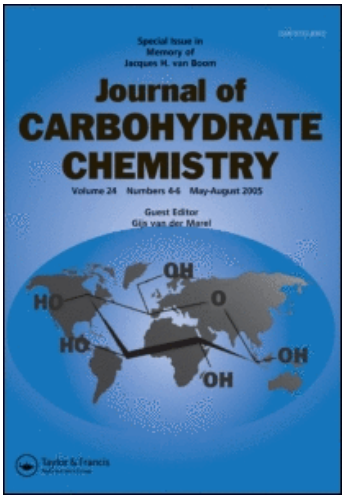

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Synthesis of a 4-Amino-4-deoxy-D-galacturonic Acid Derivative

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SYNTHESIS OF A 4-AMINO-4-DEOXY-D-GALACTURONIC ACID DERIVATIVE[1]

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ABSTRACT

The hitherto unknown methyl (methyl 4-amino-2,3-di-*O*-benzyl-4-deoxy-α-**D**-galactopyranosid)uronate (**11**) has been prepared in six steps from methyl 2,3-di-*O*-benzyl-6-*O*-(4-methoxybenzyl)-α-**D**-glucopyranoside (**1**). Treatment of **1** with methanesulfonyl chloride and subsequent substitution of the resulting 4-*O*-methanesulfonyl group with sodium azide gave under inversion at *C*-4 the 4-azido-**D**-galacto derivative **4**. After deblocking at *O*-6 of **4**, the carboxyl group was introduced by Corey oxidation and esterified with diazomethane. Conversion of the azidodeoxygalacturonate derivative **10** to the target compound **11** was achieved by reduction with H_2S in pyridine.

INTRODUCTION

In the course of a project for synthesis of modified pectin fragments and compounds which could serve as chiral building blocks for β-lactams, we were especially interested in elaborating an approach to methyl (methyl 4-amino-2,3-di-*O*-benzyl-4-deoxy-α-**D**-galacto-pyranosid)uronate (**11**). For the preparation of **11**, we have chosen the readily available methyl 2,3-di-*O*-benzyl-6-*O*-(4-methoxybenzyl)-α-**D**-glucopyranoside (**1**)[2] as the starting material.

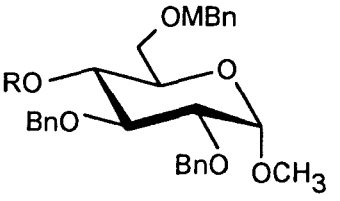
RESULTS AND DISCUSSION

Thus, **1** was treated with methanesulfonyl chloride in pyridine to give syrupy **3** in 90% yield. The ^{1}H NMR chemical shifts of the ring protons in the mesyl derivative **3** agree well with those which were observed from the chemical shifts of the 4-*O*-acetyl derivative **2**, prepared for comparing the NMR data. Therefore, acetylation and mesylation of **1** caused an expected downfield shift of the H-4 signal, from δ 3.63 - 3.77 ppm to 5.04 and 5.09 ppm, respectively.

Treatment of the 4-*O*-methanesulfonyl derivative **3** with sodium azide in *N,N*-dimethylformamide yielded the syrupy 4-azido-D-galacto derivative **4** in 86% yield. Replacement of the methanesulfonyl group by an azido group resulted in a decrease of the dihedral angle defined by H-3 / H-4 and H-4 / H-5. Thus, the vicinal coupling constants within the pyranose ring exhibit significant differences between **3** and **4** 9.1 → 3.5 Hz ($J_{3,4}$) and 10.0 → 1.3 Hz ($J_{4,5}$), indicating that compound **4** has the *galacto*-configuration. As expected, the infrared spectrum of the product **4** showed a peak for an azido group at 2115 cm^{-1}.

The *p*-methoxybenzyl group in **4** was removed by oxidation[3] with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dichloromethane-water to give, after chromatography, the 2,3-di-*O*-benzyl derivative **5** (82%). A smaller amount (12%) of the 3-*O*-benzyl derivative **6** was also isolated. Additionally, compounds **7** and **8** were used as model compounds for the interpretation of the NMR spectra of **5** and **6**. In the ^{1}H NMR spectra, acetylation of **5** caused a downfield shift (δ 0.5 ppm) for the H-6, H-6' signals of **7**. Furthermore, the ^{13}C NMR spectra of **7** showed an expected downfield shift of the C-6 signal (δ 63.5 ppm with respect to 62.3 ppm of **5**). In agreement with the β-shift effect of an acetyl group, the signal of C-5 appeared 2.3 ppm upfield for **7** in comparison with the corresponding signal of **5**. Successful dimethoxytritylation of **6** under mild conditions provided chemical evidence for a free hydroxy group at position 6. As expected, the exchange of a benzyl group at *O*-2 by an acetyl group, when comparing the ^{1}H NMR spectra of **5** with that of derivative **8**, caused a significant downfield shift (δ 3.88 ppm → 5.10 ppm). It should be noted that compounds **5** and **7** were previously prepared by Lichtenthaler et al. based on a similar synthetic route.[4]

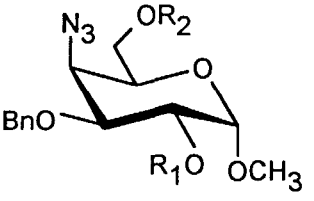
The oxidation of *N*-functionalized *gluco*-[5-9] and *manno*[10-12]-configurated sugars has been studied using potassium permanganate, or oxygen over platinum catalyst, as agents. To our best knowledge, only two synthetic examples of aminodeoxygalacturonic acids had been reported.[13,14] During our initial oxidation experiments using dimethyl sulfoxide-oxalyl chloride,[15,16] compound **9**[17] was obtained in 48% yield. This result suggested



1 R = H

2 R = Ac

3 R = Ms



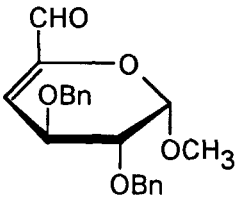
4 R_1 = Bn, R_2 = MBn

5 R_1 = Bn, R_2 = H

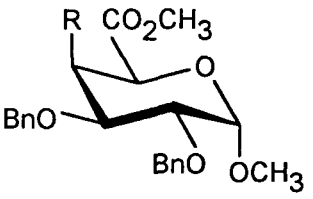
6 R_1 = R_2 = H

7 R_1 = Bn, R_2 = Ac

8 R_1 = Ac, R_2 = DMT



9



10 R = N_3

11 R = NH_2

Ac = acetyl

Bn = benzyl

MBn = 4-methoxybenzyl

Ms = methylsulfonyl

DMT = 4,4'-dimethoxytrityl

that the basic conditions of the oxidation step caused a β-elimination leading to the 4,5-unsaturated 4-deoxy-4-enodialdo derivative **9**.[5,17,18] However, the azidodeoxygalacturonic acid was obtained by oxidation with pyridinium dichromate[19,20] in *N,N*-dimethylformamide, followed by esterification with diazomethane to yield 72% of **10**.

The ^1H and ^{13}C NMR spectra of **10** are fully consistent with the assigned structure. The conversion of **5** into **10** provided, in the ^{13}C NMR spectrum, a strong downfield shift of the C-6 signal (δ 62.3 ppm → 168.5 ppm) as a result of oxidation of the primary alcohol to the carboxyl function.

Conversion of the azidodeoxygalacturonate derivative **10** to the corresponding 4-amino-4-deoxy derivative **11** was achieved in 65% yield by reduction with H_2S in pyridine. The IR, ^1H NMR and ^{13}C NMR spectral data for **11** are in full accordance with the proposed structure. The IR spectrum contained new peaks at 3350 and 3400 cm^{-1} assignable to the N-H stretching vibrations of a primary amino group, whereas the signal of a azido group (2220 cm^{-1} in **10**) disappeared. Conversion of an azido group into an amino group caused, in the ^1H NMR spectra, an expected upfield shift of the H-4 signal of **11** in comparison with **10** (δ 4.29 ppm → 3.65 ppm). Furthermore, the ^{13}C NMR spectrum showed the C-4 signal (δ 51.7 ppm) in a typical range for a carbon atom connected to an amino group.

EXPERIMENTAL

General Procedures. Melting points were determined with Boetius micro apparatus BHMK05 (RAPIDO, Dresden) and are corrected. Optical rotations were measured for solutions in a 1-dm cell with an automatic polarimeter "Polamat A" (C. ZEISS, Jena). NMR spectra were recorded with a Bruker spectrometer model WH-250 or Ac 250 P at 250 MHz for ^1H, and 62.89 MHz for ^{13}C. The following solvent systems (v/v) were used for chromatography: (A_1) 2:1, (A_2) 3:1 toluene-ethyl acetate, (B) 3:1 chloroform-acetone, and (C) 10:5:1 chloroform-ethyl acetate-methanol.

Methyl 2,3-di-*O*-Benzyl-6-*O*-(4-methoxybenzyl)-α-D-glucopyranoside (1). For preparation see ref. 2, syrup: $[\alpha]_D^{25}$ +10.6° (*c* 1.0, chloroform); lit.[2] syrup; $[\alpha]_D^{22}$ +7.7° (*c* 1.0, chloroform); ^1H NMR ($CDCl_3$) δ 3.42 (s, 3 H, glycosidic $OC\underline{H}_3$), 3.55 (dd, 1 H, $J_{2,3}$ = 9.5 Hz, H-2), 3.61 (bs, 1 H, HO-4), 3.63 - 3.77 (m, 4 H, H-4, H-5, H-6, H-6'), 3.80 (s, 3 H, $C_6H_4OC\underline{H}_3$), 3.82 (dd, 1 H, $J_{3,4}$ = 8.6 Hz, H-3), 4.51 (dd, 2 H, J = 11.8 Hz, $C\underline{H}_2Ph$), 4.65 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1), 4.73 (dd, 2 H, J = 12.3 Hz, $C\underline{H}_2Ph$), 4.77 (d,

2 H, $C\underline{H}_2Ph$), 6.85 - 7.48 (m, 14 H, arom. H); ^{13}C NMR ($CDCl_3$) δ 55.0 (2 C, 2 OCH_3), 69.2 (C-6), 69.9 (C-5), 70.9 (C-2), 72.9, 73.1, 75.2 (3 C, 3 $\underline{C}H_2Ph$), 79.6 (C-4), 81.4 (C-3), 98.0 (C-1), 113.7, 127.5, 127.8, 127.9, 128.3, 129.1, 130.0, 138.0, 138.8, 159.1 (18 C, Ph).

Methyl 4-*O*-Acetyl-2,3-di-*O*-benzyl-6-*O*-(4-methoxybenzyl)-α-D-glucopyranoside (2). Compound **1** (495 mg, 1 mmol) was dissolved in a mixture of acetic anhydride (6 mL), dry pyridine (18 mL), and 4-dimethylaminopyridine (122 mg, 1 mmol) and kept for 12 h at room temperature (TLC, solvent A_2). Ethanol (4 mL) was added at 0 °C, and, after 20 min at room temperature, the mixture was diluted with chloroform (100 mL) and poured into ice-water. The phases were separated, and the aq. phase was extracted with chloroform (50 mL). The combined organic solutions were successively washed with 10% aq. $KHSO_4$ (2 x 50 mL), water (2 x 50 mL), sat. aq. $NaHCO_3$ (3 x 50 mL), water (2 x 50 mL), dried, and concentrated. The residue was purified by column chromatography (solvent A_2) to yield **2** (510 mg, 95%), syrup: $[\alpha]_D^{25}$ +19.3° (*c* 0.95, chloroform); ^1H NMR ($CDCl_3$) δ 1.83 (s, 3 H, $C\underline{H}_3CO_2$), 3.41 (s, 3 H, glycosidic $OC\underline{H}_3$), 3.38 - 3.52 (m, 2 H, H-6, H-6'), 3.60 (dd, 1 H, $J_{2,3}$ = 9.5 Hz, H-2), 3.80 (s, 3 H, $C_6H_4OC\underline{H}_3$), 3.81 (m, 1 H, H-5), 3.92 (t, 1 H, $J_{3,4}$ = 9.3 Hz, H-3), 4.44 (dd, 2 H, J = 11.4 Hz, $C\underline{H}_2Ph$), 4.62 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1), 4.66 (dd, 2 H, J = 11.8 Hz, $C\underline{H}_2Ph$), 4.86 (dd, 2 H, J = 11.5 Hz, $C\underline{H}_2Ph$), 5.04 (dd, 1 H, $J_{4,5}$ = 10.2 Hz, H-4), 6.83 - 7.40 (m, 14 H, arom. H); ^{13}C NMR ($CDCl_3$) δ 20.6 ($\underline{C}H_3CO_2$), 55.2, 55.3 (2 C, 2 $O\underline{C}H_3$), 68.7 (2 C, C-5, C-6), 70.6 (C-4), 73.2, 73.4, 75.2 (3 C, 3 $\underline{C}H_2Ph$), 79.3 (C-3), 79.6 (C-2), 98.1 (C-1), 113.7, 127.5, 127.8, 127.9, 128.1, 128.3, 128.4, 129.4, 129.9, 138.0, 138.6, 159.2 (18 C, Ph), 169.6 ($CH_3\underline{C}O_2$).

Anal. Calcd for $C_{31}H_{36}O_8$: C, 69.39; H, 6.76. Found: C, 69.10; H, 6.72.

Methyl 2,3-Di-*O*-benzyl-6-*O*-(4-methoxybenzyl)-4-*O*-methylsulfonyl-α-D-glucopyranoside (3). To a stirred solution of **1** (4.0 g, 8 mmol) in dry pyridine (135 mL) methanesulfonyl chloride (1.6 mL, 20 mmol) was added dropwise at 0 °C. The mixture was kept for 8 h at room temperature (TLC, solvent A_1) and then poured into ice-water (300 mL). The aqueous layer was extracted with chloroform (3 x 150 mL), and the combined organic phases were successively washed with 10% aq. $KHSO_4$ (2 x 150 mL), water (2 x 150 mL), sat. aq. $NaHCO_3$ (3 x 150 mL), water (2 x 150 mL), dried, and concentrated. The residue was chromatographed (solvent A_1) to give **3** (4.10 g, 90%) as a syrup: $[\alpha]_D^{25}$ +48.2° (*c* 1.0, chloroform); ^1H NMR ($CDCl_3$) δ 2.81 (s, 3 H, $C\underline{H}_3SO_2$), 3.40 (s, 3 H, glycosidic $OC\underline{H}_3$), 3.62 (dd, 1 H, $J_{2,3}$ = 9.5 Hz, H-2), 3.80 (s, 3 H, $C_6H_4OC\underline{H}_3$), 3.67 - 3.92 (m, 3 H, H-5, H-6, H-6'), 4.03 (t, 1 H, $J_{3,4}$ = 9.1 Hz, H-3), 4.51 (dd, 2 H, J = 11.2 Hz, $C\underline{H}_2Ph$), 4.63 (d, 1 H, $J_{1,2}$ = 3.2 Hz, H-1), 4.65 (dd, 2 H, J = 9.3 Hz, $C\underline{H}_2Ph$), 4.71

(dd, 2 H, J = 11.8 Hz, C$\underline{H}_2$Ph), 5.09 (t, 1 H, $J_{4,5}$ = 10.0 Hz, H-4), 6.83 - 7.40 (m, 14 H, arom. H); ^{13}C NMR ($CDCl_3$) δ 38.6 ($\underline{C}H_3SO_2$), 55.2, 55.4 (2 C, 2 O$\underline{C}H_3$), 68.0 (C-6), 68.7 (C-5), 73.3, 75.3 (3 C, 3 $\underline{C}H_2$Ph), 78.0 (C-4), 78.8 (C-2), 80.2 (C-3) 97.6 (C-1), 113.7, 127.6, 127.7, 128.4, 128.5, 129.6, 130.1, 137.6, 138.0, 159.2 (18 C, Ph).

Anal. Calcd for $C_{30}H_{36}O_9S$: C, 62.92; H, 6.34; S, 5.60. Found: C, 62.78; H, 6.41; S, 5.86.

Methyl 4-Azido-2,3-di-*O*-benzyl-4-deoxy-6-*O*-(4-methoxybenzyl)-α-D-galacto-pyranoside (4). To a solution of **3** (4.01 g, 70 mmol) in dry *N,N*-dimethylformamide (60 mL) was added fine powdered sodium azide (4.55 g, 70 mmol) and the mixture was stirred for 32 h at 130 °C (TLC, solvent A_1). After cooling to room temperature, the solution was poured into ice-water (400 mL). The aqueous layer was extracted with chloroform (3 x 200 mL), and the combined organic phases were washed with water (3 x 200 mL), dried, and concentrated. The residue was purified by column chromatography (solvent A_1) to give **4** (3.11 g, 86%) as a syrup: $[\alpha]_D^{25}$ +11.7° (*c* 0.95, chloroform); IR (KBr) 2115 cm^{-1} (N_3); ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 3 H, glycosidic O$\underline{C}H_3$), 3.62 (m, 2 H, H-6, H-6'), 3.81 (s, 3 H, $C_6H_4O\underline{C}H_3$), 3.92 (dd, 1 H, $J_{2,3}$ = 9.4 Hz, H-2), 4.01 (m, 1 H, H-5), 4.07 (dd, 1 H, $J_{4,5}$ = 1.3 Hz, H-4), 4.10 (dd, 1 H, $J_{3,4}$ = 3.5 Hz, H-3), 4.53 (dd, 2 H, J = 11.3 Hz, C$\underline{H}_2$Ph), 4.68 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 4.80 (dd, 2 H, J = 12.0 Hz, C$\underline{H}_2$Ph), 4.83 (dd, 2 H, J = 11.9 Hz, C$\underline{H}_2$Ph),6.93 - 7.50 (m, 14 H, aromat. H); ^{13}C NMR ($CDCl_3$) δ 55.3, 55.5 (2 C, 2 O$\underline{C}H_3$), 61.7 (C-4), 67.4 (C-5), 68.9 (C-6), 73.2, 73.4, 73.8 (3 C, CH_2Ph), 76.5 (C-2), 77.9 (C-3), 98.9 (C-1), 114.1, 127.9, 128.0, 128.1, 128.2, 128.6, 129.6, 130.2, 138.5, 138.6, 159.7 (18 C, Ph).

Anal. Calcd for $C_{29}H_{33}N_3O_6$: C, 67.04; H, 6.40; N, 8.09. Found: C, 66.97; H, 6.63; N, 8.00.

Methyl 4-Azido-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranoside (5) and methyl 4-azido-3-*O*-benzyl-4-deoxy-α-D-galactopyranoside (6). To a solution of **4** (2.60 g, 5 mmol) in dichloromethane (27 mL) and water (3 mL) were added in portions 2,3-dichloro-5,6-dicyano-1,4-benzoquinone with stirring at room temperature. After 8 h (TLC, solvent B) the mixture was diluted with dichloromethane (250 mL), washed with 10% aq. $NaHCO_3$ (3 x 100 mL) and water (2 x 100 mL), dried, and concentrated. The residue was processed by column chromatography (solvent B) to give pure **5** (1.68 g, 82%) and **6** (180 mg, 12%).

Compound **5** was isolated as a syrup: $[\alpha]_D^{25}$ +13.8° (*c* 1.02, chloroform); IR (Nujol) 2110 cm^{-1} (N_3); lit.[4] syrup; $[\alpha]_D^{25}$ +3° (c 1.0, chloroform); IR (film) 2150 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.25 (bs, 1 H, OH-6), 3.37 (s, 3 H, glycosidic O$\underline{C}H_3$), 3.63 (dd, 1 H, $J_{6,6'}$ = 10.5 Hz, $J_{6',5}$ = 5.0 Hz, H-6'), 3.76 (dd, 1 H, $J_{6,5}$ = 6.8 Hz, H-6),3.82 (m, 1 H, H-

5), 3.88 (dd, 1 H, $J_{2,3}$ = 9.9 Hz, H-2), 3.95 (m, 1 H, H-4), 4.07 (dd, 1 H, $J_{3,4}$ = 3.7 Hz, H-3), 4.63 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1) 4.76 (dd, 2 H, J = 12.0 Hz, C$\underline{H}_2$Ph), 4.81 (dd, 2 H, J = 11.8 Hz, C$\underline{H}_2$Ph), 7.25 - 7.47 (m, 10 H, arom. H); ^{13}C NMR ($CDCl_3$) δ 55.4 (2 C, 2 O$\underline{C}H_3$), 61.3 (C-4), 62.3 (C-6), 68.6 (C-5), 73.2, 73.8 (3 C, 3 $\underline{C}H_2$Ph), 76.2 (C-2), 77.9 (C-3) 98.7 (C-1), 127.7, 127.8, 128.0, 128.2, 128.4, 128.5, 128.6, 138.0, 138.2 (18 C, Ph).

Compound **6** had mp 127-128 °C (from ethyl acetate-hexane); $[\alpha]_D^{25}$ +147.1° (*c* 1.0, chloroform); IR (KBr) 2110 cm^{-1} (N_3).

Anal. Calcd for $C_{14}H_{19}N_3O_5$: C, 54.36; H, 6.19; N, 13.58. Found: C, 54.45; H, 6.32; N, 13.50.

Methyl 6-*O*-Acetyl-4-azido-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranoside (7). A solution of **5** (400 mg, 1 mmol) in dry pyridine (4 mL) was treated with acetic anhydride (2 mL) at 0 °C and kept for 12 h at this temperatue (TLC, solvent A_2). Ethanol (1 mL) was added at 0 °C. After 10 min the mixture was diluted with chloroform (20 mL), and the organic layer was successively washed with water (10 mL), 15% aq. $NaHSO_4$ (2 x 10 mL), water (10 ml), sat. aq. $NaHCO_3$ (2 x 10 mL), water (10 mL), dried, and concentrated to give 7 (407 mg, 92%): mp 76-79 °C (from ethanol); $[\alpha]_D^{25}$ +9.7° (*c* 1.04, chloroform); IR (KBr) 2110 cm^{-1} (N_3); lit.[4] mp 76-78 °C; $[\alpha]_D^{25}$ +8° (*c* 0.7, chloroform); ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3 H, C$\underline{H}_3CO_2$), 3.37 (s, 3 H, glycosidic O$\underline{C}H_3$), 3.87 (dd, 1 H, $J_{2,3}$ = 10.0 Hz, H-2), 3.89 (bd, 1 H, H-4), 3.93 (m, 1 H, H-5), 4.06 (dd, 1 H, $J_{3,4}$ = 3.6 Hz, H-3), 4.15 (dd, 1 H, $J_{6,6'}$ = 11.4 Hz, $J_{6',5}$ = 5.4 Hz, H-6'), 4.21 (dd, 1 H, $J_{6,5}$ = 6.8 Hz, H-6), 4.61 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1) 4.76 (dd, 2 H, J = 12.3 Hz, C$\underline{H}_2$Ph), 4.82 (dd, 2 H, J = 11.9 Hz, C$\underline{H}_2$Ph), 7.25 - 7.45 (m, 10 H, arom. H); ^{13}C NMR ($CDCl_3$) δ 20.6 ($\underline{C}H_3CO_2$), 55.3 (O$\underline{C}H_3$), 61.4 (C-4), 63.5 (C-6), 66.3 (C-5), 73.3, 73.8 (2 C, 2 $\underline{C}H_2$Ph), 76.1 (C-2), 77.7 (C-3), 98.7 (C-1), 127.7, 127.8, 128.0, 128.4, 128.5, 138.0, 138.2 (18 C, Ph), 170.4 ($CH_3\underline{C}O_2$).

Methyl 2-*O*-Acetyl-4-azido-3-*O*-benzyl-4-deoxy-6-*O*-(4,4'-dimethoxytrityl)-α-D-galactopyranoside (8). To a stirred solution of **6** (278 mg, 0.9 mmol) in dry pyridine (4 mL) 4-dimethylaminopyridine (61 mg, 0.5 mmol) and bis(4-methoxyphenyl)chlorophenylmethane (500 mg, 1.6 mmol) were added. Stirring was continued for 2 h at ambient temperature (TLC, solvent A_1). The mixture was poured into ice-water (20 mL), the aqueous layer was extracted with chloroform (3 x 10 mL), and the combined organic phases were washed with water (2 x 10 mL), sat. aq. $NaHCO_3$ (2 x 10 mL), water (2 x 10 mL), dried, and concentrated. A solution of the residue (solvent A_2, containing 0.1% pyridine) was passed through a bed of silica gel. Conventional acetylation of the concentrated eluate (3:1 pyridine-acetic anhydride, 4 mL) led to a residue which was

processed by column chromatography (ethyl acetate 12 → 25% in toluene, containing 0.1% pyridine), to give **8** (282 mg, 48% from **6**), syrup: $[\alpha]_D^{25}$ +31.1° (c 0.97, chloroform); IR (Nujol) 2110 cm^{-1} (N_3); ^1H NMR ($CDCl_3$) δ 2.06 (s, 3 H, $C\underline{H}_3CO_2$), 3.22 (dd, 1 H, $J_{6,6'}$ = 9.6 Hz, $J_{6',5}$ = 7.2 Hz, H-6'), 3.30 (s, 3 H, glycosidic $OC\underline{H}_3$), 3.37 (dd, 1 H, $J_{6,5}$ = 5.9 Hz, H-6), 3.67 (t, 1 H, H-5), 3.74 (s, 6 H, 2 $C_6H_4OC\underline{H}_3$), 3.91 (dd, 1 H, $J_{4,5}$ = 0.9 Hz, H-4), 3.97 (dd, 1 H, $J_{3,4}$ = 3.6 Hz, H-3), 4.69 (dd, 2 H, J = 12.1 Hz, $C\underline{H}_2Ph$), 4.87 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 5.10 (dd, 1 H, $J_{2,3}$ = 10.0 Hz, H-2), 6.80 - 7.50 (m, 18 H, arom. H); ^{13}C NMR ($CDCl_3$) δ 21.0 ($\underline{C}H_3CO_2$), 55.2 (3 C, 3 $O\underline{C}H_3$), 61.4 (C-5), 62.6 (C-6), 67.4 (C-4), 70.7 (C-3), 73.0 ($\underline{C}H_2Ph$), 75.6 (C-2), 86.5 [$\underline{C}(C_6H_4OCH_3)_2C_6H_5$], 97.2 (C-1), 113.2, 126.9, 127.8, 127.9, 128.0, 128.3, 128.6, 129.2, 135.8, 136.0, 137.9, 144.9, 158.7 (30 C, Ph), 170.3 ($CH_3\underline{C}O_2$).

Anal. Calcd for $C_{37}H_{39}N_3O_8$: C, 67.98; H, 6.01; N, 6.43. Found: C, 67.75; H, 6.22; N, 6.62.

Methyl 2,3-Di-*O*-benzyl-4-deoxy-6-aldehydo-β-L-threo-hex-4-enodialdo-1,5-pyranoside (9). Into a 100-mL three-necked round bottom flask fitted with dry nitrogen gas inlet, two pressure equalizing addition funnel, thermometer, and magnetic stirrer was placed a solution of oxalyl chloride (0.4 mL, 3.9 mmol) in dry dichloromethane (10 mL). After cooling at -76 °C, a solution of dry dimethylsulfoxide (0.7 mL, 9.3 mmol) in dry dichloromethane (2 mL) was added during 2 min. Then compound **5** (798 mg, 2 mmol) in dry dichloromethane (4 mL) was added dropwise. After stirring for 15 min at -76 °C triethylamine (2.5 mL) was added dropwise, and after 5 min at -76 °C, the solution was warmed to room temperature, and stirred for an additional 15 min before being diluted with dichloromethane (30 mL). The organic phase was washed with water (15 mL), brine (4 x 15 mL), dried, and concentrated. The residue was purified by column chromatography (solvent C) to yield **9** (380 mg, 48%), syrup: $[\alpha]_D^{25}$ +146.9° (*c* 1.0, chlorofom); IR (Nujol) 1715 cm^{-1} (C=O str.); lit.[17] syrup; $[\alpha]_D$ +147.7° (*c* 0.6, chloroform); ^1H NMR ($CDCl_3$) δ 3.48 (s, 3 H, glycosidic $OC\underline{H}_3$), 3.82 (dd, 1 H, $J_{2,3}$ = 8.1 Hz, H-2), 4.50 (dd, 1 H, $J_{3,4}$ = 2.7 Hz, H-3), 4.76 (dd, 2 H, J = 12.1 Hz, $C\underline{H}_2Ph$), 4.78 (dd, 2 H, J = 12.0 Hz, $C\underline{H}_2Ph$), 4.97 (d, 1 H, $J_{1,2}$ = 2.6 Hz, H-1), 5.89 (d, 1 H, H-4), 7.25 - 7.45 (m, 10 H, arom. H), 9.19 (s, 1 H, CHO).

Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.45; H, 6.31.

Methyl (Methyl 4-Azido-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranosid)uronate (10). Compound **5** (499 mg, 1.25 mmol) was dissolved in a mixture of dry *N,N*-dimethylformamide (13 mL) and pyridinium dichromate (2.4 g, 6 mmol) and stirred under Argon for 44 h at room temperature. The solution was then poured into ice-water (300 mL), the aqueous layer extracted with chloroform (6 x 60 mL), and the combined organic

phases were washed with brine (3 x 100 mL), water (2 x 100 mL), dried, and concentrated. The residue was dissolved in 1,2-dimethoxyethane (16 mL), 1 M NaOH (6.4 mL) was added dropwise at 0 °C, and the mixture was kept for 2 h at ambient temperature. After cooling at 0 °C, 1 M HCl was added to reach a pH 1. The resulting solution was extracted with chloroform (5 x 60 mL), the combined organic layers were washed with water (100 mL), dried, and concentrated. The remaining colourless syrup was dissolved in 1,2-dimethoxyethane and treated with an excess of an ether solution of diazomethane. After 1 h, the mixture was diluted with diethyl ether (100 mL), washed with 0.1 M NaOH (2 x 70 mL), water (3 x 70 mL), dried, and concentrated. The residue was applied to a column of silica gel (solvent B) to give **10** as a syrup: $[\alpha]_D^{25}$ +31.4° (*c* 1.0, chloroform); IR (Nujol) 1750 cm^{-1} (C=O str.), 2110 cm^{-1} (N_3); ^1H NMR ($CDCl_3$) δ 3.40 (s, 3 H, glycosidic $OC\underline{H}_3$), 3.80 ($CO_2C\underline{H}_3$), 3.88 (dd, 1 H, $J_{2,3}$ = 9.9 Hz, H-2), 4.10 (dd, 1 H, $J_{3,4}$ = 3.7 Hz, H-3), 4.29 (dd, 1 H, $J_{4,5}$ = 1.8 Hz, H-4), 4.37 (d, 1 H, H-5), 4.69 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1), 4.73 (dd, 2 H, J = 11.9 Hz, $C\underline{H}_2Ph$), 4.81 (dd, 2 H, J = 11.9 Hz, $C\underline{H}_2Ph$), 7.25 - 7.45 (m, 10 H, arom. H); ^{13}C NMR ($CDCl_3$) δ 52.7, 56.2 (2 C, 2 $OC\underline{H}_3$), 62.0, 68.5, 75.4, 77.0 (C-2 - C-5), 73.3, 74.0 (2 C, 2 $C\underline{H}_2Ph$), 99.2 (C-1), 127.7, 127.9, 128.0, 128.2, 128.5, 128.6, 137.8, 138.0 (12 C, Ph), 168.5 (C-6).

Anal. Calcd for $C_{22}H_{25}N_3O_6$: C, 61.82; H, 5.89; N, 9.83. Found: C, 62.05; H, 6.11; N, 9.64.

Methyl (Methyl 4-Amino-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranosid) uronate (11). A continuous stream of H_2S was passed through a solution of **10** (855 mg, 2 mmol) and triethylamine (2 mL) in pyridine (10 mL). After 4 h (TLC, solvent B) the solution was concentrated, and the residue was co-concentrated with repeated addition of water (3 x 5 mL), dissolved in ethanol (10 mL), filtered through Celite, and concentrated. Column chromatographic purification (solvent B) afforded **11** as a syrup: $[\alpha]_D^{25}$ +51.7° (*c* 1.02, chloroform); IR (Nujol) 1770 cm^{-1} (C=O str.), 3350, 3400 cm^{-1} (NH_2); ^1H NMR ($CDCl_3$) δ 3.40 (s, 3 H, glycosidic $OC\underline{H}_3$), 3.65 (dd, 1 H, $J_{4,5}$ = 2.2 Hz, H-4), 3.75 (dd, 1 H, $J_{2,3}$ = 9.9 Hz, H-2), 3.80 ($CO_2C\underline{H}_3$), 3.92 (dd, 1 H, $J_{3,4}$ = 4.2 Hz, H-3), 4.44 (d, 1 H, H-5), 4.73 (d, 1 H, $J_{1,2}$ = 2.7 Hz, H-1), 4.73 (dd, 2 H, J = 12.0 Hz, $C\underline{H}_2Ph$), 4.73 (dd, 2 H, J = 10.0 Hz, $C\underline{H}_2Ph$), 7.25 - 7.45 (m, 10 H, arom. H); ^{13}C NMR ($CDCl_3$) δ 51.7 (C-4), 52.4, 56.0 (2 C, 2 $OC\underline{H}_3$), 69.8, 74.8, 77.2 (C-2, C-3, C-5), 72.5, 73.7 (2 C, 2 $C\underline{H}_2Ph$), 99.1 (C-1), 127.7, 127.8, 127.9, 128.1, 128.3, 128.5, 128.6, 132.0, 132.2, 138.2 (12 C, Ph), 169.8 (C-6).

Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.75; H, 6.69; N, 3.40.

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