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Note

Golgi endomannosidase inhibitor, α-D-glucopyranosyl-(1→3)-1-deoxymannojirimycin: a five-step synthesis from maltulose and examples of *N*-modified derivatives

Josef Spreitz[a] and Arnold E. Stütz[b,*]

[a]*Aglycon Company, Stremayrgasse 16, A-8010 Graz, Austria*
[b]*Institut für Organische Chemie der Technischen Universität Graz, Stremayrgasse 16, A-8010 Graz, Austria*

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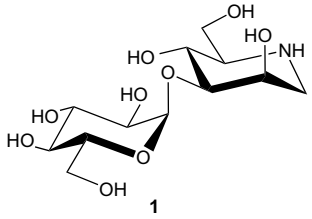
Abstract—Acid-catalysed O-acetylation of D-maltulose furnished the corresponding per-*O*-acetylated fructopyranose derivative that, after in situ deprotection at O-2 by reaction with triphenylphosphane dibromide, gave open-chain 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,3,5-tri-*O*-acetyl-6-bromo-6-deoxy-D-fructose. Standard deprotection employing sodium methoxide in methanol at −30 °C, followed by treatment of the resulting free 6-bromodeoxymaltulose with sodium azide in *N*,*N*-dimethylformamide, allowed access to 6-azidodeoxymaltulose. Hydrogenation over Pearlman's catalyst, accompanied by intramolecular reductive amination, yielded the desired title compound. This route allows access to preparative quantities and to a range of novel analogues with improved biostability.

Keywords: endo-D-Mannosidase inhibitor; Golgi endo-α-mannosidase; α-D-Glucopyranosyl-(1→3)-1-deoxymannojirimycin; Open-chain ketose

Golgi-located endo-α-D-mannosidase[1] is a unique enzyme of the early glycoprotein trimming pathway of *N*-glycoproteins that works as a bypass to the classical route of this processing cascade, which involves glucosidases I and II. By this shunt, incompletely deglucosylated glycoproteins can be avoided. Consequently, it is an important tool of the highly sophisticated quality control mechanism of glycoprotein biosynthesis.

The most powerful inhibitor of this enzyme thus far is α-D-glucopyranosyl-(1→3)-1-deoxymannojirimycin (**1**) that exhibits an excellent K_i value of 1.7 μM.[2] This compound was independently prepared by Fleet and his group[3] in 13 steps, as well as by Spiro and co-workers[4] (14 steps) by O-glucosylation of partially protected 1-deoxymannojirimycin derivatives with suitable glucosyl donors. Due to its sensitivity towards endogenous



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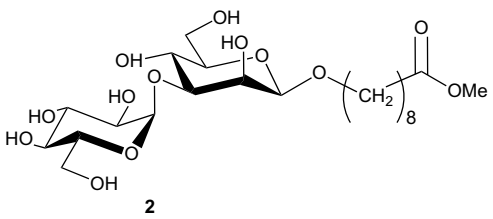

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* Corresponding author. Tel.: +43-316-873-8247; fax: +43-316-873-8740; e-mail: stuetz@orgc.tu-graz.ac.at

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α-glucosidases, useful applications, for example, as a ligand for affinity purification of endomannosidase, have been hampered.[1] More stable analogues such as thioglycosides[5] were found to be inactive.[6]

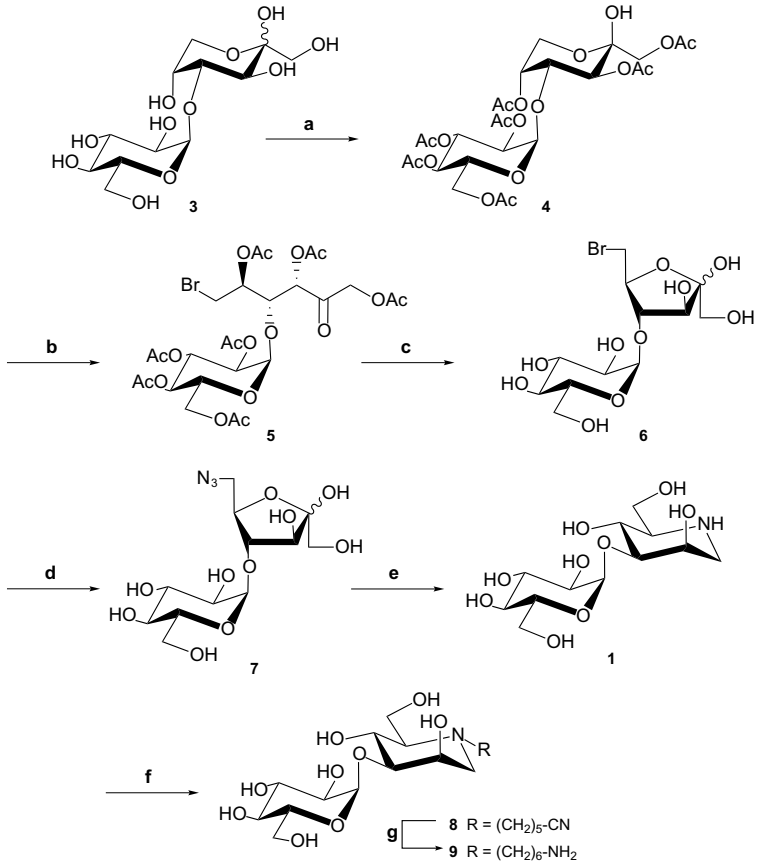
Structurally related compound **2**[7] containing a C_9 spacer arm is reasonably stable to physiological conditions, which suggested that derivatives of inhibitor **1** featuring medium chain alkyl substituents at the ring nitrogen might exhibit improved biochemical properties and could be exploited for biological studies of this interesting enzyme shunt.

Based on a simple and less time-consuming access than the published routes, such products might become useful diagnostic tools in glycobiology and glycomics research provided that the approach is suitable for scaling up.

Based on our recent synthesis of 1-deoxymannojirimycin from open-chain 1,3,4,5-tetra-*O*-acetyl-6-bromo-6-deoxy-D-fructose,[8] we relied on maltulose (**3**) as a promising starting material to avoid the glycosylation step as well as tedious protecting-group manipulations (Scheme 1). Its reaction with acetic anhydride in the presence of 4-toluenesulfonic acid yielded crystalline compound **4**. For good yields, it was found important to maintain the reaction temperature at 0 °C to avoid the formation of undesired furanoid as well as per-*O*-acetylated open-chain byproducts at the reducing end.

With commercially available triphenylphosphane dibromide in dichloromethane, practically quantitative formation of the desired open-chain bromosugar **5** took place, which by crystallisation from 2-propanol could be completely purified from triphenylphosphine oxide and was isolated in 85% yield. This nicely crystalline material was treated with sodium methoxide in methanol at −30 °C furnishing free 6-bromo-6-deoxymaltulose (**6**) as a syrup. For stability reasons, the crude product was immediately employed in the next step. Reaction with sodium azide in DMF at ambient temperature gave 6-azido-6-deoxymaltulose (**7**) as a slightly yellow syrup. Due to the low reaction temperature required to avoid side reactions, reaction times of 6–8 days were found necessary. Conventional catalytic hydrogenation of azidodeoxysugar **7** in dry methanol over $Pd(OH)_2/C$ (20%) then furnished title compound **1**.

Conveniently, this five-step sequence is based on abundant D-maltulose and only a few, inexpensive reagents. It does not involve any glycosylation reaction and allows access to compound **1** in overall yields



Scheme 1. Reagents and conditions: (a) Ac_2O, PTSA, HBr, aq NaOAc; (b) Ph_3PBr_2, Pyr., CH_2Cl_2; (c) NaOMe, MeOH; (d) NaN_3, DMF; (e) H_2, $Pd(OH)_2/C$, MeOH; (f) Br–$(CH_2)_5$–CN, Na_2CO_3, DMF; (g) H_2, Raney Ni, MeOH.

around 15% calculated from maltulose. The approach compares favourably with the previously reported routes in terms of efficacy and scaling-up potential.

N-Alkylation of compound **1** was performed in DMF with 6-bromohexanoic nitrile in the presence of sodium carbonate to give *N*-cyanopentyl derivative **8**. From this, the corresponding *N*-aminohexyl derivative **9** was obtained by conventional catalytic hydrogenation over Raney nickel in methanol. Both functional groups, the nitrile as well as the amine, should allow for a variety of modifications with a view to immobilisation and/or tagging experiments.

Gratifyingly, in preliminary stability tests employing α-glucosidase from brewer's yeast (EC 3.2.1.20) at 37 °C in pH 6.8 phosphate puffer, both *N*-alkyl derivatives exhibited considerably enhanced stabilities compared to parent compound **1** (45 min), with half lives exceeding 5 h.

1. Experimental

1.1. General methods

Melting points were recorded on a Tottoli apparatus and are uncorrected. Optical rotations were measured on a JASCO Digital Polarimeter or with a Perkin–Elmer 341 spectropolarimeter with a path length of 10 cm. NMR spectra were recorded at 200 as well as 500 MHz (^{1}H), and at 50 and 125 MHz (^{13}C). $CDCl_3$ was used as solvent for protected compounds and D_2O for free sugars. Chemical shifts are listed in δ-units (ppm) employing residual, not deuterated, solvent as the internal standard. The signals of the protecting groups were found in the expected regions and are not listed explicitly. TLC was performed on precoated aluminium sheets (E. Merck no. 5554). TLC plates were treated with concd H_2SO_4 containing 5% vanillin.

Staining of free iminoalditols was performed employing a mixture of 10% ammonium molybdate (w/v) in 10% aq H_2SO_4 containing 0.8% $CeSO_4$ (w/v).

For column chromatography Silica Gel 60 (E. Merck) was used. Mixtures of EtOAc–petroleum ether (1:10 to 3:1, v/v) were used for TLC of protected compounds. $CHCl_3$–MeOH (3:1) was employed for TLC of unprotected sugars. Purification on silica gel was performed with EtOAc–cyclohexane 10:1.

1.2. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,3,5-tri-*O*-acetyl-D-fructopyranose (4)

To an ice-cooled solution of 4-toluenesulfonic acid (1.0 g, 5.26 mmol, 0.5 equiv) in Ac_2O (100 mL), maltulose monohydrate (4.0 g, 11.1 mmol) was added portionwise over a period of 2 h. After 8 h, HBr in glacial HOAc (5 mL, 2.6 equiv) was added slowly, followed by slow addition of aq NaOAc (25%, 50 mL) to hydrolyse the 2-acetate. Excess Ac_2O was decomposed by stirring the reaction mixture with ice (200 mL) for 2 h. The mixture was extracted with CH_2Cl_2, the organic layer was washed with satd aq $NaHCO_3$, dried (Na_2SO_4) and concentrated under reduced pressure. Crystallisation of the resulting colourless syrup from Et_2O gave compound **4** [4.6 g (65%)] as colourless crystals: mp: 95–100 °C; $[\alpha]_D^{20}$ +20.5 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.36 (dd, 1H, $J_{2',3'}$ 10.3 Hz, $J_{3',4'}$ 10.0 Hz, H-3′), 5.36 (1H, $J_{3,4}$ 10 Hz, H-3), 5.32 (ddd, 1H, $J_{4,5}$ 3.6 Hz, $J_{5,6a}$ 1.3 Hz, $J_{5,6b}$ 1.8 Hz, H-5), 5.26 (d, 1H, $J_{1',2'}$ 3.8 Hz, H-1′), 5.04 (dd, 1H, $J_{4',5'}$ 10 Hz, H-4′), 4.78 (dd, 1H, H-2′), 4.30 (dd, 1H, H-4), 4.28 (dd, 1H, $J_{5',6'a}$ 4.4 Hz, $J_{6'a,6'b}$ 12.3 Hz, H-6′a), 4.22 (d, 1H, $J_{1a,1b}$ 11.9 Hz, H-1), 4.17 (ddd, 1H, $J_{5',6'b}$ 2.4 Hz, H-5′), 4.13 (dd, 1H, $J_{6'a,6'b}$ 13.1 Hz, H-6a), 4.06 (dd, 1H, H-6′b), 3.99 (d, 1H, H-1b), 3.82 (dd, 1H, H-6b); ^{13}C NMR: δ 96.5 (C-2, C-1′), 71.6, 71.1, 70.4, 70.3, 69.4, 68.4, 68.3, 66.9 (C-1, C-3, C-4, C-5, C-2′, C-3′, C-4′, C-5′), 62.1, 61.9 (C-6, C-6′). Anal. Calcd for $C_{26}H_{36}O_{18}$: C, 49.06; H, 5.70. Found: C, 49.03; H, 5.73.

1.3. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl-(1→4)-1,3,5-tri-*O*-acetyl-6-bromo-6-deoxy-D-fructose (5)

To a 6.6% solution of compound **4** (10.3 mmol) in dry CH_2Cl_2 (100 mL), pyridine (1 mL) and Ph_3PBr_2 (7.9 g, 18.7 mmol, 1.8 equiv) were added, and the mixture was stirred under reflux for 16 h, then allowed to reach ambient temperature. The yellow solution was then consecutively washed with 5% aq HCl and 5% aq $NaHCO_3$. After drying over Na_2SO_4, the solution was concentrated under reduced pressure. The remaining slightly yellow crystalline material was treated with hot 2-PrOH, and the mixture was allowed to reach ambient temperature. The precipitate was collected and again dissolved in hot 2-PrOH and allowed to crystallise to remove residual $Ph_3P{=}O$. Ketose **5** was thus obtained as colourless crystalline material (6.1 g, 85%): mp 109–110 °C; $[\alpha]_D^{20}$ +55.8 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.56 (1H, dd, $J_{3,4}$ 2.4 Hz, H-3), 5.41 (dd, 1H, $J_{2',3'}$ 10.5 Hz, $J_{3',4'}$ 9.5 Hz, H-3′), 5.21 (d, 1H, $J_{1',2'}$ 3.6 Hz, H-1′), 5.10 (ddd, 1H, $J_{4,5}$ 6.9 Hz, $J_{5,6a}$ 4.8 Hz, $J_{5,6b}$ 4.3 Hz, H-5), 5.07 (dd, 1H, $J_{4'5'}$ 10 Hz, H-4′), 5.00 (d, 1H, $J_{1a,1b}$ 17.5 Hz, H-1a), 4.91 (dd, 1H, H-2′), 4.78 (d, 1H, H-1b), 4.61 (dd, 1H, H-4), 4.23 (dd, 1H, $J_{5',6'a}$ 5.3 Hz, $J_{6'a,6'b}$ 12.5 Hz, H-6′a), 4.12 (dd, 1H, H-6′b), 4.11 (m, 1H, H-5′), 3.83 (dd, 1H, $J_{6a,6b}$ 11.6 Hz, H-6a), 3.73 (dd, 1H, H-6b); ^{13}C NMR: δ 199.5 (C-2), 98.0 (C-1′), 79.1 (C-3′), 75.5, 70.6, 70.5, 69.5, 69.1, 68.2, 67.1 (C-1, C-3, C-4, C-5, C-2′, C-4′, C-5′), 62.1 (C-6′), 31.3 (C-6). Anal. Calcd for $C_{26}H_{35}BrO_{17}$: C, 44.65; H, 5.04. Found: C, 44.61; H, 5.08.

1.4. α-D-Glucopyranosyl-(1→4)-6-bromo-6-deoxy-α/β-D-fructofuranose (6) and α-D-glucopyranosyl-(1→4)-6-azido-6-deoxy-α/β-D-fructofuranose (7)

To a slurry of compound **5** (2.0 g, 2.9 mmol) in dry MeOH (150 mL), methanolic NaOMe (10 mL, 1 N) was added dropwise at −30 °C over a period of 1 h. The reaction temperature was maintained for another 12 h. Acidic ion-exchange resin, Amberlite IR 120 (H^+), was added to reach pH 7. After filtration, the methanolic solution was passed over a short plug of silica gel and concentrated under reduced pressure. The resulting crude compound **6** (1.1–1.2 g) was unstable but sufficiently pure, and was immediately employed in the next step. ^{13}C NMR (main anomer, D_2O): δ 102.3 (C-2), 98.4 (C-1′), 83.5 (C-4), 79.1 (C-5), 75.2 (C-3), 72.8, 72.7 (C-3′, C-5′), 71.3 (C-2′), 69.6 (C-6′), 34.4 (C-6).

To a 2% solution of this compound (1.50 g, 3.70 mmol) in dry DMF, NaN_3 (3.6 g, 55.4 mmol, 15 equiv) was added, and the reaction mixture was stirred at ambient temperature for 6–8 days. The resulting mixture was cooled to 0 °C, and CH_2Cl_2 was added. The organic layer was passed over a plug of silica gel, and the silica gel was washed with CH_2Cl_2 until DMF was no longer detectable in the filtrate. Rinsing the silica gel with 2-PrOH gave crude product **7**. From this, inorganic salts were removed by repeated precipitation with 2-PrOH to furnish product **7** as a slightly yellow syrup (0.81 g), that was directly used in the next step. ^{13}C NMR (D_2O, main anomer): δ 102.3 (C-2), 98.7 (C-1′), 82.3 (C-4), 78.4 (C-5), 75.0 (C-3), 72.8, 72.7 (C-3′, C-5′), 71.4 (C-2′), 69.6 (C-4′), 62.4 (C-1), 60.6 (C-6′), 53.2 (C-6).

1.5. α-D-Glucopyranosyl-(1→3)-1,5-dideoxy-1,5-imino-D-mannitol (1)

Caution! Extreme fire hazard! To a 1% methanolic solution of azidodeoxysugar **7** (0.70 g, 1.91 mmol), $Pd(OH)_2/C$ (20%, 100 mg) was added, and the mixture was stirred under an atmosphere of hydrogen at ambient pressure and room temperature for 6 h. Removal of the catalyst by filtration, concentration of the filtrate under reduced pressure and subsequent chromatographic purification (silica gel, $CHCl_3$–MeOH–water–concd ammonia 200:200:1:1) gave free base **1** as a slightly yellow glassy foam (270 mg, 26% from bromodeoxysugar **6**). $[\alpha]_D^{20}$ +47 (*c* 1, H_2O). NMR spectral data (also recorded from **1**·HCl) were virtually identical with the published values.[3,4] ^1H NMR (D_2O, HCl): δ 5.07 (d, 1H, $J_{1',2'}$ 3.8 Hz, H-1′), 4.03 (br s, 1H, H-2), 3.75–3.58 (m, 6H, H-3′, H-5′, H-6′a, H-6′b, H-6a, H-6b), 3.50 (dd, 1H, $J_{2,3}$ 3 Hz, $J_{3,4}$ 9.6 Hz, H-3), 3.40 (dd, 1H, $J_{2',3'}$ 9.9 Hz, H-2′), 3.27 (dd, 1H, $J_{3',4'}$ 9.3 Hz, H-4′), 2.84 (dd, 1H, $J_{1a,1b}$ 14 Hz, $J_{1a,2}$ 2.7 Hz, H-1a), 2.64 (br d, 1H, H-1b), 2.39 (ddd, 1H, $J_{4,5}$ 9.9 Hz, $J_{5,6a}$ 4.1 Hz, $J_{5,6b}$ 1 Hz, H-5); ^{13}C NMR: δ 100.7 (C-1′), 83.1 (C-3), 73.0, 72.4, 71.9, 69.7, 69.1, 67.6 (C-2, C-2′, C-3′, C-4, C-4′, C-5′), 60.6 (C-5, C-6, C-6′), 48.4 (C-1). HRMS: Calcd for $[C_{12}H_{23}NO_9]Na^+$: *m*/*z* 348.3082. Found: *m*/*z* 348.3021.

1.6. α-D-Glucopyranosyl-(1→3)-*N*-(5-cyanopentyl)-1,5-dideoxy-1,5-imino-D-mannitol (8)

A solution of inhibitor **1** (110 mg, 0.338 mmol) in freshly distilled DMF (8 mL) was stirred with 6-bromohexanoic nitrile (90 μL, 0.68 mmol) in the presence of Na_2CO_3 (60 mg) at 50 °C for 70 h. The reaction mixture was then concentrated under reduced pressure, and the resulting syrup was purified on silica gel employing $CHCl_3$–MeOH–concd ammonia (200:100:3) as the solvent system to yield syrupy product **8** (110 mg, 77%). $[\alpha]_D^{20}$ +36.5 (*c* 0.3, H_2O); ^1H NMR (D_2O): δ 5.08 (d, 1H, $J_{1',2'}$ 3.9 Hz, H-1′), 4.02 (m, 1H, H-2), 3.81 (dd, 1H, $J_{6a,6b}$ 12.6 Hz, $J_{5,6a}$ 2.1 Hz, H-6a), 3.77–3.70 (m, 4H, H-6b, H-4, H-5′, H-6′a), 3.67 (1H, dd, $J_{3',4'}$ 9.5 Hz, H-3′), 3.63 (dd, 1H, $J_{6'a,6'b}$ 12.3 Hz, $J_{5',6'b}$ 5.5 Hz, H-6′b), 3.44 (dd, 1H, $J_{2,3}$ 3.4 Hz, $J_{3,4}$ 9.7 Hz, H-3), 3.42 (dd, 1H, $J_{2',3'}$ 10 Hz, H-2′), 3.29 (dd, 1H, H-4′), 2.86 (dd, 1H, $J_{1a,1b}$ 13.1 Hz, $J_{1a,2}$ 3.5 Hz, H-1a), 2.62 (m, 1H), 2.53 (m, 1H), 2.48 (dd, H-1b), 2.36 (t, 2H), 2.17 (br d, 1H, H-5), 1.56 (m, 2H), 1.39 (m, 2H), 1.28 (m, 2H); ^{13}C NMR: δ 122.3 (CN), 100.6 (C-1′), 82.9, 73.0, 72.4, 72.0, 69.8, 67.9, 67.3, 65.6, 60.7, 58.0, 55.0, 52.2 (C-1, C-2, C-3, C-4, C-5, C-6, C-2′, C-3′, C-4′, C-5′, C-6′, N–CH_2–), 26.1, 24.5, 22.3, 16.4 ($5CH_2$). HRMS: Calcd for $[C_{18}H_{32}N_2O_9]Na^+$: *m*/*z* 443.4540. Found: *m*/*z* 443.4530.

1.7. α-D-Glucopyranosyl-(1→3)-*N*-(6-aminohexyl)-1,5-dideoxy-1,5-imino-D-mannitol (9)

A solution of nitrile **8** (55 mg, 0.13 mmol) in dry MeOH was stirred with Raney Ni (200 mg) under an atmosphere of hydrogen at 50 bar for 72 h. The cloudy solution was decanted and filtered over Celite, and the catalyst, as well as the Celite, were carefully washed with MeOH–concd ammonia 1:1. The combined methanolic solutions were concentrated under reduced pressure, and the remaining residue was chromatographed ($CHCl_3$–MeOH–H_2O–concd ammonia 400:400:100:5) to give product **9** as a syrup (38 mg, 69%). $[\alpha]_D^{20}$ +38 (*c* 0.35, H_2O); ^1H NMR (H_2O): δ 5.10 (d, 1H, $J_{1',2'}$ 3.9 Hz, H-1′), 4.02 (m, 1H, H-2), 3.81 (dd, 1H, $J_{5,6a}$ 2.1 Hz, $J_{6a,6b}$ 12.5 Hz, H-6a), 3.76–3.71 (m, 4H, H-4, H-6b, H-5′, H-6′a), 3.69 (dd, 1H, $J_{3',4'}$ 9.5 Hz, H-3′), 3.65 (dd, 1H, $J_{5',6'b}$ 5.5 Hz, H-6′b), 3.45 (dd, 1H, $J_{2,3}$ 3.4 Hz, $J_{3,4}$ 8 Hz, H-3), 3.43 (dd, 1H, $J_{2',3'}$ 7.9 Hz, H-2′), 3.30 (dd, 1H, H-4′), 2.86 (dd, 1H, $J_{1a,1b}$ 13.0 Hz, $J_{1a,2}$ 3.5 Hz, H-1a), 2.64 (m, 2H), 2.59 (m, 1H), 2.50 (m, 1H), 2.46 (br d, H-1b), 2.15 (br d, H-5). 1.42–1.38 (m, 2H), 1.26–1.20 (m, 2H); ^{13}C NMR: δ 100.7 (C-1′), 83.0 (C-3), 73.0, 72.4, 72.0, 69.8, 68.0, 67.4, 65.6, 60.7, 58.1, 55.0, 52.4, 40.2 (C-1, C-2, C-2′,

C-3′, C-4, C-4′, C-5, C-5′, C-6, C-6′, C-1″, C-6″), 29.7, 26.6, 25.9, 22.9 (C-2″, C-3″, C-4″, C-5″). MS: Calcd for $[C_{18}H_{36}N_2O_9]Na^+$: m/z 447.485. Found: m/z 447.485.

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References

1. (a) Lubas, W. A.; Spiro, R. G. *J. Biol. Chem.* **1988**, *263*, 3990–3998; (b) Spiro, R. G. Processing Enzymes Involved in the Deglucosylation of *N*-Linked Oligosaccharides of Glycoproteins: Glucosidases I and II and Endomannosidase. In *Carbohydrates in Chemistry and Biology, Part II: Biology and Saccharides*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 3, pp 65–79; and references cited therein.
2. Hiraizumi, S.; Spohr, U.; Spiro, R. G. *J. Biol. Chem.* **1993**, *268*, 9927–9935.
3. Adron, H.; Butters, T. D.; Wormald, M. R.; Dwek, R. A.; Fleet, G. W. J.; Jacob, G. S. *Tetrahedron: Asymmetry* **1993**, *4*, 2011–2024.
4. Spohr, U.; Bach, M.; Spiro, R. G. *Can. J. Chem.* **1993**, *71*, 1928–1942.
5. Ding, Y.; Hindsgaul, O. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1215–1220.
6. Spiro, R. G. Personal communications to A.E.S. 2001/2002.
7. Hiraizumi, S.; Spohr, U.; Spiro, R. G. *J. Biol. Chem.* **1994**, *269*, 4697–4700.
8. Spreitz, J.; Stütz, A. E.; Wrodnigg, T. M. *Carbohydr. Res.* **2002**, *337*, 183–186; (a) Based on: Brauns, D. H. *J. Am. Chem. Soc.* **1920**, *42*, 1846–1854; (b) Pascu, E.; Rich, F. V. *J. Am. Chem. Soc.* **1933**, *55*, 3018–3024; (c) Lichtenthaler, F. W.; Klotz, J.; Flath, F.-J. *Liebigs Ann. Chem.* **1995**, 2069–2080; Hepta-*O*-acetylmaltulose was prepared following the synthesis of 1,3,4,5-tetra-*O*-acetylfructopyranose: Helferich, B.; Steinpreis, R. *Chem. Ber.* **1958**, *91*, 1794–1798.