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Synthesis of 6-deoxy-6-phenylisofagomine derivatives.

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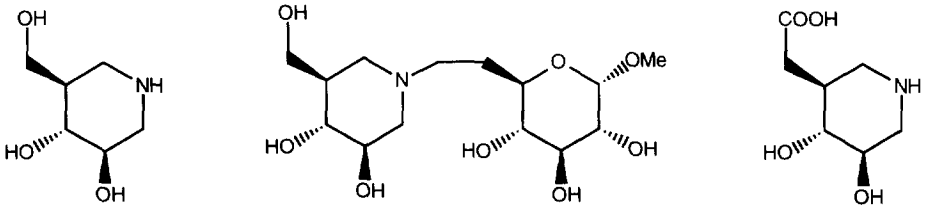
Abstract: 2-Benzyl-N-*tert*-butoxycarbonyl-1,5-imino-1,2,5-trideoxy-D-xylitol (**4**) and 5-amino-4-benzyl-4,5-dideoxy-L-xylose (**13**) were prepared in optically pure form. © 1997 Elsevier Science Ltd.

INTRODUCTION

Potent and selective glycosidase inhibitors have many interesting applications such as treatment of AIDS,[1] diabetes[2] or cancer[3] as well as crop protection. It has recently been found that monosaccharide analogues with nitrogen in place of anomeric carbon are potent glycosidase inhibitors.[4-13] For instance isofagomine (**1**), a substituted hydroxypiperidine that resembles glucose, is the most potent inhibitor known of almond β-glucosidase.[4] Interestingly the disaccharide analogue **2** inhibits yeast α- and almond β-glucosidase at levels comparable to **1**, but two α-glucosidases with specificity for the aglycon, glucoamylase and isomaltase, are inhibited much stronger or much weaker, respectively, by **2** than **1**. This suggests that oligosaccharide analogues with one (or more) anomeric carbon atom replaced with a nitrogen atom would be more selective glycosidase inhibitors. We therefore decided to explore this, and realised that a flexible route to larger analogues of **2** could be through peptide synthesis using **3** followed by reduction of the amide bonds. In this paper we report our successful synthetic efforts to obtain a synthetic equivalent for **3**, 2-benzyl-N-*tert*-butoxycarbonyl-1,5-imino-1,2,5-trideoxy-D-xylitol (**4**).



1 **2** **3**

Fig 1

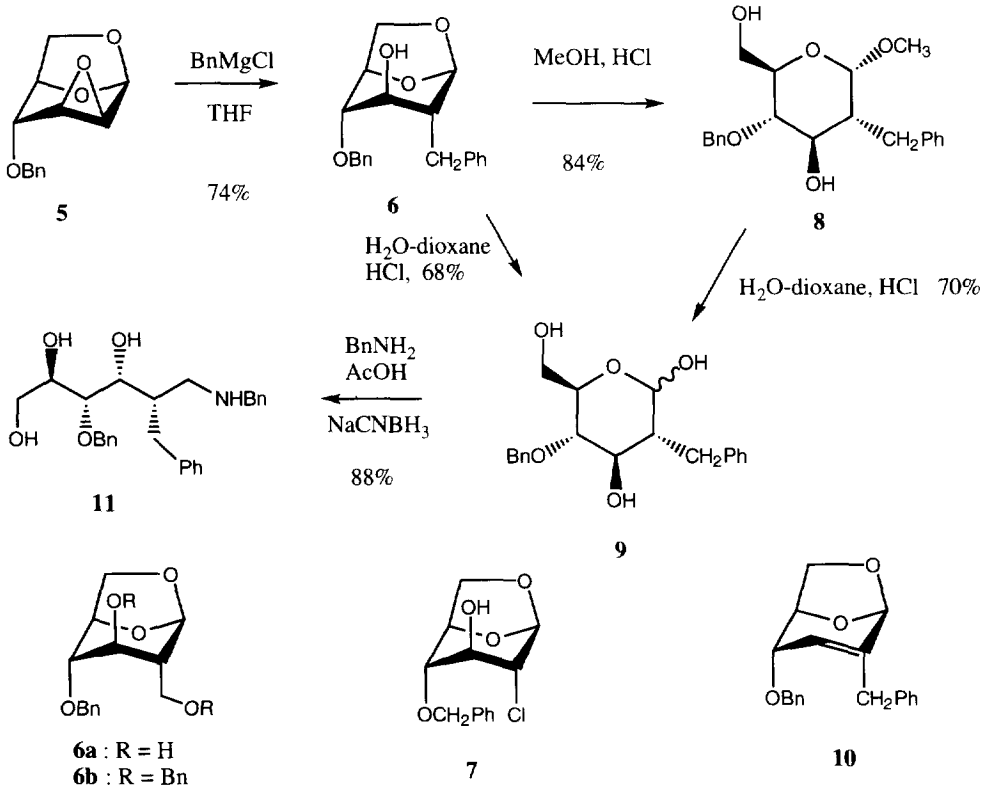
RESULTS AND DISCUSSION

For synthesising **3** modification of the previous isofagomine synthesis was necessary. However as the carboxylic group was incompatible with many steps of the synthesis, it had to be masked. The phenyl group

is a useful synthetic equivalent for a carboxylic acid, as it can be converted into the latter by ozonolysis.[14] It was therefore decided to synthesise the phenyl equivalent of **3**.

The synthesis started with known epoxide **5**, available from starch in 5 steps.[15] Reaction of **5** with benzylmagnesium chloride in THF gave the 2-benzyl derivative **6**, the expected product from epoxide opening in the 2-position, in 74 % yield. Opening of the epoxide with chloride was a side reaction giving the 2-chloride **7** in 16% yield.[16]

Hydrolysis of the 1,6-anhydride gave considerable problems. Our previous experience with this reaction had revealed ambiguous results. Initially it was found that hydrolysis of the hydroxymethyl analogue **6a** (1,6-anhydro-4-*O*-benzyl-2-deoxy-2-hydromethyl-β-D-glucopyranose) in aqueous H_2SO_4 proceeded smoothly to the hemiacetal in good yield.[5] However later studies showed that the corresponding perbenzylated compound **6b** (1,6-anhydro-3,4-di-*O*-benzyl-2-deoxy-2-benzoxymethyl-β-D-glucopyranose) during acidic hydrolysis underwent elimination reaction to give a complex mixture of products.[17] Similarly **6**, when subjected to

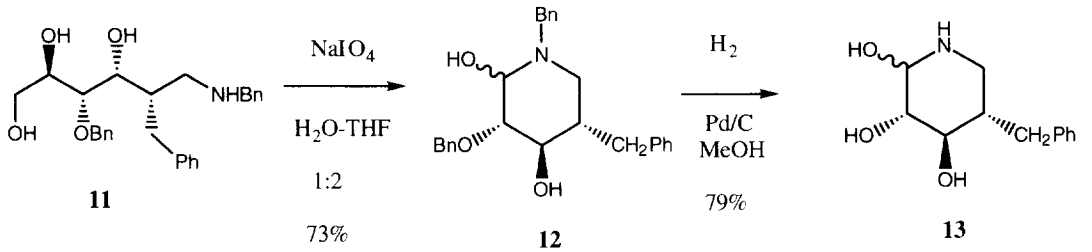


Scheme 1

hydrolysis in dilute H_2SO_4, gave a complex mixture of products. An important difference between **6a** and **6** (or **6b**) was that the former was soluble in water, while the latter was not. Therefore hydrolysis of **6** (or **6b**) had to be carried out heterogeneously or with a cosolvent, which apparently affected the reaction pathway unfavorably. Little help could be obtained from the literature as the review by Czerny on levoglucosan chemistry only suggested use of dilute H_2SO_4 for hydrolysis of the 1,6-anhydro bond.[18] After some experimentation it was found however that careful hydrolysis of **6** with aqueous HCl/dioxane was possible giving 68 % of **9** together with 18 % of **10**. Prolonged hydrolysis time gave less of the desired product **9**. The

structure of **10** was elucidated by 2D NMR and confirmed by mass spectroscopy giving a molecular peak of 308. Hence the problems with hydrolysis of this type of structure, which we had also encountered earlier, were undoubtedly due to favorable elimination of the 3-substituent.

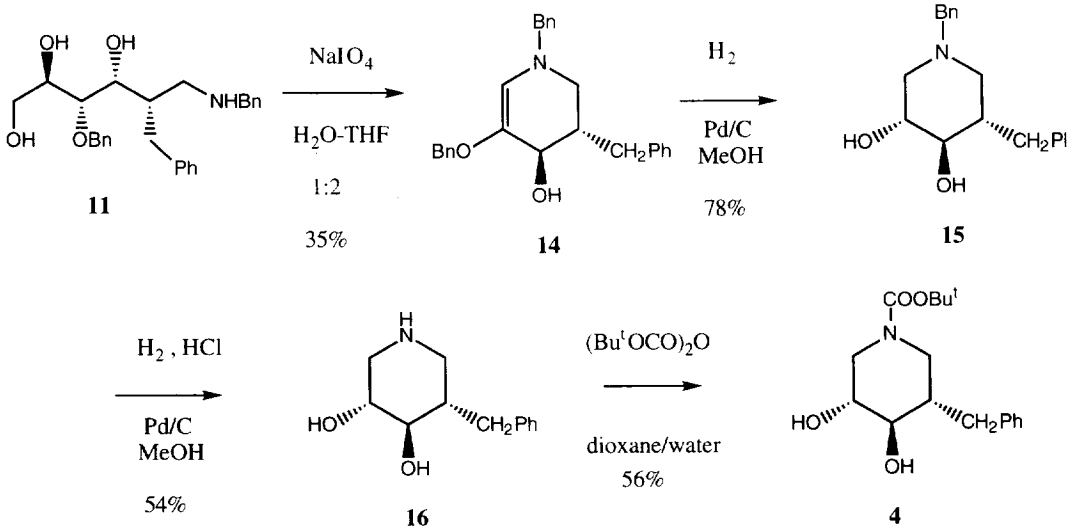
The search of the literature had revealed, that HCl catalysed methanolysis had been carried out successfully on the allyl analogue of **6** (2-allyl-1,6-anhydro-4-*O*-benzyl-2-deoxy-β-D-glucopyranose).[19] Since we expected the elimination reactions to be favored by the $^1C_4$ conformation of **6**, a solution might be first methanolysis of **6**, and then hydrolysis of the methyl glycoside. Methanolysis of **6** in HCl/MeOH did give in a smooth and fast reaction the methyl glycoside **8** in 84 % yield. Only the α-anomer was obtained as could be seen from a small J_{12} in the ^{1}H-NMR spectrum.



Scheme 2

Hydrolysis of **8** with aqueous HCl/dioxane at 100 °C for 1 h gave the hemiacetal **9** in 70 % yield. Thus the overall yield of direct hydrolysis of **6** to **9** was higher even though **10** was formed, and was therefore usually preferred.

Reductive amination of **9** with 2 equivalents of benzylamine, a catalytic amount of acetic acid and $NaCNBH_3$ in MeOH at 50 °C for 1 day gave **11** in 88 % yield.

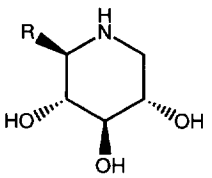


Scheme 3

Now periodate cleavage of **11** was a tricky transformation. Treatment of **11** with excess $NaIO_4$ (5 equivalents) in water-THF followed by careful concentration of the solution with evacuation at low

temperature allowed isolation of the hemiaminal **12**. Hydrogenolysis of the hemiaminal with H_2 and Pd/C gave surprisingly the unprotected hemiaminal **13**.

However when the periodate cleavage product was subjected to concentration at elevated temperature and longer time the enamine **14** was obtained. Reduction of **14** was stereoselective giving the *trans*-isomer **15** in 78 % yield. Finaly hydrogenolysis gave the unprotected piperidine **16**, in 54 % yield. This compound was protected with a BOC-group to give **4** in 56% yield.



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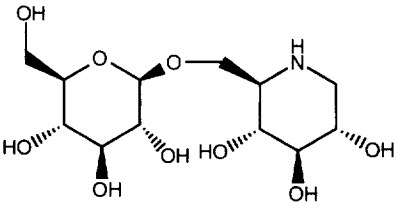

18

Fig 2

To investigate the effect of a bulky substituent inplace of the hydroxymethyl group in isofagomine, compound **13** was tested for inhibition of α-glucosidase (bakers yeast), β- glucosidase (almonds) and isomaltase (bakers yeast). No inhibition was observed at a concentration of **13** of 0.4 mM. We compared this biological activity with 1-deoxynojirimycin analogues (**17**) with bulky substituents in place of the hydroxymethyl group. A number of such compounds have been prepared,[20-24] but only glycosidase inhibition of one of these, the natural product **18**, has been investigated.[24] It was found that **18** (like **13**) did not inhibit bakers yeast α-glucosidase and almond β- glucosidase. This suggests that nojirimycin and isofagomine binds in a structurally similar manner.

In this paper we have synthesised a 6-deoxy-6-phenyl analogue of isofagomine as a precursor for a isofagomine based peptide. Future work will explore that possibility.

ACKNOWLEDGEMENTS

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EXPERIMENTAL SECTION

^{13}C-NMR and ^{1}H-NMR spectra were recorded on a Varian Gemini 200 instrument. D_2O was used as solvent with DHO (^{1}H-NMR: δ 4.7 ppm) and acetone (^{1}H-NMR: δ 2.05 ppm; ^{13}C-NMR: δ 29.8 ppm) as reference. With $CHCl_3$ as solvent TMS and $CHCl_3$ (^{13}C-NMR: δ 76.93 ppm) were used as references. Mass spectra were obtained on a VG TRIO-2 instrument. Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 141 polarimeter. Concentrations were performed on a rotary evaporator at a temperature below 40 °C. Dry tetrahydrofuran and diethyl ether were prepared by distillation from sodium and benzophenone.

2-Benzyl-4-O-benzyl-2-deoxy-1,6-anhydro-β-D-glucopyranose (**6**).

To a solution of 1,6:2,3-dianhydro-4-*O*-benzyl-β-D-mannopyranose (**5**, 3.75 g, 0.016 mol) in THF (20 ml), was added a solution of benzylmagnesium chloride (80 ml, 2 M) over a period of 5 min. The mixture was refluxed for 1 hour. After cooling NH_4Cl solution (1 M, 500 ml) was added carefully, followed by an

extraction with EtOAc (3 x 200 ml). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to give an yellow oil (5.81 g) containing **6** and **7**. The residue was purified by flash chromatography with 25% petroleum ether 75% ether as eluant to give first pure **6** (3.87 g, 74 %) and then the sideproduct **7** (0.69 g, 16 %). **6**: $[\alpha]_D^{22}$ = - 43.3° (*c* 1.35; MeOH), ^{1}H-NMR ($CDCl_3$): δ 7.2-7.5 (m, 10 H, Ar), 5.45 (s, 1H, H-1), 4.7 (m, 3H, Bn, H-4), 4.1 (d, 1H, H-6a), 3.7 (m, 2H, H-5, H-6b), 3.45 (s, 1H, H-3), 2.9 (d, 2H, H-2'), 2.1 (s, 1H, H-2). MS(EI): m/z 326.1518 (M^+), calc. for $C_{20}H_{22}O_4$: 326.1518. **7**: $[\alpha]_D^{22}$ = + 84.8° (*c* 1.4; MeOH) ^{1}H-NMR ($CDCl_3$): δ 7.2-7.5 (m, 5H, Ar), 5.55 (s, 1H, H-1), 4.75 (d, 1H, Bn), 4.7 (d, 1H, Bn), 4.6 (m, 1H H-4), 4.1 (m, 1H, H-3), 4.0 (d, 1H, H-6a), 3.7 (m, 1H, H-5), 3.6 (d, 1H, H-6b) 3.4 (s, 1H, H-2). MS(EI): m/z 270.0659 (M^+), calc. for $C_{13}H_{15}ClO_4$: 270.0659.

	C-1	C-2	C-3	C-4	C-5	C-6	C-2'	OBn	NBn	OMe	Ph
4	49.7*	37.4#	77.0†	67.0†	51.1*	------	40.4#	80.4θ	155.2θ	28.8θ	126.0-129.5; 139.8
5	97.1	47.3*	53.9*	73.4#	71.1#	65.3	-----	71.6#	------	------	127.4-128.1; 137.2
6	103.8	48.2	75.3*	79.1*	69.3*	65.9	35.8	72.0*	------	------	126.8-129.7; 138-9
7	102.8	58.6	75.9*	79.2*	73.0*	67.0	-----	72.4*	------	------	128.5-129.2; 138.1
8	99.7	48.8	75.3*	80.2*	73.5*	62.5	34.0	71.5*	------	------	126.6-129.6; 138.8; 140.3
9	92.9 96.7	48.7 49.3	75.4* 75.7*	80.7* 79.9*	73.0* 73.2*	62.7 62.2	34.0 32.5	71.6* 71.6*	------ ------	------ ------	126.6-130.7; 138.6, 140.3
10	99.0	143.7	118.9	74.5*	73.8*	64.1	35.9	71.1*	------	------	127.0-129.9; 137.7; 139.9
11	50.0*	42.5*	73.5#	78.6#	72.7#	64.2	35.4	73.0#	53.6*	------	126.7-129.4; 137.5; 138.3; 140.1
12	98.5 91.6	84.4* 81.8*	77.7* 77.6*	43.5 44.1	66.5 62.3	------ ------	35.0‡ 34.8‡	74.9* 74.4*	73.0* 72.0*	------ ------	126.7-129.5; 138.1; 138.8; 139.3; 139.7
13	98.2 93.2	76.6* 74.2*	74.8* 70.8*	44.5 44.8	65.2 61.0	------ ------	34.1‡ 34.2‡	------ ------	------ ------	------ ------	126.1-129.1; 140.2
14	97.6	153.5	63.1*	42.0	55.0#	------	37.2‡	69.4*	56.1#	------	126.4-129.9; 137.7; 138.7; 141.1
15	58.5*	41.4#	71.1†	75.5†	63.4*	------	37.1#	------	60.0*	------	126.6-130.0; 138.6; 140.5
16	47.0*	38.3#	67.0†	63.1†	48.5	------	33.8#	------	------	------	126.5-129.2; 139.1

Table 1. ^{13}C-NMR chemical shift in $CDCl_3$ (except for **13** and **16** which were in $(CD_3)_2SO$). * , # and † marked shifts may have the opposite assignment. θ marked shifts are from the *tert*-butyloxycarbonyl group. ‡ these shifts are C-4'.

Methyl 2-benzyl-4-O-benzyl-2-deoxy-α-D-glucopyranoside (**8**).

To a solution of 1,6-anhydro-2-benzyl-4-*O*-benzyl-2-deoxy-β-D-glucopyranose (**6**, 2.30 g, 7.0 mmol) in methanol (125 ml) was added conc. HCl (10 ml). The mixture was refluxed for an hour, poured into saturated $NaHCO_3$ (200 ml) and extracted with $CHCl_3$ (3 x 100 ml). The combined organic layers were dried over $MgSO_4$, and evaporated under reduced pressure. Recrystalisation of the solid residue from methanol/water afforded a white crystalline compound. Yield of **8**: 2.11 g (84 %). Mp: 139-141°C. $[\alpha]_D^{22}$ = + 95.3° (*c* 1.5; MeOH). ^{1}H-NMR ($CDCl_3$): δ 7.2-7.5 (m, 10H, Ar), 4.8 (d, 1H, *J* 11 Hz, Bn), 4.7 (d, 1H, *J* 11 Hz, Bn), 4.2 (d, 1H, *J* 4 Hz, H-1), 3.8 (m, 3H, H-3, H-6a, H-6b), 3.7 (m, 1H, H-5), 3.4 (dd, 1H, *J* 9.5 and 8

Hz, H-4), 3.25 (s, 3H, Me), 3.15 (dd, 1H, *J* 12.5 and 4.5 Hz, H-2'a), 2.55 (d, 1H, *J* 12.5 and 11 Hz, H-2'b), 2.0 (bs, 2H, OH's), 1.95 (m, 1H, H-2).

2-Benzyl-4-O-benzyl-2-deoxy-αβ-D-glucopyranose (**9**). From **6**.

1,6-Anhydro-2-benzyl-4-*O*-benzyl-2-deoxy-β-D-glucopyranose (**6**, 2.0 g, 6.1 mmol) was dissolved in a mixture of 1,4-dioxane and water (1:1, 125 ml). Conc. HCl (10 ml) was addded, and the mixture was refluxed for an hour. The volume was reduced to 50 ml, saturated $NaHCO_3$ (100 ml) was added, and then an extraction with $CHCl_3$ (3 x 100 ml) was carried out. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to give an yellow oil. From flash chromatography of the crude product using 5 % methanol in CH_2Cl_2 as eluant two products were isolated. First **9** (white foam) was obtained (1.43 g, 68 %, $[\alpha]_D^{22} = +72.0°$ (*c* 1.3; MeOH), ^{1}H-NMR ($CDCl_3$): δ 7.2-7.5 (m, 10H, Ar), 4.7 (m, 3H), 3.0-4.0 (m, 7H), 2.5-2.9 (m, 2H), 1.8-2.0 (m, 1H) and then **10** (clear oil, 0.34 g, 18 %, $[\alpha]_D^{22} = +127.4°$ (*c* 1.3; MeOH), ^{1}H-NMR ($CDCl_3$): δ 7.2-7.5 (m, 10H, Ar), 5.4 (s, 1H, H-1), 5.35 (m, 1H, H-3), 4.8 (ddd, 1H, *J* 7, 3.5 and 2 Hz, H-5), 4.7 (s, 2H, Bn), 3.9 (dd, 1H, J 8 and 7 Hz, H-6a), 3.55 (m, 1H, H-4), 3.45 (s, 2H, H-2'), 3.4 (dd, 1H, *J* 8 and 2 Hz, H-6b). MS(EI): m/z 308 (M^+)).

2-Benzyl-4-O-benzyl-2-deoxy-αβ-D-glucopyranose (**9**). From **8**.

Methyl 2-benzyl-4-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**8**, 3.00 g, 8.4 mmol) was dissolved in a mixture of 1,4-dioxane and water (1:1, 125 ml). Conc. HCl (10 ml) was addded, and the mixture was refluxed for an hour. The volume was reduced to 50 ml, saturated $NaHCO_3$ (100 ml) was added, and then an extraction with $CHCl_3$ (3 x 100 ml) was carried out. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to give an yellow oil. The crude product was purified by flash chromatography with 5 % methanol in CH_2Cl_2 as eluant. Yield of **9**: 2.02 g (70 %).

1-Amino-2-benzyl-1-N-benzyl-4-O-benzyl-1,2-dideoxy-D-glucitol (**11**).

To a solution of 2-benzyl-4-*O*-benzyl-2-deoxy-αβ-D-glucopyranose (**9**, 1.88 g, 5.4 mmol) in methanol (75 ml), benzylamine (1.17 g, 10.8 mmol), acetic acid (0.98 g, 16.3 mmol) and sodiumcyanoborhydride (0.68 g, 10.8 mmol) were added. The mixture was stired at 50° C for one day, poured into water (150 ml) and extracted with $CHCl_3$ (3 x 150 ml). The combined organic layers were washed with brine (300 ml), dried over $MgSO_4$ and evaporated to dryness. Flash chromatography of the crude product using a stepwise gradient of 5-20 % methanol in CH_2Cl_2 as eluant gave the pure product (**11**, 2.09 g, 88 %) as a thick clear oil. On standing the product crystalised to give a hard white solid. Mp: 65-70°C. $[\alpha]_D^{22} = +7.0°$ (*c* 1.25; MeOH). ^{1}H-NMR ($CDCl_3$): δ 7.0-7.4 (m, 15H, Ar), 4.8 (d, 1H, *J* 11.5 Hz, Bn), 4.6 (d, 1H, *J* 11.5 Hz, Bn), 3.5-4.1 (m, 11H, H-3, H-4, H-5, H-6a, H-6b, NBn, OH's, NH), 2.9 (dd, 1H, *J* 12.5 and 8 Hz, H-1a), 2.8 (dd, 1H, *J* 12.5 and 4 Hz, H-1b), 2.55 (dd, 1H, *J* 12.5 and 3 Hz, H-2'a), 2.3 (m, 2H, H-2, H-2'b).). MS(FAB): m/z 436 (M+1)).

5-Amino-4-benzyl-5-N-benzyl-2-O-benzyl-4,5-dideoxy-L-xylose (**12**).

1-Amino-2-benzyl-1-*N*-benzyl-4-*O*-benzyl-1,2-dideoxy-D-glucitol (**11**, 50 mg, 0.11 mmol) was dissolved in a 1:1 mixture of THF and water (3:1, 20 ml) and sodium periodate (122 mg, 0.57 mmol) was added. After stirring for an hour the mixture was poured into saturated $NaHCO_3$ (20 ml) and extracted with CH_2Cl_2 (3 x 15 ml). The combined organic phases were dried over $MgSO_4$, and evaporated to dryness under reduced pressure. The crude product was purified by flash chromatography using 5% methanol in CH_2Cl_2 as eluant. Yield of **12**: 34 mg (73 %). The product was a 1:1 mixture of α and β-anomers. It was used directly in the next step. ^{1}H-NMR ($CDCl_3$): δ 7.1-7.4 (m, 30H, Ar), 5.2 (d, 1H, *J* 3.5 Hz, H-1α), 5.0 (d, 1H, *J* 11.5 Hz, OBn), 4.5-4.8 (m, 4H, 3 OBn, H-1β), 3.0-3.8 (m, 14H, H-2, H-3, H-5a, H-5b, NBn, OH), 2.6 (bs, 2H, OH), 2.3 (2dd, 2H, H-4'a), 2.0 (m, 4H, H-4, H-4'b).).

5-Amino-4-benzyl-4,5-dideoxy-L-*xylose* (**13**).

5-Amino-4-benzyl-5-*N*-benzyl-2-*O*-benzyl-4,5-dideoxy-L-xylose (**12**, 34 mg, 0.084 mmol) was dissolved in methanol (10 ml) and a catalytic amount of palladium (10 mg, 10 % Pd-Carbon) was added. The mixture was hydrogenated at atmospheric pressure for 48 hours, filtered through celite and evaporated to dryness under reduced pressure. Yield of **13**: 17 mg (90 %). The compound was a 1:2 mixture of α- and β-anomers. $[\alpha]_D^{22} = \pm 0°$ (*c* 0.85, H_2O). ^{1}H-NMR ($CDCl_3$), β-anomer: δ 7.1-7.4 (m, 5H, Ar), 6.5 (d, 1H, *J* 7 Hz, OH), 5.0 (d, 1H, *J* 6 Hz, OH), 4.9 (d, 1H, *J* 4 Hz, OH), 4.2 (t, 1H, *J* 7 Hz, H-1), 2.9-3.6 (m, 6H, H-2, H-3, H-4'a, H-5a, H-5b, NH), 2.2 (dd, 1H, *J* 13 and 10 Hz, H-4'b), 1.7 (m, 1H, H-4). α-anomer: δ 7.1-7.4 (m, 5H, Ar), 6.1 (d, 1H, *J* 4 Hz, OH), 4.9 (m, 1H, H-1), 4.8 (d, 1H, *J* 6 Hz, OH), 4.5 (d, 1H, *J* 7 Hz, H-1), 2.9-3.6 (m, 6H, H-2, H-3, H-4'a, H-5a, H-5b, NH), 2.3 (dd, 1H, H-4'b), 1.7 (m, 1H, H-4).

2-Benzyl-N-tert-*butoxycarbonyl-1,5-imino-1,2,5-trideoxy*-D-*xylitol* (**4**).

1-Amino-2-benzyl-1-*N*-benzyl-4-*O*-benzyl-1,2-dideoxy-D-glucitol (**11**, 1.0 g, 2.3 mmol) was dissolved in a mixture of water and THF (1:3, 30 ml), and $NaIO_4$ (1.23 g, 5.7 mmol) was added. After stiring for 3 hours the mixture was poured into saturated $NaHCO_3$ (50 ml) and extracted with $CHCl_3$ (3 x 50 ml). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure (13 mm Hg, 40°C). The crude product was purified by flash chromatography using 5 % methanol in CH_2Cl_2 as eluant to give sirupy **14** (0.32 g, 35 %, ^{1}H-NMR ($CDCl_3$): δ 7.3-7.5 (m, 15H, Ar), 7.2 (d, 1H, *J* 1.7 Hz, H-1), 4.8 (s, 2H, OBn), 3.7 (d, 1H, *J* 12 Hz, NBn), 3.6 (d, 1H, *J* 12 Hz, NBn), 3.1 (s, 1H, OH), 2.7 (m, 3H, H-3, H-5a, H-5b), 2.4 (m, 2H, H-4'a, H-4'b), 2.0 (m, 1H, H-4).).

The product **14** (0.20 g, 0.52 mmol) was dissolved in methanol (20 ml), and a catalytic amount of palladium (30 mg, 10 % Pd-Carbon) was added. The mixture was hydrogenated at 50 bar for 24 hours, filtered, and evaporated to dryness. The crude product, **15** was used without further purification in the next step.

To a solution of the crude **15** in methanol (20 ml) an equivalent of HCl (0.52 ml, 1 M HCl) was added together with with a catalytic amount of palladium (20 mg, 10 % Pd-Carbon). After hydrogenation for another 24 hours at 50 bar the mixture was filtered and evaporated to dryness under reduced pressure. Yield of **16**: 40 mg (31 %, two steps).

The crude **16** (40 mg, 0.16 mmol) was dissolved in a 1:1 mixture of water and 1,4-dioxane (10 ml). NaOH (0.33 ml, 1.0 M) and di-*tert*-butyl-dicarbonate (43 mg, 0.20 mmol) were added and the mixture was stired over night. After addition of water (15 ml) the reaction mixture was extracted with $CHCl_3$ (2 x 15 ml). The combined organic phases were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Flash chromatography af the crude material with 5 % MeOH in CH_2Cl_2 as elutant gave 28 mg of pure product (**4**, 56 %). $[\alpha]_D^{22} = + 5.5°$ (*c* 1.3; MeOH). ^{1}H-NMR ($CDCl_3$): δ 7.1-7.4 (m, 5H, Ar), 4.2 (dd, 1H, *J* 12.3 and 3.5 Hz, H-5a), 4.0 (bm, 1H, H-3), 3.5 (ddd, 1H, *J* 14, 10.5 and 3.5 Hz, H-4), 2.2-2.5 (m, 2H, H-1a, H-2'a), 2.4 (dd, 1H, *J* 12.3 Hz and 10.5 Hz, H-5b), 2.0 (bd, 1H *J* 12.3 Hz, H-2'b), 1.7 (m, 1H, H-1b), 1.4 (s, 9H, Me_3C), 1.0 (q, 1H, *J* 12.3 Hz, H-2).).

Measurements of glycosidase inhibition.

This was carried out as described previously.[10]

REFERENCES

1. Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W *Proc. Natl. Acad. Sci. U.S.A.* **1988** *85* 9229-33.
2. Robinson, K. M.; Begovic, M. E.; Rhinehart, B. L. Heineke, E. W.; Ducep, J. -B.; Kastner, P. R.; Marshall, F. N.; Danzin, C. *Diabetes* **1991** *40* 825-830.

3. Bernacki, R. J.; Niedbala, M. J.; Korytnyk, W. *Cancer and Metastasis Reviews* **1985** *4* 81-102.
4. Jespersen, T. M.; Dong, W.; Skrydstrup,T.; Sierks, M.R.; Lundt, I.; Bols, M *Angew. Chem. Int. Ed. Eng.* **1994** *33* 1778-1779.
5. Jespersen, T. M.; Bols, M.; Sierks, M.R.; Skrydstrup,T. *Tetrahedron* **1994** *50* 13449-13460.
6. Dong, W.; Jespersen, T. M.; Skrydstrup,T.; Bols, M.; Sierks, M.R. *Biochemistry* **1996** *35* 2788-95.
7. Ichikawa, Y.; Igarashi, Y. *Tetrahedron Lett.* **1995** *36* 4585-6.
8. Igarashi, Y.; Ichikawa, M.; Ichikawa, Y. *Tetrahedron Lett.* **1996** *37* 2707-2708.
9. Hansen, A.; Tagmose, T. M.; Bols, M. *J. Chem. Soc. Chem. Comm.* **1996** 2649-50.
10. Hansen, A.; Tagmose, T. M.; Bols, M. *Tetrahedron* **1997** *53* 697-706.
11. Ichikawa, M.; Igarashi, Y.; Ichikawa, Y. *Tetrahedron Lett.* **1995** *36* 1767-1770.
12. Ichikawa, M.; Ichikawa, Y. *Bioorg. Med. Chem.* **1995** *3* 161-165.
13. Bols, M.; Persson, M. P.; Butt, W. M.;Jørgensen, M.; Christensen, P.; Hansen, L. T. *Tetrahedron Lett.* **1996** *37* 2097-2100.
14. Hvidt, T; Szarek, W. A.; MacLean, D. B. *Can. J. Chem.* **1988** *66* 779-882.
15. Trnka, T.; Czerny, M. *Collect Czech. Chem. Commun.* **1971** *36* 2216-25.
16. Note that when BnMgCl in THF is placed is cooled Bn_2Mg can precipitate out leaving mostly $MgCl_2$ in solution. Reacting this solution with **5** therefore gives mainly **7**.
17. Barbaud, C.; Bols, M.; Lundt, I.; Sierks, M. R. *Tetrahedron* **1995** *51* 9063-78.
18. Cerny, M.; Stanek, J. Jr. *Adv. Carbohydr. Chem. Biochem.* **1977** *34* 23-177.
19. Ermolenko, M. S.; Olesker, A.; Lukacs G. *Tetrahedron Lett.* **1994** *35* 711-4.
20. Delinck, D. L.; Margolin, A. L. *Tetrahedron Lett.* **1990** *31* 3093-6.
21. Martin, S. F., Chen, H. -J.; Yang, C. -P. *J. Org. Chem.* **1993** *58* 2867-73.
22. Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984** *25* 165-8.
23. Kilonda, A.; Compernolle, F.; Toppet, S.; Hoornaert, G. J. *Tetrahedron Lett.* **1994** *35* 9047-50.
24. Asano, N.; Oseki, K.; Tomioka, E.; Kizu, H.; Matsui, K. *Carbohydr. Res.* **1994** *259* 243-256.

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