Stereoselective Synthesis of C-Amino-Substituted D-Mannopyranosides. Easy Preparation of Novel Inhibitors for Mannosidases

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Received October 3, 1996

Introduction

C-Glycosides are becoming useful as building blocks[1] for the total synthesis of various types of physiologically active natural products such as palytoxin,[2] brevetoxin,[3] and polyether antibiotics.[4] In addition, they are used in enzymatic and metabolic studies. As a result, new and stereoselective synthetic methods for C-pyranosides have been developed in the last few years. The biological interest in these products lies in their potential inhibitory action on glycosidases. Thus, assays of glycosidase inhibitors as potential therapeutic agents against HIV, diabetes, and cancer testify to the increasing demand for these products.[5] On the basis of the knowledge of the enzyme's active site for glycosidases, a wide variety of C-glycosides have been designed. It has been postulated, and in some cases demonstrated, that the agent responsible for the hydrolysis of the O-glycosidic bond is a carboxyl group of an amino acid residue. In theory, any C-glycoside could inhibit these enzymes; however, if the C-bridge is correctly modified, the inhibitory power can be enhanced. Thus, C-glycopyranoses with an amine group on the carbon bridge, which can form an ammonium salt intermediate with the carboxyl group, are potent inhibitors for glycosidases.[6] Similarly, diazo sugar derivatives have been described as irreversible inhibitors by alkylation of the carboxylic acid.[7] This paper reports a new, stereoselective method for the synthesis of C-pyranoses with a hydroxyl group on the C-bridge by using stabilized sulfur ylides, which have previously been used to prepare epoxy amides in a stereoselective fashion, by condensation with aldehydic sugars.[8] Preliminary experiments with glycofuranosides showed the proposed approach to be a highly efficient and stereoselective method of preparing C-glycofuranosides.[9] Our earlier results for the condensation of stabilized sulfur ylides with readily, available protected glycopyranoses to produce epoxy amides in high yields and with high stereoselectivity revealed the usefulness and efficiency of our method.[10] Fully protected monosaccharides such as the 2,3;4,6-di-*O*-isopropylidene-D-mannopyranose (**2**)[11] were an appropriate choice for synthesizing C-glycopyranoses by the same approach. In this paper, we report the condensation of mannopyranose **2** with the sulfur ylide **1a**, which is generated *in situ* from the sulfonium salt **1b** by the "two-phase method".[12] Intramolecular cyclization of the resulting epoxides leads to C-glycopyranoses containing a hydroxyl group on the carbon bridge. These products are of interest on account of the synthetic flexibility of the hydroxyl group. Thus, we converted **4** into the amino derivative and subjected it to enzyme inhibition experiments. The discovery of new inhibitors for mannosidases is of great interest owing to the frequent occurrence of mannose residues in the carbohydrate chains of mammalian surface cells (mannosidases are involved in the biosynthesis of those chains).[13]

Results and Discussion

Thus, **2** was reacted with the sulfonium salt **1b**, in methylene chloride and 10% sodium hydroxide solution, to obtain almost quantitatively and with complete stereoselectivity epoxy amide **3**.[10] Alternatively, the condensation could be accomplished by the same "two-phase method" but using 50% sodium hydroxide. In this case, however, too long exposure times, or excess base, led to the isolation of C-mannopyranose **4** together with small amounts of epoxide **5** and α-C-glycoside **6** (Scheme 1).

We must emphasize that this method provides an easy and efficient stereoselective two-chiral carbon integration of pyranoses to acyclic epoxy amides and can be considered an alternative to the very well-known multistep method based on the Wittig reaction and Sharpless epoxidation.[14] The absolute configurations of the two new chiral sites were established by chemical degradation of product **3** with periodic acid to afford epoxy aldehyde **7**. The optical rotation of **7** was compared with that for the product obtained by reaction of the well-known epoxy amide **8** with periodic acid, which gave epoxide **9**.

Treatment of epoxy amide **3** with sodium hydride in anhydrous THF at rt led to C-mannopyranose **4** in virtually quantitative yield and with complete stereoselectivity. The establishment of the absolute configuration of the starting epoxy amide allowed the configuration of the resulting cyclic product to be assigned. Furthermore, NMR spectroscopic data were in agreement with the proposed configurations and unequivocally revealed a β-configuration in the light of the coupling constant value

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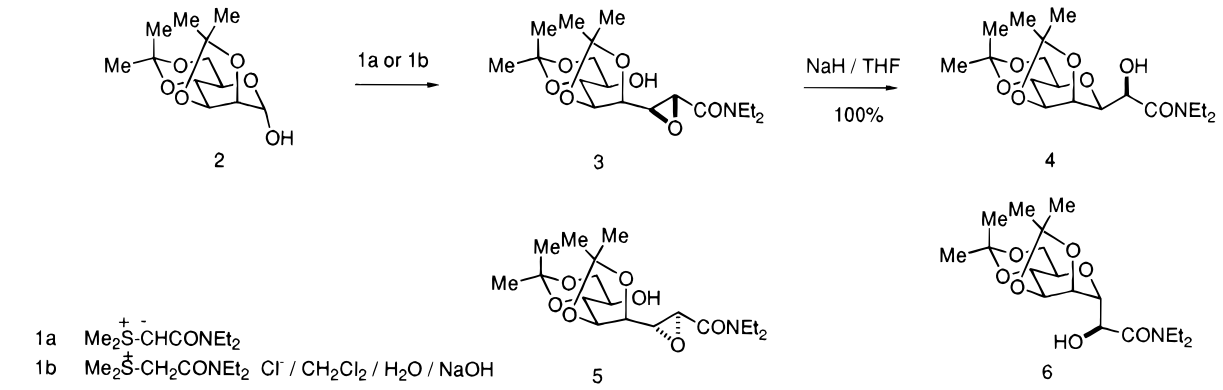
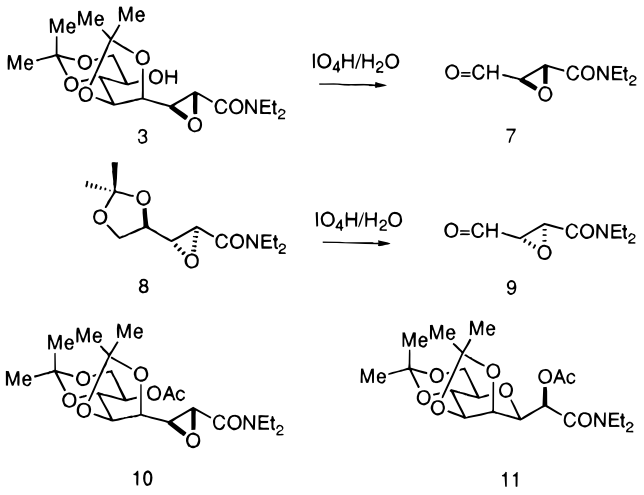
Scheme 1



Scheme 2



$J_{2,3}$ = 8.9 Hz. Acetylated derivatives of **3** and **4** (**10** and **11** respectively) were synthesized in order to confirm the structural assignment (Scheme 2).

C-Mannopyranoside **4** was successfully converted into the amino derivative by conventional reactions. Firstly, **4** was treated with tosyl chloride in pyridine to give the corresponding tosylated product **12** in 98% yield. Treatment with sodium azide in refluxing DMF gave the azide derivative **13** in 75% yield after purification by column chromatography on silica gel. Azide **13** was transformed into the amino derivatives **14** and **15** in quantitative yields by reaction with triphenylphosphine and lithium aluminum hydride, respectively (Scheme 3). While **15** required no further purification, attempts to purify the amino derivative **14** from the crude reaction mixture by column chromatography on silica gel proved impossible. Consequently, **14** was transformed into the less polar carbamate Boc derivative **16**, which was readily purified.

The products, depicted in Figure 1, were obtained from **4**, **16**, and **15**, respectively, by acid hydrolysis with 2 N HCl. Whereas the products **17** and **19** were obtained in quantitative yields and with a high degree of purity, the hydrolysis of **16** furnished a mixture of products in which **18** was the major compound (*ca*. 30% from the crude mixture). Mild hydrolysis conditions were attempted, but in all cases the results were unsuccessful. For this reason, we decided to perform the inhibition experiments with the C-mannopyranoses **17** and **19**. These biological assays utilized commercially available β-mannosidase (isolated from snails) and *p*-nitrobenzyl β-mannoside as the substrate.[15] These preliminary results revealed that **17** and **19** showed inhibitory activity against β-mannosidase. We are currently continuing these biological studies with these and other related products in order to determine the K_i values.

(15) β-Mannosidase was purchased from Sigma-Aldrich, ref M-9400.

Experimental Section

Melting points are uncorrected. NMR spectral data were obtained in $CDCl_3$, unless other solvents are stated. Chemical shifts (δ, ppm), relative to the residual solvent peaks. Microanalyses were performed by the "Servicio de Microanálisis de la Universidad de Málaga". Silica gel for column chromatography was Merck silica gel 60 No. 7736. Preparative thin-layer chromatography was performed on Merck silica gel 60 No. 7747.

Condensation of Sulfonium Salt 1 with 2,3:4,6-Di-*O*-isopropylidene-α-D-mannopyranose (2). To a solution containing 1.0 g (3.84 mmol) of **2**[11] in 10 mL of dichloromethane, 2.5 mL of a 10% solution of NaOH in water, and 0.933 g (4.41 mmol) of dimethylsulfonium (*N*,*N*-diethylcarbamoyl)methylide (**1b**) were added. After 2 h under vigorous stirring, the crude mixture was diluted with 20 mL of water, and the organic layer was separated. The aqueous phase was extracted with *tert*-butylmethyl ether (5 × 20 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The crude mixture was purified by column chromatography on silica gel (3:1 hexane:EtOAc) to provide 1.4 g of product **3** (98%). When the reaction was performed using 50% NaOH and starting from 1 g of **2**, the result, after purification by column chromatography on silica gel, was 0.955 g of β-C-glycoside **4** (67%), 0.085 g of epoxy amide **5** (6.0%), and 0.170 g of α-C-glycoside **6** (12%).

***N*,*N*-Diethyl-2,3-anhydro-4,5:6,8-di-*O*-isopropylidene-D-*erythro*-L-*altro*-octonamide (3):** $[\alpha]^{20}_D$ −58.6° (*c* 7.5, MeOH); IR 3416, 2996, 1653 cm^{-1}; ^{1}H NMR δ 4.52 (dd, 1H, J = 6.7, 2.9 Hz), 3.98 (t, 1H, J = 6.7 Hz), 3.89 (dd, 1H, J = 7.2, 2.9 Hz), 3.64 (ddd, 1H, J = 9.9, 7.3 Hz), 3.56 (d, 1H, J = 2.0 Hz), 3.48 (dd, 1H, J = 6.7, 2.0 Hz), 3.55−3.30 (m, 6H), 1.49, 1.48, 1.37, 1.34 (4s, 12H), 1.25 and 1.12 (2t, 6H, J = 7.2, 7.1 Hz); ^{13}C NMR δ 168.5, 109.5, 98.8, 76.7, 75.3, 72.0, 64.8, 63.6, 55.7, 52.1, 41.6, 40.9, 28.4, 26.7, 25.4, 19.1, 14.7, 12.3; MS *m*/*z* 358 (M^+ − 15, 5), 300 (1.2), 272 (16.6), 214 (7.3), 198 (1.9), 131 (6.6), 100 (100), 72 (36.9), 59 (58.3). Anal. Calcd for $C_{18}H_{31}O_7N$: C, 57.90; H, 8.31; N, 3.75. Found: C, 57.60; H, 8.40; N, 3.76.

***N*,*N*-Diethyl-2,3-anhydro-4,5:6,8-di-*O*-isopropylidene-D-*erythro*-L-*gluco*-octonamide (5):** $[\alpha]^{20}_D$ −88.9° (*c* 0.9, MeOH); IR 3416, 2996, 1653 cm^{-1}; ^{1}H NMR δ 4.26 (dd, 1H, J = 7.7, 3.7 Hz), 4.12 (dd, 1H, J = 7.7, 4.9 Hz), 3.61 (d, 1H, J = 1.9 Hz), 3.34 (dd, 1H, J = 4.9, 1.9 Hz), 3.95−3.55 (m, 4H), 3.55−3.30 (2dq, 4H), 1.44, 1.41, 1.37 (3s, 12H), 1.23, 1.12 (2t, 6H, J = 6.8, 6.8 Hz); ^{13}C NMR δ 165.7, 110.2, 98.7, 78.3, 74.7, 72.6 64.3, 63.3, 57.5, 51.3, 41.4, 40.7, 28.0, 26.8, 26.4, 19.3, 14.5, 12.7; MS *m*/*z* 358 (M^+ − 15, 4), 300 (1.2), 272 (15), 214 (8.3), 198 (2.4), 130 (7.4), 100 (100), 72 (36.7), 59 (49.6), 43 (34.6).

***N*,*N*-Diethyl-3,7-anhydro-4,5:6,8-di-*O*-isopropylidene-D-*erythro*-L-*allo*-octonamide (6):** $[\alpha]^{20}_D$ −88.9° (c 9.5, MeOH); IR 3453, 2997, 2944, 2884, 1648 cm^{-1}; ^{1}H NMR δ 4.68 (d, 1H, J = 9.2 Hz), 4.27 (dd, 1H, J = 5.1, 2.3 Hz), 4.03 (dd, 1H, J = 9.2, 2.3 Hz), 4.02 (dd, 1H, J = 7.8, 5.1 Hz), 3.75 (dd, 1H, J = 10.6, 5.7 Hz), 3.65 (dd, 1H, J = 9.9, 7.9 Hz), 3.54 (dd, 1H, J = 10.6,

Scheme 3

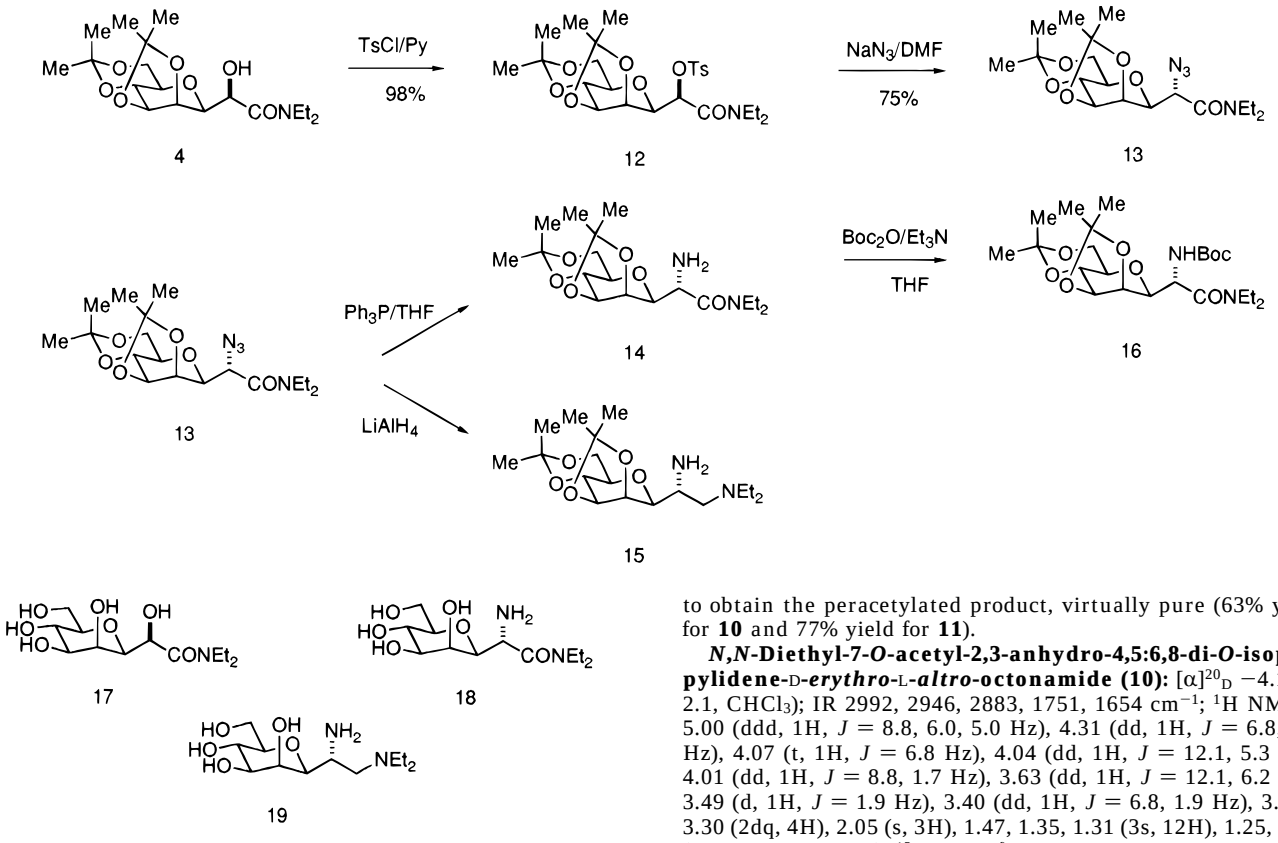


Figure 1.

10.0 Hz), 3.05 (ddd, 1H, J = 10.0, 9.9, 5.7 Hz), 3.55−2.87 (2dq, 4H), 1.52, 1.46, 1.38, 1.31 (4s, 12H), 1.18, 1.05 (2t, 6H, J = 7.1, 7.1 Hz); ^{13}C NMR δ 168.8, 109.5, 99.7, 77.2, 76.1, 73.0, 72.9, 71.6, 70.0, 61.8, 42.5, 41.1, 28.9, 28.4, 26.2, 18.8, 14.7, 12.9; MS m/z 358 (M^+ − 15, 3.3), 283 (0.9), 273 (8.8), 215 (7.7), 190 (2.6), 131 (22.1), 100 (100), 72 (46.4), 43 (34.5).

***N,N*-Diethyl-3,7-anhydro-4,5:6,8-di-*O*-isopropylidene-D-*erythro*-L-*manno*-octonamide (4).** To a solution containing 7.6 g (0.02 mol) of epoxide **3** in 20 mL of anhydrous THF was added 4 g of 60% sodium hydride. The suspension was stirred under a nitrogen atmosphere and at rt for 3 h, after which time the reaction was complete as checked by TLC analysis. The suspension was then filtered and the filtrate washed with ether. The ether solution was then washed with a saturated aqueous solution of ammonium chloride and water, and the combined aqueous phases were extracted with chloroform (3 × 1). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to obtain 7.6 g of the pure pyranose **4** as a colorless syrup (100%): $[\alpha]^{20}_D$ −57.4° (c 9.6, $HCCl_3$); IR 3444, 2936, 1637 cm^{-1}; ^{1}H NMR δ 4.57 (d, 1H, J = 8.9 Hz), 4.40 (dd, 1H, J = 5.0, 2.2 Hz), 3.96 (dd, 1H, J = 7.8, 5.0 Hz), 3.70 (dd, 1H, J = 14.2, 7.2 Hz), 3.65 (dd, 1H, J = 10.0, 7.8 Hz), 3.59 (dd, 1H, J = 8.9, 2.2 Hz), 3.55−3.10 (2dq, 4H), 3.15 (dd, 1H, J = 14.2, 7.2 Hz), 2.93 (ddd, 1H, J = 9.9, 7.3, 7.2 Hz), 1.47, 1.41, 1.31 (3s, 12H), 1.08, 1.05 (2t, 6H, J = 7.2, 7.2 Hz); ^{13}C NMR δ 171.5, 109.3, 99.3, 79.0, 75.6, 73.2, 72.8, 69.7, 65.6, 61.6, 40.9, 40.4, 28.6, 28.2, 26.1, 18.5, 13.7, 12.2; MS m/z 358 (M^+ − 15, 9.1), 297 (2.9), 273 (20.5), 215 (15.1), 202 (11.6), 130 (24.1), 100 (100), 72 (41.4), 43 (30.1). Anal. Calcd for $C_{18}H_{31}O_7N$: C, 57.90; H, 8.31; N, 3.75. Found: C, 57.97; H, 8.17; N, 3.51.

Treatment of Epoxy Amide 3 and Mannopyranoside 4 with Acetic Anhydride. Synthesis of the Acetylated Products 10 and 11: General Procedure. The product (1.34 mmol) was dissolved in 2 mL of anhydrous pyridine, and to the resulting mixture was then added 0.4 mL of acetic anhydride at rt. After 12 h, the solution was diluted with cold water (4 mL) and extracted with chloroform (5 mL, 3 × 1). The organic phase was then washed once with 2 N HCl (5 mL), saturated sodium bicarbonate (5 mL), and water (5 mL). Finally, it was dried over anhydrous sodium sulfate, filtered, and concentrated to obtain the peracetylated product, virtually pure (63% yield for **10** and 77% yield for **11**).

***N,N*-Diethyl-7-*O*-acetyl-2,3-anhydro-4,5:6,8-di-*O*-isopropylidene-D-*erythro*-L-*altro*-octonamide (10):** $[\alpha]^{20}_D$ −4.1° (c 2.1, $CHCl_3$); IR 2992, 2946, 2883, 1751, 1654 cm^{-1}; ^{1}H NMR δ 5.00 (ddd, 1H, J = 8.8, 6.0, 5.0 Hz), 4.31 (dd, 1H, J = 6.8, 1.6 Hz), 4.07 (t, 1H, J = 6.8 Hz), 4.04 (dd, 1H, J = 12.1, 5.3 Hz), 4.01 (dd, 1H, J = 8.8, 1.7 Hz), 3.63 (dd, 1H, J = 12.1, 6.2 Hz), 3.49 (d, 1H, J = 1.9 Hz), 3.40 (dd, 1H, J = 6.8, 1.9 Hz), 3.55−3.30 (2dq, 4H), 2.05 (s, 3H), 1.47, 1.35, 1.31 (3s, 12H), 1.25, 1.12 (2t, 6H, J = 7.1 Hz); ^{13}C NMR δ 170.1, 165.6, 110.0, 99.7, 76.9, 75.4, 69.0, 67.3, 61.9, 55.3, 52.1, 41.6, 40.9, 26.7, 26.4, 25.4, 20.9, 20.6, 14.8, 12.9; MS m/z 400 (M^+ − 15, 4.5), 342 (1.6), 272 (8.4), 242 (4.4), 214 (3.8), 142 (6.9), 130 (3.9), 100 (100), 58 (7.7), 43 (98.2).

***N,N*-Diethyl-2-*O*-acetyl-3,7-anhydro-4,5:6,8-di-*O*-isopropylidene-D-*erythro*-L-*manno*-octonamide (11):** $[\alpha]^{20}_D$ = −81.3° (c 2.6, $CHCl_3$); IR 3002, 2953, 2896, 1750, 1657 cm^{-1}; ^{1}H NMR δ 5.45 (d, 1H, J = 9.5 Hz, H-2), 4.30 (dd, 1H, J = 5.2, 2.5 Hz), 4.17 (dd, 1H, J = 9.5, 2.5 Hz), 4.03 (dd, 1H, J = 8.0, 5.2 Hz), 3.79 (dd, 1H, J = 10.7, 5.6 Hz), 3.66 (dd, 1H, J = 10.0, 8.0 Hz), 3.56 (dd, 1H, J = 10.7, 10.0 Hz), 3.07 (ddd, 1H, J = 10.1, 10.0, 5.7 Hz), 3.55−3.20 (2dq, 4H), 2.06 (s, 3H), 1.51, 1.47, 1.38, 1.30 (3s, 12H), 1.22, 1.06 (2t, 6H, J = 7.1 Hz); ^{13}C NMR δ 169.4, 167.3, 109.4, 99.5, 75.6, 72.8, 69.7, 67.4, 61.5, 41.7, 40.6, 28.7, 28.2, 26.0, 20.2, 18.6, 13.7, 12.3; MS m/z 400 (M^+ − 15, 9.4), 356 (5.3), 300 (6.1), 244 (16.6), 202 (26.1), 142 (20.8), 100 (100), 72 (47.5), 59 (13.0), 43 (62.3).

Periodic Acid Oxidation of Epoxy Amides 3 and 5. Synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-*N,N*-Diethyl-2,3-Epoxy-3-formylpropionamide (7) and (9). A solution containing 0.050 g (0.134 mmol) of the epoxy amide in 2 mL of water was treated with 0.13 g (0.572 mmol) of periodic acid. After 24 h, the reaction was complete and produced epoxy aldehydes **7** and **9**, respectively, in quantitative yield. The specific rotation of **7** was +10.2 (c 1.2, H_2O), and that of **9** was −8.97. A reference sample of epoxy amide **8** was treated with periodic acid under similar conditions to obtain epoxy aldehyde **9** with a negative specific rotation [−8.9° (c 1.2, H_2O)].[12]

***N,N*-Diethyl-3,7-anhydro-4,5:6,8-di-*O*-isopropylidene-2-*O*-tosyl-D-*erythro*-L-*manno*-octonamide (12).** To a solution of 7.6 g (0.02 mol) of pyranose **4** in 50 mL of anhydrous pyridine was added 6.5 g of *p*-toluenesulfonyl chloride (50% excess) at 0 °C, and the crude mixture was allowed to stand at rt for 12 h. Then, cold water was added, and the mixture extracted with chloroform (50 mL, 4 × 1). The combined organic layers were washed once with 1 N HCl (100 mL), saturated sodium hydrogen carbonate, and water, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain 10.5 g (98%) of **12** as a white solid: mp 61 °C; $[\alpha]^{20}_D$ −51.4° (c 0.5, $CHCl_3$); IR 2998, 1653, 1381, 1217 cm^{-1}; ^{1}H NMR δ 7.74 (d, 2H, J = 8.2 Hz), 7.26 (d, 2H, J = 8.2 Hz), 5.48 (d, 1H, J = 9.2 Hz, H-2), 4.26 (dd, 1H, J = 5.2, 2.4 Hz), 4.07 (dd, 1H, J = 9.2, 2.4 Hz), 3.98 (dd, 1H, J = 7.8, 5.2 Hz), 3.75 (dd, 1H, J = 10.4, 5.6 Hz), 3.63 (dd, 1H, J =

10.0, 7.8 Hz), 3.52 (dd, 1H, J = 10.4, 10.0 Hz), 3.42−3.20 (2dq, 4H), 3.03 (dt, 1H, J = 10.0, 5.6 Hz), 2.38 (s, 3H), 1.49, 1.44, 1.35, 1.25 (4s, 12H), 1.18, 0.96 (2t, 6H, J = 7.1, 7.0 Hz); ^{13}C NMR δ 165.4, 144.7, 133.4, 129.4, 127.7, 109.5, 99.4, 75.3, 72.7, 72.1, 70.9, 69.8, 61.4, 41.7, 40.6, 28.6, 28.1, 25.8, 21.3, 18.5, 13.8, 12.0; MS m/z 512 (M^+ − 15, 3), 412 (1), 356 (11), 314 (18), 242 (9), 155 (18), 142 (9), 100 (100), 91 (20), 72 (29). Anal. Calcd for $C_{25}H_{37}O_9NS$: C, 56.92; H, 7.02; N, 2.65. Found: C, 56.75; H, 7.12; N, 2.49.

***N,N*-Diethyl-3,7-anhydro-2-azido-2-deoxy-4,5:6,8-di-*O*-isopropylidene-D-*erythro*-L-*gluco*-octonamide (13).** A suspension containing 2 g (3.79 mmol) of the tosyl derivative **12** and 2 g of sodium azide (8-fold excess) in 20 mL of DMF was heated under reflux for 3 h, after which time the reaction was complete. Then, the crude mixture was cooled and diluted with 50 mL of chloroform. Next, the organic solution was washed with water twice and the aqueous solution extracted with chloroform (50 mL, 2 × 1). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under high vacuum to remove the solvents. Column chromatography on silica gel (eluent 8:1 Hex:AcOEt) of the resulting syrup provided 1.1 g of the pure azido derivative **13** as a white solid (75%): mp 101 °C; $[\alpha]^{20}_D$ = −36.7° (*c* 2.7, $CHCl_3$); IR 2997, 2113, 1641, 1381, 1217 cm^{-1}; ^{1}H NMR δ 4.29 (dd, 1H, J = 9.1, 2.4 Hz), 4.19 (d, 1H, J = 9.1 Hz), 4.17 (dd, 1H, J = 5.7, 2.4 Hz), 4.01 (dd, 1H, J = 8.0, 5.7 Hz), 3.93 (dd, 1H, J = 10.9, 5.7 Hz), 3.69 (t, 1H, J = 10.9 Hz), 3.64 (dd, 1H, J = 10.0, 8.0 Hz), 3.56−3.22 (4q, 4H), 3.12 (ddd, 1H, J = 10.9, 8.0, 5.7 Hz), 1.47, 1.45, 1.37, 1.19 (4s, 12H), 1.18, 1.06 (2t, 6H, J = 7.1, 7.0 Hz); ^{13}C NMR δ 165.6, 109.5, 99.5, 76.3, 75.9, 73.1, 72.7, 69.3, 61.7, 58.6, 42.5, 40.9, 28.8, 28.2, 25.9, 18.5, 14.3, 12.7; MS m/z 355 (M^+ − 15−28, 6), 312 (3), 201 (5), 183 (6), 143 (17), 127 (10), 101(12), 100 (29), 85 (12), 72 (100), 59 (20), 43 (40). Anal. Calcd for $C_{18}H_{30}O_6N_4$: C, 54.27; H, 7.53; N, 14.07. Found: C, 54.55; H, 7.52; N, 13.94.

***N,N*-Diethyl-2-amino-3,7-anhydro-2-deoxy-4,5:6,8-di-*O*-isopropylidene-D-*erythro*-L-*gluco*-octonamide (14).** To a solution containing 0.54 g (1.54 mmol) of azido derivative **13** in 5 mL of THF was added 0.5 g of triphenylphosphine (25% excess). The crude mixture was stirred at rt for 12 h, and 15 mL of water was added. The mixture was kept under strong stirring for a further 12 h more and then separated. The aqueous solution was extracted with THF (5 mL, 3 × 1). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to obtain a crude mixture consisting of the amino derivative **14** and triphenylphosphine oxide. Purification by column chromatography on silica gel (eluent 1:1 Hex:AcOEt and then AcOEt) was unsuccessful, and pure amino derivative **14** was isolated in a low yield. This required derivatization of **14** to a lower polarity product, viz. the Boc-amino **16**, which is described below. **14**: IR 3386, 3320, 2998, 1653, 1381 cm^{-1}; ^{1}H NMR δ 4.15 (dd, 1H, J = 8.1, 2.4 Hz), 3.97 (dd, 1H, J = 5.7, 2.4 Hz), 3.90 (dd, 1H, J = 8.0, 5.7 Hz), 3.89 (dd, 1H, J = 10.5, 5.7 Hz), 3.87 (d, 1H, J = 8.1 Hz), 3.71 (t, 1H, J = 10.5 Hz), 3.55 (dd, 1H, J = 10.0, 8.0 Hz), 3.55−3.20 (4q, 4H), 3.14 (ddd, 1H, J = 10.5, 8.0, 5.7 Hz), 1.49, 1.47, 1.39, 1.21 (4s, 12H), 1.19, 1.08 (2t, 6H, J = 7.1, 7.0 Hz); ^{13}C NMR δ 170.7, 109.3, 99.5, 79.7, 75.9, 73.4, 73.1, 69.6, 61.8, 52.5, 42.4, 40.7, 28.9, 28.4, 25.9, 18.7, 14.4, 12.9; MS m/z 372 (M^+, 1), 357 (M^+ − 15, 9), 273 (14), 272 (100), 214 (53), 156 (77), 138 (13), 129 (35), 100 (26), 85 (13), 72 (56), 69 (35), 43 (30).

2-Amino-3,7-anhydro-1,2-dideoxy-1-(diethylamino)-4,5:6,8-di-*O*-isopropylidene-D-*erythro*-L-*gluco*-octitol (15). A solution of 2 mL of anhydrous THF containing 0.1 g of the azido derivative **13** was treated with 0.1 g of lithium aluminum hydride (10-fold excess) under a nitrogen atmosphere at rt. The suspension was vigorously stirred for 1 h. Then, 2 mL of a 10% aqueous solution of KOH was added slowly and at 0 °C to remove the excess hydride. Next, the crude mixture was extracted with dichloromethane (3 × 1). The organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain 0.1 g of a white solid corresponding to the pure diamino derivative **15** (100%). No further purification was required. **15**: mp 92 °C; $[\alpha]^{20}_D$ −36.9° (*c* 0.5, $CHCl_3$); IR 3401, 2977, 1380, 1241, 1217 cm^{-1}; ^{1}H NMR δ 4.11 (dd, 1H, J = 5.3, 2.4 Hz), 3.96 (dd, 1H, J = 8.0, 5.3 Hz), 3.83 (dd, 1H, J = 10.5, 5.8 Hz), 3.67 (dd, 1H, J = 10.5, 7.2 Hz), 3.62 (dd, 1H, J = 8.0, 5.3 Hz), 3.53 (dd, 1H, J = 6.4, 2.4 Hz), 3.14 (m, 1H), 3.03 (ddd, 1H, J = 7.2, 5.8, 5.3 Hz), 2.44 (m, 5H), 2.21 (dd, 1H, J = 12.4, 8.9 Hz), 1.47, 1.43, 1.35, 1.27 (4s, 12H), 0.92 (t, 6H, J = 7.1 Hz); ^{13}C NMR δ 109.5, 99.4, 78.5, 76.3, 74.8, 73.1, 69.5, 61.8, 54.9, 50.3, 47.6, 28.9, 28.3, 26.0, 18.7, 11.7; MS m/z 343 (M^+ − 15, 4), 115 (2), 100 (1), 87 (21), 86 (100), 71 (13), 57 (10), 43 (10). Anal. Calcd for $C_{18}H_{34}O_5N_2$: C, 60.33; H, 9.49; N, 7.82. Found: C, 59.84; H, 9.40; N, 7.26.

***N,N*-Diethyl-3,7-anhydro-2-[(*tert*-butoxycarbonyl)amino]-2-deoxy-4,5:6,8-di-*O*-isopropylidene-D-*erythro*-L-*gluco*-octonamide (16).** To a solution of the crude mixture resulting from the reaction of azide **13** (0.30 g) with triphenylphosphine in 5 mL of THF were added 0.30 g of triethylamine and 0.70 mL of Boc_2O. After 12 h, the solution was concentrated to dryness under vacuum to obtain a syrup. Column chromatography on silica gel (eluent 8:1 Hex:AcOEt) of the resulting syrup provided 0.31 g of the pure Boc-derivative **16** as a colorless liquid (75%). **16**: $[\alpha]^{20}_D$ −61.4° (*c* 2.1, $CHCl_3$); IR 3338, 2991, 1707, 1636, 1382 cm^{-1}; ^{1}H NMR δ 4.07 (dd, 1H, J = 5.4, 2.3 Hz), 3.98 (d, 1H, J = 8.1 Hz), 3.92 (dd, 1H, J = 8.1, 2.3 Hz), 3.84 (dd, 1H, J = 10.9, 5.8 Hz), 3.67 (m, 3H), 3.55−3.30 (4q, 4H), 3.08 (m, 1H), 1.47, 1.44, 1.41, 1.37 (4s, 12H), 1.38 (s, 9H), 1.18, 1.06 (2t, 6H, J = 7.1, 7.0 Hz): ^{13}C NMR δ 168.8, 157.5, 109.5, 99.5, 77.8, 76.1, 73.2, 72.9, 69.5, 61.8, 51.2, 42.5, 40.5, 28.9, 28.4, 26.1, 18.8, 28.2, 27.6, 14.1, 12.8; MS m/z 415 (M^+ − 57, 3), 330 (27), 272 (26), 142 (1), 100 (100), 72 (67), 33 (30). Anal. Calcd for $C_{23}H_{40}O_8N_2$: C, 58.47; H, 8.47; N, 5.93. Found: C, 58.20; H, 8.40; N, 5.80.

Acid Hydrolysis of Pyranoses 4, 15, and 16. Synthesis of the Unprotected Mannopyranoses 17, 19, and 18. General Procedure. A solution of 0.1 mmol of the sugar derivative in 1 mL of absolute ethanol was treated with 0.2 mL of 2 N HCl at rt for 1 h. Then the crude mixture was concentrated to dryness under high vacuum to obtain the unprotected sugar derivative quantitatively as a syrup. Redissolution in water and subsequent lyophilization gave crystalline products.

***N,N*-Diethyl-3,7-anhydro-D-*erythro*-L-*manno*-octonamide (17):** $[\alpha]^{20}_D$ −23.5° (*c* 2.0, H_2O); ^{1}H NMR (MeOD−D_2O) δ 4.52 (d, 1H, J = 8.1 Hz), 3.61−3.4 (m, 7H), 3.2−3.1 (m, 4H), 1.1−1.0 (2t, 6H, J = 7.1 Hz); ^{13}C NMR (MeOD−D_2O) δ 173.7, 81.1, 79.8, 75.3, 68.9, 67.9, 65.7, 61.9, 43.2, 42.1, 14.4, 12.8.

***N,N*-Diethyl-2-amino-3,7-anhydro-2-deoxy-D-*erythro*-L-*gluco*-octonamide (18).** These data were obtained from the crude mixture: ^{1}H NMR (MeOD−D_2O) δ 4.57 (d, 1H, $J_{2,3}$ = 8.8 Hz), 3.92−3.80 (m, 2H), 3.72−3.49 (m, 4H), 3.42−3.15 (m, 5H), 1.15 and 1.07 (2t, 6H, J = 7.1 Hz); ^{13}C NMR (MeOD−D_2O) δ 173.4, 81.7, 81.2, 75.4, 70.5, 68.4, 62.8, 52.5, 44.7, 42.2, 14.7, 13.1.

2-Amino-3,7-anhydro-1,2-dideoxy-1-(diethylamino)-D-*erythro*-L-*gluco*-octitol (19): $[\alpha]^{20}_D$ +7.27° (*c* 1.6, H_2O); ^{1}H NMR (MeOD−D_2O) δ 4.20−4.09 (m, 2H), 3.97−3.89 (m, 2H), 3.80 (d, 1H, J = 8.3 Hz), 3.75−3.50 (m, 3 H), 3.48−3.40 (m, 2H), 3.36 (q, 4H), 1.35 (t, 6H, J = 7.1 Hz); ^{13}C-NMR (MeOD−D_2O) δ 79.7, 73.1, 72.9, 69.7, 65.8, 60.6, 51.4, 48.4, 7.6.

Acknowledgment. This research was funded by the Dirección General de Investigación y Científica Técnica (Ref. PB94-1487) and the Dirección General de Universidades e Investigación. Consejería de Educación y Ciencia. Junta de Andalucía (group FQM 0158). F.S.-G. acknowledges the award of a research grant from the Consejería de Educación y Ciencia de la Junta de Andalucía.

Supporting Information Available: Compound characterization data inclusive of NMR peak assignments and copies of NMR spectra (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO961875S