Available online at www.sciencedirect.com
SCIENCE DIRECT®
Carbohydrate Research 341 (2006) 1498–1504
Carbohydrate RESEARCH

Synthesis of polyhydroxy amino acids based on D- and L-alanine from D-*glycero*-D-*gulo*-heptono-1,4-lactone

Romina V. Gómez, Adriana A. Kolender and Oscar Varela*

CIHIDECAR-CONICET, Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Pabellón II, Ciudad Universitaria, 1428 Buenos Aires, Argentina

Received 19 January 2006; received in revised form 14 March 2006; accepted 19 March 2006
Available online 18 April 2006

Abstract—2-Amino-2,3-dideoxy-D-*manno*-heptonic acid (**7**) has been synthesized from 2,5,6,7-tetra-*O*-acetyl-3-deoxy-D-*gluco*-heptono-1,4-lactone (**1**), which was readily prepared from D-*glycero*-D-*gulo*-heptono-1,4-lactone. O-Deacetylation of **1** followed by treatment with 13:1 (v/v) 2,2-dimethoxypropane/acetone in the presence of *p*-toluenesulfonic acid gave methyl 3-deoxy-4,5:6,7-di-*O*-isopropylidene-D-*gluco*-heptonate (**3**) as a crystalline product (80% yield). The free hydroxyl group (OH-2) of **3** was mesylated and substituted by azide to give the corresponding azide derivative **5**. Hydrogenolysis and further hydrolysis of the ester function of **5** afforded α-amino acid **7** (43% overall yield from **1**). Compound **7** is an analog of L-alanine having a polyhydroxy chain attached to C-3. The diastereoisomer of **7** at C-2, 2-amino-2,3-dideoxy-D-*gluco*-heptonic acid (**12**) was also prepared from **3**, by a route that involved 2,3-dideoxy-2-iodo derivative **8** as a key intermediate.

Keywords: Sugar amino acids; Polyhydroxy amino acids; D-Alanine; L-Alanine; Acetonation

1. Introduction

Carbohydrate-based polymers can be obtained by either grafting a polymeric chain with carbohydrates or incorporating a carbohydrate moiety in the backbone. The resulting polymers have been investigated as potential biomaterials, particularly as scaffolds for the controlled delivery of drugs, and in the food, fiber, and coating industries.[1,2]

Biocompatible polymers that are made of naturally occurring building blocks are preferred for biomedical applications because their degradation products are usually nontoxic and can be properly metabolized by living tissues.[3,4] Considering this point of view, amino acids derived from carbohydrates could be one of the most promising candidates as monomeric precursors of polyamides.[5,6] Peptidomimetics and peptides derived from sugar amino acids are able to form inherent high ordered structures and show varied properties, which depend on the sugar amino acid composition and sequence.[7]

In our laboratory, we have synthesized ω-amino acids derived from hexoses,[8–10] and their polymerization reactions have been studied.[10,11] Similarly, polycondensation of *O*-protected 6-amino-6-deoxy-D-gluconate,[12] D-allonate,[13] and D-galactonate[14] has been described, and amino acids derived from pentoses have also been synthesized[15] and polymerized.[16]

On the other hand, carbohydrates play an important role in their interactions with proteins, and polymeric materials bearing pendant carbohydrate chains serve as cell surface mimics.[17] Therefore, we describe here a convenient synthesis of a sugar derived α-amino acid that can be seen as an L-alanine analog, bearing a 4-carbon polyhydroxyl chain at C-3. For comparison, the diastereoisomeric amino acid, having the opposite configuration at C-2, was also prepared. The polycondensation of the L-amino acid should lead to a stereoregular polyalanine selectively substituted at C-3 by a polyol.

* Corresponding author. Tel./fax: +54 11 4576 3352; e-mail: varela@qo.fcen.uba.ar

0008-6215/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carres.2006.03.028

2. Results and discussion

3-Deoxy compound **1** (Scheme 1) was prepared from commercially available D-*glycero*-D-*gulo*-heptono-1,4-lactone following a known procedure.[18] O-Deacetylation of **1** with sodium methoxide afforded crystalline 3-deoxy-D-*gluco*-heptono-1,4-lactone (**2**). The ^{1}H NMR spectrum of **2** allowed a first order analysis, and showed large values for the coupling constants of H-2 ($J_{2,3} = 8.9$ Hz, $J_{2,3'} = 11.2$ Hz) indicating that H-2 is axially oriented and it lies out of the angle formed by H-3 and H-3′, in the preferred E_3 conformation of these types of lactones.[18,19]

The introduction of an amino group at C-2 required the selective activation of HO-2 and the protection of the remaining hydroxyl groups. For our purposes, such protecting groups should be readily removed under smooth acidic conditions. Therefore, we decided to employ acetonides as protecting groups taking into account the fact that isopropylidenation of aldonolactones with 2,2-dimethoxypropane usually leads to lactone opening and formation of isopropylidene derivatives of the corresponding methyl ester of the aldonic acid.[9,20,21] Furthermore, we took into account that the configuration of the C-4–C-7 fragment of **2** has the arabino stereochemistry, and it is known that open chain derivatives of arabinose are fully protected on acetonation.[22] As expected, the treatment of lactone **2** with 13:1 (v/v) 2,2-dimethoxypropane/acetone in the presence of *p*-toluenesulfonic acid afforded the 4,5:6,7-di-*O*-isopropylidene derivative of methyl ester **3** in 80% yield. The free hydroxyl group at C-2 of **3** was sulfonylated with mesyl chloride in pyridine to give **4**.

The ^{1}H NMR spectra of compounds **3** and **4** indicated a preference in solution for the planar zigzag conformation, somewhat distorted by the two dioxolane rings attached to the chain. The large value for $J_{5,6}$ (>8 Hz) suggested an anti-disposition for H-5 and H-6, and the coupling constants of H-3,3′with H-2 and H-4 are also indicative of conformational stability for the C-1–C-4 segment.

Treatment of **4** with sodium azide in DMF afforded azide derivative **5** in 87% yield. The ^{1}H NMR spectrum of **5** showed similar coupling constants for the protons of the C-4–C-7 fragment as those in **3** and **4**, suggesting a similar conformation. Changes in $J_{2,3}$ and $J_{2,3'}$ values should be expected as a result of the inversion of the configuration of C-2. However, the coupling constants in **5** appeared averaged, and also the value of $J_{3',4}$ was somewhat smaller than that in **4**, indicating conformational mobility for the C-1–C-4 fragment. In fact, the introduction of azide on C-2 generates a 1,3-parallel N,O-interaction in the planar zigzag conformation that may be relieved by clockwise rotation of the C-2–C-3 linkage. The contribution of the resulting sickle conformer (Fig. 1) to the conformational equilibrium was in agreement with the observed coupling constant values and with the cross-peaks between H-2–H-3′, H-3′–H-5, H-3–H-4, and H-4–H-6 in the NOESY spectrum of **5**.

The hydrogenolysis of the azide group of **5** was performed using Pd/C as catalyst and a mixture of EtOAc/$CHCl_3$ as solvent. Under these conditions, the hydrogen chloride smoothly released by hydrogenation of chloroform does not produce hydrolysis of the isopropylidene protecting groups.[23] The ester function of the resulting compound **6** was hydrolyzed with KOH

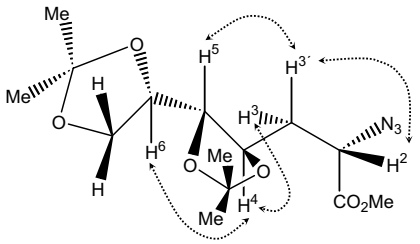
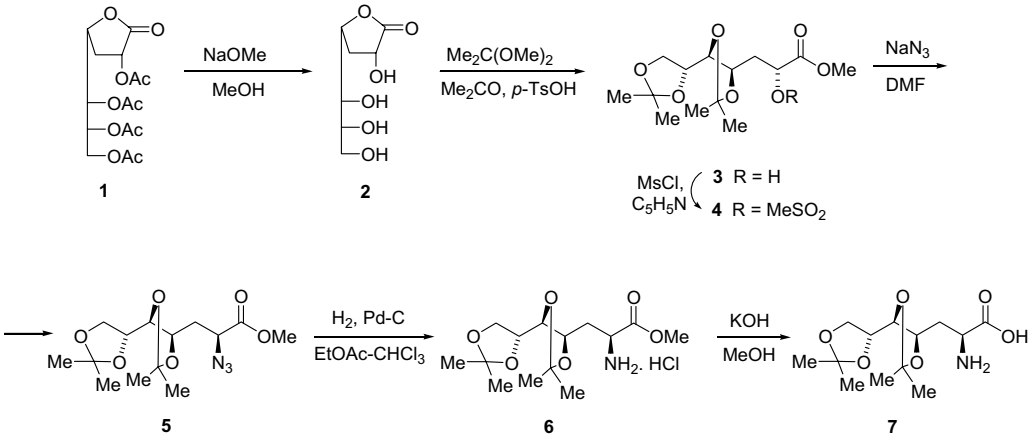


Figure 1. Contribution of a sickle conformer and observed NOEs for **5**.



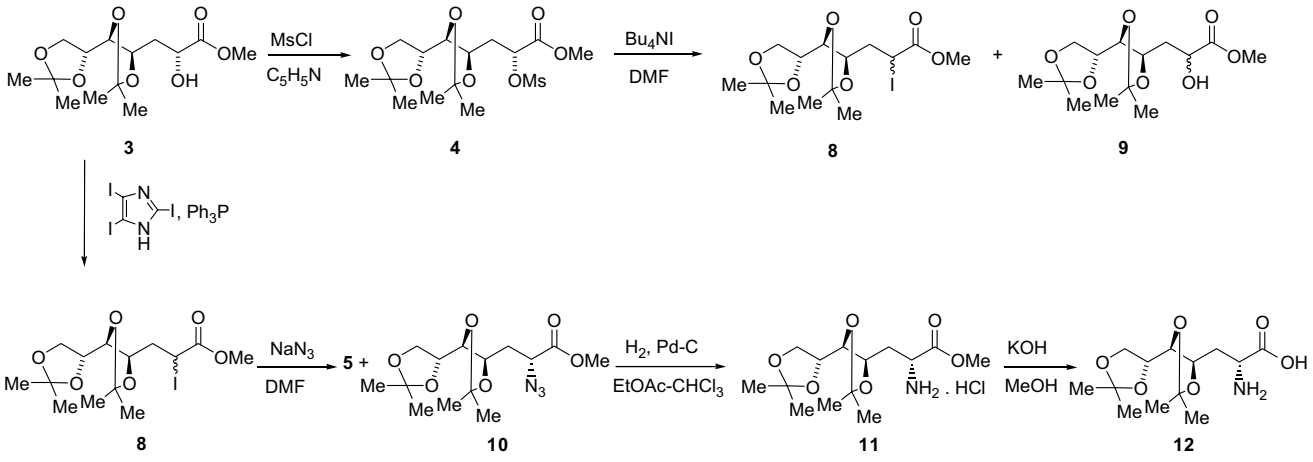
Scheme 1.

in methanol to afford the target α-amino acid **7**, which was purified by ion-exchange chromatography using BioRad AG_1X_2 (AcO^- form) resin. The salts were eliminated by washing with water and compound **7** was recovered by eluting the column with 0.02 M aqueous pyridinium acetate buffer (pH 5). The ^1H NMR spectrum of **7** showed a coupling constant pattern for H-4–H-7 similar to that of the intermediates **3**–**5**, indicating a similar conformation for the C-4–C-7 segment. However, in contrast to azide derivative **5**, the *J* values in **7** are indicative of conformational stability for the C-1–C-4 segment, and suggest a preference for the planar zigzag conformation, in spite of the N,O-parallel interaction. The NOESY spectrum of **7**, recorded in $CDCl_3$, supported the structure proposed, as it showed cross-peaks between H-2–H-3, H-2–H-4, H-3–H-4, H-3′–H-5, and H-4–H-6. The planar conformation could be stabilized by hydrogen bonding of the NH, acting as donor, and the O-4 as acceptor. In fact, the recent studies of L-serine, an amino acid analog of **7**, in aqueous solution by FT-IR and FT-Raman agreed with a zwitterionic structure. An optimization of the molecular geometry by quantum mechanical calculations confirmed that the optimized structure of L-serine contained two intra-molecular hydrogen bonds for the NH; the stronger with one oxygen of the carboxylate, and a weaker interaction with the HO group of the chain.[24]

As polymerization of amino acid derivatives usually takes place under alkaline conditions, to ensure that the α-carbon to the carboxylate does not isomerize, we prepared the epimeric amino acid for comparison. For the synthesis of the analog of alanine in the D-series, we employed in first instance mesylate **4** as a key intermediate. A double inversion of C-2 would lead to the target azide, epimer of **5**. For the substitution of the mesylate, iodide salts were used as nucleophiles[25] under varied conditions (Scheme 2). However, the substitution could not be satisfactorily accomplished. The highest yield (23%) reached for 2-iodide **8** was on the treatment of **4** with tetra-*n*-butylammonium iodide in DMF, but **8** was in fact a mixture of isomers at C-2. This product was accompanied by a larger amount (61%) of a mixture of diastereoisomeric alcohols **9**.

Iodine reagents were then employed for the direct substitution of hydroxyl groups by halogens.[25] Thus, attempted reaction of the hydroxyl function of **3** with *N*-iodosuccinimide and triphenylphosphine[26] did not produce the expected **8**, but partial removal of the protecting *O*-isopropylidene groups took place instead. The hydrolysis of ketal functions is known to be promoted by iodine.[25] More satisfactory results were obtained when **3** was treated with 2,4,5-triiodoimidazole and triphenylphosphine in toluene at reflux.[27] In this case, 2-deoxy-2-iodo derivative **8** was obtained in 73% yield, as an epimeric mixture, which could not be separated by column chromatography. The ^1H NMR spectrum of **8** showed that the ratio of 2*R* and 2*S* diastereoisomers was approximately 1:1. The signals of H-2, 3, and 3′ of each isomer could be readily identified, as they appeared in a clean region of the spectrum. Also, the signals of the methyl group of each isomer were clearly differentiated. The ^{13}C NMR spectrum of **8** showed the resonance of the carbon bonded to iodine at a very high field (17.6 and 13.9 ppm, for the (2*R*) and (2*S*) isomers, respectively). The identity of these signals was established by 2D HETCOR experiments.

Epimeric mixture **8** was treated with sodium azide in DMF to give the corresponding 2*S* and 2*R* azides (**5** and **10**, respectively), which could be separated by column chromatography. The ^1H NMR spectrum of **10** was similar to those of **3** and **4**, as they bear the same configuration at C-2. The large values of the coupling constants $J_{2,3}$ and $J_{3',4}$ (10.8 and 10.1 Hz, respectively) and the small ones for $J_{2,3'}$ and $J_{3,4}$ (3.8 and 2.4 Hz, respectively) indicated a preference of **10** for the planar zigzag conformation. The detected NOEs in the NOESY



Scheme 2.

spectrum of **10** between H-2–H-3′, H-3–H-4, H-3′–H-5, and H-4–H-6 gave further support to that conformation. Azide **10** was subjected to hydrogenation, using the same conditions as those described for analog **5**, to give **11**. Alkaline hydrolysis of the ester function of **11** afforded target amino acid **12**, which was desalted by ion-exchange chromatography as for analog **7**. The ^{1}H NMR spectrum of **12** showed similar coupling constant values for the C-4–C-7 segment as those of **7**, indicating a similar conformation. However, although the C-1–C-4 region of **12** is free of parallel interactions in the planar zigzag conformation, the relatively small values of $J_{2,3}$ and $J_{2,3'}$ suggest a clockwise rotation of the C-2–C-3 bond. The resulting conformation could be again stabilized by an intra-molecular hydrogen bonding between the NH and O-4.

3. Experimental

3.1. 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, by charring with a solution of 5% (v/v) sulfuric acid in EtOH, containing 0.5% *p*-anisaldehyde or, in the case of compounds **7** and **12**, by charring with a solution of ninhydrin in acetone. 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. For selected compounds, NOESY spectra were recorded. IR spectra (films) were recorded with a Nicolet 510P FT-IR spectrometer.

3.2. 3-Deoxy-D-*gluco*-heptono-1,4-lactone (2)

A solution of 2,5,6,7-tetra-*O*-acetyl-3-deoxy-D-*gluco*-heptono-1,4-lactone[18] (**1**, 1.00 g, 2.77 mmol) in 0.05 M sodium methoxide in CH_3OH (85 mL) was stirred at rt for 4 h. The mixture was treated in batch with Dowex 50W (H^+) resin (pH 4–5), filtered, and concentrated. The syrup crystallized from EtOAc/CH_3OH (10:1) to give **2** (0.48 g, 90%) as slightly yellow crystals; mp 105–106 °C; $[\alpha]_D$ −44 (*c* 1.0, H_2O); IR (KBr) 3334 (OH), 2947 (CH), 1763 (CO) cm^{-1}; ^{1}H NMR (D_2O): δ 4.73 (ddd, 1H, $J_{3,4} = 5.5$ Hz, $J_{3',4} = 10.7$ Hz, $J_{4,5} = 2.3$ Hz, H-4), 4.64 (dd, 1H, $J_{2,3} = 8.9$ Hz, $J_{2,3'} = 11.2$ Hz, H-2), 3.73 (dd, 1H, $J_{6,7} = 2.7$ Hz, $J_{7,7'} = 11.8$ Hz, H-7), 3.65 (ddd, 1H, $J_{5,6} = 8.7$ Hz, $J_{6,7'} = 6.1$ Hz, H-6), 3.54 (dd, 1H, H-7′), 3.47 (dd, 1H, $J_{4,5} = 2.3$ Hz, H-5), 2.54 (ddd, 1H, $J_{3,3'} = 12.4$ Hz, H-3), 2.08 (dd, 1H, H-3′); ^{13}C NMR (D_2O): δ 180.2 (C-1), 79.1 (C-4), 73.5, 72.8, 70.5 (C-2, 5, 6), 65.3 (C-7), 34.5 (C-3). Anal. Calcd for $C_7H_{12}O_6$: C, 43.75; H, 6.29. Found: C, 43.21; H, 6.33.

3.3. Methyl 3-deoxy-4,5:6,7-di-*O*-isopropylidene-D-*gluco*-heptonate (3)

To a suspension of **2** (0.45 g, 2.49 mmol) in a mixture of anhydrous acetone (0.70 mL) and 2,2-dimethoxypropane (9.0 mL) was added *p*-toluenesulfonic acid monohydrate (0.20 g, 1.05 mmol). The mixture was stirred at rt for 4 h, when TLC (1:1, hexane/EtOAc) showed a main spot having $R_f = 0.58$. The reaction mixture was made neutral with 25% (v/v) aqueous (aq) ammonium hydroxide; it was filtered, and concentrated. The residue was purified by flash chromatography using mixtures of increasing polarity of hexane/EtOAc (from 20:1 to 5:1), to afford **3** (0.57 g, 80%) as a crystalline solid; mp 70–71 °C; $[\alpha]_D$ +10 (*c* 1.0,$CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.42 (dd, 1H, $J_{2,3} = 9.0$ Hz, $J_{2,3'} = 3.5$ Hz, H-2), 4.14 (ddd, 1H, $J_{3,4} = 3.2$ Hz, $J_{3',4} = 9.1$ Hz, $J_{4,5} = 7.7$ Hz, H-4), 4.11 (dd, 1H, $J_{6,7} = 6.2$ Hz, $J_{7,7'} = 8.5$ Hz, H-7), 4.02 (ddd, 1H, $J_{5,6} = 8.2$ Hz, $J_{6,7'} = 5.0$ Hz, H-6), 3.93 (dd, 1H, H-7′), 3.79 (s, 3H, CH_3O), 3.58 (t, 1H, H-5), 3.08 (br s, 1H, HO), 2.08 (ddd, 1H, $J_{3,3'} = 14.1$ Hz, H-3), 2.02 (ddd, 1H, H-3′), 1.39 (×2), 1.36, 1.32 (3s, 12H, $2(CH_3)_2C$); ^{13}C NMR ($CDCl_3$): δ 175.1 (C-1), 109.7, 109.4 (Me_2C), 81.2, 77.0, 76.9 (C-4, 5, 6), 68.4 (C-2), 67.8 (C-7), 52.5 (OCH_3), 38.0 (C-3), 27.3, 27.0, 26.7, 25.3 ($(CH_3)_2C$). Anal. Calcd for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95. Found: C, 55.38; H, 7.85.

3.4. Methyl 3-deoxy-4,5:6,7-di-*O*-isopropylidene-2-*O*-methylsulfonyl-D-*gluco*-heptonate (4)

To a stirred solution of compound **3** (0.57 g, 1.88 mmol) in anhydrous pyridine (2.7 mL) was added methanesulfonyl chloride (0.215 g, 1.88 mmol). After stirring at rt for 1 h, an additional amount of methanesulfonyl chloride (0.215 g, 1.88 mmol) was added. When TLC (1:1, hexane/EtOAc) monitoring showed complete conversion of **3** ($R_f = 0.58$) into a less polar product ($R_f = 0.70$), the mixture was concentrated and the residue purified by flash chromatography, using as eluent mixtures of hexane/EtOAc (from 20:1 to 5:1), to afford crystalline **4** (0.65 g, 90%); mp 61–62 °C; $[\alpha]_D$ +44 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.22 (dd, 1H, $J_{2,3} = 11.0$ Hz, $J_{2,3'} = 3.0$ Hz, H-2), 4.12 (dd, 1H, $J_{6,7} = 6.2$ Hz, $J_{7,7'} = 8.6$ Hz, H-7), 4.05 (ddd, 1H,

$J_{3,4} = 2.6$ Hz, $J_{3',4} = 10.2$ Hz, $J_{4,5} = 7.6$ Hz, H-4), 4.00 (ddd, 1H, $J_{5,6} = 8.4$ Hz, $J_{6,7'} = 5.0$ Hz, H-6), 3.91 (dd, 1H, H-7′), 3.82 (s, 3H, OCH_3), 3.53 (dd, 1H, H-5), 3.14 (s, 3H, CH_3SO_2), 2.31 (ddd, 1H, $J_{3,3'} = 14.3$ Hz, H-3), 2.09 (ddd, 1H, H-3′), 1.39, 1.37, 1.34, 1.32 (4s, 12H, $(CH_3)_2C$); ^{13}C NMR ($CDCl_3$): δ 169.7 (C-1), 109.8, 109.6 (Me_2CO), 81.3, 76.8, 75.4 (×2) (C-2, 4, 5, 6), 67.8 (C-7), 52.9 (OCH_3), 38.8 (CH_3SO_2), 35.6 (C-3), 27.3, 26.9, 26.8, 25.2 ($(CH_3)_2C$). Anal. Calcd for $C_{15}H_{26}O_9S$: C, 47.11; H, 6.85; S, 8.38. Found: C, 47.08; H, 6.83; S, 8.36.

3.5. Methyl 2-azido-2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*manno*-heptonate (5)

A solution of **4** (0.65 g, 1.70 mmol) in dry DMF (16 mL) was stirred with sodium azide (0.22 g, 3.40 mmol) at 70 °C for 6 h. At the end of this time, TLC (3:1, hexane/EtOAc) indicated complete conversion of **4** into a less polar product ($R_f = 0.53$). The reaction mixture was concentrated and the residue extracted with CH_2Cl_2, filtered, and the solvent evaporated. The oily product was subjected to flash chromatography with hexane/EtOAc (from 20:1 to 7:1) to give syrupy **5** (0.49 g, 87%), which became solid upon cooling, but melted at rt; $[\alpha]_D$ −16 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 4.19 (dd, 1H, $J_{2,3} = 6.1$ Hz, $J_{2,3'} = 7.2$ Hz, H-2), 4.14 (dd, 1H, $J_{6,7} = 6.1$ Hz, $J_{7,7'} = 8.6$ Hz, H-7), 4.07 (ddd, 1H, $J_{3,4} = 2.6$ Hz, $J_{3',4} = 7.4$ Hz, $J_{4,5} = 7.6$ Hz, H-4), 4.01 (ddd, 1H, $J_{5,6} = 8.5$ Hz, $J_{6,7'} = 5.1$ Hz, H-6), 3.93 (dd, 1H, H-7′), 3.80 (s, 3H, CH_3O), 3.59 (dd, 1H, H-5), 2.28 (ddd, 1H, $J_{3,3'} = 14.2$ Hz, H-3), 2.06 (ddd, 1H, H-3′), 1.41, 1.37, 1.35, 1.34 (4s, 12H, $(CH_3)_2C$); ^{13}C NMR ($CDCl_3$): δ 170.7 (C-1), 109.8, 109.4 (Me_2CO), 81.6, 77.1, 76.9 (C-4, 5, 6), 67.9 (C-7), 59.3 (C-2), 52.6 (OCH_3), 35.2 (C-3), 27.0, 26.9, 26.7, 25.2 ($(CH_3)_2C$). Anal. Calcd for $C_{14}H_{23}N_3O_6$: C, 51.06; H, 7.04; N, 12.76. Found: C, 51.26; H, 7.08; N, 12.55.

3.6. 2-Amino-2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*manno*-heptonic acid (7)

Compound **5** (0.49 g, 1.49 mmol) dissolved in a mixture of EtOAc (10 mL) and $CHCl_3$ (0.4 mL) was hydrogenated at 30 psi in the presence of 10% Pd/C (70 mg). After 1 h, the catalyst was filtered and the filtrate concentrated to a hygroscopic syrup, which was characterized as methyl 2-amino-2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*manno*-heptonate hydrochloride (**6**, 0.48 g, 95%); ^1H NMR (D_2O): δ 4.25 (ddd, 1H, $J = 5.5$, 6.3, 12.0 Hz), 4.14 (m, 3H), 3.91 (dd, 1H, $J = 4.8$, 9.2 Hz), 3.80 (m, 1H), 3.76 (s, 3H, CH_3O), 2.32 (ddd, 1H, $J = 2.5$, 6.0, 14.8 Hz, H-3), 2.09 (ddd, 1H, $J = 7.3$, 10.4, 14.8 Hz, H-3′), 1.38, 1.35, 1.34, 1.31 (4s, 12H, $(CH_3)_2C$); ^{13}C NMR (DMSO-d_6): δ 169.4 (C-1), 108.9 (×2) (Me_2CO), 80.6, 75.8, 74.9 (C-4, 5, 6), 66.5 (C-7), 52.6 (OCH_3), 49.8 (C-2), 34.0 (C-3), 26.8, 26.7, 26.4, 25.2 ($(CH_3)_2C$). Crude **6** (0.48 g, 1.42 mmol) was dissolved in a 0.05 M solution of KOH in CH_3OH (85 mL) containing water (0.5 mL). The hydrolysis of the ester was followed by TLC (40:10:1, EtOAc/CH_3OH/Et_3N), which showed the conversion of **6** ($R_f = 0.60$) into more polar **7** ($R_f = 0$). When the reaction was complete, the mixture was neutralized with 1 M aq hydrochloric acid, and the volume was reduced to 2 mL. This solution was applied to a column filled with BioRad AG_1X_2 (AcO^- form) resin and eluted with water (30 mL) and then with a buffer of 0.02 M aq pyridinium acetate (pH 5). The fractions that resulted positive in the ninhydrin test were collected and concentrated, after addition of pyridine (5 mL). Compound **7** (0.33 g, 81%) was obtained as colorless crystals; mp 175 °C (decomp.); $[\alpha]_D$ +13 (*c* 1.0, H_2O); ^1H NMR (D_2O): δ 4.29 (ddd, 1H, $J_{5,6} = 6.6$ Hz, $J_{6,7} = 6.7$ Hz, $J_{6,7'} = 5.0$ Hz, H-6), 4.17 (dd, 1H, $J_{7,7'} = 9.0$ Hz, H-7), 4.15 (ddd, 1H, $J_{3,4} = 2.5$ Hz, $J_{3',4} = 10.1$ Hz, $J_{4,5} = 7.8$ Hz, H-4), 3.95 (dd, 1H, H-7), 3.82 (dd, 1H, H-5), 3.81 (ddd, 1H, $J_{2,3} = 4.5$ Hz, $J_{2,3'} = 9.7$ Hz, H-2), 2.38 (ddd, 1H, $J_{3,3'} = 15.0$ Hz, H-3), 1.96 (ddd, 1H, H-3′), 1.42, 1.40, 1.38, 1.35 (4s, 12H, $(CH_3)_2C$); ^1H NMR ($CDCl_3$): δ 7.94 (br s, 2H, NH_2), 4.24 (dd, 1H, $J_{2,3} = 2.0$ Hz, $J_{2,3'} = 9.2$ Hz, H-2), 4.18 (ddd, 1H, $J_{3,4} = 2.0$ Hz, $J_{3',4} = 9.7$ Hz, $J_{4,5} = 8.2$ Hz, H-4), 4.12 (dd, 1H, $J_{6,7} = 6.2$ Hz, $J_{7,7'} = 8.5$ Hz, H-7), 4.07 (ddd, 1H, $J_{5,6} = 8.0$ Hz, $J_{6,7} = 4.6$ Hz, H-6), 3.95 (dd, 1H, H-7′), 3.60 (dd, 1H, H-5), 2.56 (dt, 1H, $J_{3,3'} = 14.4$ Hz, H-3), 2.07 (ddd, 1H, H-3′), 1.40 (×2), 1.37, 1.33 (3s, 12H, $(CH_3)_2C$); ^{13}C NMR (D_2O): δ 174.6 (C-1), 111.4 (×2) (Me_2CO), 81.2, 78.4, 76.4 (C-4, 5, 6), 66.7 (C-7), 54.9 (C-2), 35.3 (C-3), 27.0, 26.6, 26.3, 24.8 ($(CH_3)_2C$). Anal. Calcd for $C_{13}H_{23}NO_6 \cdot 0.5H_2O$: C, 52.34; H, 8.10; N 4.69. Found: C, 51.71; H, 8.08; N, 4.72.

3.7. Methyl 2,3-dideoxy-2-iodo-4,5:6,7-di-*O*-isopropylidene-D-*gluco*- and D-*manno*-heptonate (8)

3.7.1. From 4. Methyl 3-deoxy-4,5:6,7-di-*O*-isopropylidene-2-methylsulfonyl-D-*gluco*-heptonate (**4**, 0.17 g, 0.445 mmol) was dissolved in DMF (2 mL), and tetrabutylammonium iodide (0.52 g, 1.4 mmol) was added. The reaction mixture was heated at 75 °C for 3 h, and then at 115 °C for 3 h. The solution was cooled to rt and diluted with CH_2Cl_2, washed with water, dried ($MgSO_4$), and the solvent was evaporated. The crude product was subjected to purification by column chromatography using mixtures of hexane/EtOAc (from 5:1 to 3:2). Two main fractions were isolated, the less polar product ($R_f = 0.88$; 3:2, hexane/EtOAc) was identified as the mixture of epimers **8** (0.042 g, 23%); $[\alpha]_D$ +82 (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$): isomer (2*S*): δ 4.58 (dd, 1H, $J_{2,3} = 10.9$ Hz, $J_{2,3'} = 4.6$ Hz, H-2), 2.72

(ddd, 1H, $J_{3,4} = 3.9$ Hz, $J_{3,3'} = 14.2$ Hz, H-3), 2.23 (ddd, 1H, $J_{3',4} = 7.8$ Hz, H-3′); isomer (2*R*): δ 4.56 (dd, 1H, $J_{2,3} = 9.6$ Hz, $J_{2,3'} = 5.5$ Hz, H-2), 2.36 (ddd, 1H, $J_{3,4} = 3.0$ Hz, $J_{3,3'} = 14.7$ Hz, H-3), 2.03 (ddd, 1H, $J_{3',4} = 9.6$ Hz, H-3′); ^{13}C NMR ($CDCl_3$): δ 171.9, 171.7 (C-1), 109.7, 109.4 (Me_2C), 52.8 (CH_3O), 27.1, 27.0, 26.9, 26.8, 25.2 (($CH_3)_2C$). The following signals for each isomer could be assigned: isomer (2*R*): δ 81.0, 79.1, 76.9 (C-4, 5, 6), 67.7 (C-7), 39.6 (C-3), 17.6 (C-2); isomer (2*S*): δ 80.7, 78.8, 76.7 (C-4, 5, 6), 67.6 (C-7), 40.6 (C-3), 13.9 (C-2). Anal. Calcd for $C_{14}H_{23}IO_6$: C, 40.59; H, 5.60; I, 30.64. Found: C, 40.70; H, 5.56; I, 30.38.

Further fractions of the column afforded a mixture of methyl 3-deoxy-4,5:6,7-di-*O*-isopropylidene-D-*gluco*- and D-*manno*-heptonate (**9**, 0.083 g, 61%). The NMR spectra of **9** showed the signals corresponding to the (2*R*) isomer (**3**), and those of the (2*S*) component: ^{13}C NMR ($CDCl_3$): δ 174.7 (C-1), 109.7, 109.4 (Me_2C), 81.4, 77.3, 76.9 (C-4, 5, 6), 68.7 (C-2), 67.8 (C-7), 52.5 (OCH_3), 37.7 (C-3), 27.1, 26.6, 25.3 (($CH_3)_2C$).

3.7.2. From 3, using triphenylphosphine-2,4,5-triiodoimidazole. To a solution of **3** (0.58 g, 1.90 mmol) in anhydrous toluene (43 mL) were added PPh_3 (2.07 g, 7.9 mmol) and 2,4,5-triiodoimidazole[28] (1.815 g, 4.1 mmol). The mixture was heated under argon at 120 °C (bath) for 4 h. After cooling to rt, satd aq $NaHCO_3$ (25 mL) was added. Iodine was then added to the mixture until the organic layer remained reddish brown for 10 min. After extraction with toluene (2 × 30 mL), the organic layer was washed with 5% aq $NaHSO_3$ (to remove excess of I_2), and then with water (30 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (20:1, toluene/acetone) to afford **8** (0.57 g, 73%), which showed the same properties as product **8** described above (Section 3.7.1).

3.8. Methyl 2-azido-2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*manno*-heptonate (5) and methyl 2-azido-2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*gluco*-heptonate (10)

To a solution of **8** (0.197 g, 0.47 mmol) in anhydrous DMF (6.0 mL) was added NaN_3 (62 mg, 0.95 mmol). After stirring for 3 h at 70 °C, the solvent was evaporated and the resulting solid was suspended in EtOAc and filtered. The solution was concentrated and the residue was purified by column chromatography (CH_2Cl_2). The first component of the mixture ($R_f = 0.57$; 95:5, CH_2Cl_2/EtOAc) was isolated and identified as (2*R*) isomer **10** (0.060 g, 39%); mp 52 °C; $[\alpha]_D$ +32 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.18 (dd, 1H, $J_{2,3} = 10.8$ Hz, $J_{2,3'} = 3.8$ Hz, H-2), 4.14 (dd, 1H, $J_{6,7} = 6.1$ Hz, $J_{7,7'} = 8.5$ Hz, H-7), 4.10 (ddd, 1H, $J_{3,4} = 2.4$ Hz, $J_{3',4} = 10.1$ Hz, $J_{4,5} = 7.6$ Hz, H-4), 4.03 (ddd, 1H, $J_{5,6} = 8.5$ Hz, $J_{6,7'} = 4.9$ Hz, H-6), 3.93 (dd, 1H, H-7′), 3.81 (s, 3H, CH_3O), 3.54 (dd, 1H, H-5), 2.13 (ddd, 1H, $J_{3,3'} = 14.0$ Hz, H-3), 2.03 (ddd, 1H, H-3′), 1.40, 1.39, 1.37, 1.34 (4s, 12H, $(CH_3)_2C$); ^{13}C NMR ($CDCl_3$): δ 170.9 (C-1), 109.7, 109.5 (Me_2C), 81.2, 76.9, 76.4 (C-4, 5, 6), 67.8 (C-7), 59.5 (CH_3O), 52.7 (C-2); 35.5 (C-3), 27.2, 26.9, 26.7, 25.1 (($CH_3)_2C$). Anal. Calcd for $C_{14}H_{23}N_3O_6$: C, 51.06; H, 7.04; N, 12.76. Found: C, 51.33; H, 7.10; N, 12.67. Further fractions from the column afforded more polar azide **5** (0.069 g, 44%), which had the same physical and spectral properties as the product described in Section 3.5.

3.9. 2-Amino-2,3-dideoxy-4,5:6,7-di-*O*-isopropylidene-D-*gluco*-heptonic acid (12)

Compound **10** (0.050 g, 0.153 mmol) was hydrogenated under the conditions described for **5**, to give **11** (0.048 g, 95%); ^{1}H NMR (Me_2SO-d_6): δ 4.10 (ddd, 1H, $J_{3,4} = 10.2$ Hz, $J_{3',4} = 2.5$ Hz, $J_{4,5} = 7.5$ Hz, H-4), 4.04 (m, 2H, H-6,7), 3.79 (dd, 1H, $J_{6,7'} = 8.2$ Hz, $J_{7,7'} = 11.4$ Hz, H-7′), 3.62 (s, 3H, CH_3O), 3.55 (t, 1H, $J_{5,6} = 7.2$ Hz, H-5), 3.46 (ddd, 1H, $J_{2,3} = 4.1$ Hz, $J_{2,3'} = 9.8$ Hz, H-2), 1.80 (ddd, 1H, $J_{3,3'} = 13.7$ Hz, H-3), 1.74 (ddd, 1H, H-3′), 1.32, 1.27 (2s, 12H, $(CH_3)_2C$); ^{13}C NMR (Me_2SO-d_6): δ 176.0 (C-1); 108.8, 108.3 (Me_2C), 80.5, 76.0 (×2) (C-4, 5, 6), 66.5 (C-7), 51.6, 51.5 (C-2, CH_3O), 38.1 (C-3); 27.2, 26.9, 26.5, 25.2 (($CH_3)_2C$). Crude **11** (0.048 g, 0.15 mmol) was dissolved in a 0.05 M solution of methanolic KOH and, after hydrolysis of the ester function, the work-up described for amino acid **7** was followed. Analogous **12** (0.042 g, 92%) was obtained as a crystalline product; mp 175 °C (decomp.); $[\alpha]_D$ +21 (*c* 0.5, H_2O); ^{1}H NMR (D_2O): δ 4.18 (ddd, 1H, $J_{5,6} = 6.3$ Hz, $J_{6,7} = 6.4$ Hz, $J_{6,7'} = 4.8$ Hz, H-6), 4.06 (dd, 1H, $J_{7,7'} = 8.9$ Hz, H-7), 3.91 (ddd, 1H, $J_{3,4} = 2.5$ Hz, $J_{3',4} = 10.0$ Hz, $J_{4,5} = 7.8$ Hz, H-4), 3.87 (dd, 1H, $J_{2,3} = 6.5$ Hz, $J_{2,3'} = 3.5$ Hz, H-2), 3.83 (dd, 1H, H-7), 3.74 (ddd, 1H, H-5), 2.21 (ddd, 1H, $J_{3,3'} = 15.2$ Hz, H-3), 2.05 (ddd, 1H, H-3′), 1.31, 1.29, 1.25, 1.22 (4s, 12H, $(CH_3)_2C$); ^{13}C NMR (D_2O): δ 174.4 (C-1), 111.9, 111.7 (Me_2C), 81.4, 76.9, 76.6 (C-4, 5, 6), 66.9 (C-7), 53.9 (C-2), 34.2 (C-3); 27.2, 26.8, 26.5, 25.0 (($CH_3)_2C$). Anal. Calcd for $C_{13}H_{23}NO_6 \cdot H_2O$: C, 50.80; H, 8.20; N, 4.56. Found: C, 50.87; H, 7.84; N, 4.70.

Acknowledgments

We are indebted to the University of Buenos Aires (Project X059), the National Research Council of República Argentina (CONICET) and the National Agency for Promotion of Science and Technology (ANPCYT-PICT 13922) for financial support. O.V. and A.A.K. are Research Members of CONICET.

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. Törmälä, P. *Adv. Mater.* **1992**, *4*, 589–591.
4. Vainiopää, S.; Rokkanen, P.; Törmälä, P. *Prog. Polym. Sci.* **1989**, *14*, 679–716.
5. Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491–514.
6. Schweizer, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 230–253.
7. van Well, R. M.; Marinelli, L.; Altona, C.; Erkelens, K.; Siegal, G.; van Raaij, M.; Llamas-Saiz, A. L.; Kessler, H.; Novellino, E.; Lavecchia, A.; van Boom, J. H.; Overhand, M. *J. Am. Chem. Soc.* **2003**, *125*, 10822–10829.
8. Romero Zaliz, C. L.; Varela, O. *J. Carbohydr. Chem.* **2001**, *20*, 689–701.
9. Romero Zaliz, C. L.; Varela, O. *Tetrahedron: Asymmetry* **2003**, *14*, 2579–2586.
10. Romero Zaliz, C. L.; Varela, O. *ARKIVOC* **2005**, 201–208.
11. Romero Zaliz, C. L.; Varela, O. *Tetrahedron: Asymmetry* **2005**, *16*, 97–103.
12. 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*, 299–305.
13. Hunter, D. F. A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2003**, *14*, 3831–3839.
14. Mayes, B. A.; Stetz, R. J. E.; Watterson, M. P.; Edwards, A. A.; Ansell, C. W. G.; Tranter, G. E.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2004**, *15*, 627–638.
15. Zamora, F.; Bueno, M.; Molina, I.; Orgueira, H. A.; Varela, O.; Galbis, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 1811–1818.
16. Bueno, M.; Zamora, F.; Molina, I.; Orgueira, H. A.; Varela, O.; Galbis, J. A. *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *55*, 3645–3653.
17. Sparks, M. A.; Williams, K. W.; Whitesides, G. M. *J. Med. Chem.* **1993**, *36*, 778–783.
18. Jeroncic, L. O.; Fernández Cirelli, A.; Lederkremer, R. M. *Carbohydr. Res.* **1987**, *167*, 175–186.
19. (a) Varela, O.; Fernández Cirelli, A.; Lederkremer, R. M. *Carbohydr. Res.* **1982**, *100*, 424–430; (b) Moradei, O.; du Mortier, C.; Varela, O.; Lederkremer, R. M. *J. Carbohydr. Chem.* **1991**, *10*, 469–479.
20. Regeling, H.; Rouville, E.; Chittende, G. J. F. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 461–464.
21. Long, D. D.; Stetz, R. J. E.; Nash, R. J.; Marquess, D. G.; Lloyd, J. D.; Winters, A. L.; Asano, N.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 901–908.
22. Horton, D.; Varela, O. *Carbohydr. Res.* **1984**, *134*, 205–214.
23. Secrist, J. A., III; Logue, M. W. *J. Org. Chem.* **1972**, *37*, 335–336.
24. Ramírez, F. J.; Tuñón, I.; Silla, E. *Chem. Phys.* **2004**, *303*, 86–96.
25. Vaino, A. R.; Szarek, W. A. *Adv. Carbohydr. Chem. Biochem.* **2000**, *56*, 44–50.
26. Bose, A. K.; Lal, B. *Tetrahedron Lett.* **1973**, *40*, 3937–3940.
27. (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978–980; (b) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866–2869.
28. Garegg, P. J.; Samuelsson, B. *Synthesis* **1979**, 813–814.