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Synthesis of regioisomeric, stereoregular AABB-type polyamides from chiral diamines and diacids derived from natural amino acids

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Abstract—Two regioisomeric and stereoregular AABB-type polyamides have been synthesized using L-glutamic acid **1** and L-alaninol **4** as sources of chirality. From **4**, two derivatives of chiral diamines were prepared and regioselectively condensed with pentachlorophenyl 5-oxo-(*S*)-2-tetrahydrofurancarboxylate **3**, derived from **1**. Manipulation of functional groups and convenient deprotections led to the ammonium salts of *N*-[1′-amino-(*S*)-2′-propyl]- and *N*-[(*S*)-2′-amino-1′-propyl]-5-oxo-(*S*)-2-tetrahydrofurancarboxyamide **11** and **15**, respectively, in which the building blocks derived from **1** and **4** are linked through an amido group. Compounds **11** and **15** are, in fact, α,ω-amino acids having amino and lactone groups, and hence activated for polycondensation. Thus, polymerization of **11** took place under regio- and stereo-control to afford stereoregular poly[*N*-(1′-amino-(*S*)-2′-propyl)-carboxyamido-(*S*)-2-hydroxypentan-5-oic acid] (**16**). Similar polycondensation of **15**, under the optimized conditions employed for the synthesis of **16**, gave the regioisomeric polyamide **17**, which exhibited a molecular weight lower than that of **16**. The thermal and spectroscopic properties of optically active AABB-polyamides **16** and **17** are described.

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1. Introduction

Among the hydrolytically sensitive polymers, polyamides have attracted considerable attention. As the amide bond is quite polar, polyamides tend to be hydrophilic compounds that usually show high melting temperatures and good material properties, even at relatively low molecular weights. The introduction of functionalities and stereocenters in a polymeric chain allows control of the physical and mechanical properties of the polymer. Such functionalities are either added to the main chain or occur as pendant groups, and are usually aimed at improving both abiotic and biotic hydrolytic degradation of the material.[1–4] For the construction of chain-modified polyamides, regrowing natural products have been widely used as starting materials. In particular, carbohydrates and amino acids are frequently employed, as they provide varied functionalities and chirality to the monomeric precursors.[1–4]

Polyamides derived from naturally occurring amino acids [poly(amino acids)] can be employed for many different purposes, from medical, pharmaceutical and personal care applications to the domains of agriculture and environment.[5] Therefore, they have been the subject of intensive studies and their synthesis is a topic of current interest. New and modified methods of synthesis continue to appear in the literature.[1,4,6] However, the chemical synthesis of co-poly(amino acids) by common procedures, such as the *N*-carboxyanhydride method,[7,8] have the major disadvantage that there is no control of the sequence of the amino acids in the chain. The control of the sequence (regioregularity) and the stereochemistry (stereoregularity) in the polymerization of non-symmetric monomers is a challenging task, as the occurrence of regioisomerism leads to non-regular polymers. We have succeeded in synthesizing regio- and stereo-regular AABB-type polyamides from common monosaccharides[9–11] or amino acids.[12–14] Herein, we report our results on the synthesis of regio- and stereo-regular AABB-type polyamides based on the natural amino acids L-alanine and L-glutamic acid. They were employed as the source of chirality in the synthesis of chiral diamines and a chiral diacid, precursors of the polyamides. These building blocks were conveniently assembled to generate activated α,ω-amino acids, which could be employed for polycondensation reactions.

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2. Results and discussion

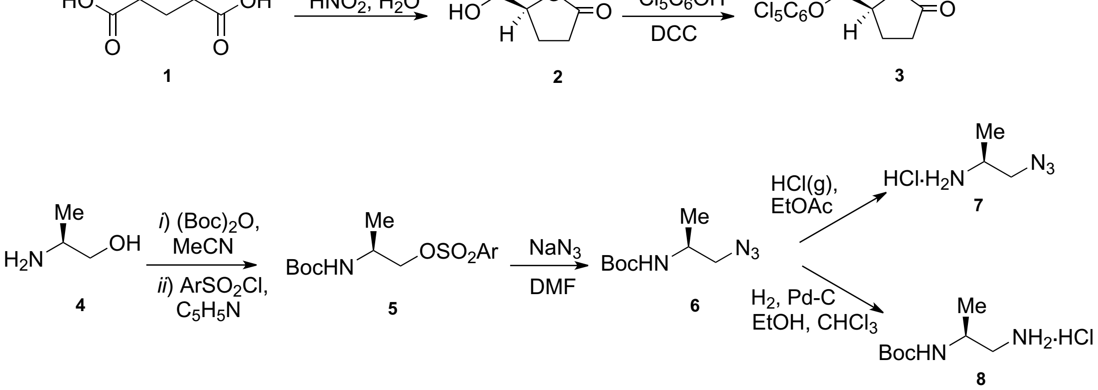
Deamination of L-glutamic acid **1** with nitrous acid afforded the γ-lactone derivative of (2*S*)-hydroxy-pentanedioic acid **2**.[15] The carboxylic acid function of **2** was converted into the pentachlorophenyl ester **3** (Scheme 1).[14] For the L-alanine-derived components of the monomers, commercially available L-alaninol [(*S*)-2-amino-1-propanol, **4**] was employed as a starting material. As shown in Scheme 1, manipulation of the functional groups from **4** led selectively to the hydrochloride salts of amines **7**[16] and **8**, via the common intermediate **6**.

Hydrogenation of **6**, or acid removal of the *N*-*tert*-butyloxycarbonyl group of **7**, would produce the same diamine, which could be polycondensed with **3** as both reactive functionalities, the pentachlorophenyl[9,17] ester and the lactone,[10,18–20] are prone to undergo aminolysis. However, such a polycondensation should lead to a non-regular AABB-type polyamide due to non-regioselective additions of non-equivalent amino groups to non-equivalent carboxyl functions. Similarly, the polymerization of tartaric acid derivatives with L-lysine produces an aregic polyamide.[21] To overcome the difficulties related to the dissymmetry of the chiral-building blocks, if the preparation of a regioregular polyamide is intended, we have designed and synthesized two precursors **10** and **12** of the α,ω-amino acid monomers **11** and **13**. Thus, compounds **10** and **12** were prepared by the regioselective addition of the amine function of **7** or **8** to the pentachlorophenyl ester of **3**. A higher reactivity for this group, compared with that of the lactone, could be anticipated as pentachlorophenolate is a good leaving group, while the rate of aminolysis of the ester should be enhanced by the presence of an electron withdrawing substituent on the α-carbon that further polarized the carbonyl group.[22] As expected, releasing the amino group of hydrochlorides **7** or **8** with *N*,*N*-diisopropylethylamine (DIPEA), followed by reaction with the pentachlorophenyl ester of **3**, led regioselectively to the corresponding adducts **10** and **12** (Scheme 2). Formation of regioisomeric hydroxy amides, resulting from aminolysis of the lactone, was not detected.

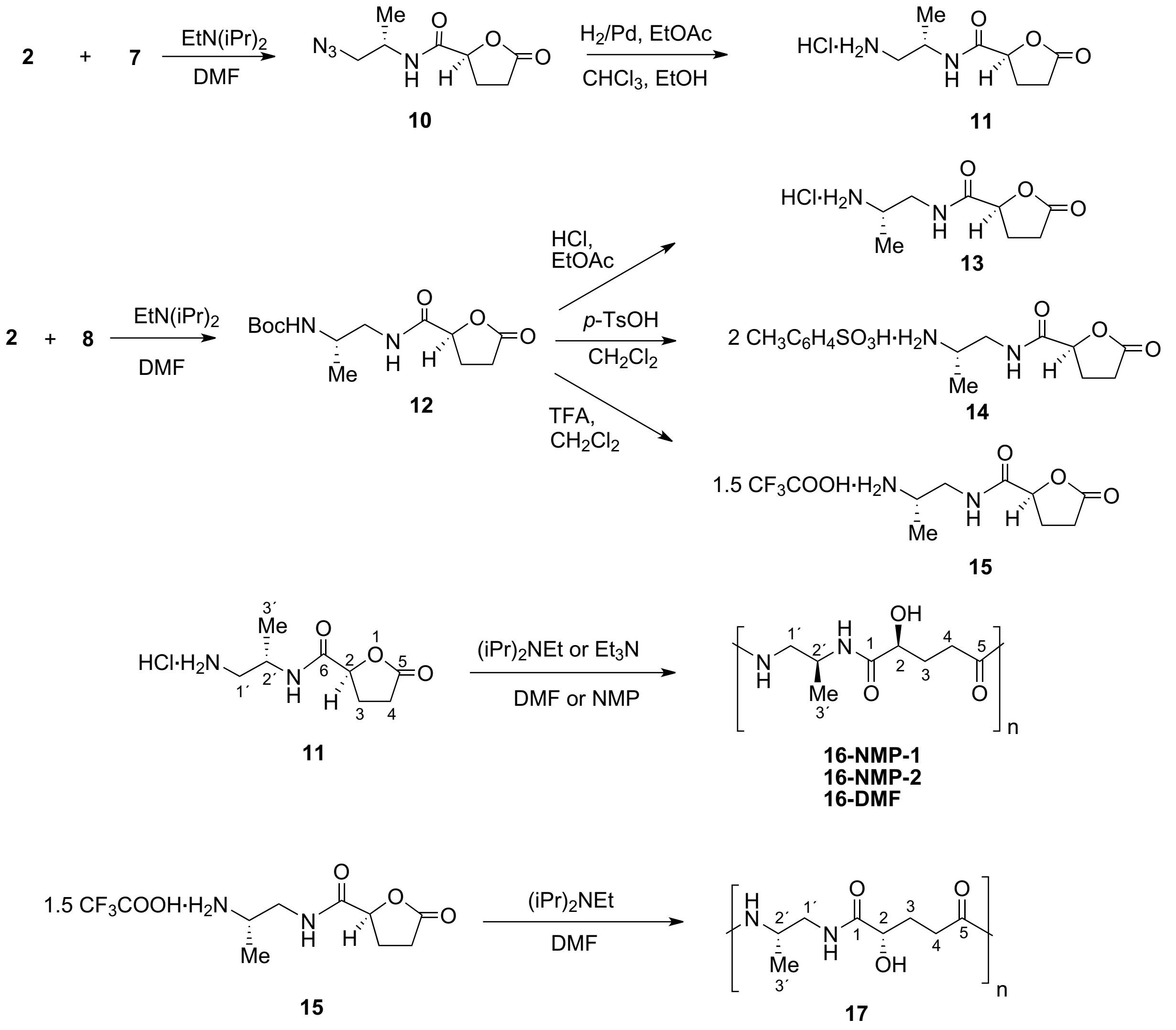
Hydrogenolysis of the azide group of **10** with Pd/C in EtOAc–$CHCl_3$–EtOH gave the hydrochloride derivative **13**. The hydrogen chloride generated in situ by hydrogenation of chloroform led to the formation of the ammonium salt,[23] while the lactone group was not affected. However, removal of the *N*-Boc protecting group of **12** with a solution of hydrogen chloride in EtOAc, led to the expected **13** accompanied by the hydroxy acid produced by hydrolysis of the lactone. This fact was evidenced, in the ^1H NMR spectrum of the product, by the strong upfield shifting of the double doublet due to H-2, from δ 4.95 in **13** to ~4.00 ppm in the hydroxy acid, as a consequence of the lactone opening. Furthermore, satellite resonances to those corresponding to **13** were observed in the ^{13}C NMR spectrum. The intensity of the satellites increased on the standing of the product in solution for longer periods.

The polymerization of α,ω-amino acid monomers **11** and **13** was next studied. The resulting polyamides were regioisomeric as they only differ in the disposition of the diamine unit in the polymeric chain. They were also stereoregular, as the formation of amide bonds was defined by the functionalities (lactone and amine) of the monomeric precursors. To optimize the polymerization conditions for **11**, two different tertiary amines and solvents were employed. The presence of a tertiary amine (DIPEA or Et_3N) was required to release the amino group of **11** from the hydrochloride; *N*-Methyl-2-pyridone (NMP) and *N*,*N*-dimethylformamide (DMF) were employed as aprotic, polar solvents to avoid precipitation of oligomers during the polymerization, which results in low molecular weights.

Polymerization of **11** in NMP using DIPEA as a base, afforded a brownish material **16-NMP-1** which was difficult to purify. The DIPEA was not completely miscible with NMP, even under vigorous stirring. Replacement of DIPEA by Et_3N led to homogeneous solutions, and to an improvement in the yield of the polyamide (**16-NMP-2**). Also, this polymer exhibited a molecular weight ($M_n = 2300$) somewhat higher than that determined for **16-NMP-1** ($M_n = 1600$). The molecular weights (M_n) were estimated by the spectral integration end-group analysis



Scheme 1.



Scheme 2.

method. Thus, the ^{1}H NMR spectrum (DMSO-d_6) of the polyamides showed a small peak at ∼2.9 ppm that was attributed to the methylene protons (H-1′a, 1′b) adjacent to the terminal NH_2 group of the polymer chain. Also, the resonance of H-2 (adjacent to the lactone carboxylate) was considered, as it appears in a clean region of the spectra (δ 4.89 ppm).

Polymerization of **11** in DMF containing DIPEA led to better results. In this case, a gel-like mass was formed and the polyamide **16-DMF** was isolated as a white solid by precipitation from MeOH–ethyl ether (1:3). The yield of **16-DMF** (89%) and its M_n value (5100, ^{1}H NMR) were higher than those determined for **16-NMP-1** and **16-NMP-2**. These materials exhibited very similar ^{1}H and ^{13}C NMR spectra and their FTIR spectra were also alike.

The molecular weight distribution for **16-DMF** was determined by size exclusion chromatography (SEC), using THF as the mobile phase. To dissolve the polyamide in this solvent, it was subjected to trifluoroacetylation.[24] From the SEC chromatogram M_w (4900), M_n (4827) and polydispersity values (1.015) were obtained.

The thermal behavior of **16-DMF** was studied by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Thus, DSC during the first heating cycle (Fig. 1, trace a) showed a broad range transition (18–95 °C), probably due to the loss of water, followed by an endotherm (ΔH 23.5 J g^{-1}) corresponding to the melting transition (T_m 183 °C). If the heating was continued, immediately after the melting, decomposition of the sample was observed (T_d 250 °C). This was confirmed by TGA (Fig. 2), which showed a gradual loss of mass (4.6%) between 36 and 95 °C, followed by decomposition (onset = 197 °C, endset = 263 °C, mid point 248 °C), with a total weight loss of 26.3%. Therefore, a DSC experiment was conducted by heating the sample until the T_m was reached, after which it was cooled. During the cooling, a glass transition (T_g) took place at 79 °C (Fig. 1, trace b). This T_g was also observed in a second heating cycle (Fig. 1, trace c), but no other

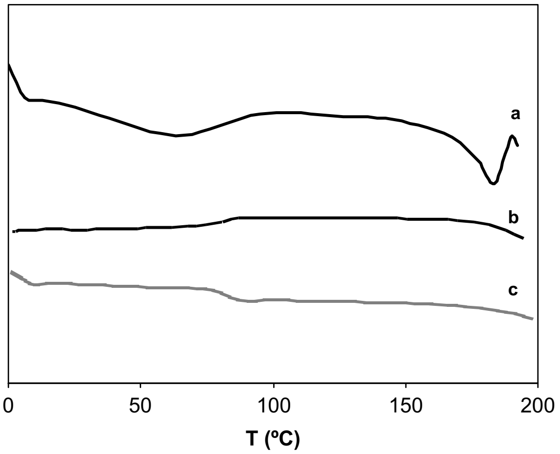


Figure 1. DSC thermogram for polyamide **16**. (a) First heating cycle, (b) cooling and (c) second heating cycle.

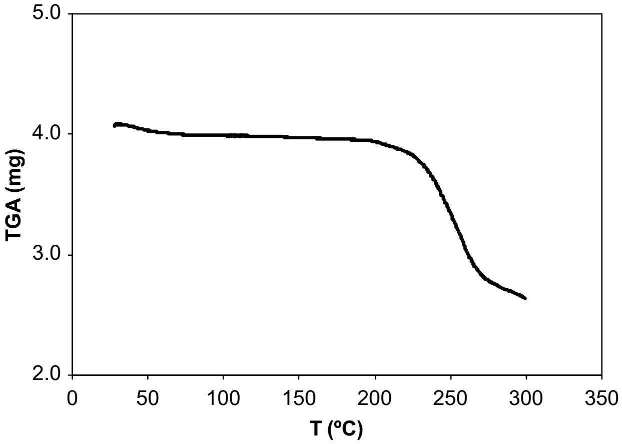


Figure 2. Thermogravimetric analysis (TGA) for polyamide **16**.

thermal transitions occurred, indicating that the polyamide does not crystallize from the melting. These results seem to indicate that **16-DMF** precipitated from solution is only slightly crystalline.

The optimized conditions employed for the polymerization of **11** were applied to **13**. In this case, the polycondensation was unsuccessful, as it led to pale brown, syrupy products, which could not be purified. As already mentioned, amino lactone **13** was accompanied by the hydroxy acid formed by hydrolysis of the lactone. We investigated the preparation of other monomeric salts from **12**, taking into account that polymerizations are severely affected by the presence of impurities as well as by the non stoichiometric ratio of reacting groups.[25] Organic acids were used for the removal of the *N*-Boc protecting group, to prevent the opening of the lactone. Thus, when *p*-toluenesulfonic acid was employed, an excess of this reagent was required for the complete removal of the carbamate, and *p*-toluenesulfonate **14** was obtained as a crystalline product. The NMR spectra of **14** indicated that the salt contained as much as twice the expected amount of *p*-TsOH. The elemental analysis confirmed that **14** is in fact a ditosylate. As for **13**, polymerization of **14** was not satisfactory and syrupy products contaminated with *p*-TsOH–Et_3N were isolated.

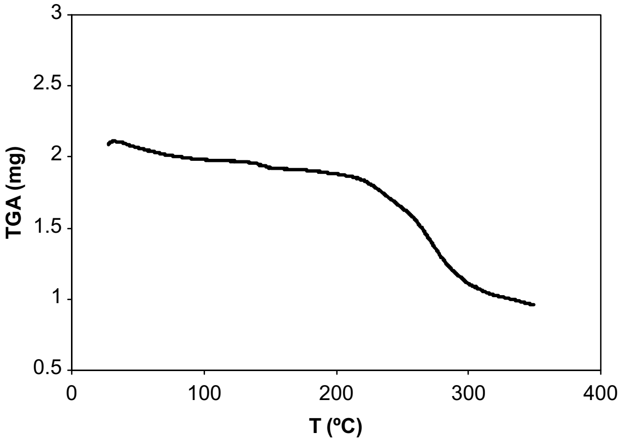


Figure 3. Thermogravimetric analysis (TGA) for polyamide **17**.

The best results were obtained when the polymerization was conducted starting from the trifluoroacetate **15**, obtained by hydrolysis with trifluoroacetic acid (TFA) of the *N*-Boc protecting group of **12**. The polycondensation was conducted under the optimized conditions employed for the polymerization of **11**, using DMF as the solvent and Et_3N as a base. After purification the solid polyamide **17** was obtained in 61% yield.

The ^1H and ^{13}C NMR spectra of **17** showed rather broad signals, suggesting that we were dealing with a rather heterogeneous material. A preliminary determination of the molecular weight by ^1H NMR spectral integration of end-groups, gave a relatively low M_n value (1400). The SEC analysis of the polyamide **17**, as the *N*-trifluoroacetyl derivative,[24] confirmed a low molecular weight ($M_w = 1160$, $M_n = 930$) and a substantial degree of polydispersity (1.25). In agreement with this result, the Maldi-MS spectrum of **17** revealed a distribution of oligomers having from 3 to 10 repeating units. From the mass and intensity of the peaks, number and average molecular weights ($M_w = 1310$, $M_n = 1090$) were calculated.

The DSC analysis of **17** showed that thermal transitions did not take place in the temperature range of 30–200 °C. A similar behavior was observed during the cooling of the sample, or during a second heating cycle. These results are indicative that **17** is an amorphous material. From TG measurements (Fig. 3), it was established that the decomposition of **17** starts at 197 °C, with a temperature of decomposition (T_d) of 262 °C and a total weight loss of 41.6%.

3. Conclusion

α,ω-Amino acid co-monomers were prepared by the regioselective formation of an amide linkage between chiral diamines and a chiral pentanedioic acid derivative. The diamines were prepared from L-alaninol and the diacid from L-glutamic acid. The co-monomers were synthesized to ensure regio- and stereo-selectivity in the polymerization. This reaction took place by intermolecular attack of the terminal amine group to the lactone function, which acts as an active ester. When the amino group is linked to a primary carbon, the polycondensation, under optimized conditions, led to an optically active, stereoregular polyamide that exhibited a relatively high molecular weight. However, under similar conditions, the co-monomer that carries the amino group on a more hindered secondary carbon yielded a low molecular weight polymer. These results constitute as an additional example to the known fact that relatively minor structural changes in the participating monomers have a strong influence in the degree of polymerization.

4. Experimental

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 on a Bruker AC-200 or Bruker AMX-500 spectrometers. 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 the 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. Maldi-MS measurements were performed using a laser desorption time-of-flight mass spectrometer Bruker Daltonics OmniFlex instrument. Differential scanning chromatography (DSC) was conducted with a Mettler DSC 822, with thermal system Star e (software 6.1). Samples of about 5 mg were heated at a rate of 10 °C min^{-1}, and then cooled to room temperature, at the same rate. Thermogravimetric analysis (TG) was performed in a Shimadzu TGA-51 instrument.

4.1. Pentachlorophenyl 5-oxo-(*S*)-2-tetrahydrofuran-carboxylate 3

This compound was prepared from L-glutamic acid **1** as previously described.[14]

4.2. (*S*)-2-*N*-(*tert*-Butoxycarbonyl)amino-1-propylamine hydrochloride 8

1-Azido-(*S*)-2-(*N*-*tert*-butoxycarbonyl)aminopropane **6**[16] (0.70 g, 3.50 mmol) dissolved in 10:1:2 EtOAc–EtOH–$CHCl_3$ (18 mL) was hydrogenated at 45 psi and room temperature, in the presence of 10% Pd/C (70 mg). After 6 h, the catalyst was filtered, and the residue washed with MeOH. The filtered and washing liquids were pooled and concentrated to give a solid, which was recrystallized from MeOH–ethyl ether to give **8** (0.62 g, 85%); mp = 172–173 °C, $[\alpha]_D = +2.1$ (*c* 1, DMSO); ^1H NMR (DMSO-d_6, 500 MHz) δ 8.10 (br s, 3H, NH_3^+), 6.87 (d, 1H, $J = 7.8$ Hz, N*H*), 3.71 (m, 1H, H-2), 2.76 (m, 2H, H-1a, 1b), 1.39 (s, 9H, $(CH_3)_3CO$), 1.07 (d, 3H, $J = 6.8$ Hz, H-3); ^{13}C NMR (DMSO-d_6, 125.3 MHz) δ 155.1 (NCO_2), 78.1 (Me_3CsO), 44.2, 43.1 (C-1, 2), 28.2 $[(CH_3)_3CO]$, 18.2 (C-3). Anal. Calcd for $C_8H_{18}N_2O_2\cdot 1.2HCl$: C, 44.08; H, 8.82; N, 12.86. Found: C, 43.92; H, 8.88; N, 13.04.

4.3. *N*-(1′-Amino-(*S*)-2′-propyl)-5-oxo-(*S*)-2-tetrahydrofurancarboxyamide hydrochloride 11

A solution of **3** (1.19 g, 3.15 mmol) in dry DMF (17 mL) and *N*,*N*-diisopropylethylamine (DIPEA, 1.12 mL) was cooled to 0 °C and a solution of **7**[16] (0.43 g, 3.15 mmol) in dry DMF (17 mL) was added dropwise. The mixture was stirred at room temperature for 16 h and then the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (80 mL) and successively extracted with 50 mL portions of water, aqueous 10% NaOH, water, aqueous 10% HCl, and water. The organic layer was dried over $MgSO_4$ and concentrated to afford **10** (0.57 g, quantitative), which was homogeneous ($R_f = 0.50$) by TLC (EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.45 (br s, 1H, N*H*), 4.79 (t, 1H, $J = 7.6$ Hz, H-2), 4.11 (m, 1H, H-2′), 3.40 (dd, 1H, $J = 4.9$, 12.3 Hz, H-1′a), 3.31 (dd, 1H, $J = 5.1$, 12.3 Hz, H-1′b), 2.63–2.23 (m, 4H, H-3a, 3b, 4a, 4b), 1.16 (d, 3H, $J = 6.8$ Hz, H-3′); ^{13}C NMR ($CDCl_3$, 125.3 MHz) δ 175.6 (C-6), 168.8 (C-5), 77.3 (C-2), 55.2 (C-1′), 44.9 (C-2′), 27.6, 25.6 (C-3, 4), 17.8 (C-3′). Crude **10** (0.57 g) was dissolved in 10:1:2 EtOAc–EtOH–$CHCl_3$ (15 mL) and hydrogenated at 45 psi in the presence of 10% Pd/C (70 mg) for 6 h. The catalyst was filtered and the filtrate was concentrated to give a syrup, which crystallized upon addition of dry ethyl ether to a methanolic solution, to afford **11** (0.65 g, 91.5%); mp = 169–171 °C, $[\alpha]_D = +40.0$ (*c* 1.0, DMSO); ^1H NMR (DMSO-d_6, 200 MHz) δ 8.43 (d, 1H, $J = 8.0$ Hz, CON*H*), 8.19 (br s, 3H, NH_3^+), 4.89 (dd, 1H, $J = 5.5$, 7.7 Hz, H-2), 4.06 (m, 1H, $J = 6.7$ Hz, H-2′), 2.86 (d, 2H, $J = 6.7$ Hz, H-1′a, 1′b), 2.55–2.15 (m, 4H, H-3a, 3b, 4a, 4b), 1.13 (d, 1H, $J = 6.7$ Hz, H-3′); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 176.9, 169.3 (C-5, 6), 76.9 (C-2), 42.8 (C-1′, 2′), 27.1, 25.3 (C-3, 4), 17.8 (C-3′). Anal. Calcd for $C_8H_{14}N_2O_3\cdot HCl$: C, 43.15; H, 6.79; N, 12.58. Found: C, 43.11; H, 6.82; N, 12.45.

4.4. *N*-[(*S*)-2′-*N*-(*tert*-Butoxycarbonyl)amino-1′-propyl]-5-oxo-(*S*)-2-tetrahydrofuran carboxyamide 12

A solution of **3** (1.08 g, 2.8 mmol) in dry DMF (16 mL) and *N*,*N*-diisopropylethylamine (DIPEA, 1.0 mL) was cooled to 0 °C and a solution of **8** (0.60 g, 2.85 mmol) in dry DMF (16 mL) was slowly added, over a period of 2 h, under Ar. The reaction mixture was stirred for 16 h at room temperature and concentrated. The resulting residue, which showed by TLC (EtOAc) a main spot having $R_f = 0.40$, was subjected to column chromatography using hexane–EtOAc (from 5:1 to 3:1). Concentration of the fractions that contained the main product ($R_f = 0.40$) afforded **12** (0.56 g, 70%) as a crystalline solid, which was recrystallized from ethyl ether–hexane. mp = 136–138 °C; $[\alpha]_D = -17.2$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.98 (br s, 1H, N*H*), 4.84 (t, 1H, $J = 7.1$ Hz, H-2), 4.58 (t, 1H, $J = 7.2$ Hz, N*H*), 3.84 (m, 1H, H-2′), 3.42 (d, 1H, $J = 13.1$ Hz, H-1′a), 3.14 (dd, 1H, $J = 8.9$, $J = 13.1$ Hz, H-1′b), 2.65–2.50 and 2.39 (2 m, 3H and 1H, respectively, H-3a, 3b, 4a, 4b), 1.44 [$(CH_3)_3CO$], 1.43 (d, 3H, $J = 6.8$ Hz, H-3′); ^{13}C NMR ($CDCl_3$, 125.3 MHz) δ 175.8 (C-6), 170.0 (C-5), 155.8 (NCO_2), 79.8 (Me_2CO), 46.4, 45.7 (C-1′, 2′), 28.4 [$(CH_3)_3CO$], 27.5, 25.9, (C-3, 4), 18.7 (C-3′). Anal. Calcd for $C_{13}H_{22}N_2O_5$: C, 54.53; H, 7.74; N, 9.78. Found: C, 54.50; H, 7.82; N, 9.73.

4.5. *N*-[(*S*)-2′-Amino-1′-propyl]-5-oxo-(*S*)-2-tetrahydrofurancarboxyamide hydrochloride 13

To a solution of **12** (0.40 g, 1.40 mmol) in dry EtOAc (4.0 mL) was added a solution of EtOAc (4.0 mL) saturated with hydrogen chloride. The mixture was stirred for 5 h at room temperature and then concentrated to afford crude **13** (0.30 g, 95%), which could not be induced to crystallize. Examination of this product by NMR spectroscopy revealed the presence of the lactone (major) and its ring-opening product, the corresponding hydroxy ester. The ^1H NMR spectrum of a preparation enriched in **13** showed the following signals: ^1H NMR (DMSO-d_6, 200 MHz) δ 8.58 (br s, 1H, CON*H*), 8.12 (br s, 3H, NH_3^+), 4.95 (dd, 1H, $J = 5.7$, 7.7 Hz, H-2), 3.28 (m, 3H, H-1′a, 1′b, 2′), 2.58–2.10 (m, 4H, H-3a, 3b, 4a, 4b), 1.16 (d, 3H, $J = 6.2$ Hz, H-3′); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 176.8 (C-6), 170.1 (C-5), 76.8 (C-2′), 41.7 (C-1′), 27.1, 25.5 (C-3,4), 16.0 (C-3′). Signals having smaller intensities due to the hydroxy acid were also observed: δ 70.0 (C-2), 46.7 (C-2′), 41.4 (C-1′), 29.3, 29.2 (C-3, 4), 16.0 (C-3′).

4.6. *N*-[(*S*)-2′-Amino-1′-propyl]-5-oxo-(*S*)-2-tetrahydrofurancarboxyamide *p*-toluenesulfonate 14

To a solution of **12** (0.254 g, 0.89 mmol) in dry CH_2Cl_2 (5.0 mL) was added *p*-toluenesulfonic acid (0.306 g, 1.78 mmol). The mixture was stirred at room temperature for 5 h. After evaporation of the solvent, the solid residue was recrystallized from EtOAc, to afford **14** (0.286 g, 61%); mp = 126–127 °C; $[\alpha]_D = +10.6$ (*c* 0.6, DMSO); ^1H NMR (500 MHz, DMSO-d_6) δ 8.00 (br t, 1H, $J = 5.8$ Hz, *H*NCO) 7.68 (d, 4H, $J = 8.0$ Hz, H-aromatic), 7.66 (s, 3H, NH_3^+), 7.13 (d, 4H, $J = 8.0$ Hz, H-aromatic), 4.78 (dd, 1H, $J = 7.7$, $J = 6.0$ Hz, H-2), 3.57 (m, 1H, H-2′), 3.48 (m, 1H, H-1′a), 3.31 (m, 1H, H-1′b), 2.41–2.27 and 2.16 (2 m, 3H and 1H, respectively, H-3a, 3b, 4a, 4b), 2.34 (s, 6H, ArCH_3), 1.20 (d, 3H, $J = 6.4$ Hz, H-3′);^{13}C NMR (50.3 MHz, DMSO-d_6) δ 177.4 (C-6), 171.1 (C-5), 141.1, 140.9, 129.1, 125.8 (C-aromatic), 77.6 (C-2), 48.2, 42.6 (C-1′, 2′), 27.6, 25.5 (C-3, 4), 21.4 (ArCH_3), 16.4 (C-3′). Anal. Calcd for $C_8H_{14}N_2O_3 \cdot 2CH_3C_6H_4SO_3H$: C, 49.79, H, 5.70; N, 5.28; S, 12.08. Found: C, 49.55; H, 5.57; N, 5.63; S, 11.61.

4.7. *N*-[(*S*)-2′-Amino-1′-propyl]-5-oxo-(*S*)-2-tetrahydrofurancarboxyamide trifluoroacetate 15

A solution of **12** (0.35 g, 1.22 mmol) in dry CH_2Cl_2 (4.0 mL) containing TFA (0.28 mL, 3.66 mmol) was stirred at room temperature for 5 h, when TLC (EtOAc) showed that the starting **12** ($R_f = 0.40$) had been completely consumed. The mixture was concentrated to afford **15** (0.40 g, 92%) as a slightly yellow syrup that resisted crystallization from various solvents; $[\alpha]_D = +5.8$ (*c* 1, DMSO); ^1H NMR (500 MHz, DMSO-d_6) δ 8.41 (br t, 1H, $J \approx 6.0$ Hz, *H*NCO), 7.84 (s, 3H, NH_3^+), 4.89 (dd, 1H, $J = 6.1$, $J = 8.0$ Hz, H-2), 3.33–3.21 (m, 3H, H-1′a, 1′b, 2′), 2.54–2.41 and 2.14 (2 m, 3H and 1H, respectively, H-3a, 3b, 4a, 4b), 1.15 (d, 3H, $J = 6.2$ Hz, H-3′); ^{13}C NMR (125.3 MHz, DMSO-d_6) δ 176.8 (C-6), 170.4 (C-5), 158.4, (F_3CCO_2H), 76.9 (C-2), 46.6, 41.8 (C-1′, 2′), 27.1, 25.4 (C-3, 4), 16.0 (C-3′). Anal. Calcd for $C_8H_{14}N_2O_3 \cdot 1.5F_3CCO_2H$: C, 36.97; H, 4.34; N, 7.84. Found: C, 36.48; H, 4.23; N, 7.60.

4.8. Poly[*N*-(1′-amino-(*S*)-2′-propyl)-carboxyamido-(*S*)-2-hydroxypentan-5-oic acid] 16

4.8.1. Polymerization of 11 in *N*-methyl-2-pyridone (NMP)–DIPEA. To a suspension of **11** (90 mg, 0.40 mmol) in NMP (0.23 mL) was added DIPEA (0.13 mL, 0.75 mmol) under Ar. The vial was sealed and the mixture vigorously stirred at 70 °C for 5 days. The resulting brownish gel was dissolved in MeOH (1 mL) and filtered through a diatomaceous earth bed. The filtrate was diluted with ethyl ether to afford **16-NMP** (37 mg, 50%); ^1H NMR (500 MHz, DMSO-d_6) δ 7.87 (br t, 1H, $J = 5.6$ Hz, *H*NCO-5), 7.55 (d, 1H, $J = 8.2$ Hz, *H*NCO-1), 5.53 (d, 1H, $J = 4.0$ Hz, HO), 3.85 (m, 2H, H-2, 2′), 3.10 (dd, 2H, $J = 5.6$, $J = 6.5$ Hz, H-1a′,1′b), 2.15 (m, 2H, H-4a, 4b), 1.88 (m, 1H, H-3a), 1.67 (m, 1H, H-3b), 1.02 (d, 3H, $J = 6.7$ Hz, H-3′), ^{13}C NMR (DMSO-d_6, 125.3 MHz) δ 173.1, 172.5 (HN*C*O), 70.4 (C-2), 44.2, 43.3 (C-1′, 2′), 31.1, 30.3 (C-3, 4), 17.9 (C-3′); $M_n = 1600$ (estimated by NMR).

4.8.2. Polymerization of 11 in NMP-ET_3N. Monomer **11** (0.29 g, 1.31 mmol) was suspended in NMP (0.70 mL) and Et_3N (0.40 mL, 2.62 mmol) was added at room temperature, under Ar. The solution was stirred for 16 h at 70 °C, when formation of a gel was observed. After the addition of NMP (0.70 mL), stirring was continued at 70 °C for 4 days. The resulting slightly yellow gel was dissolved in dry MeOH (5 mL) and a solid was obtained upon the addition of ethyl ether (10 mL). The solid was recovered by centrifugation, and it was washed three times with ethyl ether to afford **16-NMP-2** (0.17 g, 70%). This polyamide showed the same spectral properties as the one synthesized above (4.1.8.1); $M_n = 2300$ (estimated by NMR).

4.8.3. Polymerization of 11 in DMF–DIPEA. Compound **11** (0.337 g, 1.51 mmol) was dissolved in dry DMF (1 mL) and DIPEA (0.53 mL, 3.04 mmol) was added under Ar. The vial was sealed and the mixture vigorously stirred at 50 °C for 5 days. The resulting gel was dissolved in dry

MeOH (5 mL) and the polymer was precipitated with ethyl ether (15 mL). The solid was collected by centrifugation and it was purified by dissolution in MeOH and precipitation with ethyl ether; the solid was washed with ethyl ether (three times). The polyamide **16-DMF** was obtained as a white solid (0.25 g, 89%); $[\alpha]_D = -27.4$ (c 1, DMSO); which showed the same spectral properties as **16-NMP-1** and **16-NMP-2**; FTIR: 3436 (s, OH), 3333, 3261 (s, NH), 1651, 1635 (vs, amide I), 1570 cm^{-1} (vs, amide II); $M_w = 4900$, $M_n = 4827$, polydispersity = 1.025 (SEC); $M_n = 5100$ (estimated by NMR). Anal. Calcd for $C_8H_{14}N_2O_3 \cdot 0.5H_2O$: C, 49.17; H, 7.74; N, 14.34. Found: C, 49.22; H, 7.56; N, 14.24.

4.9. Poly[*N*-[(*S*)-2′-amino-1′-propyl]-carboxyamido-(*S*)-2-hydroxypentan-5-oic acid] 17

To a solution of **15** (0.397 g, 1.33 mmol) in dry DMF (1 mL) was added DIPEA (0.35 mL, 2.0 mmol) under Ar. The mixture was stirred at 50 °C for 5 days and processed as described for the preparation of **16-DMF**. The polyamide **17** (0.151 g, 61%) was obtained as a yellowish solid; $[\alpha]_D = -15.0$ (c 0.5, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.90–7.75 (m, NH), 3.86 (m, 2H, H-2, 2′), 3.09 (m, 2H, H-1′a, 1′b), 2.12 (m, 2H, H-3a, 3b), 1.88 (m, 1H, H-4a), 1.68 (m, 1H, H-4b), 1.05 (m, 3H, H-3′); ^{13}C NMR (125, DMSO-d_6) δ 173.8–171.7 (C-1, C-5), 70.4 (C-2), 44.3, 43.2 (C-1, C-2′), 31.2, 30.3 (C-3, C-4), 17.9 (C-3′); FTIR: 3317 (br s, NH), 3098 (w, amide B), 1652 (vs, amide I), 1562 cm^{-1} (vs, amide II); $M_w = 1160$, $M_n = 930$, polydispersity = 1.25 (SEC); $M_w = 1310$, $M_n = 1090$, polydispersity = 1.20 (Maldi-MS). Anal. Calcd for $(C_8H_{14}N_2O_3)_n \cdot nH_2O$: C, 47.05; H, 7.90; N 13.72. Found: C, 47.51; H, 8.41; N, 14.10.

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References

1. Okada, M. *Prog. Polym. Sci.* **2002**, *27*, 87–133.
2. Varela, O.; Orgueira, H. A. *Adv. Carbohydr. Chem. Biochem.* **1999**, *55*, 137–174.
3. Gonsalves, K. E.; Mungara, P. M. *Trends Polym. Sci.* **1996**, *4*, 25–31.
4. Thiem, J.; Bachmann, F. *Trends Polym. Sci.* **1994**, *2*, 425–432.
5. Obst, M.; Steinbüchel, A. *Biomacromol.* **2004**, *95*, 1166–1176.
6. Sanda, F.; Endo, T. *J. Synth. Org. Chem.* **2001**, *59*, 648–658.
7. Kricheldorf, H. R. *α-Amino acids-N-Carboxyanhydrides and Related materials*; Springer: New York, 1987.
8. Pascal, R.; Cottet, H.; Boiteau, L.; Danger, G. *J. Am. Chem. Soc.* **2006**, *128*, 7412–7413.
9. Bueno, M.; Zamora, F.; Molina, I.; Orgueira, H. A.; Varela, O.; Galbis, J. A. *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *35*, 3643–3645.
10. Orgueira, H. A.; Varela, O. *J. Polym. Sci.: Part A, Polym. Chem.* **2001**, *39*, 1024–1030.
11. Romero Zaliz, C. L.; Varela, O. *Tetrahedron: Asymmetry* **2005**, *16*, 97–103.
12. Orgueira, H. A.; Varela, O. *Tetrahedron: Asymmetry* **1997**, *8*, 1383–1589.
13. Orgueira, H. A.; Bueno, M.; Funes, J. L.; Galbis, J. A.; Varela, O. *J. Polym. Sci.: Part A, Polym. Chem.* **1998**, *36*, 2741–2748.
14. Orgueira, H. A.; Erra-Balsells, R.; Nonami, H.; Varela, O. *Macromolecules* **2001**, *34*, 687–695.
15. Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449–1452.
16. Gómez, R. V.; Orgueira, H.; Varela, O. *Arkivoc* **2003**, *X*, 201–208.
17. Bueno, M.; Galbis, J. A.; García-Martín, M. G.; de Paz, M. V.; Zamora, F.; Muñoz-Guerra, S. *J. Polym. Sci., Part A: Polym. Chem.* **1995**, *33*, 229–305.
18. Lederkremer, R. M.; Varela, O. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 125–209.
19. Chen, L.; Kiely, D. E. *J. Org. Chem.* **1996**, *61*, 5847–5851.
20. Kiely, D. E.; Chen, L.; Lin, T. *J. Polym. Sci.: Part A: Polym. Chem.* **2000**, *38*, 594–603.
21. Bou, J. J.; Muñoz-Guerra, S. *Polymer* **1995**, *36*, 181–186.
22. Sanui, K.; Tanaka, H.; Suzuki, T. *J. Polym. Sci., Polym. Chem. Ed.* **1977**, *15*, 2531–2534.
23. Secrist, J. A., III; Logue, A. M. W. *J. Org. Chem.* **1972**, *37*, 335–336.
24. Jacobi, E.; Schuttenberg, H.; Schulz, R. C. *Makromol. Chem. Rapid Commun.* **1980**, *1*, 397–402.
25. Schule, E. C. Encyclopedia of Polymer Science and Technology. In *Polyamides Plastics*; Bikales, N. M., Conrad, J., Eds.; John Wiley: New York, 1969; pp 460–482.