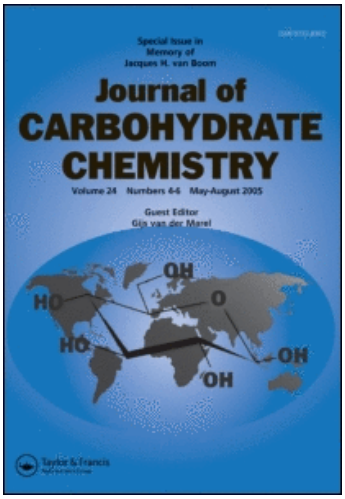

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis of the Antibiotic 1,5-dideoxy-1,5-imino-d-mannitol

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To cite this Article Broxterman, H. J. G. , Neefjes, J. J. , Van der Marel, G. A. , Ploegh, H. L. and Van Boom, J. H.(1988) 'Synthesis of the Antibiotic 1,5-dideoxy-1,5-imino-d-mannitol', Journal of Carbohydrate Chemistry, 7: 3, 593 — 603
To link to this Article: DOI: 10.1080/07328308808057553
URL: http://dx.doi.org/10.1080/07328308808057553

J. CARBOHYDRATE CHEMISTRY, 7(3), 593-603 (1988)

SYNTHESIS OF THE ANTIBIOTIC 1,5-DIDEOXY-1,5-IMINO-D-MANNITOL

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Received February 2, 1988 - Final Form May 18, 1988

ABSTRACT

Easily accessible benzyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (1) was converted in six steps into benzyl 2,3-*O*-isopropylidene-5-*N*-benzyl-5-deoxy-6-*O*-benzyl-α-D-mannofuranoside or benzyl 2,3-*O*-isopropylidene-5-azido-5-deoxy-6-*O*-benzyl-α-D-mannofuranoside. Both compounds afforded, after hydrogenolysis and acidolysis, 1-deoxymannojirimycin in an overall yield of 38% based on 1.

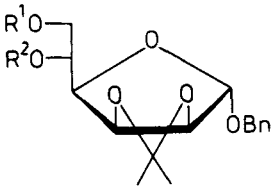
INTRODUCTION

The polyhydroxylated piperidine 1,5-dideoxy-1,5-imino-D-mannitol (1-deoxymannojirimycin, 11) inhibits a specific mannosidase of glycoprotein processing.[1,2] Up to now, several approaches to the preparation of 1,5-dideoxy-1,5-imino-D-mannitol (11)[3-7] have been published. In a previous paper,[8] we showed that 1,5-dideoxy-1,5-imino-D-glucitol (C-2 epimer of 11) was easily accessible from D-glucose. We now report that 1-deoxymannojirimycin (11) can be synthesised starting from D-mannose following a closely related route revealing unexpected pitfalls.

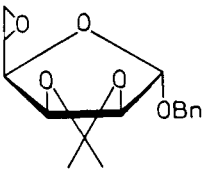
RESULTS AND DISCUSSION

The L-gulofuranoside 5 is an important intermediate in the preparation of the target molecule 11. We reasoned that compound 5 would be

accessible by adopting the same synthetic route applied earlier by us in the synthesis of the C-2 epimer of compound 5 (i.e. 1,2-*O*-isopropylidene-3,6-di-*O*-benzyl-β-L-idofuranose). Thus mesylation of benzyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (1), obtained[5] in three steps from D-mannose, afforded 2 in an excellent yield. The primary mesylate group in 2 could easily be substituted[9] with potassium acetate in the presence of a crown-ether to give the 6-*O*-acetyl derivative 3. Contrary to our expectation,[9] we found that treatment of the 5-*O*-mesyl-6-*O*-acetyl mannofuranoside derivative 3 with excess potassium *tert*-butyloxide in *tert*-butanol gave a complex mixture of products from which the desired oxirane 4 was isolated in a rather low yield (20%). However the yield could be increased by executing the ring-closure in the aprotic polar solvent *N,N*-dimethylformamide and by using an equimolar amount of potassium *tert*-butyl oxide. In this way compound 4 having the L-gulo configuration was obtained in a yield of 91%. Regioselective opening[10] of the 5,6-anhydro function in 4 with sodium benzyl oxide furnished 5 (72% based on 1). Triflation of 5 with trifluoromethanesulfonic anhydride in the presence of pyridine afforded 6 in a nearly quantitative yield. Substitution of the triflate function in 6 by *Walden* inversion with a small excess of lithium azide in *N,N*-dimethylformamide was rather disappointing. TLC analysis of the crude reaction mixture revealed the presence of one major product, the ^{1}H and ^{13}C NMR data of which were in agreement with the 5,6-*cis*-enolether derivative 9. In addition, the required 5-azido derivative 7 could be isolated in a yield of 30%. In this respect it is interesting to note that *Walden* inversion, under the aforementioned condition, of the 5-*O*-triflate group in 1,2-*O*-isopropylidene-3,6-di-*O*-benzyl-5-*O*-trifluoromethanesulfonyl-β-L-idofuranose[8] proceeded quantitatively. Any attempt to favour the formation of 7 by increasing the amount of nucleophile or the nucleophilicity of the azide-ion failed. The yield of required 7 amounted to 50% by executing the substitution in a mixture of *N,N*-dimethylformamide and toluene. However, purification of 7 was, due to the small difference in R_f value of 7 and 9, rather cumbersome. The latter disadvantage could be overcome by using benzylamine, instead of lithium azide, as the nucleophilic source. Thus prolonged treatment of 6 with benzylamine in toluene afforded the 5-*N*-benzyl mannofuranoside derivative 8, having a much lower mobility than the, also in this case, formed side product 9. In this way, compound 8 could



1 $R^1=R^2=H$
2 $R^1=R^2=Ms$
3 $R^1=Ac$, $R^2=Ms$



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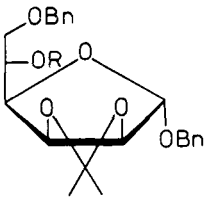
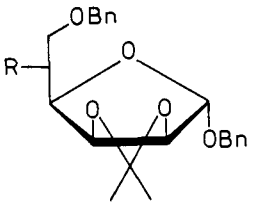
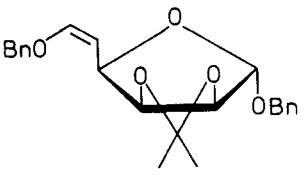


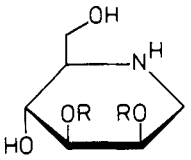
5 R=H
6 R=Tf



7 $R=N_3$
8 R=NHBn



9



10 R,R=$C(CH_3)_2$
11 R=H

Bn=$CH_2C_6H_5$, Ms=SO_2CH_3, Ac=$COCH_3$, Tf=SO_2CF_3

be isolated, after purification by column chromatography, in a yield of 56%. Hydrogenolysis of **8** with palladium(II) hydroxide gave crude **10**, the acetonide function of which was removed by acidic hydrolysis to afford crystalline 1,5-dideoxy-1,5-imino-D-mannitol (**11**) in 38% yield (based on **1**). In a similar fashion, the azido derivative **7** could also be smoothly converted to **11**.

In conclusion the data presented in this paper indicate that the mannofuranoside derivative **1** is a convenient starting product for the preparation of the valuable antibiotic 1-deoxymannojirimycin.

EXPERIMENTAL

General Procedures. Acetonitrile was dried by refluxing with CaH_2 for 16 h, then distilled and stored over molecular sieves 4 nm. Pyridine was dried by refluxing with CaH_2 for 16 h and then distilled, redistilled from *p*-toluenesulfonyl chloride (60 g/L), redistilled from KOH

(40 g/L) and stored over molecular sieves (0.4 nm). Toluene and dichloromethane were dried by refluxing with P_2O_5 (5 g/L) for 2 h and then distilled. Toluene was stored over sodium wire. Dichloromethane was stored over basic aluminum oxide. *N,N*-Dimethylformamide was stirred with CaH_2 for 16 h and then distilled under reduced pressure and stored over molecular sieves (0.4 nm). Methanol and ethanol were dried by refluxing with magnesium methyloxide and magnesium ethyloxide, respectively, distilled and stored over molecular sieves (0.3 nm). Benzyl alcohol was freshly distilled before use. Benzylamine was distilled from zinc dust and stored over molecular sieves (0.4 nm). All solvents were stored under a nitrogen atmosphere.

Melting points are uncorrected. TLC analysis was carried out on silica gel (Schleicher & Schull, F 1500 LS 254). Compounds were visualized by UV light or by spraying with the appropriate reagents. Compounds containing alkene functions were visualized by spraying the TLC plates with $KMnO_4$ (1%) in aqueous Na_2CO_3 (2%); sugars were visualized by treatment with conc. H_2SO_4/methanol (2/8, v/v) followed by charring at 140°C for a few minutes. Compounds containing NH functions were visualized by spraying the TLC plates with a tolidine solution after treatment of the TLC plates with chlorine. Column chromatography was carried out on Merck Kieselgel (230-400 mesh, ASTM). Evaporations were carried out below 40°C under reduced pressure (15 mm or 0.5 mm Hg). ^1H NMR spectra were measured at 300 MHz using a Bruker WM-300 spectrometer equipped with an ASPECT-2000 computer operating in the Fourier transform mode. ^{13}C NMR spectra were measured at 50.1 MHz using a Jeol JNM-FX 200 spectrometer on line with a JEC 980 B computer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane (TMS) as internal standard.

Benzyl 2,3-O-isopropylidene-5,6-di-O-mesyl-α-D-mannofuranoside (2). Twice, a solution of benzyl 2,3-*O*-isopropylidene-α-D-mannofuranoside[5] (1) (180 mmol) in pyridine (100 mL) was evaporated and then the compound was again dissolved in the same solvent (290 mL). The solution was cooled (0°C) and methane sulfonyl chloride (474 mmol, 33.3 mL) was added. The reaction mixture was stirred for 16 h at 0-5°C. TLC analysis (methanol/dichloromethane, 4/96, v/v) of the reaction mixture showed complete conversion of the starting material. The reaction mixture was poured into water (1 l; 50°C) under vigorous stirring, the mixture was allowed

to cool to 4°C and the residue was isolated by filtration to give **2**. Crude **2** was washed with water (2 x 250 mL; 0°C), dried *in vacuo* and crystallised from ethyl acetate and petroleum ether (40-60°C) to give pure **2** (177 mmol; 98%) as white needles: mp 102-103°C; R_f 0.76 (methanol/ dichloromethane, 4/96, v/v); ^1H NMR ($CDCl_3$) δ 7.35 (m, 5H, $H_{arom.}$ benzyl), 5.11 (s, 1H, H1), 5.05 (ddd, 1H, H5, $J_{5,6}$ 2.1 Hz, $J_{5,6'}$ 4.8 Hz), 4.79 (dd, 1H, H3, $J_{3,4}$ 3.6 Hz), 4.70 (dd, 1H, H6, $J_{6,6'}$ 11.6 Hz), 4.69 (d, 1H, H2, $J_{2,3}$ 5.8 Hz), 4.59 (AB, 2H, CH_2 benzyl), 4.52 (dd, 1H, H6'), 4.28 (dd, 1H, H4, $J_{4,5}$ 8.0 Hz), 3.14 (s, 3H, CH_3 mesyl), 3.09 (s, 3H, CH_3 mesyl), 1.48 and 1.32 (2 x s, 6H, $(CH_3)_2C$); ^{13}C NMR ($CDCl_3$) δ 136.6 (s, $C_{arom.}$ benzyl), 128.3, 128.0 and 127.8 (3 x d, $CH_{arom.}$ benzyl), 112.9 (s, $\underline{C}(CH_3)_2$), 105.0 (d, C1), 84.7 (d, C5), 78.5, 76.4 and 76.0 (3 x d, C2, C3 and C4), 69.0 (t, C6), 38.3 and 37.3 (2 x q, 2 x CH_3 mesyl), 25.7 and 24.5 (2 x q, $(\underline{C}H_3)_2C$).

Anal. Calcd for $C_{18}H_{26}O_{10}S_2$: C, 46.34; H, 5.62; S, 13.7. Found: C, 45.9; H, 5.51; S, 14.0.

Benzyl 2,3-O-isopropylidene-5-O-mesyl-6-O-acetyl-α-D-mannofuranoside (3). Twice, a solution of compound **2** (173 mmol) in acetonitrile (300 mL) was evaporated and then compound **2** was again dissolved in the same solvent (1750 mL), after which dry potassium acetate (1700 mmol) and 18-crown-6 (17.3 mmol) were added. The mixture was refluxed for 20 h and the reaction was monitored by TLC analysis (*n*-hexane/ether, 1/2, v/v). After cooling to room temperature the mixture was filtered, the residue washed with dichloromethane (300 mL) and the combined filtrates evaporated *in vacuo*. The crude product was crystallised from abs ethanol (500 mL) to give **3** (124 mmol; 71%) as white needles. The mother liquor was concentrated *in vacuo* and applied to a Kieselgel (300 g) column, which after elution with petroleum ether (60-80°C)/ ethyl acetate (3/2, v/v) and concentration of the appropriate fractions gave another portion of homogeneous **3** (31 mmol; 18%): mp 80.7-81.3°C; R_f 0.33 (hexane/ether, 1/2, v/v); ^1H NMR ($CDCl_3$) δ 7.38-7.27 (m, 5H, $H_{arom.}$ benzyl), 5.10 (s, 1H, H1), 5.07 (ddd, 1H, H5, $J_{5,6}$ 2.3 Hz, $J_{5,6'}$ 6.0 Hz), 4.78 (dd, 1H, H3, $J_{3,4}$ 3.6 Hz), 4.68 (d, 1H, H2, $J_{2,3}$ 5.8 Hz), 4.60 (dd, 1H, H6, $J_{6,6'}$ 12.6 Hz), 4.54 (AB, 2H, CH_2 benzyl), 4.32 (dd, 1H, H6'), 4.19 (dd, 1H, H4, $J_{4,5}$ 8.3 Hz), 3.11 (s, 3H, CH_3 mesyl), 2.10 (s, 3H, CH_3 acetyl), 1.48 and 1.32 (2 x s, 6H, $(CH_3)_2C$); ^{13}C NMR ($CDCl_3$) δ 170.2 (s, C=O

acetyl), 136.8 (s, $C_{arom.}$ benzyl), 128.4-127.9 (3 x d, $CH_{arom.}$ benzyl), 112.9 (s, $\underline{C}(CH_3)_2$), 105.2 (d, C1), 84.7 (d, C5), 78.8, 77.1 and 76.6 (3 x d, C2, C3 and C4), 69.0 (t, CH_2 benzyl), 63.5 (t, C6), 38.4 (q, CH_3 mesyl), 25.8 and 24.7 (2 x q, $(\underline{C}H_3)_2C$), 20.6 (q, CH_3 acetyl).

Anal. Calcd for $C_{19}H_{26}O_9S$: C, 53.0; H, 6.09; S, 7.45. Found: C, 52.8; H, 6.06; S, 7.93.

Benzyl 2,3-O-isopropylidene-5,6-anhydro-β-L-gulofuranoside (4). Benzyl 2,3-*O*-isopropylidene-5-*O*-mesyl-6-*O*-acetyl-α-D-mannofuranoside (3) (130 mmol) was dissolved in dry *N,N*-dimethylformamide (500 mL), cooled (0°C) and a solution of potassium *tert*-butyl oxide (156 mmol) in dry *N,N*-dimethylformamide (280 mL) was added dropwise over a period of 0.5 h. After 0.5 h at 0°C, TLC analysis (ether/petroleum ether (40-60°C), 1/2, v/v) of the reaction mixture showed complete conversion of compound 3. The mixture was diluted with H_2O (250 mL), neutralized (acetic acid/water, 1/1, v/v) and concentrated *in vacuo*. The resulting syrup was diluted with dichloromethane (750 mL) and extracted with two portions of water (150 mL). The organic layer was dried with Na_2SO_4, concentrated *in vacuo* and applied to a column of Kieselgel (800 g). Elution was effected with petroleum ether (40-60°C)/ether (10/0 to 7/3, v/v) and concentration of the appropriate fractions gave compound 4 (118 mmol; 91%) as a colourless oil, which crystallized upon standing: mp 79-80 °C; R_f 0.45 (ether/petroleum ether (40-60°C), 1/2, v/v); ^1H NMR ($CDCl_3$) δ 7.37-7.29 (m, 5H, $H_{arom.}$ benzyl), 5.17 (s, 1H, H1), 4.76 (dd, 1H, H3, $J_{3,4}$ 3.8 Hz), 4.66 (d, 1H, H2, $J_{2,3}$ 5.7 Hz), 4.59 (AB, 2H, CH_2 benzyl), 3.57 (dd, 1H, H4, $J_{4,5}$ 6.8 Hz), 3.27 (ddd, 1H, H5, $J_{5,6}$ 4.4 Hz, $J_{5,6'}$ 2.7 Hz), 2.92 (t, 1H, H6, $J_{6,5}$ $J_{6,6'}$ 4.5 Hz), 2.66 (dd, 1H, H6'), 1.50 and 1.31 (2 x s, 6H, $(CH_3)_2C$); ^{13}C NMR ($CDCl_3$) δ 138.8 (s, $C_{arom.}$ benzyl), 128.0 126.4 (d, $CH_{arom.}$ benzyl), 112.4 (s, $\underline{C}(CH_3)_2$), 105.0 (d, C1), 84.6, 82.1 and 80.1 (3 x d, C2, C3 and C4), 68.4 (t, CH_2 benzyl), 49.6 (d, C5), 43.0 (t, C6), 25.5 and 24.2 (2 x q, $(\underline{C}H_3)_2C$).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.7; H, 6.90. Found: C, 65.69; H, 6.87.

Benzyl 2,3-O-isopropylidene-6-O-benzyl-β-L-gulofuranoside (5). To a suspension of sodium hydride (4.8 g, 200 mmol) in dry *N,N*-dimethylformamide (220 mL) was added dropwise benzyl alcohol (34 mL, 330 mmol). After stirring the mixture for 15 min at 0°C, the temperature of the mixture

was allowed to rise to room temperature and a solution of benzyl 2,3-*O*-isopropylidene-5,6-anhydro-β-L-gulofuranoside (4) (110 mmol) in dry *N,N*-dimethylformamide (275 mL) was added dropwise in 30 min. After stirring for 16 h at room temperature, TLC analysis (ether/light petroleum ether, 1/1, v/v) showed complete conversion of the starting compound. The reaction mixture was neutralized with 50% acetic acid in water, concentrated *in vacuo*, and concentrated several times with water. The residue was dissolved in dichloromethane (750 mL) and washed with two portions of a saturated NaCl solution (300 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was applied to a column of Kieselgel (700 g) and elution was effected with dichloromethane/acetone (100/0 to 95/5, v/v). The appropriate fractions were concentrated to give compound **5** (100 mmol, 91%) as a colourless oil, which crystallised upon standing: mp 59°C; R_f 0.46 (ether/ petroleum ether (40-60°C), 1/1, v/v); ^1H NMR ($CDCl_3$) δ 7.34-7.28 (m, 10H, $H_{arom.}$ 2 x benzyl), 5.15 (s, 1H, H1), 4.71 (dd,1H, H3, $J_{3,4}$ 3.5 Hz), 4.66 (d, 1H, H2, $J_{2,3}$ 5.8 Hz), 4.59 (AB, 2H, CH_2 benzyl), 4.57 (AB, 2H, CH_2 benzyl), 4.23 (dq, 1H, H5, $J_{5,OH}$ 2.2 Hz, $J_{5,6} \approx J_{5,6'}$ 5.2 Hz), 4.12 (dd, 1H, H4, $J_{4,5}$ 5.3 Hz), 3.68 (ABM, 2H, H6 and H6', $J_{6,6'}$ 9.5 Hz), 3.02 (d,1H, OH), 1.46 and 1.28 (2 x s, 6H, $(CH_3)_2C$); ^{13}C NMR ($CDCl_3$) δ 137.7 and 137.0 (2 x s, 2 x $C_{arom.}$ benzyl), 128.1-127.0 (d, $CH_{arom.}$ benzyl), 112.3 (s, $\underline{C}(CH_3)_2$), 104.7 (d, C1), 85.1, 80.1, 79.0 and 69.3 (4 x d, C2, C3, C4 and C5), 73.2, 70.6 and 69.3 (3 x t, C6 and 2 x CH_2 benzyl), 25.6 and 24.2 (2 x q, $(\underline{C}H_3)_2C$).

Anal. Calcd for $C_{23}H_{28}O_6$: C, 69.0; H, 7.05; Found: C, 68.89; H, 7.07.

Benzyl 2,3-O-isopropylidene-5-O-trifluoromethanesulfonyl-6-O-benzyl-α-D-gulofuranoside (6). A solution of compound 5 (15 mmol) in dry dichloromethane (30 ml) was added dropwise to a cooled (-20°C) suspension of trifluoromethanesulfonic anhydride (5.05 mL, 30.0 mmol), pyridine (34.5 mmol, 2.8 mL) and 15 g of activated molecular sieves (0.4 nm) in dry dichloromethane (90 mL). The mixture was stirred for 1 h at -20°C under a nitrogen atmosphere, after which TLC analysis (ether/light petroleum ether, 2/1, v/v) showed complete conversion of the starting material. The reaction mixture was filtered, washed with an ice cold aqueous solution of saturated $NaHCO_3$ (100 mL) and ice cold water (100

mL). The organic layer was dried with $MgSO_4$, filtered, concentrated and twice concentrated with dry toluene (25 mL) (water bath temperature 20°C). The resulting syrup was used without further purification for the synthesis of compounds **7** and **8**: R_f 0.76 (ether/petroleum ether (40-60°C), 1/1, v/v); ^1H NMR ($CDCl_3$) δ 7.38-7.25 (m, 10H, $H_{arom.}$ 2 x benzyl), 5.19 (dt, 1H, H-5, $J_{5,6} = J_{5,6'} = 2.4$ Hz), 5.11 (s, 1H, H-1), 4.69-4.61 (m, 4H, CH_2 benzyl, H-2 and H-3), 4.60 (d, 1H, CH_2 benzyl, $J_{A,B} = 12.0$ Hz), 4.47 (d, 1H, CH_2 benzyl), 4.37 (dd, 1H, H-4, $J_{4,5} = 8.9$ Hz), 3.89 (ABM, 2H, H-6 and H-6', $J_{6,6'} = 12.0$ Hz), 1.42 and 1.21 (2 x s, 6H, $C(CH_3)_2$).

Benzyl 2,3-O-isopropylidene-5-azido-5-deoxy-6-O-benzyl-α-D-manno-furanoside (7). The crude 5-*O*-trifluoromethanesulfonate **6** (1 mmol) was dissolved in dry *N,N*-dimethylformamide (6 mL) or a mixture of dry *N,N*-dimethylformamide and dry toluene (1/3, v/v, 6 mL) and lithium azide (2 mmol), tetrabutylammonium azide (2 mmol) or the lithium azide 12-crown-4 complex (2 mmol) was added, the mixture was stirred for 8 h at ambient temperature under a nitrogen atmosphere. TLC analysis (ether/light petroleum ether, 2/1, v/v) showed complete conversion of **6**. The reaction mixture was concentrated *in vacuo*, diluted with dichloromethane (30 mL), washed twice with water (15 mL), dried with $MgSO_4$, concentrated and applied to a Kieselgel column (9 g). Elution was effected with light petroleum ether (50 mL) to give **9** as a light yellow oil (0.4 mmol; 40%): R_f 0.70 (ether/petroleum ether (40-60°C), 1/1, v/v); ^1H NMR ($CDCl_3$) δ 7.38-7.28 (m, 10H, $H_{arom.}$ 2 x benzyl), 6.33 (dd, 1H, H6), 5.13 (ddd, 1H, H4, $J_{4,5}$ 8.8 Hz, $^4J_{4,6}$ 0.8 Hz), 5.07 (s, 1H, H1), 4.87 (s, 2H, CH_2 benzyl), 4.77 (dd, 1H, H5, $J_{5,6}$ 6.3 Hz), 4.72 (d, 1H, CH_2 benzyl, $J_{A,B} = 11.7$ Hz), 4.68 (dd, 1H, H3, $J_{3,4}$ 3.2 Hz), 4.65 (d, 1H, H2, $J_{2,3}$ 5.8 Hz), 4.47 (d, 1H, CH_2 benzyl), 1.47 and 1.31 (2 x s, 6H, $(CH_3)_2C$).

Further elution of the column by light petroleum ether/ether (85/15, v/v, 50 mL) gave **7**, after concentration of the appropriate fractions, as a colourless syrup (0.5 mmol; 50%): R_f 0.65 (ether/ petroleum ether (40-60°C), 1/1, v/v); IR 2100 cm^{-1} (azide); ^1H NMR ($CDCl_3$) δ 7.38-7.23 (m, 10H, 2 x $H_{arom.}$ benzyl), 5.05 (s, 1H, H1), 4.79 (dd, 1H, H3, $J_{3,4}$ 3.4 Hz), 4.64 (d, 1H, H2, $J_{2,3}$ 5.8 Hz), 4.62 (AB, 2H, CH_2 benzyl), 4.50 (AB, 2H, CH_2 benzyl), 3.97 (dd, 1H, H4, $J_{4,5}$ 9.8 Hz), 3.87 (ddd, 1H, H5, $J_{5,6}$ 2.2 Hz, $J_{5,6'}$ 6.2 Hz), 3.85 (dd, 1H, H6, $J_{6,6'}$ 10.2 Hz), 3.65 (dd, 1H,

H6'), 1.45 and 1.33 (2 x s, $(CH_3)_2C$); ^{13}C NMR ($CDCl_3$) δ 137.8 and 137.0 (2 x s, $C_{arom.}$ benzyl), 112.5 (s, $(CH_3)_2\underline{C}$), 105.4 (d, C1), 84.6, 79.5 and 77.6 (3 x d, C2, C3 and C4), 73.4, 70.4 and 68.9 (3 x t, C6 and 2 x CH_2 benzyl), 59.3 (d, C5), 25.9 and 24.6 (2 x q, $(\underline{C}H_3)_2C$).

Anal. Calcd for $C_{23}H_{27}N_3O_5$: C, 64.9; H, 6.40; N, 9.88. Found: C, 64.78; H, 6.24; N, 9.51.

Benzyl 2,3-O-isopropylidene-5-N-benzyl-6-O-benzyl-α-D-mannofuranoside (8). The crude 5-*O*-trifluoromethanesulfonate **6** (20 mmol) was dissolved in dry toluene (180 mL) and benzylamine (200 mmol, 21.8 mL) was added. The reaction mixture was stirred for 14 days at ambient temperature under a nitrogen atmosphere. The reaction was monitored by TLC analysis (3% acetone in toluene). After completion, the mixture was diluted with dichloromethane (200 mL) and washed with two portions of water (200 mL). The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and applied to a Kieselgel column (150 g). Elution was effected with toluene/acetone (100/0 to 97/3, v/v). Concentration of the appropriate fractions gave pure **8** (11.2 mmol, 56%) which crystallised upon standing. A small quantity of **8** was recrystallised from dichloromethane and *n*-hexane for analytical purposes: mp 86°C; R_f 0.58 (ether/ petroleum ether (40-60°C), 2/1, v/v), 0.45 (3% acetone in toluene); ^1H NMR ($CDCl_3$) δ 7.40-7.28 (m, 15H, $H_{arom.}$ 3 x benzyl), 5.03 (s, 1H, H1), 4.86 (dd, 1H, H3, $J_{3,4}$ 3.4 Hz), 4.64 (d, 1H, CH_2 benzyl, J_{AB} 10.7 Hz), 4.63 (d, 1H, H2, $J_{2,3}$ 5.9 Hz), 4.53 (s, 2H, CH_2 benzyl), 4.39 (d, 1H, CH_2 benzyl), 4.11 (dd, 1H, H4, $J_{4,5}$ 9.2 Hz), 3.90 (AB, 2H, CH_2 benzyl), 3.71 (dd, 1H, H6, $J_{6,6'}$ 9.7 Hz), 3.62 (dd, 1H, H6'), 3.20 (ddd, 1H, H5, $J_{5,6}$ 3.3 Hz, $J_{5,6'}$ 4.1 Hz), 1.40 and 1.31 (2 x s, 6H, $(CH_3)_2C$); ^{13}C NMR ($CDCl_3$) δ 140.9, 138.4 and 137.4 (3 x s, $C_{arom.}$ benzyl), 128.4-126.6 (d, $CH_{arom.}$ benzyl), 112.1 (s, $\underline{C}(CH_3)_2$), 104.9 (d, C1), 84.9, 80.0 and 79.7 (3 x d, C2, C3 and C4), 73.3 (t, C6), 68.8 and 68.7 (2 x t, 2 x CH_2 O-benzyl), 55.2 (d, C5), 51.5 (t, CH_2 N-benzyl), 26.0 and 24.9 (2 x q, $(\underline{C}H_3)_2C$).

Anal. Calcd for $C_{30}H_{35}NO_5$: C, 73.6; H, 7.21; N, 2.86. Found: C, 73.8; H, 7.16; N, 2.68.

1,5-Dideoxy-1,5-imino-D-mannitol (11). A: A solution of the 5-*N*-benzyl-mannofuranoside derivative **8** (12 mmol) in ethanol/water/acetic acid (5/1/1, v/v/v, 90 mL) was shaken with palladium(II) hydroxide on carbon 20% (moisture ca. 50%, 11.9 g) under a hydrogen atmosphere (400

kPa) for 48 h at room temperature. TLC analysis (*n*-propanol/water/triethylamine, 600/400/5, v/v/v) showed complete conversion of the starting material. The palladium catalyst was removed by filtration and the filtrate was concentrated to a volume of ca. 10 mL, *in vacuo*. The residue was diluted with water (total volume 70 mL) and a few drops of concentrated hydrochloric acid were added (pH 2). The solution was stirred for 48 h at ambient temperature, and the reaction was monitored by TLC analysis (*n*-propanol/water/triethylamine, 600/400/5, v/v/v). The reaction mixture was diluted with water (100 mL), treated with Amberlyte IRA-400 [OH^-] (pH 10.6) and concentrated *in vacuo*. Lyophilization of the residue gave homogeneous 1,5-dideoxy-1,5-imino-D-mannitol (11) in almost quantitative yield. Crystallization from a mixture of abs methanol and diethyl ether (5/1, v/v) gave 11 (11 mmol, 92%) as colourless crystals: mp 185°C {Lit.[5] mp 185-187°C}; $[\alpha]_D^{20}$ -40° (c= 1.35, H_2O) {Lit.[5] $[\alpha]_{578}^{20}$ -39° (H_2O)}; R_f 0.25 (*n*-propanol/water/triethylamine, 600/400/5, v/v/v); ^{1}H-NMR (D_2O, pD 7.20) δ 4.09 (dt, 1H, H2, $J_{2,3}$ 3.2 Hz), 3.86 (dd, 1H, H6, $J_{6,6'}$ 11.9 Hz), 3.78 (dd, 1H, H6'), 3.71 (t, 1H, H4, $J_{4,5}$ 9.7 Hz), 3.61 (dd, 1H, H3, $J_{3,4}$ 9.7 Hz), 3.12 (dd, 1H, H1, $J_{1,1'}$ 14.0 Hz, $J_{1,2}$ 2.3 Hz), 2.95 (dd, 1H, H1', $J_{1',2}$ 1.6 Hz), 2.74 (ddd, 1H, H5, $J_{5,6}$ 3.1 Hz, $J_{5,6'}$ 5.3 Hz), these chemical shift values are in agreement with previously reported[7] values; ^{13}C-NMR (D_2O, pD 9.49) δ 76.3, 70.5 and 69.9 (3 x d, C2, C3 and C4), 63.0 (d, C5), 62.8 (t, C6), 50.5 (t, C1).

Anal. Calcd for $C_6H_{13}NO_4$: C, 44.17; H, 8.03; N, 8.58. Found: C, 43.97; H, 8.35; N, 8.21.

B: A solution of benzyl 2,3-*O*-isopropylidene-5-azido-5-deoxy-6-*O*-benzyl-α-D-mannofuranoside (7) (2.73 mmol) was converted to 11 as described above and yielded after crystallization from abs methanol and diethyl ether (5/1, v/v) pure 11 (2.60 mmol, 95%) as colourless crystals. Analytical and spectral data of compound 11 thus obtained were in excellent agreement with 11 obtained under A.

REFERENCES

1. U. Fuhrmann, E. Bauze, G. Legler, and H. Ploegh, *Nature*, 307, 755 (1984).

2. U. Fuhrmann, E. Bauze, and H. Ploegh, *Biochimica et Biophysica Acta*, **825**, 95 (1985).

3. R. C. Bernotas, and B. Ganem, *Tetrahedron Lett.*, **26**, 1123 (1985).

4. K. Leontein, B. Lindberg, and J. Lönngren, *Acta Chem. Scand.*, Ser. **B36**, 515 (1982).

5. G. Legler, and E. Jülich, *Carbohydr. Res.*, **128**, 61 (1984).

6. G. W. J. Fleet, and P. W. Smith, *Tetrahedron Lett.*, **26**, 1469 (1985).

7. H. Seito, H. Takeno, and M. Hashimoto, *Chem. Pharm. Bull.*, **34**, 2642 (1986).

8. H. J. G. Broxterman, G. A. van der Marel, J. J. Neefjes, H. L. Ploegh, and J. H. van Boom, *Recl. Trav. Chim. Pays-Bas*, **106**, 571, (1987).

9. C. A. A. van Boeckel, T. Beetz, J. N. Vos, A. J. M. de Jong, S. F. van Aelst, R. H. van den Bosch, J. M. R. Mertens, and F. A. van der Vlugt, *J. Carbohydr. Chem.*, **4**, 293 (1985).

10. R. L. Whistler, and R. E. Gramera, *J. Org. Chem.*, **29**, 2609 (1964).