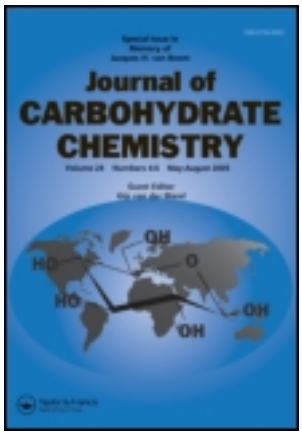


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lcar20

SYNTHESIS OF 6-AMINO-6-DEOXY-2,3,4,5- TETRA-O-METHYL-D-GALACTONIC ACID, A KEY PRECURSOR OF A STEREOREGULAR POLYAMIDE

Carmen L. Romero Zaliz [a] & Oscar Varela [b]

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

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

Published online: 16 Aug 2006.

To cite this article: Carmen L. Romero Zaliz & Oscar Varela (2001) SYNTHESIS OF 6-AMINO-6-DEOXY-2,3,4,5- TETRA-O-METHYL-D-GALACTONIC ACID, A KEY PRECURSOR OF A STEREOREGULAR POLYAMIDE , Journal of Carbohydrate Chemistry, 20:7-8, 689-701

To link to this article: http://dx.doi.org/10.1081/CAR-100108283

J. CARBOHYDRATE CHEMISTRY, 20(7&8), 689–701 (2001)

SYNTHESIS OF 6-AMINO-6-DEOXY-2,3,4,5-TETRA-*O*-METHYL-D-GALACTONIC ACID, A KEY PRECURSOR OF A STEREOREGULAR POLYAMIDE[1]

Carmen L. Romero Zaliz and Oscar Varela*

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

ABSTRACT

The title compound (**17**) was synthesized by two alternative sequences, starting from D-galactose diacetonide (**1**) and from methyl 6-*O*-tosyl-α-D-galactopyranoside (**9**). Compound **1** was converted into the 6-bromo-6-deoxy derivative **2** or mesylated to **3**. Nucleophilic substitution of the leaving group in **2** and **3** by sodium azide led to the 6-azido-6-deoxy derivative **4**, which on treatment with methanol under acidic conditions afforded a mixture of the corresponding methyl β-furanoside (**5**) and α-pyranoside (**6**). Methylation of the free hydroxyl groups of **5** and **6** gave the respective per-*O*-methyl derivatives **7** and **8**. In order to maintain the size of the sugar ring during the sequence, compound **8** was alternatively prepared from **9**, by acetylation, substitution by azide and per-*O*-methylation. Hydrolysis of the glycoside followed by oxidation and further 5-*O*-methylation afforded the 6-azido-6-deoxy carboxylic acid **16** which was converted into **17** (38% overall yield from **9**) by hydrogenolysis of the azide function.

INTRODUCTION

Modified polyamides containing other functional groups besides the peptide bond are interesting materials with novel technical and biomedical applications.[2,3] Because of their stereochemical diversity, and their commercial availability, carbohydrates constitute highly convenient starting compounds for the synthesis of

polymers which contain several stereocenters in the main chain. Many examples of the synthesis and application of carbohydrate-based polymers have been reported.[2,4] Particularly, in our laboratory we have described the synthesis of AABB-type polyhydroxypolyamides, which are analogs of polyhydroxylated nylons.[5–7] We have also reported the synthesis of ω-aminoacids derived from pentoses and L-glutamic acid,[8] which have been employed as monomers in the preparation of stereoregular AB-type polyamides.[9] Similarly, derivatives of 6-amino-6-deoxy-D-gluconic acid have been obtained,[10] and their polymerization to the corresponding chiral polyamide has been studied.[11] Also, various 6-amino-6-deoxy-D-aldonic acids, their lactams and some derivatives have been prepared,[12] although 6-amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid (**17**) has not been previously synthesized. Furthermore, galactonic acid derivatives possess a regular distribution of chiral centers (*R*, *S*, *S*, *R*) in the chain, and the symmetry of the galactaryl units (alternating axis of symmetry between C-3 and C-4) led to an extended zigzag conformation of the carbohydrate in AABB-type polygalactaramides,[13] which results in alignment of the molecules in the solid state by interchain attractive forces providing polymers of improved mechanical properties. An optically active, stereoregular polygalactaramide may be prepared by polycondensation of bifunctional monomers derived from **17**. Therefore, we wish to report here two alternative routes for the synthesis of the amino acid **17**, starting from D-galactose derivatives.

RESULTS AND DISCUSSION

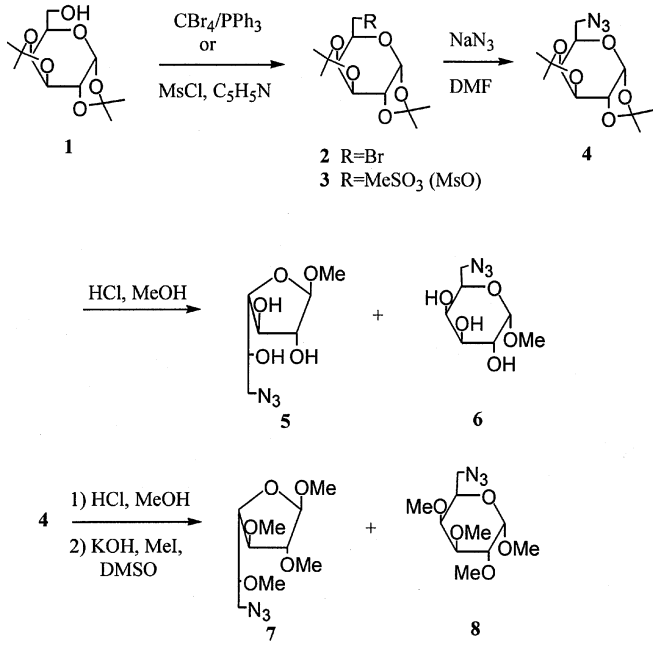
To introduce an amino group at position 6 of galactose, the readily available[14] 1,2:3,4-diacetonide derivative **1** was employed as starting material. The free hydroxyl group at C-6 of **1** was substituted by bromine, using the procedure based on carbon tetrabromide-triphenylphosphine.[15] The ^{1}H NMR spectrum of the 6-bromo derivative **2** showed strong distortion of the normal $^4C_1$ conformation of the sugar ring (for example, $J_{2,3} = 2.5$ Hz for trans disposed protons) because of the two fused isopropylidene rings. This result was in agreement with previous reports[16] on derivatives of **1**.

As compound **2** was obtained in a rather moderate yield (65%), the free 6-OH group of **1** was alternatively converted into a leaving group by mesylation under standard conditions. The 6-*O*-mesyl derivative **3** was obtained as a crystalline product in 89% yield.

Nucleophilic substitution of bromine by azide in **2** led to the 6-azide derivative **4** in 72% yield. The same reaction when applied to **3** required more vigorous conditions (higher temperature and longer reaction time) and the yield of **4** was lower (55%). Therefore, the overall yield of **4** via **2** (47%) was similar to that obtained via **3** (49%). The bromide **2** and the azide **4** had been previously prepared by substitution of the 6-chlorosulfonyl derivative of **1**, in 30% and 26% yield, respectively.[17] The azide function was not reduced to an amine until the last step of the synthesis because of its higher stability towards acidic and basic conditions, and also against oxidation.[18]

Treatment of **4** with a solution of aqueous HCl in methanol, under reflux,

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



Scheme 1.

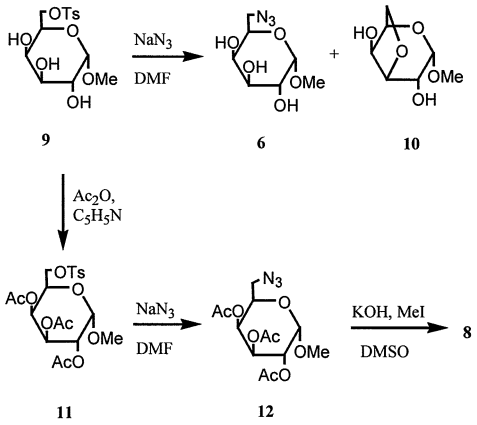
caused removal of the isopropylidene groups and the formation of two methyl glycosides, which were separated by column chromatography. The less polar product was identified by NMR spectroscopy as the β-furanoside **5**; the ^{13}C NMR spectrum was very similar to that described for other β-D-galactofuranosides,[19,20] which also presented characteristic resonances at low field for C-1, C-2 and C-4. Furthermore, the small coupling constant between H-1 and H-2 ($J_{1,2} < 1$ Hz) indicated a *trans* relationship for these protons and hence a β configuration for the glycoside. Also, in coincidence with methyl[19] and *p*-nitrophenyl β-D-galactofuranosides,[20] compound **5** showed a large negative optical rotation value. The other component of the original mixture was methyl 6-azido-6-deoxy-β-D-galactopyranoside (**6**), which had an identical melting point with the product described in the literature,[17] and spectral data which agreed with a β-pyranoside structure. When the progress of the reaction of methanolysis of **4** was monitored by TLC it was observed that, as expected, the furanoside **5** was formed first; at longer reaction times, its concentration in the mixture decreased and the thermodynamically favored **6** became the main product.

Methylation of the crude mixture of methanolysis of **4**, with methyl iodide-potassium hydroxide in dimethyl sulfoxide (DMSO) afforded a mixture, from which the per-*O*-methyl furanoside (**7**) and pyranoside (**8**) were isolated by column chromatography. However, as both compounds **7** and **8** lead, by chemical transformations, to the per-*O*-methyl derivative of 6-azido-6-deoxy-D-gluconic acid (**16**), the direct precursor of the amino acid **17**, in further preparations the mixture of glycosides was employed in the synthetic sequence (see below) to avoid tedious chromatographic separations.

Alternatively, a synthesis of **16** was designed to facilitate NMR analysis. The starting material was methyl α-D-galactopyranoside, which was readily tosylated at the primary hydroxyl group[21] to afford the monotosylate **9**.

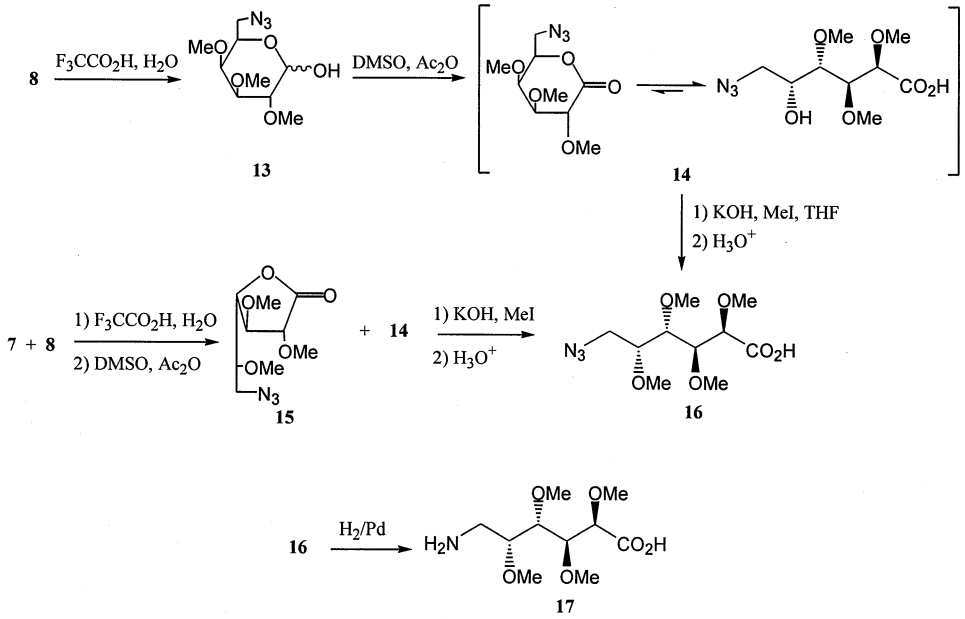
Attempted substitution of **9** with sodium azide in *N*,*N*-dimethylformamide (DMF) afforded two main products, which were separated by column chromatography. The one having higher mobility by TLC was characterized as methyl 3,6-anhydro-α-D-galactopyranoside (**10**), which is the major product formed by treatment of **9** with sodium hydroxide.[21] The other component of the mixture, isolated in 48 % yield, was the expected glycoside **6**. Hanessian[22] also reported a low yield for the reaction of **9** with sodium azide under conditions similar to those we employed. The formation of **10** as a by-product indicates that **9** underwent intramolecular attack of HO-3 to C-6 with nucleophilic displacement of the tosylate and formation of a cyclic ether bond. In order to avoid this reaction, the free hydroxyl groups of **9** were acetylated under standard conditions to afford the 2,3,4-tri-*O*-acetyl derivative **11** in almost quantitative yield. Treatment of **11** with a mixture of sodium azide in DMF at high temperature gave **12** in 79% yield. Compound **12** was directly converted into the per-*O*-methyl derivative **8** (81% yield) by reaction with MeI-KOH in DMSO.

Hydrolysis of the methyl glycoside **8** afforded 6-azido-6-deoxy-2,3,4-tri-*O*-methyl-D-galactopyranose (**13**) as a 2.3:1 ratio ofα/β anomers. Pfitzner-Moffat oxidation[23] (DMSO-acetic anhydride) of the hemiacetal function led to a single product, as shown by TLC (R_f 0.60, 1:1 hexane-EtOAc) of the reaction mixture. This product was isolated by flash chromatography and identified as the lactone **14**. However, this was a rather unstable compound, as it was always accompanied by the corresponding 5-hydroxy acid, the lactone ring opening product. The proportion of the latter increased gradually when **14** was dissolved in chloroform saturated with water. The structures of the two species involved in this equilibrium were established on the basis of their spectral data. Thus, the H-5



Scheme 2.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



Scheme 3.

signal in the ^{1}H NMR spectrum of the lactone was shifted downfield with respect to the same signal in the acid, due to the effect of the opening of the lactone ring. Also, the singlets of the methyl groups appeared all at higher field in the acid. Moreover, the ^{13}C NMR spectrum showed the carbonyl carbon signal of the lactone at higher field than that of the acid, in agreement with values reported for the C-1 signals of aldonic acids and their lactones.[24] Methylation of the HO-5 in **14** was performed with MeI-KOH in tetrahydrofuran (THF). As partial esterification of the carbonyl function is possible under these conditions, water was added to the reaction mixture in order to hydrolyze the ester that could be formed.

Compound **16** was also prepared by the alternative route already mentioned, starting from **4**. Methanolysis of **4** gave a mixture of glycosides **5** and **6** in a 3:1 ratio. The mixture was subjected to methylation, hydrolysis of the methyl glycosides and oxidation. For all the steps the crude products were employed and the 1,4-lactone derivative **15** was spectroscopically identified in the reaction mixture of oxidation, together with the 1,5-lactone (**14**). The mixture was methylated under the conditions described for the methylation of pure **14**, as both components (**14** and **15**) lead to **16**. However, the yield of **16** by this sequence was rather poor; and the other route starting from **9**, was more convenient as the yield was higher (40%, compared to 16% when starting from **1** via **4**), and the products obtained in each step were easier to handle. The final product **17** was obtained by hydrogenolysis of the azide **16**.

EXPERIMENTAL

General Methods. Melting points (mp) were determined with a Fisher-Johns apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on 0.2 mm silica gel 60 F_{254} (Merck) aluminum supported plates. Visualization of the spots was effected by charring with a solution of 5% sulfuric acid in EtOH, containing 0.5% *p*-anisaldehyde. Column chromatography was performed with silica gel 60 (230–400 mesh, Merck). Optical rotations were measured with a Perkin-Elmer Model 343 digital polarimeter at 25°C in the solvent indicated in each individual case. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC 200 or on a Bruker AMX-500 spectrometers. TMS was employed as an internal standard for solutions in $CDCl_3$.

6-Bromo-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (2). To a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactose[14] (**1**, 2.50 g, 9.62 mmol) in anhydrous pyridine (56 mL) was added triphenylphosphine (5.03 g, 19.20 mmol) and carbon tetrabromide (4.77 g, 14.37 mmol). The solution was warmed to 35°C and stirred for 16 h, and then at 50°C for an additional 48 h. The pyridine was evaporated in vacuum, and the resulting syrup was extracted with hexane (3 × 60 mL). The residue was dissolved in CH_2Cl_2 (100 mL), filtered, and the filtrate was washed with water (3 × 100 mL). The organic extract was dried ($MgSO_4$) and concentrated. Chromatographic purification of the residue (10:1 PhMe-EtOAc) afforded **2** (2.03 g, 65%), which recrystallized from MeOH gave mp 56–57°C; $[\alpha]_D$ −62° (*c* 1.0, $CHCl_3$), lit.[17] mp 52–53.5°C, $[\alpha]_D$ −58.9°; ^{1}H NMR (200 MHz, $CDCl_3$) δ5.54 (d, 1 H, $J_{1,2}$ = 5.1 Hz, H-1), 4.63 (dd, 1 H, $J_{2,3}$ = 2.5, $J_{3,4}$ = 8.0 Hz, H-3), 4.37 (dd, 1 H, $J_{4,5}$ = 1.8 Hz, H-4), 4.32 (dd, 1 H, H-2), 3.97 (ddd, 1 H, $J_{5,6}$ = 7.0, $J_{5,6'}$ = 6.8 Hz, H-5), 3.51 (dd, 1 H, $J_{6,6'}$ = 10.2 Hz, H-6), 3.41 (dd, 1 H, H-6′), 1.54, 1.44, 1.35, 1.33 (4 s, 12 H, C*H*$_3$); the ^{13}C NMR spectrum was identical with that previously reported.[17]

Anal. Calcd for $C_{12}H_{19}BrO_5$: C, 44.59; H, 5.94. Found: C, 44.73, H, 6.07.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-methylsulphonyl-α-D-galactopyranose (3). To a solution of compound **1** (3.70 g, 14.23 mmol) in dry pyridine (22 mL) cooled to 0°C, was slowly added methanesulphonyl chloride (2.20 mL, 28.45 mmol). The mixture was stirred at room temperature for 2 h and then poured into water with stirring. The syrupy residue was dissolved in CH_2Cl_2 (100 mL), and the solution was successively washed with 10% aq HCl, satd aq $NaHCO_3$ and water. The organic layer was dried ($MgSO_4$) and concentrated to afford a solid, which was crystallized from MeOH. Compound **3** (4.28 g, 89%) was recrystallized from the same solvent; mp 119°C, $[\alpha]_D$ −69° (*c* 0.8, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.55 (d, 1 H, $J_{1,2}$ = 5.1 Hz, H-1), 4.64 (dd, 1 H, $J_{3,4}$ = 7.7, $J_{4,5}$ = 2.6 Hz, H-4), 4.38 (d, 2 H, $J_{5,6} \approx J_{5,6'} \approx$ 6.0 Hz, H-6, 6′), 4.35 (dd, 1 H, $J_{2,3}$ = 2.2 Hz, H-3), 4.12 (dt, 1 H, H-5), 3.10 (s, 3 H, C*H*$_3$Ar), 1.55, 1.46, 1.37 (× 2) (3 s, 12 H, (C*H*$_3$)$_2$C); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 109.8, 108.9 (*C*Me$_2$), 96.1 (C-1), 70.5 (× 2), 70.2, 68.9 (C-2, 3, 4, 5), 66.2 (C-6), 37.7 (*C*H$_3$SO$_2$), 25.8, 25.7, 24.7, 24.2 (C(*C*H$_3$)$_2$).

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Anal. Calcd for $C_{13}H_{22}O_8S$: C, 46.13; H, 6.57; S, 9.48. Found: C, 46.45; H, 6.65; S, 9.20.

6-Azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (4). a) Starting from **2**. Compound **2** (1.19 g, 3.68 mmol) dissolved in dry DMF (28 mL) was treated with sodium azide (0.83 g, 12.77 mmol) at 80°C for 60 h. The mixture was concentrated in vacuum, and the residue was suspended in CH_2Cl_2 and filtered. The filtrate was concentrated, and the resulting syrup was applied to a chromatographic column (10:1 PhMe-EtOAc) to afford oily **4** (0.76 g, 72%); $[\alpha]_D$ −107° (*c* 1.2, $CHCl_3$), lit.[17] $[\alpha]_D$ −96.9°; ^{1}H NMR (500 MHz, $CDCl_3$) δ5.51 (d, 1 H, $J_{1,2}$ = 4.8 Hz, H-1), 4.60 (dd, 1 H, $J_{2,3}$ = 2.3, $J_{3,4}$ = 7.7 Hz, H-3), 4.30 (dd, 1 H, H-2), 4.16 (dd, 1 H, $J_{4,5}$ 1.9 Hz, H-4), 3.88 (ddd, 1 H, $J_{5,6}$ = 7.8, $J_{5,6'}$ = 5.3 Hz, H-5), 3.47 (dd, 1 H, $J_{6,6'}$ = 12.6 Hz, H-6), 3.33 (dd, 1 H, H-6′), 1.52, 1.43, 1.33, 1.31 (4 s, 12 H, CH_3); the ^{13}C NMR spectrum was identical with that already described.[17]

Anal. Calcd for $C_{12}H_{19}N_3O_5$: C, 50.51; H, 6.73. Found: C, 50.32; H, 6.58.

b) Starting from **3**. Compound **3** (3.01 g, 9.36 mmol) dissolved in DMF (50 mL) was treated with sodium azide (1.22 g, 18.77 mmol) at 100°C. After 20 h the temperature was raised to 120°C, and the heating was continued for an additional 72 h. The same work-up and chromatographic purification as in a) led to compound **4** (1.46 g, 55%) which showed the same physical and spectroscopic properties as the product reported in a).

Methyl 6-Azido-6-deoxy-β-D-galactofuranoside (5) and Methyl 6-Azido-6-deoxy-β-D-galactopyranoside (6). A solution of **4** (0.30 g, 1.05 mmol) in MeOH (5 mL) containing conc aq HCl (0.015 mL) was heated under reflux for 10 h. The mixture was neutralized with AG3-X4 resin, filtered and concentrated. TLC examination revealed two main spots having R_f 0.52 and 0.40 (10:1 CH_2Cl_2-MeOH). The mixture was subjected to column chromatography (2:1 EtOAc-hexane). From the first fractions of the column was isolated the furanoside **5** (0.14 g, 61%); $[\alpha]_D$ −112° (*c* 1.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.89 (bs, 1 H, $J_{1,2}$ <1 Hz, H-1), 4.21–3.92 (m, 4 H, H-2, 3, 4, 5), 3.54 (dd, 1 H, $J_{5,6}$ = 7.7, $J_{6,6'}$ = 12.3 Hz, H-6), 3.42 (dd, 1 H, $J_{5,6'}$ = 5.5 Hz, H-6′), 3.40 (s, 3 H, OCH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 108.9 (C-1), 85.2 (C-4), 79.9 (C-2), 78.0 (C-3), 69.6 (C-5), 55.0 (O*C*H_3), 53.9 (C-6).

Anal. Calcd for $C_7H_{13}N_3O_5$.0.3 H_2O: C, 37.42, H, 6.11, N, 18.71. Found: C, 37.67; H, 6.08; N, 18.57.

From the next fractions of the column was obtained the pyranoside 6 (0.06 g, 26%); mp 173°C (lit.[22] 172–173°C); $[\alpha]_D$ +154° (*c* 0.8, H_2O); ^{1}H NMR (200 MHz, DMSO-d_6) δ 4.58 (d, 1 H, $J_{1,2}$ = 3.3 Hz, H-1), 3.74 (d, 1 H, $J_{2,3}$ = 8.8 Hz, H-2), 3.64–3.53 (m, 3 H, H-3, 4, 5), 3.48 (dd, 1 H, $J_{5,6}$ = 9.1, $J_{6,6°}$ = 13.2 Hz, H-6), 3.29 (s, 3 H, OCH_3), 3.22 (dd, 1 H, $J_{5,6'}$ = 3.7 Hz, H-6′); ^{13}C NMR (50.3 MHz, DMSO-d_6) δ 100.3 (C-1), 69.7, 69.5, 69.2, 68.0 (C-2, 3, 4, 5), 54.6 (O*C*H_3), 51.3 (C-6).

Methyl 6-Azido-6-deoxy-2,3,5-tri-*O*-methyl-β-D-galactofuranoside (7) and Methyl 6-Azido-6-deoxy-2,3,4-tri-*O*-methyl-α-D-galactopyranoside (8). Compound **4** (1.04 g, 3.65 mmol) was treated with MeOH (20 mL) containing conc aq HCl (0.05 mL) as described above. The crude mixture of galactosides **5** and **6** (0.81 g, 3.70 mmol) was dissolved in DMSO (7 mL) and freshly powdered KOH (2.4 g) was added. Upon addition of methyl iodide (1.4 mL) the mixture was stirred, in the dark, at room temperature. After 3 h it was poured into water (50 mL) and extracted with CH_2Cl_2 (5 × 30 mL). The organic extract was washed with water, dried, ($MgSO_4$) and concentrated. TLC of the syrup showed two main spots having R_f 0.62 and 0.32 (2:1 PhMe-EtOAc). The mixture was chromatographed with 5:1 PhMe-EtOAc. Concentration of the first eluate afforded the oily compound **7** (0.45 g, 47%); $[\alpha]_D$ −101° (*c*. 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (s, 1 H, H-1), 3.98 (dd, 1 H, $J_{3,4}$ = 6.1, $J_{4,5}$ = 4.6 Hz, H-4), 3.65 (d, 1 H, $J_{2,3}$ = 1.6 Hz, H-2), 3.59 (dd, 1 H, H-3), 3.52 (s, 3 H, OCH_3), 3.47 (ddd, 1 H, $J_{5,6}$ = 7.3, $J_{5,6'}$ = 4.5 Hz, H-5), 3.39 (dd, 1 H, $J_{6,6'}$ = 12.8 Hz, H-6), 3.38, 3.36, 3.34 (3s, 9 H, OCH_3), 3.31 (dd, 1 H, H-6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 106.4 (C-1), 89.1, 85.0 (C-2, 4), 81.1, 79.6 (C-3, 5), 59.1, 57.8, 57.3, 54.6 (O*C*H_3), 51.0 (C-6).

Anal. Calcd for $C_{10}H_{19}N_3O_5$: C, 45.96; H, 7.34; N, 16.08. Found: C, 46.22; H, 7.47; N, 15.84.

Compound 8 (0.17 g, 18%) was isolated from further fractions of the column; mp 30–31°C, $[\alpha]_D$ +92° (*c*. 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 3.78 (ddd, 1 H, $J_{4,5} \approx 1.0$, $J_{5,6}$ = 6.3, $J_{5,6'}$ = 5.2 Hz, H-5), 3.60 (dd, 1 H, $J_{2,3}$ = 10.3 Hz, H-2), 3.57–3.53 (m, 2 H, H-4, 6), 3.51 (dd, 1 H, $J_{3,4}$ = 3.1 Hz, H-3), 3.54, 3.48, 3.47, 3.40 (3 s, 9 H, OCH_3), 3.24 (dd, 1 H $J_{6,6'}$ = 12.4 Hz, H-6′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.9 (C-1), 80.3, 77.6, 76.6 (C-2, 3, 4), 69.5 (C-5), 61.2, 58.9, 58.3, 55.3 (O*C*H_3), 51.1 (C-6).

Anal. Calcd for $C_{10}H_{19}N_3O_5$: C, 45.96; H, 7.34; N, 16.08. Found: C, 46.23; H, 7.24; N, 15.89.

Methyl 6-Azido-6-deoxy-β-D-galactopyranoside (6) and Methyl 3,6-Anhydro-α-D-galactopyranose (10). Sodium azide (0.25 g, 3.85 mmol) was added to a solution of the tosylate **9**[21] (0.50 g, 1.44 mmol) in dry DMF (8 mL) and the suspension was heated to 100°C for 24 h, when TLC showed two main spots (R_f 0.71 and 0.64, 10:1 EtOAc-MeOH) and complete consumption of the starting material **9**. The solvent was evaporated, and the residue was suspended in MeOH, filtered and evaporated. Column chromatography (20:1 EtOAc-MeOH) afforded a compound having R_f 0.64, which was identified as **10** (0.07 g, 28%); mp 131°C; $[\alpha]_D$ +72° (*c* 0.7, H_2O), lit.[21] mp 140°C, $[\alpha]_D$ +80°.

Evaporation of the fractions which contained the more polar product led to the expected azide derivative **6** (0.15 g, 48%), which had the same physical and spectral properties as the product previously synthesized from **4**.

Methyl 2,3,4-Tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside (11). To a solution of **9**[21] (1.50 g, 4.31 mmol) in dry pyridine (7.5 mL) was added

acetic anhydride (2 mL), and the mixture was stirred at room temperature for 20 h. After addition of MeOH (2 mL) the solution was stirred for 1 h and then concentrated. The resulting syrup was dissolved in CH_2Cl_2 (100 mL) and the solution washed with 10 % aq HCl, satd aq $NaHCO_3$, and water, dried ($MgSO_4$) and the solvent evaporated. Compound **11** (1.96 g, 96%) was obtained in crystalline form and then recrystallized from EtOH: mp 131–132°C; $[\alpha]_D$ +94° (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, 2 H, *J* 8.4 Hz, H-aromatic), 7.35 (d, 2 H, H-aromatic), 5.40 (dd, 1 H, $J_{3,4}$ = 3.3, $J_{4,5}$ = 1.1 Hz, H-4), 5.34, (dd, 1 H, $J_{2,3}$ = 10.6 Hz, H-3), 5.08 (dd, 1 H, $J_{1,2}$ = 3.7 Hz, H-2), 4.94 (d, 1 H, H-1), 4.17 (ddd, 1 H, $J_{5,6}$ = 6.6, $J_{5,6'}$ = 5.7 Hz, H-5), 4.09 (dd, 1 H, $J_{6,6'}$ = 9.9 Hz, H-6), 4.00 (dd, 1 H, H-6′), 3.36 (s, 3 H, OCH_3), 2.46 (s, 3 H, ArCH_3), 2.07, 2.05, 1.96 (3 s, 9 H, CH_3CO); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.3, 169.9, 169.7 (*C*OCH$_3$), 145.1, 132.6, 129.9, 128.0 (*C*-aromatic), 97.2 (C-1), 68.0 (× 2), 67.3, 66.9, 66.2 (C-2, 3, 4, 5, 6), 55.6 (O*C*H$_3$), 21.6 (Ar*C*H$_3$), 20.7, 20.5, 20.4 (*C*H$_3$CO).

Anal. Calcd for $C_{20}H_{26}O_{11}S$: C, 50.62; H, 5.53. Found: C, 50.78; H, 5.51.

Methyl 6-Azido-6-deoxy-2,3,4-tri-*O*-acetyl-α-D-galactopyranoside (12). To a solution of **11** (1.96 g, 4.12 mmol) in DMF (30 mL) was added sodium azide (0.82 g, 12.62 mmol) and the mixture was heated at 80°C for 16 h and then at 110°C for an additional 8 h. The solvent was evaporated, and the residue was suspended in CH_2Cl_2 (100 mL) and filtered. The filtrate was concentrated and the resulting syrup was purified through a short column of silica gel (3:1 hexane-EtOAc) to afford crystalline **12** (1.12 g, 79%); mp 79–80°C; $[\alpha]_D$ +126° (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.41 (dd, 1 H, $J_{3,4}$ = 3.3, $J_{4,5}$ = 0.7 Hz, H-4), 5.35 (dd, 1 H, $J_{2,3}$ = 10.4 Hz, H-3), 5.15 (dd, 1 H, $J_{1,2}$ = 3.7 Hz, H-2), 5.03 (d, 1 H, H-1), 4.12 (ddd, 1 H, $J_{5,6}$ = 8.4, $J_{5,6'}$ = 4.4 Hz, H-5), 3.46 (s, 3 H, CH_3O), 3.45 (dd, 1 H, $J_{6,6'}$ = 12.8 Hz, H-6), 3.15 (dd, 1 H, H-6′), 2.16, 2.09, 1.98 (3 s, 9 H, CH_3CO); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 170.3, 170.2, 169.8 (CH$_3$*C*O), 97.2 (C-1), 69.0, 68.1, 67.9, 67.5 (C-2, 3, 4, 5), 55.6 (*C*H$_3$O), 50.8 (C-6), 20.8, 20.6 (*C*H$_3$CO).

Anal. Calcd for $C_{13}H_{19}N_3O_8$: C, 45.21; H, 5.56; N, 12.17. Found: C, 44.94; H, 5.61; N, 11.95.

Methyl 6-Azido-6-deoxy-2,3,4-tri-*O*-methyl-α-D-galactopyranoside (8). Potassium hydroxide (6 g) was added to a solution of compound **12** (2.13 g, 6.17 mmol) in DMSO (21 mL). To the vigorously stirred solution MeI (5 mL) was added. After 0.5 h the mixture was processed as described for the preparation of the same product starting from **4**. Chromatographic purification led to **8** (1.31 g, 81%) which showed the same properties as those previously described.

6-Azido-6-deoxy-2,3,4-tri-*O*-methyl-α,β-D-galactopyranose (13). A solution of **8** (1.41 g, 5.40 mmol) in trifluoroacetic acid (14 mL) and water (6 mL) was placed in a sealed tube and heated at 90°C under a static argon atmosphere. After 20 h an additional amount of trifluoroacetic acid was added (2 mL) and the heating was continued for 8 h. The yellowish solution was concentrated, and the syrup

was purified by column chromatography (2:1 EtOAc-hexane) to afford crystalline **13** (1.12 g, 84%); mp 45–47°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ (anomeric region) 5.38 (d, 0.7 H, $J_{1,2}$ = 3.3 Hz, H-1α), 4.55 (d, 0.3 H, $J_{1,2}$ = 7.0 Hz, H-1β); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (α anomer) 91.0 (C-1), 84.0, 80.0, 76.1, 69.3 (C-2, 3, 4, 5), 61.2, 58.9, 58.2 (*C*H_3O), 50.9 (C-6); β anomer: 97.5 (C-1), 81.8, 75.2, 73.3, 73.2 (C-2, 3, 4, 5), 61.2, 61.0, 58.5 (*C*H_3O), 50.8 (C-6).

Anal. Calcd for $C_9H_{17}N_3O_5$: C, 43.71; H, 6.94. Found: C, 43.44; H, 7.01.

6-Azido-6-deoxy-2,3,4-tri-*O*-methyl-D-galactonic acid (14). To a solution of **13** (1.06 g, 4.29 mmol) in DMSO (13 mL, 190 mmol) was added acetic anhydride (8.7 mL, 97 mmol), and the mixture was stirred at room temperature for 24 h. Upon addition of water (20 mL) an oil was formed, and the water solution was separated and extracted with CH_2Cl_2 (4 × 20 mL). The oil and extracts were combined, washed with water, dried ($MgSO_4$) and concentrated. The residue, which showed by TLC a main spot having R_f 0.60 (1:1 hexane-EtOAc), was purified by flash chromatography (2:1 hexane-EtOAc) to afford oily lactone **14** (0.83 g, 78%) slightly contaminated by a polar product ($R_f \approx 0$); $[\alpha]_D$ +97° (*c* 1.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.24 (ddd, $J_{4,5}$ = 1.8, J = 6.2, J = 7.8 Hz, H-5), 4.05 (d, 1 H, $J_{2,3}$ = 9.5 Hz, H-2), 3.88 (dd, 1 H, $J_{3,4}$ = 2.2 Hz, H-4), 3.70, 3.61, 3.54 (3 s, 9 H, C*H*$_3$O), 3.69–3.45 (m, 3 H, H-3, 6, 6′); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 169.1 (C-1), 82.0, 78.8, 77.0, 73.8 (C-2, 3, 4, 5), 61.0, 60.9, 58.6 (*C*H_3O), 50.3 (C-6).

On standing in a chloroform solution with a drop of D_2O the lactone was gradually converted into the polar product, which was identified as the corresponding acid. A mixture enriched in the acid (≈ 70%) had $[\alpha]_D$ +57° (*c* 0.8, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) of **14** (acid form) δ 4.78 (bs, 1 H, CO_2H), 3.98 (d, 1 H, $J_{2,3}$ = 2.2 Hz, H-2), 3.93 (ddd, 1 H, $J_{4,5}$ = 1.5, $J_{5,6}$ = 7.3, $J_{5,6'}$ = 5.5 Hz, H-5), 3.81 (dd, 1 H, $J_{3,4}$ = 8.8 Hz, H-2), 3.62–3.44 (m, 2 H, H-4, 6), 3.50, 3.47, 3.44 (3 s, 9 H, C*H*$_3$O), 3.35 (dd, 1 H, $J_{6,6'}$ = 12.4 Hz, H-6′); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 174.2 (C-1), 80.8, 79.2, 79.0, 69.8 (C-2, 3, 4, 5), 60.5, 60.2, 58.8 (*C*H_3O), 54.1 (C-6).

Anal. Calcd for $C_9H_{17}N_3O_6$: C, 41.05; H, 6.52; N, 15.96. Found: C, 41.16; H, 6.39; N, 15.77.

6-Azido-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid (16). a) Starting from **14**. Freshly powdered KOH (0.65 g) was added to a solution of **14** (0.47 g, 1.90 mmol) in THF (2 mL). To this suspension was added MeI (0.5 mL), and the mixture was stirred in the dark for 17 h, then poured into water (10 mL) and stirred for another 0.5 h. The mixture was extracted with CH_2Cl_2 (2 × 30 mL), the aq phase was acidified (pH 3) with conc aq HCl and extracted with ethyl ether (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to a syrup, which was chromatographed (4:1 hexane-EtOAc) to afford oily **16** (0.42 g, 79%); $[\alpha]_D$ −11° (*c*. 1.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43 (bs, CO_2H), 4.05 (d, 1 H, $J_{2,3}$ = 2.1 Hz, H-2), 3.88 (dd, 1 H, $J_{3,4}$ = 9.1 Hz, H-3),

3.68–3.39 (m, 4 H, H-4, 5, 6, 6′), 3.53, 3.50, 3.48, 3.42 (4 s, 12 H, C*H*$_3$O); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 175.6 (*C*O), 80.8, 79.2, 79.0, 78.8 (C-2, 3, 4, 5), 60.7, 59.8, 58.8, 58.5 (*C*H$_3$O), 50.7 (C-6).

Anal. Calcd for $C_{10}H_{19}N_3O_6.0.5\ H_2O$: C, 41.96; H, 6.99; N, 14.69. Found: C, 41.85; H, 6.70; N, 14.48.

b) Starting from **14** and **15**, prepared from **4**. Compound **4** (0.20 g, 0.70 mmol) was treated with an HCl solution of methanol to give a mixture of **5** and **6** in 3:1 ratio (estimated by ^{1}H NMR). This mixture was subjected to methylation, hydrolysis and oxidation in the conditions described above (crude products were employed in all the steps). The product of this sequence was purified by column chromatography (4:1 hexane-EtAc) affording a syrup (80 mg, 46%) in which the lactone **15** was spectroscopically identified as the major component (the lactone **14** was the other). Compound **15**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.20 (dd, 1 H, $J_{3,4}$ = 7.0, $J_{4,5}$ = 3.0 Hz, H-4), 4.08 (d, 1 H, $J_{2,3}$ = 7.3 Hz, H-2), 4.00 (dd, 1 H, H-3), 3.69, 3.54, 3.50 (3 s, 9 H, OC*H*$_3$), 3.54–3.38 (m, 3 H, H-5, 6, 6′); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.8 (C-1), 81.8, 80.6, 79.0, 78.6 (C-2, 3, 4, 5), 59.6, 58.7, 58.4 (*C*H$_3$O), 50.3 (C-6′).

Methylation of the mixture of **14** and **15** (73 mg, 0.50 mmol) as described in a) led to **16** (61 mg, 74%), which had the same properties as the product described above.

6-Amino-6-deoxy-2,3,4,5-tetra-*O*-methyl-D-galactonic acid (17). Compound **16** (70 mg, 0.25 mmol) dissolved in 2 M HCl (1 mL) was hydrogenated at room temperature and normal pressure in the presence of 10 % PD-C (10 mg) for 4 h. The catalyst was filtered, and the filtrate was concentrated. The residue was dissolved in water (0.5 mL) and applied to a column of Dowex 50 W (H^+ form). The column was eluted with water and then with 0.5 M aq pyridine. Upon evaporation of the solvent syrupy **17** (0.06 g, 96 %) was obtained. Highly hygroscopic crystals were obtained from MeOH-ether, mp 161°C, $[\alpha]_D$ +13° (MeOH); ^{1}H NMR (200 MHz, D_2O) δ 3.72–3.63 (m, 3 H, H-2, 3, 4), 3.42, 3.39, 3.30 (× 2) (3 s, 13 H, OC*H*$_3$ and H-5), 3.25 (dd, 1 H, $J_{5,6}$ = 4.0, $J_{6,6'}$ = 13.5 Hz, H-6), 3.09 (dd, 1 H, $J_{5,6'}$ = 7.7 Hz, H-6); ^{13}C NMR (50.3 MHz, D_2O) δ 179.0 (C-1), 81.9, 81.4, 80.6, 77.8 (C-2, 3, 4, 5), 61.1, 60.1, 59.9, 58.5 (O*C*H$_3$), 41.3 (C-6).

Anal Calcd for $C_{10}H_{21}NO_6.1.5\ H_2O$: C, 43.15; H. 8.71; N, 5.03. Found: C, 43.34; H, 8.74; N, 4.75.

ACKNOWLEDGMENTS

Financial support from ANPCyT (National Agency for Promotion of Science and Technology, PICT 01698) and from the University of Buenos Aires (Project TW70) is gratefully acknowledged. O. V. is a Research Member of the National Research Council of República Argentina (CONICET), C. L. R. Z. is a Research Fellow from ANPCyT.

REFERENCES

1. Dedicated to Professor Joachim Thiem on the occasion of his 60th birthday.
2. Varela, O.; Orgueira, H. A. Synthesis of Chiral Polyamides from Carbohydrate Derived Monomers. Adv. Carbohydr. Chem. Biochem. **1999**, *55*, 137–174.
3. Gonsalves, K. E.; Mungara, P. M. Synthesis and Properties of Degradable Polyamides and Related Polymers. Trends Polym. Sci. **1996**, *4*, 25–31.
4. Thiem, J.; Bachmann, F. Carbohydrate-derived Polyamides. Trends Polym. Sci. **1994**, *2*, 425–432.
5. Orgueira, H. A.; Varela, O. Stereocontrolled Synthesis of Stereoregular, Chiral Analogs of Nylon 5,5 and Nylon 5,6. Tetrahedron: Asymmetry **1997**, *8*, 1383–1389.
6. Orgueira, H. A.; Erra-Balsells, R.; Nonami, H.; Varela, O. Synthesis of Chiral Polyhydroxy Polyamides Having Chains of Defined Regio and Stereoregularity. Macromolecules **2001**, *34*, 687–695.
7. Orgueira, H. A.; Varela, O. Synthesis and Characterization of Stereoregular AABB-Type Polymannaramides. J. Polym. Sci., Part A: Polym. Chem. **2001**, *39*, 1024–1030.
8. Zamora, F.; Bueno, M.; Molina, I.; Orgueira, H. A.; Varela, O.; Galbis, J. A. Synthesis of Carbohydrate-based Monomers that are Precursors for the Preparation of Stereoregular Polyamides. Tetrahedron: Asymmetry **1996**, *7*, 1811–1818.
9. Bueno, M.; Zamora, F.; Molina, I.; Orgueira, H. A.; Varela, O.; Galbis, J. A. Synthesis and Characterization of Optically Active Polyamides Derived from Carbohydrate-based Monomers. J. Polym. Sci., Part A: Polym. Chem. **1997**, *55*, 3645–3653.
10. Bueno Martínez, M.; Zamora Mata, F.; Ugalde Donoso, M. T.; Galbis Pérez, J. A. Some Derivatives of 6-Amino-6-deoxy-D-gluconic acid that are Precursors for the Synthesis of Polyamides. Carbohydr. Res. **1992**, *230*, 191–195.
11. Bueno, M.; Galbis, J. A.; García-Martín, M. G.; de Paz, M. V.; Zamora, F.; Muñoz-Guerra, S. Synthesis of Stereoregular Polygluconamides from D-Glucose and D-Glucosamine. J. Polym. Sci., Part A: Polym. Chem. **1995**, *33*, 299–305.
12. Kefur, K.; Kefurtova, Z.; Jary, J. 6-amino-6-deoxyhexonolactams. Collect. Czech. Chem. Commun. **1988**, *53*, 1795–1805, and references therein.
13. Kiely, D. E.; Chang, L.; Lin, T. H. Synthetic Polyhydroxypolyamides from Galactaric, Xylaric, D-Glucaric, and D-Mannaric Acids and Alkylenediamine Monomers - Some Comparisons. J. Polym. Sci., Part A: Polym. Chem. **2000**, *38*, 594–603.
14. Schmidt, O. T. Isopropylidene Derivatives. In *Methods in Carbohydrate Chemistry*, Vol II, Academic, New York, **1963**, 324. Calinaud, P.; Gelas, J. Synthesis of Isopropylidene, Benzylidene, and Related Acetals. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker, New York, **1996**, 21.
15. Chen, S. Y.; Joullié, M. M. Use of D-Ribonolactone in Organic Synthesis. 2. Scope and Utility. J. Org. Chem. **1984**, *49*, 2168–2176.
16. Cone, C.; Hough, L. A P.M.R. Study of the Conformation of Some Derivatives of Di-*O*-isopropylidene-arabinopyranose. Carbohydr. Res. **1965**, *1*, 1–9.
17. Bundle, D. R. Displacement of Sugar Chlorosulphates by Bromide, Azide, and Acetate; a Convenient Synthesis of Methyl 3,6-Dideoxy-β-D-*ribo*-hexopyranoside. J. Chem Soc., Perkin Trans. I **1979**, 2751–2755.
18. Sheradsky, T. Azides as Synthetic Starting Materials. In *The Chemistry of the Azido Group*; Patai, S., Ed.; Interscience, New York, **1971**, 333.
19. Marino, C.; Varela, O.; Lederkremer, R. M. Synthesis of Galactofuranose Dissacharides of Biological Significance. Carbohydr. Res. **1989**, *190*, 65–76.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

20. Varela, O.; Marino, C.; Lederkremer, R. M. Synthesis of *p*-Nitrophenyl β-D-galactofuranoside. A Convenient Substrate for β-Galactofuranosidase. Carbohydr. Res. **1986**, *155*, 247–251.
21. Lewis, B. A.; Smith, F.; Stephen, A. M. 2,5- and 3,6-Anhydrosugars and their Derivatives. In *Methods in Carbohydrate Chemistry*, Vol II, Academic, New York, **1963**, 174.
22. Hanessian, S. Sugar Lactams. III. Synthesis of Five-, Six-, and Seven-Membered Analogs. J. Org. Chem. **1969**, *34*, 675–681.
23. Green, J. W. Oxidative Reactions and Degradations. In *The Carbohydrates, Chemistry and Biochemistry*, Pigman, W. and Horton, D., Eds.; Vol IB, Academic, New York, **1980**, 1142.
24. Bock, K.; Pedersen, C. Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Monosaccharides. Adv. Carbohydr. Chem. Biochem. **1983**, *41*, 27–66.

Received May 9, 2001
Accepted September 19, 2001

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016