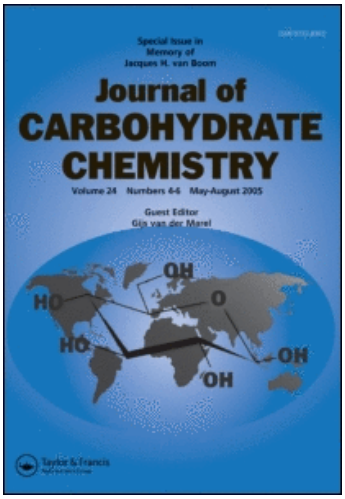

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ANALOGUES OF MORANOLINE AND MDL 73945. METHYL 6(5)-DEOXY-6(5)-(MORPHOLIN-4-YL)-α-D-GLYCOSIDES AS GLUCOSIDASE INHIBITORS

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ABSTRACT

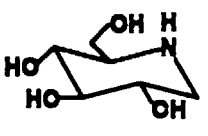
Methyl 2,3,4-tri-*O*-acetyl-6-*O*-(*p*-tolylsulfonyl)-α-D-glucopyranoside (**6**), or its iodo analogue **7**, were subjected to nucleophilic displacement with morpholine to give **8**, deacetylation of which gave methyl 6-deoxy-6-(morpholin-4-yl)-α-D-glucopyranoside (**3**). Similarly, **11**, **12** and **21** were prepared. The 6-deoxy-6-iodo derivative **16** was subjected to nucleophilic displacement with morpholine and subsequent acetylation to give **15**. Deacetylation of **15** gave **17**. The kinetic studies for the inhibition of β-D-glucosidase from *sweet almond* and using *o*-nitrophenyl β-D-glucopyranoside as substrate exhibited a K_i value for **21** on the same order as 1-deoxynojirimycin whereas for **3**, a K_i value of lesser order was observed.

INTRODUCTION

Various therapeutic effects have been reported for glycosidase inhibitors.[1-18] 1-Deoxynojirimycin (**1**, DNM, moranoline) is a potent inhibitor for all types of mammalian α-glucosidases and it is useful against the HIV virus.[4] Its lipophilic

derivative *N*-butyl-DNM shows a more potent antiviral activity both in vitro and in animal models.[13] Its perbutyroylated ester derivative was developed to eliminate the gastrointestinal side effects associated with its oral administration.[17] A series of oxygen-substituted *N*-alkyl-DNM derivatives which showed potent glucosidase activity has been developed in order to alleviate the toxic effects resulting from the amphiphilic character of the decyl side chain group.[15-18] A combination therapy of azasugars with nucleoside antivirals may offer a greater utility of azasugars due to their value as *N*-glycoprotein processing inhibitors.[19] The respective derivative of DNJ, 1,5-dideoxy-1,5-[(6-deoxy-1-*O*-methyl-6-α-D-glucopyranosyl)imino]-D-glucitol (MDL 73945) is a selective and potent intestinal α-glucohydrolase inhibitor that reduces the glycemic and insulin responses to a carbohydrate load in rats and monkeys and has a long duration of action.[20] Thus, such inhibitors are potential beneficial drugs for the treatment of diabetes and some are being evaluated clinically.[21,22]

The design of glycosidase inhibitors with a high degree of specificity and potency has attracted much attention during the last few years.[23-25] Various amines have been reported as competitive inhibitors.[26,27] Consideration of the structure of 1-deoxynojirimycin and its analogues has led to a correlation which shows that the β-hydroxyalkylamine residue is an important feature in such inhibitors. The skeleton of MDL 73945 (**2**) has a unique feature in which the nitrogen of the deoxynojirimycin is linked to the C-6 of a 6-deoxyglucoside. Consequently, we planned to design glycosidase inhibitors having this unique structural element by replacing the 1-deoxynojirimycin ring by a simple cyclic amine ring characterized by a close similarity to the DNM moiety. A six membered ring, which has a chair conformation



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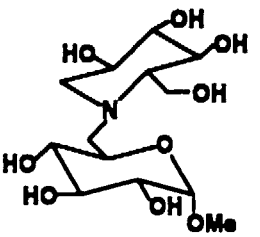

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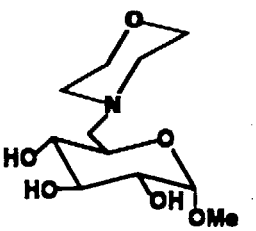
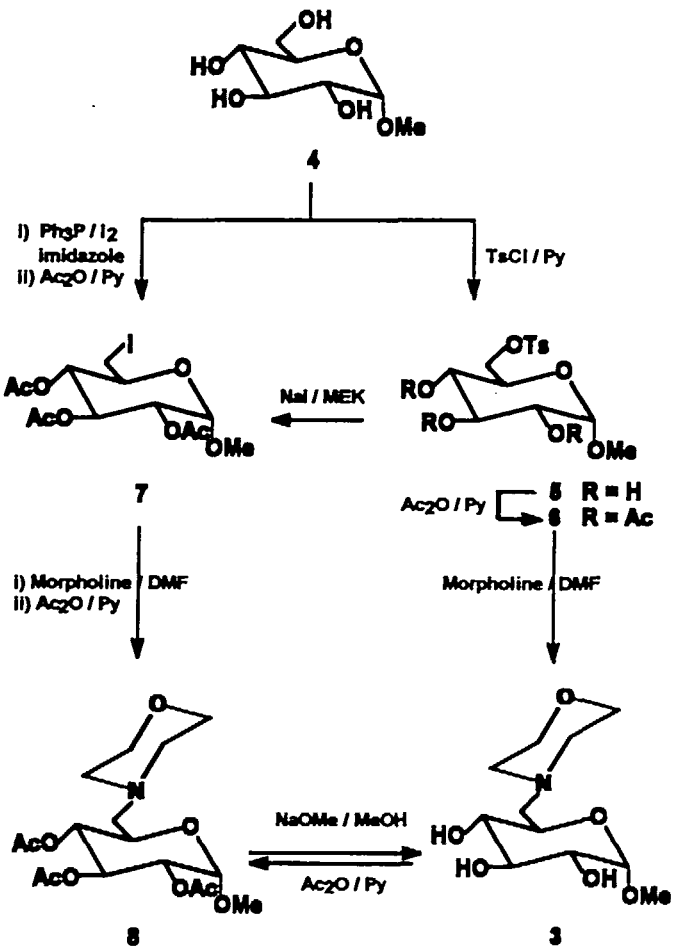


3

and possesses a hidden β-hydroxyethylamine residue was considered, thus the designed targets selected in this work are constructed by replacing the DNM part in MDL 73945 by a morpholine ring.

RESULTS AND DISCUSSION

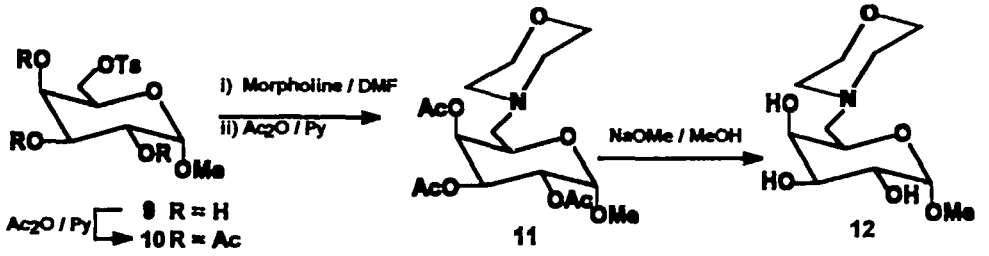
The first target to be synthesized was the gluco analogue, methyl 6-deoxy-6-(morpholin-4-yl)-α-D-glucopyranoside (**3**). Selective tosylation of **4** gave methyl 6-*O*-(*p*-tolylsulfonyl)-α-D-glucopyranoside (**5**).[28] Nucleophilic displacement of the 6-



Scheme 1

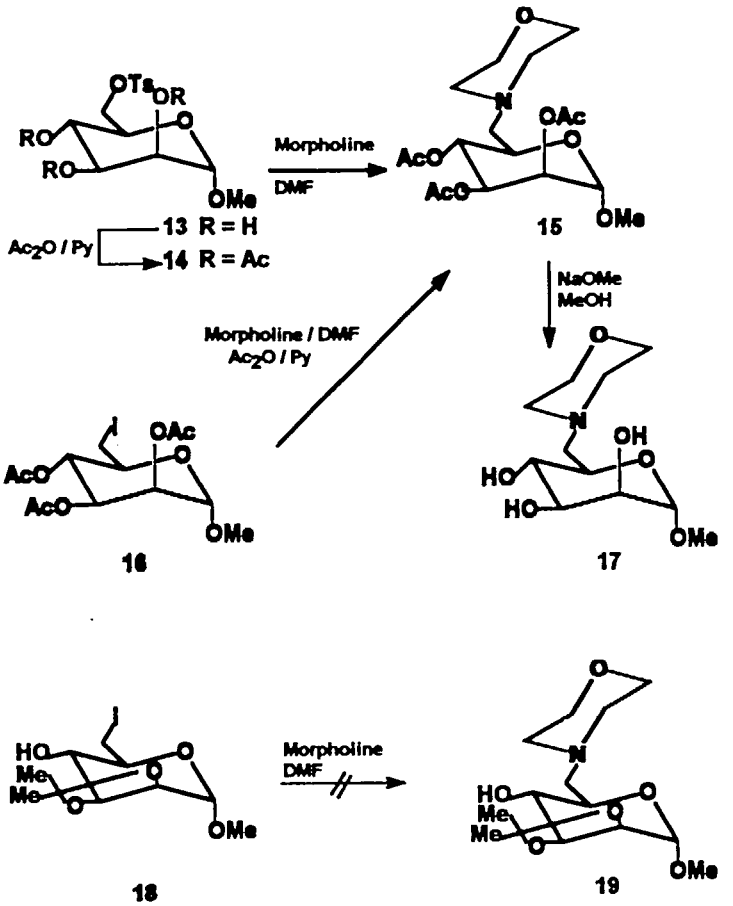
tosyloxy group in **5** by morpholine gave the target compound **3**, but in low yield. Acetylation of **5** followed by displacement with iodide ion gave **7**, which was also synthesized from **4** by the direct iodination with triphenylphosphine/iodine/imidazole and subsequent acetylation.[29] The iodide was found to be a better precursor for the nucleophilic displacement with morpholine, and gave the desired product **8** in addition to partially deacetylated derivatives. Acetylation of the reaction mixture gave **8**, whereas subsequent deacetylation gave the required target compound **3** in a high yield.

The synthesis of the D-galacto analog **12** and **17** was carried out by a similar approach (Scheme 2) from methyl α-D-galactopyranoside.[30] Nucleophilic displacement of the tosyloxy group of **10** with morpholine gave **11** accompanied by some partially deacetylated products. Attempted purification by chromatography or deacetylation to give **12** proved to be troublesome; however, acetylation of the reaction mixture followed by flash chromatography afforded **11**.



Scheme 2

The 6-*O*-tosyl mannoside **13**[31] was acetylated to give **14** which was treated with morpholine and acetylated to give **15**. However, it was not possible to separate the latter product from a contaminant by-product. Alternatively, the 6-deoxy-6-iodo derivative **16**[32] was subjected to nucleophilic displacement with morpholine and subsequent acetylation to give **15**. Other attempts to synthesize the manno analogue by the nucleophilic displacement of the iodide **18**[33] led to mixtures which could not be purified. This could be attributed to the partial loss of the isopropylidene



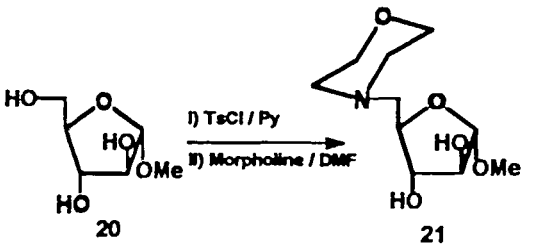
Scheme 3

group resulting from morpholine hydroiodide produced in the reaction. Deisopropylidenation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with morpholinium tosylate salt in an aprotic solvent has been observed.

The last target compound in this series was methyl 5-deoxy-5-(morpholin-4-yl)-α-D-arabinofuranoside (**21**) which was prepared by the nucleophilic displacement of the 5-tosyloxy group with morpholine in DMF. The latter was prepared by the selective tosylation of methyl-α-D-arabinofuranoside (**20**).

INHIBITION STUDIES

The inhibitory activity of methyl 6-deoxy-6-(morpholin-4-yl)-α-D-



Scheme 4

glucopyranoside (**3**) and methyl 5-deoxy-5-(morpholin-4-yl)-α-D-arabinofuranoside (**21**) on the hydrolysis of *o*-nitrophenyl β-D-glucopyranoside (ONPG) by β-D-glucosidase from *sweet almond* was determined under the following conditions: total reaction volume 1050 μL, pH 6.8 (0.07 M potassium dihydrogen phosphate and disodium hydrogenphosphate buffer), temperature 30 °C, enzyme activity 0.49 U/mL, stock solution of inhibitor 1.799 mM at pH 6.8, and substrate concentrations of 20.00, 10.00, 5.00, 3.33, 2.50 and 2.00 mM. The assay method was based on measuring the continuous release of *o*-nitrophenol from *o*-nitrophenyl β-D-glucopyranoside by the action of the enzyme. The Michaelis-Menten constant (K_m) at pH 6.8 was determined to be 6.9 mM by Lineweaver-Burk plots (Figs. 1 and 2). The inhibition constants (K_i) of the compounds **3** and **21** were determined and found to be 1.3×10^{-4} and 7.2×10^{-5} M, respectively and the inhibition was found to be competitive. The constants are similar to that of 1-deoxynojirimycin [K_i 1.8×10^{-5} M][34] and the furanoside **21** is more active than the pyranoside **3**. These results demonstrate that replacement of deoxynojirimycin in MDL 73945 by a simple heterocyclic ring is a valuable approach to the discovery of potent inhibitors.

EXPERIMENTAL

General method. Melting points are uncorrected. Optical rotations were measured at 20 °C with a Perkin-Elmer 241 MC polarimeter. NMR spectra were recorded with Bruker AC 250 MHz and 200 MHz spectrometers. Chemical shifts δ are reported in ppm relative to TMS as internal standard, and described as: s(singlet),

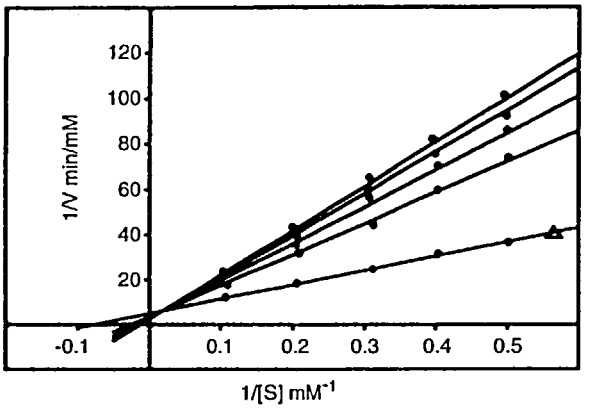


Fig. 1. Lineweaver-Burk plot in the presence or absence (Δ) of 3.

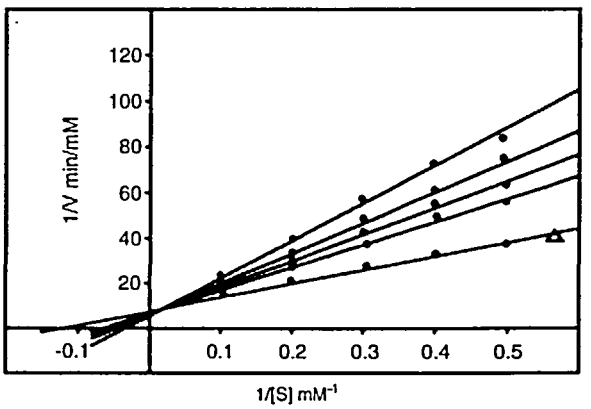


Fig. 2. Lineweaver-Burk plot in the presence or absence (Δ) of 21.

d(doublet), t(triplet), q (quartet), m(multiplet), or brs (broad singlet). Column chromatography was performed under normal pressure with silica gel MERCK, 70-230 mesh ASTM and 230-400 mesh ATSM for flash chromatography. Mass spectra were recorded using electron ionization (EI) on a Varian MAT 311A spectrometer and fast atom bombardment (FAB) on a Kratos MS 50 spectrometer. UV data were recorded with a Philips PU 8740 UV/VIS spectrometer. IR spectra were recorded

with a Unicam SP 1025 spectrometer. Microanalyses were performed in the unit of Microanalysis at Alexandria University.

Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-(morpholin-4-yl)-α-D-glucopyranoside (8). A solution of 7 (2.00 g, 4.70 mmol) in dry dimethylformamide (7.00 mL), was treated with morpholine (1.19 g, 14.0 mmol). The mixture was heated under reflux for 18 h. The solvent was concentrated to dryness and the residue was dissolved in chloroform. The solution was washed with water, dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford a syrup, which was purified by column chromatography on silica gel with ethyl acetate-petroleum ether (5:2). Fractions enriched with the product were collected and concentrated to give a syrup (1.41 g), which was dissolved in dry pyridine (4.30 mL), cooled to 0 °C, and then treated with acetic anhydride (4.30 mL). The reaction mixture was kept overnight at room temperature, and then poured into ice-water, whereby an oil separated. The water layer was decanted, and the oil was washed several times with water to yield a syrup which was crystallized from ethanol. Recrystallization from the same solvent furnished compound **8** as a white needles (0.63 g, 35%); mp 181-183 °C; $[\alpha]_D^{20}$ +0.6 (*c* 0.1, $CHCl_3$); IR (KBr) 1241 (C-O), and 1747 cm^{-1} (C=O); ^1H NMR (200 MHz,$CDCl_3$): δ 1.99 (s, 3 H, OAc), 2.01 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 2.25-2.57 (m, 6 H, 2 NCH_2, H-6, 6'), 3.39 (s, 3 H, OMe), 3.67 (t, 4 H, *J* 4.6 Hz, 2 OCH_2), 4.60-4.75 (m, 1 H, H-5), 4.85 (dd, 1 H, $J_{4,5}$ 3.4, $J_{3,4}$ 10.2 Hz, H-4), 4.88-4.92 (m, 1 H, H-2), 4.96 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.52 (t, 1 H, $J_{3,4}$ 10.2 Hz, H-3); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 170.42, 170.21, 169.63 (3 OAc), 97.32 (C-1), 70.40 (C-2), 70.26 (C-3), 69.11 (C-4), 65.63 (C-5), 63.94 (C-6), 58.47 (2 OCH_2), 57.58 (OMe), 53.95 (2 NCH_2), 20.98, 20.65, 20.55 (3 OAc); EI MS *m/z* (%): 389 (M^{+}, 12), 358 (9), 330 (17), 270 (7), 184 (7) 168 (6), 128 (35), 100 (100).

Anal. Calcd for $C_{17}H_{27}NO_9$ (389.402): C, 52.44; H, 6.98; N, 3.59. Found: C, 52.41; H, 7.34; N, 3.71.

Methyl 6-deoxy-6-(morpholin-4-yl)-α-D-glucopyranoside (3).

Method A. Compound **3** was prepared from **5** (2.00 g, 5.75 mMol) under the same conditions used above and isolated as a syrup (0.10 g, 7.00%).

Method B. A stirred solution of compound **8** (0.95 g, 2.40 mmol) in dry methanol (10.0 mL) was cooled to 0 °C and then treated with a freshly prepared solution of 0.1 M sodium methoxide (3.00 mL). Stirring was then continued at room temperature for 1 h. The solution was stirred with Amberlite IR-120 (H^+) until the solution became neutral. The resin was filtered off, and the solution was concentrated under reduced pressure to afford a syrup, which was purified by column chromatography on silica gel, and eluted with ethyl acetate-methanol (7:1) to give **3** (0.60 g, 94.0%); $[\alpha]^{20}_D$ +16.5 (*c* 1, $CHCl_3$); IR (NaCl) 3366 cm^{-1} (OH); ^1H NMR (250 MHz, $CDCl_3$): δ 2.51-2.59 (m, 2 H, H-6,6'), 2.65-2.78 (m, 4 H, 2 NCH_2), 3.34-3.37 (m, 1 H, H-5), 3.41 (s, 3 H, OMe), 3.53 (dd, 1 H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.7 Hz, H-2), 3.71-3.78 (m, 6 H, 2 OCH_2, H-3, 4), 4.65 (brs, 3 H, 3 OH), 4.71 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 99.65 (C-1), 74.65, 73.45, 71.61 (C-2, 3, 4), 66.57 (C-5, 2 OCH_2), 61.27 (C-6), 55.42 (OMe), 54.26 (2 NCH_2); FAB MS (MeOH / NBOH) *m/z* (%): 264 (M^{+} + 1, 60), 263 (15), 232 (10).

Anal. Calcd for $C_{11}H_{21}NO_6$ (263.29): C, 50.18; H, 8.03; N, 5.32. Found: C, 49.98; H, 8.10; N,5.00.

Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-(morpholin-4-yl)-α-D-galactopyranoside (11). Compound **11** was prepared from **10** (1.46 g, 3.0) under the conditions used above for the synthesis for **8.** The product was crystallized from ethanol to give **11** (0.80 g, 68.0%), mp 152-154 °C; $[\alpha]^{20}_D$ + 0.8 (*c* 0.1, $CHCl_3$); IR (KBr) 1251 (C-O) and 1742 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 1.94 (s, 3 H, OAc), 2.04 (s, 3 H, OAc), 2.10 (s, 3 H, OAc), 2.29-2.55 (m, 6 H, 2 NCH_2, H-6, 6'), 3.36 (s, 3 H, OMe), 3.63 (t, 4 H, *J* 4.4 Hz, 2 OCH_2), 4.09 (t, 1 H, *J* 6.0 Hz, H-5), 4.94 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 5.09 (dd, 1 H, $J_{1,2}$ 3.8, $J_{2,3}$ 10.8 Hz,H-2), 5.29 (dd, 1 H, $J_{3,4}$ 3.4, $J_{2,3}$ 10.8 Hz, H-3), 5.44 (brd, 1 H, H-4); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 170.41, 170.20, 169.89 (3 OAc), 97.38 (C-1), 69.77, 68.20, 67.73, 66.49, 65.68 (C-2, 3, 4, 5, 6), 58.30 (2 OCH_2), 55.88 (2 NCH_2), 54.16 (OMe), 20.80, 20.65, 20.62 (3 OAc); EI MS *m/z* (%): 389 (M^{+}, 9), 358 (10), 330 (17), 270 (4), 100 (100).

Anal. Calcd for $C_{17}H_{27}NO_9$ (389.402): C, 52.44; H, 6.98; N, 3.59. Found: C, 51.98; H, 6.62; N, 3.43.

Methyl 6-deoxy-6-(morpholin-4-yl)-α-D-galactopyranoside (12). Compoud **12** was prepared from **11** (0.60 g, 1.50 mmol) under the same conditions used for the synthesis of **3** to afford compound **13** as white crystals (0.20 g, 49.0%), mp 134-136 °C; IR (KBr): 3266-3365 cm^{-1} (OH); ^1H NMR (200 MHz, $CDCl_3$): δ 2.43-2.53 (m, 3 H, H-6, 6, OH), 2.74-2.83 (m, 5 H, 2 NCH_2, OH), 3.39 (s, 3 H, OMe), 3.67-3.75 (m, 6 H, 2 OCH_2, H-5, OH), 3.77-3.81 (m, 1 H, H-4), 3.86 (dd, 1 H, $J_{3,4}$ 3.8, $J_{2,3}$ 10.0 Hz, H-3), 4.08 (brd, 1 H, H-2), 4.78 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1).

Anal. Calcd for $C_{11}H_{21}NO_6$ (263.29): C, 50.18; H, 8.03; N, 5.32. Found: C, 50.48; H, 8.26; N, 5.00.

Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-(morpholin-4-yl)-α-D-manno-pyranoside (15).

Method A. Compound **15** was prepared from **16** (4.30 g, 10.0 mmol) under the same conditions used for **8** to afford a syrup which was crystallized from ether to give **15** (0.90 g, 23.0%), mp 110-111 °C; IR (KBr): 1226 (C-O) and 1751 cm^{-1} (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 1.97 (s, 3 H, OAc), 2.02 (s, 3 H, OAc), 2.11 (s, 3 H, OAc), 2.37-2.65 (m, 6 H, 2NCH_2, H-6, 6'), 3.38 (s, 3 H, OMe), 3.69 (t, 4 H, *J* 4.4 Hz, 2 OCH_2), 3.94 (m, 1 H, H-5), 4.67 (s, 1 H, H-1), 5.12-5.21 (m, 2 H, H-2, 4), 5.30 (dd, 1 H, $J_{3,4}$ 10.4, $J_{2,3}$ 3.2 Hz, H-3), 5.32 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1).

Anal. Calcd for $C_{17}H_{27}NO_9$ (389.402): C, 52.44; H, 6.98; N, 3.59. Found: C, 52.37; H, 7.30; N, 3.58.

Method B. Compound **15** was prepared from **14** (1.00 g, 2.10 mmol) under the same conditions used above for **8** to yield a product (0.70 g, 85.0%) identical with that obtained from method A.

Methyl 6-deoxy-6-(morpholin-4-yl)-α-D-mannopyranoside (17). Compound **17** was prepared from compound **15** (0.60 g, 1.54 mmol) under the same conditions for the synthesis of **3** to give a syrupy product **17** (0.20 g, 49.0%); IR (NaCl): 3396 cm^{-1} (OH); ^1H NMR (200 MHz, $CDCl_3$): δ 2.52-2.57 (m, 2 H, H-6, 6), 2.65-2.81 (m, 4 H, 2NCH_2), 3.31 (s, 3 H, OMe), 3.64-3.68 (m, 8 H, 2 OCH_2, H-2, 3, 4, 5), 4.64 (s, 1 H, H-1), 5.08 (brs, 3 H, 3 OH).

Anal. Calcd for $C_{11}H_{21}NO_6$ (263.29): N, 5.32. Found: N, 5.75.

Methyl 5-deoxy-5-(morpholin-4-yl)-α-D-arabinofuranoside (21). Compoud **21** was prepared from **20** (0.50 g, 1.57 mmol) under the conditions used for the synthesis for **3** to give a yellowish-brown syrup product **21** (0.05 g, 15.0%). $[\alpha]^{20}_{D}$ +1.5 (*c* 0.1, $CHCl_3$); ^{1}H NMR (200 MHz, DMSO-d_6): δ 2.37-2.47 (m, 2 H, H-5), 2.49-2.50 (m, 4 H, 2 NCH_2), 2.60-2.63 (m, 1 H, OH), 3.21-3.47 (m, 10 H, H-3, 4, OMe, 2 OCH_2, OH), 3.51-3.53 (m, 2 H, H-1, 2); ^{13}C NMR (62.5 MHz, DMSO-d_6): δ 87.20 (C-1), 76.80 (C-4), 66.01 (C-2, 3), 65.99 (2 OCH_2, C-5), 51.53 (OMe), 45.96 (2 NCH_2). FAB MS (MeOH / NBOH): *m/z* (%): 234 ($M^{\cdot+}$ + 1, 21), 192 (15), 154 (100).

Anal. Calcd for $C_{10}H_{19}NO_5$ (233.264): C, 51.49; H, 8.20; N, 6.00. Found: C, 51.01; H, 7.99; N,5.71.

INHIBITION STUDIES

The inhibitory activity of compounds **3** and **21** on the hydrolysis of *o*-nitrophenyl β-D-glucopyranoside was determined. Buffer substances (potassium dihydrogenphosphate and disodium hydrogenphosphate) were purchased from Fluka and used as received. β-D-glucosidase (*sweet almond*) and *o*-nitrophenyl β-D-glucopyranoside were obtained from Boehringer, Mannheim. The buffer solution (pH 6.8) was prepared by mixing 50 mL of potassium dihydrogenphosphate solution (0.07 M) and 50 mL disodium hydrogenphosphate solution (0.07 M). β-D-Glucosidase (2.45 U) in the buffer solution (5.00 mL) was used for assay. ONPG (82.2 mg) was dissolved in the buffer solution (6.50 mL). Inhibitor concentrations of 0.856, 0.571, 0.285 and 0.142 mM were used to determine the K_i value. At each inhibitor concentration, six substrate concentrations 20.0, 10.0, 5 00, 3.33, 2.50 and 2.00 mM were used.

To a 1.00 mL disposable cuvette was added buffer solution (500 μL) and ONPG-solution (500 μL). The solution was thermally equilibrated at 30 °C. The reaction was started by addition of 50.0 μL of β-D-glucosidase solution. Liberation

of ONPG was monitored using a PU 8740 UV/VIS-spectrophotometer, for 4 min (λ = 405 nm), and the initial hydrolysis rate was calculated.

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