Disaccharides as Endomannosidase Inhibitors: Syntheses of α-Homomannojirimycin and β-Homomannojirimycin Linked to D-Glucose and D-Mannose

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4-*O*-(α-D-Glucopyranosyl)-αHMJ (Glcα1,4HMJ), 4-*O*-(α-mannopyranosyl)-αHMJ (Manα1,4αHMJ), 4-*O*-(α-glucopyranosyl)-βHMJ (Glcα1,4βHMJ), and 4-*O*-(α-mannopyranosyl)-βHMJ (Manα1, 4βHMJ) were synthesized as endomannosidase inhibitors which are potentially useful both for probing the pathways of *N*-linked glycoprotein processing and for the chemotherapy of some viral diseases.

Key words endomannosidase inhibitor; deoxynojirimycin; α-homomannojirimycin; β-homomannojirimycin; *N*-linked glycoprotein; anti human immunodeficiency activity

Polyhydroxylated mono- and bicyclic nitrogen heterocycles, in which nitrogen is substituted for oxygen in the carbohydrate ring, have provided an important class of glycosidase inhibitors.[1] Recently, various potent exoglycosidase inhibitors were synthesized, such as castanospermine,[2] deoxynojirimycin (DNJ),[3,4] deoxymannojirimycin (DMJ)[5–7] and swainsonine (Fig. 1). Although there are many potential applications of such materials, one area in which such compounds have made a major contribution has been in the investigation of the processing of *N*-linked oligosaccharides. The major route for *N*-linked oligosaccharide biosynthesis in most cell types is *via* the sequential hydrolysis of a cotranslationally transferred, triglucosylated oligosaccharide by exoglycosidases of the intracellular membrane compartment.

Oligosaccharide maturation to a high mannose,[7] hybrid, or complex type, requires that the glucose units are removed by α-glucosidase I, which hydrolyzes the terminal α-1,2 linked glucose residue, and by α-glucosidase II, which removes the inner two α-1,3 linked glucose residues[3,8]; this initiates the processing which ultimately leads to mature complex and hybrid type *N*-linked oligosaccharides. The initial removal of glucose units may be inhibited by the use of basic nitrogen mimics such as DNJ, an inhibitor of both glucosidase I and glucosidase II. DMJ, although a rather poor inhibitor of many α-mannosidases, is a powerful and specific inhibitor of mannosidase I but has little effect on mannosidase II; in contrast, swainsonine and simpler synthetic analogues of mannofuranose, such as the 6-deoxy-6-fluoromannofuranose analogue, are inhibitors of mannosidase II. All these derivatives of glucose or mannose inhibit only exoglycosidases; no report of their inhibition of endoglycosidases has appeared.

However, cells that are grown in the presence of α-glucosidase inhibitors or which are mutationally negative for these enzymes, retain the ability to form fully matured glycans by invoking a glucosidase-independent pathway that uses a Golgi-located endo-α-mannosidase.[3,8] This apparently constitutive enzyme converts Glc_3-, Glc_2-, and $Glc_1Man_9GlcNAc_2$ oligosaccharides to a $Man_8GlcNAc_2$ isomer and is not inhibited by a number of compounds that are potent exoglycosidase inhibitors, such as castanospermine, DNJ, DMJ and swainsonine (Fig. 1).

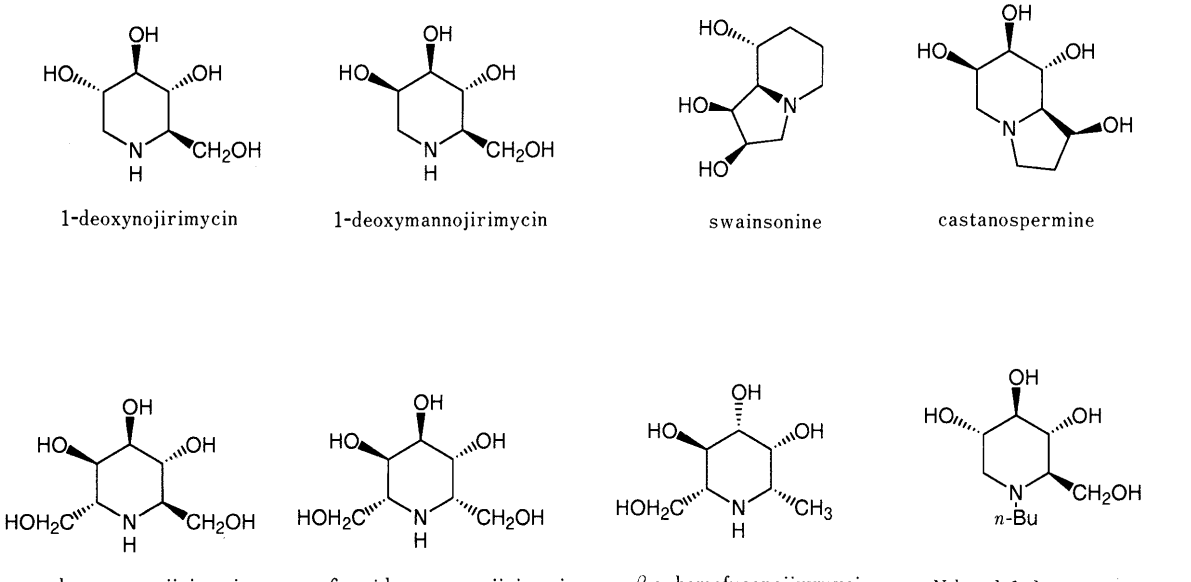

Fig. 1. Glycosidase Inhibitors

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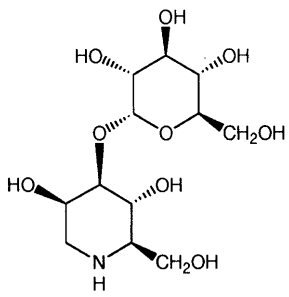
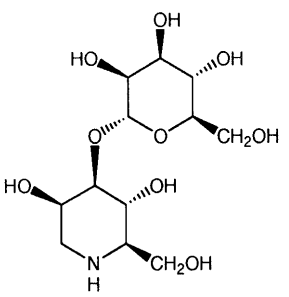


Glcα1,3DMJ



Manα1, 3DMJ

Fig. 2. Endomannosidase Inhibitors

Since the endomannosidase cleaves Glcα1,3Man, it was postulated that a suitable inhibitor would be a disaccharide possessing a glucose unit α1—3 linked to a mannose analogue such as DMJ or swainsonine.[9-12] Recently, various azadisaccharides, Glcα1,3DMJ and Glcα1,3swainsonine, have been synthesized, and it was reported that *in vitro*, Glcα1,3DMJ was the most potent endo-α-mannosidase inhibitor (Fig. 2).

Since it was reported that C-1 groups of mannojirimycin derivatives were needed for selectivity of α- and β-mannosidase inhibition,[13,14] we considered that the α-isomer of a disaccharide containing a mannojirimycin derivative would inhibit endo-α-mannosidase, and the β-isomer would be an endo-β-mannosidase inhibitor. In addition, since the C–C bond linkage of the C-1 group of mannojirimycin is more stable than that of the C–O bond to hydrolysis *in vivo*, we designed mannose analogues having a 1-hydroxymethyl group at the C-1 site, *i.e.*, α- and β-homomannojirimycin.

We describe in this report the syntheses of monoazasaccharide of 1-α-homomannojirimycin (α-HMJ) (**1**), 1-β-homomannojirimycin (β-HMJ) (**2**), and disaccharides of 4-*O*-(α-D-glucopyranosyl)-α-HMJ (Glcα1,4α-HMJ) (**3**), 4-*O*-(α-D-mannopyranosyl)-α-HMJ (Manα1,4α-HMJ) (**4**), 4-*O*-(α-D-glucopyranosyl)-β-HMJ (Glcα1,4β-HMJ) (**5**), and 4-*O*-(α-D-glucopyranosyl)-β-HMJ (Manα1,4β-HMJ) (**6**) (Fig. 3).

The availability of compounds **3**—**6** not only will allow further biochemical dissection of the *N*-linked glycoprotein processing pathway, but also has potential for augmenting α-glucosidase inhibitor-mediated therapies for infectious agents. For example, human immunodeficiency virus (HIV) may be rendered non-infectious by the formation of completely glucosylated *N*-linked oligosaccharides. Because Golgi endomannosidase is capable of acting as a salvage pathway, coadministration of **3** or **4** with castanospermine, butylDNJ (**2**) and other naturally occurring and synthetic glucosidase inhibitors may provide a potentially better therapeutic strategy for treatment of such diseases than would the use of a glucosidase I inhibitor by itself.

Synthesis of Glucose Derivative and Mannose Derivative 2,3,4,6-Tetra-*O*-benzyl glucose and 2,3,4,6,-tetra-*O*-benzyl mannose were purchased from the Sigma Chemical Company and converted into 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl trichloroacetoimidate (**20**) and 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl trichloroacetoimidate (**21**) with trichloroacetonitrile and sodium hydride in 66% and 68% yields, respectively.

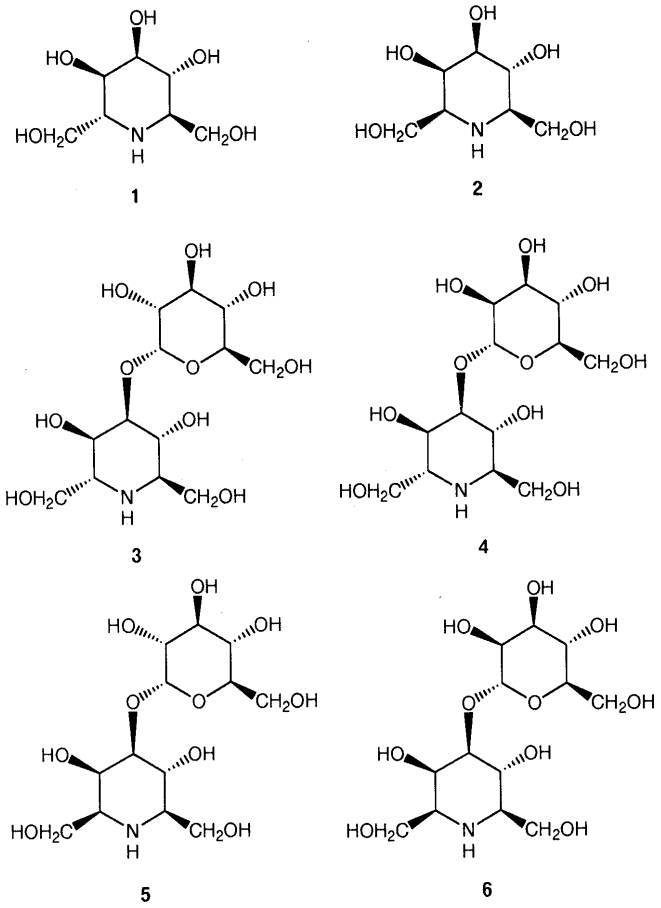


Fig. 3

Synthesis of Glcα1,4α-HMJ and Manα1,4α-HMJ α-Homomannojirimycin (**1**) was synthesized by the reported method,[13,15] and its derivatives were prepared by the following method. The secondary amino group in **7** was protected with benzyloxycarbonyl chloride (ZCl) and saturated aqueous $NaHCO_3$ to give **8** in 65% yield. The two free hydroxy groups in **8** were treated with benzyl trichloroacetimidate in the presence of a catalytic amount of trifluoromethanesulfonic acid (TFMSA) to afford the dibenzyl ether (**9**) in 60% yield. The acetonide and silyl groups of **9** were cleaved with trifluoroacetic acid and water (1 : 1) to give **10** in 55% yield, and then the primary alcohol of **10** was reprotected with *tert*-butyldimethylchlorosilane (TBDMSCl) and imidazole in dimethyl formamide (DMF) at −30 °C to afford the α-HMJ derivative (**11**) in 48% yield. The α-HMJ derivative (**11**) was condensed with a glucose derivative (**20**) by using a catalytic amount of TFMSA in DMF to give **22** in 10% yield. Compound **22** was deprotected by hydrogenolysis in MeOH in the presence of a catalytic amount of palladium black and treatment with a trace of concentrated hydrochloric acid to afford **3**. Manα1, 4α-HMJ (**4**) was synthesized in the same way as used for compound **3**, that is, the α-HMJ derivative (**11**) was linked in 7% yield to the mannose derivative (**21**) to afford **23**, which, on hydrogenation followed by hydrolysis, gave Manα1, 4α-HMJ (**4**) in 40% yield (Chart 1).

Synthesis of Glcα1,4βHMJ and Manα1,4βHMJ 5-

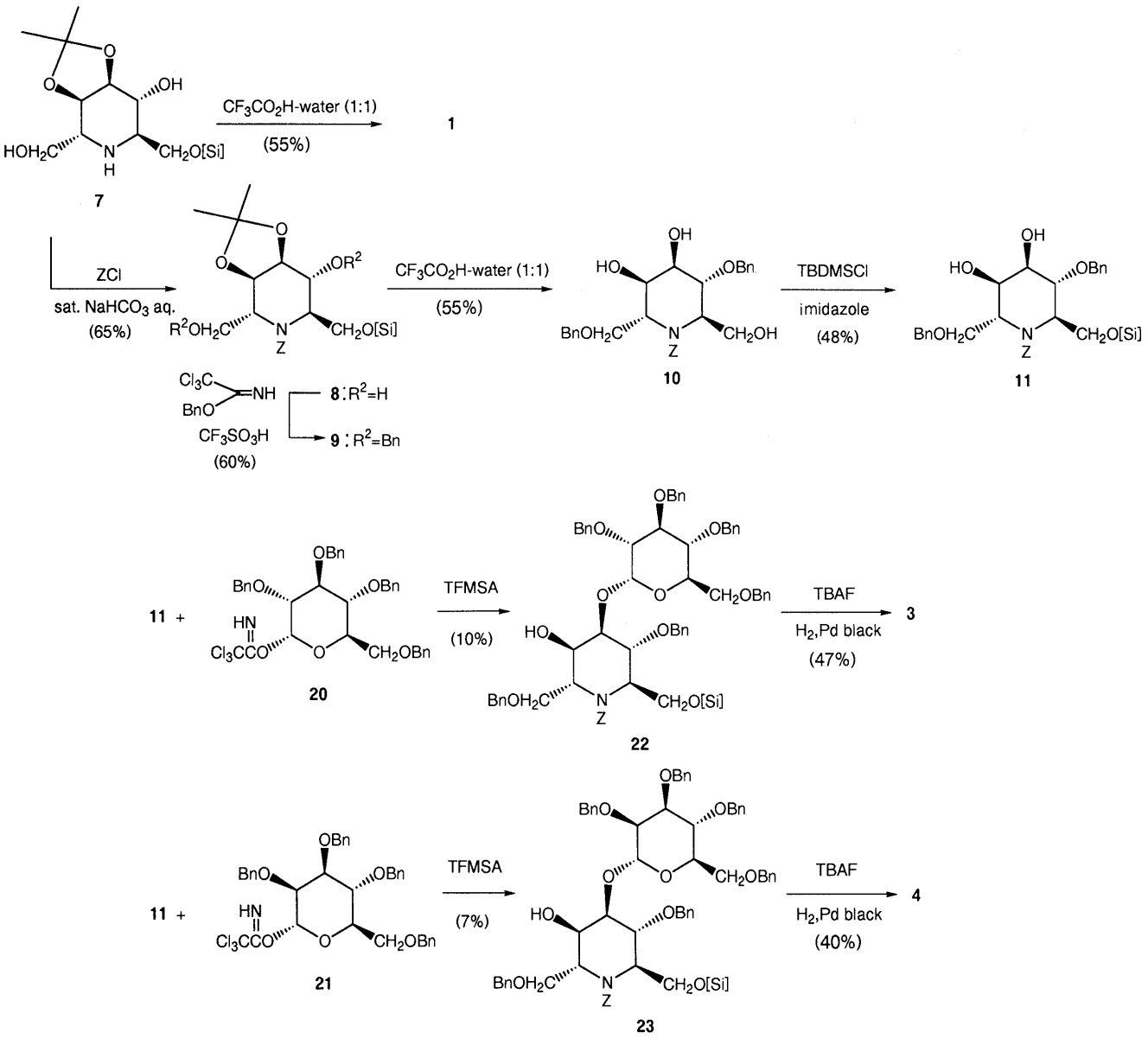


Chart 1

Azido-5-deoxy-D-mannolactone (**12**) was prepared as previously described.[3,8,16] For the synthesis of **2** and its derivative (**19**), compound **12** was treated with Tebbe's reagent[17] to give the 1-methylene sugar (**13**) in 20% yield, or in the case of using dicyclopentadienyldimethyltitanium[18,19] in 60% yield. Oxidation with osmium tetraoxide of **13** afforded the diol (**14**) [60% yield], which, on hydrogenation in methanol in the presence of platinum oxide, gave the piperidine ring compound **15**[3,8,16] in quantitative yield. Removal of the protecting groups of **15** with aqueous trifluoroacetic acid gave **2** in 55% yield. The secondary amino group in **15** was protected with ZCl and saturated aqueous $NaHCO_3$ gave **16** in 62% yield, and the two free hydroxyl groups in **16** were converted into the dibenzyl ether (**17**) by treatment with benzyl trichloroacetimidate in the presence of a catalytic amount of TFMSA [52% yield]. The acetonide and silyl groups of **17** were cleaved with trifluoroacetic acid and water (1 : 1) to give **18** in 52% yield, and then the primary alcohol of **18** was reprotected with TBDMSCl and imidazole in DMF at $-30\,^{\circ}C$ to afford the β-HMJ derivative (**19**) in 45% yield (Chart 2).

The β-1-HMJ derivative (**19**) was condensed to the glucose derivative (**20**) by using a catalytic amount of TFMSA in DMF to afford compound **24** in 15% yield.[11] Hydrogenolysis of **24** in methanol in the presence of palladium black and a trace of concentrated aqueous hydrochloric acid gave Glcα1,4βHMJ (**5**) in 45% yield.[11] Next, Manα1,4βHMJ (**6**) was synthesized in the same way as described for compound **5**. The β-HMJ derivative (**19**) was linked to the mannose derivative (**21**) by using a catalytic amount of TFMSA in DMF to give compound **25** [5% yield], which, on hydrogenation followed by hydrolysis, afforded Manα1,4βHMJ (**6**) in 35% yield (Chart 3).[20]

The structures of all compounds were characterized by proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy, as well as infrared (IR) spectroscopy, elemental analyses, and fast-atom bombardment (FAB) mass spectroscopy.

Experimental

All melting points are uncorrected. Optical rotations were measured with a JASCO DIP-140 digital polarimeter. IR spectra were recorded on a JASCO A-202 infrared spectrometer. ^{1}H-NMR spectra were taken on a JEOL JNM-GX270 (270 MHz) spectrometer. ^{13}C-NMR spectra were recorded with a JEOL JNM-GX270 (67.5 MHz) spectrometer. ^{1}H and ^{13}C chemical shifts (δ) are given in ppm relative to Me_4Si ($\delta=0$) in $CDCl_3$ or CD_3OD, or to sodium 4,4-dimethyl-4-silapentane-1-sulfonate hydrate (DSS, $\delta=0$ in D_2O) as an internal standard. The abbreviations of signal patterns are as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Column chromatography was carried out on Silica gel 60 (70—230 mesh, Merck). Gel filtration was performed on Sephadex LH-20 (Pharmacia). Thin-layer chromatography (TLC) on Silica gel 60-F_{254} (Merck) was used to monitor the reaction and to ascertain the purity of the reaction products. The spots were visualized by spraying the plates with 5% aqueous sulfuric acid and then heating.

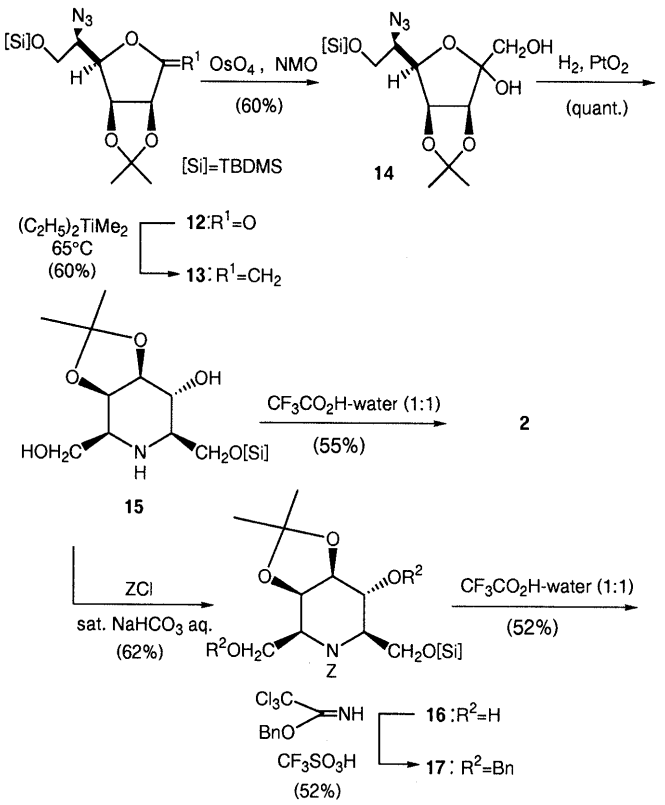


Chart 2

α-Homomannojirimycin (**1**) and its derivatives, β-homomannojirimycin, 5-azido-6-*tert*-butyldimethylsilyl-5-deoxy-2, 3-*O*-isopropylidene-D-mannolactone (**12**)[13,16] were synthesized by the reported methods, and $[\alpha]_D$, IR, ^{1}H-NMR, and ^{13}C-NMR data were in complete agreement with the reported data.

***N*-Benzyloxycarbonyl-7-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-2,6-dideoxy-2,6-imino-D-*glycero*-D-*talo*-heptitol (8)** Benzyloxycarbonyl chloride (0.35 ml, 2.4 mmol) was added dropwise to a stirred solution of compound **7** (350 mg, 2.0 mmol) in ether (5 ml) and saturated aqueous $NaHCO_3$ (25 ml) at room temperature over 12 h. The reaction mixture was extracted with ether (20 ml) three times. The organic layer was dried over anhydrous $MgSO_4$, and concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography using AcOEt–*n*-hexane (1 : 3) to afford **8** (625 mg, 65%) as a colorless oil. $[\alpha]_D$ −22.0° ($c=1.22$, MeOH). IR (neat): 1690 (C=O) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.01 (6H, s, $SiMe_2$), 0.89 (9H, s, Si^tBu), 1.38, 1.47 (each 3H, s, CMe_2), 2.44—3.10 (2H, m, H-2, H-6), 3.67—3.69 (1H, m, H-3), 3.75—3.82 (2H, m, H-7, H-7′), 3.83—3.95 (2H, m, H-1, H-1′), 4.00—4.25 (2H, m, H-4, H-5), 5.10—5.25 (2H, m, $COOCH_2$-Ph), 7.25—7.39 (5H, m, Ph). ^{13}C-NMR (CD_3OD) δ: −5.6 (2×q, $SiMe_2$), 20.5 (s, $SiCMe_3$), 25.6 (3×q, $SiCMe_3$), 26.8, 28.2 (2×s, 2×CMe), 56.5, 57.1 (2×d, C-6), 59.3, 60.3 (2×d, C-2), 63.4, 63.9 (2×t, C-1), 64.6, 65.2 (2×t, C-7), 72.9, 73.1 (2×d, C-3), 75.6, 76.1 (2×d, C-4), 81.3, 81.8 (d, C-5), 109.1, 111.2 (s, CMe_2), 127.1, 127.3, 127.5, 128.4, 128.5 (5×d, $COOCH_2Ph$), 133.1, 133.6 (2×s, CPh), 149.5, 152.2 (2×s, C=O). *Anal.* Calcd for $C_{24}H_{39}NO_7Si$: C, 59.85; H, 8.16; N, 2.91. Found: C, 59.52; H, 8.01; N, 2.97.

***N*-Benzyloxycarbonyl-7-*O*-*tert*-butyldimethylsilyl-1,5-di-*O*-benzyl-3,4-*O*-isopropylidene-2,6-dideoxy-2,6-imino-D-*glycero*-D-*talo*-heptitol (9)** A mixture of compound **8** (480 mg, 1.0 mmol) and benzyl trichloroacetoimidate (760 mg, 3.0 mmol) in CH_2Cl_2–cyclohexane (1 : 1) (10 ml) was stirred at room temperature. The reaction mixture was stirred with TFMSA (15 mg, 0.1 mmol) at −10 °C under argon for 2 h and then at 0 °C for 24 h. The solution was concentrated to dryness, and the residue was chromatographed on silica gel using AcOEt–*n*-hexane (1 : 5)

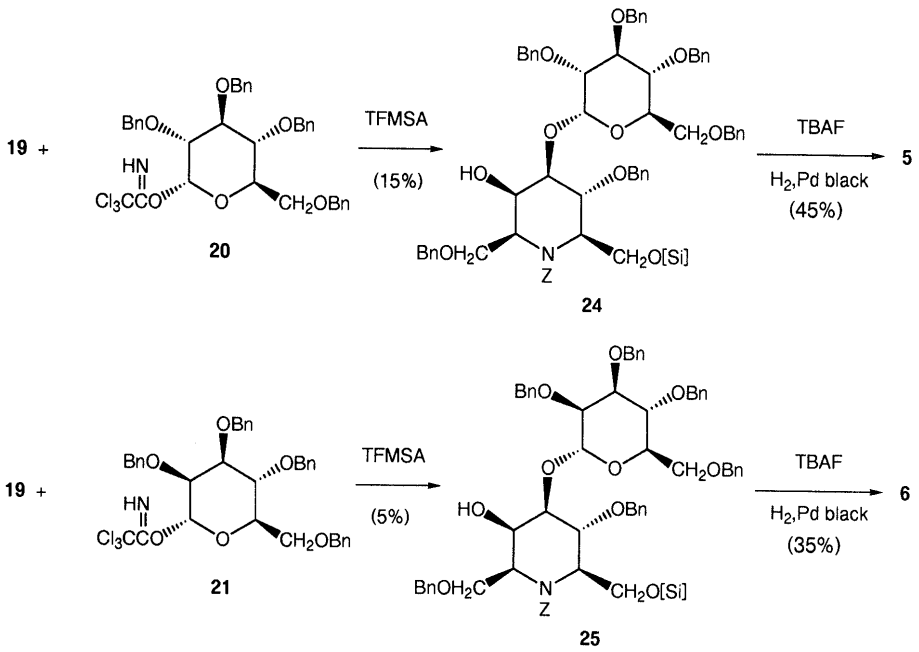


Chart 3

to give **9** (397 mg, 60%) as a white powder. $[\alpha]_D$ +1.8° (c=1.12, $CHCl_3$). IR (KBr): 1695 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s, SiMe$_2$), 0.86 (9H, s, Si^{t}Bu), 1.35, 1.49 (each 3H, s, CMe$_2$), 3.65—4.78 (9H, m, H-1, H-1′, H-2, H-3, H-4, H-5, H-6, H-7, H-7′), 4.60—4.68 (4H, m, 2×CH$_2$Ph), 5.01—5.15 (2H, m, COOCH$_2$-Ph), 7.13—7.35 (15H, m, 3×Ph). ^{13}C-NMR ($CDCl_3$) δ: −5.6 (2×q, SiMe$_2$), 18.3 (s, SiCMe$_2$), 25.7, 25.8, 25.9 (3×q, SiCMe$_3$), 25.7, 30.3 (2×q, CMe$_2$), 57.1 (d, C-6), 67.0, 67.7 (2×t, COOCH$_2$Ph), 72.5, 72.7 (2×t, CH$_2$Ph), 109.0 (s, CMe$_2$), 126.5, 126.7, 126.9, 127.0, 127.3, 127.5 127.8, 128.1, 128.2, 128.7, 129.2, 129.5 (15×d, CHPh), 135.8, 136.5, 137.6 (3×s, CPh), 161.2 (s, C=O). *Anal.* Calcd for $C_{38}H_{51}NO_7Si$: C, 68.95; H, 7.77; N, 2.12. Found: C, 68.56; H, 7.65; N, 2.27.

***N*-Benzyloxycarbonyl-1,5-di-*O*-benzyl-2,6-dideoxy-2,6-imino-D-*glycero*-D-*talo*-heptitol (10)** Compound **9** (330 mg, 0.5 mmol) was reacted with trifluoroacetic acid–water (1 : 1) (10 ml) at room temperature for 3 h. After removal of the solvent, the residue was chromatographed on silica gel using CH_2Cl_2–MeOH (10 : 1) to give **10** (140 mg, 55%) as a colorless oil. $[\alpha]_D$ −1.3° (c=1.03, MeOH). IR (neat): 3400 (br OH), 1695 (C=O) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.75—2.88 (2H, m, H-7, H-7′), 4.50—4.68 (4H, m, 2×CH$_2$Ph), 5.01—5.14 (2H, m, COOCH$_2$Ph), 7.24—7.33 (15H, m, Ph). ^{13}C-NMR (CD_3OD) δ: 67.9, 68.5 (2×t, COOCH$_2$Ph), 72.5, 72.7 (2×t, CH$_2$Ph), 109.0 (s, CMe$_2$), 127.5, 127.7, 128.0, 128.2, 128.6, 128.9, 130.6 (15×d, CHPh), 161.8 (s, C=O). *Anal.* Calcd for $C_{29}H_{33}NO_7$: C, 68.62; H, 6.55; N, 2.76. Found: C, 68.44; H, 6.61; N, 2.87.

***N*-Benzyloxycarbonyl-1,5-di-*O*-benzyl-7-*O*-*tert*-butyldimethylsilyl-2,6-dideoxy-2,6-imino-D-*glycero*-D-*talo*-heptitol (11)** Imidazole (51 mg, 0.75 mmol) and TBDMSCl (90 mg, 0.6 mmol) were added to a stirred solution of compound **10** (255 mg, 0.5 mmol) in DMF (5 ml) at −40 °C under argon. The mixture was stirred at the same temperature for 2 h, diluted with AcOEt (50 ml), and successively washed with AcOEt and water. The organic layer was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residual product was purified by column chromatography using AcOEt–*n*-hexane (1 : 3) to afford **11** (149 mg, 48%) as a colorless oil. $[\alpha]_D$ −1.0° (c=1.05, MeOH). IR (neat): 3401 (br OH), 1698 (C=O) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.04 (6H, s, SiMe$_2$), 0.89 (9H, s, Si^{t}Bu), 4.50—4.78 (4H, m, 2×CH$_2$Ph), 5.11—5.15 (2H, m, COOCH$_2$Ph), 7.25—7.35 (15H, m, Ph). ^{13}C-NMR (CD_3OD)δ: −5.6 (2×q, SiMe$_2$), 18.1 (s, SiCMe$_3$), 25.7, 25.9, 26.0 (3×q, SiCMe$_3$), 67.2 (t, COOCH$_2$Ph), 72.7, 72.9 (2×t, CH$_2$Ph), 127.5, 127.8, 127.9, 128.1, 128.2, 128.5, 129.0, 129.5 (15×d, 3×Ph). *Anal.* Calcd for $C_{35}H_{47}NO_7Si$: C, 67.60; H, 7.62; N, 2.25. Found: C, 67.44; H, 7.74; N, 2.30. FAB-MS m/z: 622 $(M+H)^+$.

Protected Glcα1,4αHMJ (22) A catalytic amount of TFMSA was added to a solution of **11** (127 mg, 0.2 mmol) and **20** (136 mg, 0.2 mmol) in CH_2Cl_2 at 0 °C under argon. The reaction mixture was stirred at room temperature for 24 h, and adjusted to pH 7.0 with IRA-94S. The resin was filtered off, and the filtrate was concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel using AcOEt–*n*-hexane (1 : 5) to give **22** (23 mg, 10%) as a colorless oil. $[\alpha]_D$ +6.1° (c=0.34, $CHCl_3$). IR (neat): 1698 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.12 (6H, s, SiMe$_2$), 0.77 (9H, s, Si^{t}Bu), 2.75—5.18 (30H, m), 5.98 (1H, d, $J_{1,2}$=2.9 Hz, 2H-1), 7.25—7.37 (35H, m, Ph). *Anal.* Calcd for $C_{69}H_{81}NO_{12}Si$: C, 72.41; H, 7.13; N, 1.22. Found: C, 72.32, H, 7.35 N, 1.27.

Glcα1,4αHMJ (3) A solution of 1 N tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF, 5 ml) was added to a stirred solution of **22** (100 mg, 0.09 mmol) at room temperature over 1 h. The mixture was evaporated *in vacuo*, and the residue was dissolved in MeOH (5 ml). A catalytic amount of palladium black was added to the solution, and the mixture was stirred at room temperature for 12 h. Then, the resin was filtered off, and the filtrate was concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography using CH_2Cl_2 : MeOH : H_2O = (60 : 60 : 10) to afford **3** (15 mg, 47%) as a white powder. $[\alpha]_D$ +20.4° (c=0.21, MeOH). IR (KBr): 3402 (br OH, NH) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.55—2.91 (2H, m, 1H-2, 1H-6), 3.28—3.65 (3H, m, 1H-4, 2H-2, 2H-4), 3.71-3.94 (8H, m, 1H-1, 1H-1′, 1H-7, 1H-7′, 2H-3, 2H-5, 2H-6, 2H-6′), 3.89 (1H, d, J=9.7 Hz, 1H-5), 4.35 (1H, s, 1H-3), 5.18 (1H, d, $J_{1,2}$=2.0 Hz, 2H-1). FAB-MS m/z: 356 $(M+H)^+$.

Protected Manα1,4αHMJ (23) A catalytic amount of TFMSA was added to a solution of **11** (124 mg, 0.2 mmol) and **21** (136 mg, 0.2 mmol) in CH_2Cl_2 at 0 °C under argon. The reaction mixture was stirred at room temperature for 24 h, and adjusted to pH 7.0 with IRA-94S. The resin was filtered off, and the filtrate was concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel using AcOEt–*n*-hexane (1 : 5) to give **23** (16 mg, 7%) as a colorless oil. $[\alpha]_D$ +10.7° (c=0.24, $CHCl_3$). IR (neat): 1675 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.01 (6H, s, SiMe$_2$), 0.89 (9H, s, Si^{t}Bu), 3.42—4.98 (29H, m), 5.11—5.16 (2H, m, COOCH$_2$Ph), 7.12—7.36 (35H, m, Ph). *Anal.* Calcd for $C_{69}H_{81}NO_{12}Si$: C, 72.41; H, 7.13; N, 1.22. Found: C, 72.38, H, 7.43; N, 1.31.

Manα1,4αHMJ (4) A solution of 1 N TBAF in THF (5 ml) was added to a stirred solution of **23** (100 mg, 0.09 mmol) at room temperature over 1 h. The mixture was evaporated *in vacuo*, and the residue was dissolved in MeOH (5 ml). A catalytic amount of palladium black was added to the solution, and the mixture was stirred at room temperature for 12 h. Then, the resin was filtered off, and the filtrate was concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography using CH_2Cl_2–MeOH–H_2O (60 : 60 : 10) to afford **4** (13 mg, 40%) as a white powder. $[\alpha]_D$ +11.4° (c=0.22, MeOH). IR (KBr): 3400 (br OH, NH) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.55—2.78 (2H, m, 1H-2, 1H-6), 3.31—3.67 (4H, m, 1H-4, 2H-4, 2H-5), 3.70—3.98 (6H, m, 1H-1, 1H-1′, 1H-5, 1H-7, 1H-7′, 2H-3, 2H-6, 2H-6′), 4.11 (1H, s, 2H-2), 4.20—4.24 (1H, m, 1H-3), 5.18 (1H, s, 2H-1). FAB-MS m/z: 356 $(M+H)^+$.

2,5-Anhydro-1-deoxy-3,4-*O*-isopropylidene-5-azido-6-*O*-*tert*-butyldimethylsilyl-D-manno-hept-enitol (13) A solution of dicyclopentadienyldimethyltitanium (1.75 g, 4.2 mmol) in dry toluene (20 ml) and compound **12** (1.50 g, 4 mmol) was stirred in the dark for 24 h at 65 °C under argon. After completion of the reaction, as checked by TLC, the brownish reaction mixture was concentrated and applied to a column of silica gel. Elution with AcOEt : *n*-hexane = 1 : 3 afforded the methylenated compound **13** (850 mg, 60%) as a yellow oil. $[\alpha]_D$ +58.8° (c=1.00, $CHCl_3$). IR (neat): 2096 (N_3), 1460 (C=CH$_2$) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.09 (6H, s, SiMe$_2$), 0.91 (9H, s, Si^{t}Bu), 1.39, 1.48 (each 3H, s, CMe$_2$), 3.70—3.77 (1H, m, H-5), 3.83 (1H, dd, $J_{6,6'}$=10.4 Hz, $J_{5,6}$=5.94 Hz, H-6), 3.94 (1H, dd, $J_{3,4}$=3.5 Hz, $J_{4,5}$=9.7 Hz, H-4), 4.06 (1H, dd, $J_{6,6'}$=10.7 Hz, $J_{5,6'}$=2.4 Hz, H-6′), 4.26 (1H, dd, H_{cis}), 4.47 (1H, d, H_{trans}), 4.76 (1H, dd, $J_{2,3}$=5.7 Hz, $J_{3,4}$=3.5 Hz, H-3), 5.04 (1H, d, $J_{2,3}$=5.9 Hz, H-2). ^{13}C-NMR ($CDCl_3$) δ: −5.6 (2×q, SiMe$_2$), 18.3 (s, SiCMe$_3$), 25.6 (3×q, SiCMe$_3$), 25.9, 26.8 (2×q, CMe$_2$), 61.1 (d, C-5), 63.9 (t, C-6), 78.7 (d, C-3), 79.7 (2×d, C-2, C-4), 86.8 (t, C=CH$_2$), 113.4 (s, CMe$_2$), 161.4 (s, C-1). *Anal.* Calcd for $C_{16}H_{29}N_3O_4Si$: C, 54.06; H, 8.22; N, 11.83. Found: C, 54.32; H, 8.14; N, 12.01. FAB-MS m/z: 356 $(M+H)^+$.

6-*O*-*tert*-Butyldimethylsilyl-2,5-anhydro-1-deoxy-3,4-*O*-isopropylidene-D-psicofuranose (14) A solution of compound **13** (256 mg, 0.72 mmol) in acetone (6 ml) was cooled in ice, then 0.4 ml of a 2.5% solution of osmium tetraoxide in *tert*-butyl alcohol was added, followed after 5 min by *N*-methylmorpholine-*N*-oxide (90 mg, 0.72 mmol). The reaction mixture was stirred overnight at room temperature. Water (0.4 ml) and sodium sulfite (32 mg) were added and stirring continued for 15 min. Extraction with dichloromethane (3×100 ml) followed by usual drying over anhydrous magnesium sulfate afforded a crude oil. Purification by column chromatography gave pure **14** (171 mg, 60%) as an anomeric mixture (α : β = 3 : 7). $[\alpha]_D$ −18.4° (c=1.00, $CHCl_3$). IR (neat): 3406 (OH), 2096 (N_3) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.10 (6H, s, SiMe$_2$), 0.92 (9H, s, Si^{t}Bu), 1.34, 1.47 (each 3H, s, CMe$_2$), 2.77 (1H, s, CH$_2$OH), 3.67—3.79 (4H, m, H-5, H-6, CH$_2$OH), 3.98—4.01 (2H, m, H-4, H-6′), 4.56 (1H, d, $J_{2,3}$=5.9 Hz, H-2), 4.86 (1H, dd, $J_{3,4}$=3.8 Hz, H-3). ^{13}C-NMR ($CDCl_3$) δ: −5.6 (2×q, SiMe$_2$), 18.2 (s, SiCMe$_3$), 25.7 (3×q, SiCMe$_3$), 24.5, 25.9 (2×q, 2×CMe), 61.1 (d, C-5), 64.2 (t, C-6), 64.3 (t, CH$_2$OH), 77.1 (d, C-4), 80.4 (d, C-3), 84.5 (d, C-2), 104.8 (s, C-1), 112.9 (s, CMe$_2$). *Anal.* Calcd for $C_{16}H_{31}N_3O_6Si$: C, 49.34; H, 8.02; N, 10.79. Found: C, 48.88; H, 7.92; N, 10.56.

7-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-isopropylidene-2,6-dideoxy-2,6-imino-D-*glycero*-D-*talo*-heptitol (15) A solution of **14** (170 mg, 0.43 mg) in MeOH (20 ml) was hydrogenated under atmospheric pressure of H_2 in the presence of platinum dioxide (20 mg) at room temperature for 12 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed on a column of silica gel (CH_2Cl_2–MeOH, 10 : 1) to give **15** (quant.) as a colorless oil. $[\alpha]_D$ −6.5° (c=0.80, $CHCl_3$). IR (neat): 3416 (br OH, NH) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.08 (6H, s, SiMe$_2$), 0.92 (9H, s, Si^{t}Bu), 1.37, 1.52 (each 3H, s, CMe$_2$), 2.51 (1H, ddd, $J_{2,3}$=9.7 Hz, $J_{1,2}$=4.9 Hz, H-2), 3.08 (1H, ddd, $J_{5,6}$=8.1 Hz, $J_{6,7}$=2.4 Hz, H-6), 3.62 (1H, dd, $J_{2,3}$=10.3 Hz, H-4), 3.74—3.78 (2H, m, H-7 and H-7′), 3.82 (1H, dd, C-1), 3.92 (1H, dd, $J_{1,1'}$=11.6 Hz, $J_{1',2}$=4.3 Hz, H-1′), 4.00 (1H, dd,

$J_{4,5}=5.4$ Hz, H-5), 4.17 (1H, dd, $J_{4,5}=5.1$ Hz, $J_{3,4}=2.4$ Hz, H-4). ^{13}C-NMR ($CDCl_3$) δ: −5.6 (2×q, $SiMe_2$), 18.2 (s, $SiCMe_3$), 26.0 (3×q, $SiCMe_3$), 26.7, 28.3 (2×s, 2×CMe), 56.2 (d, C-6), 57.9 (d, C-2), 63.9 (d, C-1), 64.7 (t, C-7), 73.0 (d, C-3), 75.6 (d, C-4), 81.4 (d, C-5), 109.9 (s, CMe_2). *Anal.* Calcd for $C_{16}H_{33}NO_5Si$: C, 55.30; H, 9.57; N, 4.03. Found: C, 55.46; H, 9.61, N, 3.87. FAB-MS *m/z*: 348 $(M+H)^+$.

2,6-Dideoxy-2,6-imino-D-*glycero*-D-*talo*-heptitol (β-Homomannojirimycin) (2) A solution of compound **15** (100 mg, 0.29 mmol) in trifluoroacetic acid–water (1 : 1, 10 ml) was stirred at room temperature for 1 h, then evaporated with toluene three times, and the residue was chromatographed on silica gel with CH_2Cl_2: MeOH (20 : 1) to give **2** (31 mg, 55%) as a colorless oil. $[\alpha]_D$ −4.3° (*c*=1.30, MeOH). IR (neat): 3442 (br OH, NH) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.45 (1H, ddd, $J_{6,7}=2.6$ Hz, $J_{6,7'}=5.6$ Hz, $J_{6,5}=9.5$ Hz, H-6), 2.72 (1H, dd, $J_{2,1}=6.2$ Hz, $J_{2,1'}=6.5$ Hz, H-2), 3.29 (1H, dd, $J_{4,3}=2.6$ Hz, $J_{4,5}=9.5$ Hz, H-4), 3.48 (1H, t, $J_{5,4}=J_{5,6}=9.5$ Hz, H-5), 3.60—3.64 (3H, m, H-1, H-1′, H-7′), 3.77 (1H, dd, $J_{7,6}=2.6$ Hz, $J_{7,7'}=11.0$ Hz, H-7), 3.80 (1H, d, $J_{3,2}=2.6$ Hz, H-3). ^{13}C-NMR (CD_3OD) δ: 60.5 (d, C-2), 62.6 (d, C-6), 62.9 (t, C-7), 63.5 (t, C-1), 70.5 (d, C-3), 70.8 (d, C-4), 77.4 (d, C-5). *Anal.* Calcd for $C_7H_{15}NO_5$: C, 43.52; H, 7.83; N, 7.25. Found: C, 43.82; H, 7.77; N, 7.33. FAB-MS *m/z*: 194 $(M+H)^+$.

***N*-Benzyloxycarbonyl-7-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-2,6-dideoxy-2,6-imino-D-*glycero*-D-*talo*-heptitol (16)** As described for **8**, benzyloxycarbonylchloride (0.35 ml, 2.4 mmol) was added dropwise to a stirred solution of compound **15** (347 mg, 2.0 mmol) in ether (5 ml) and saturated aqueous $NaHCO_3$ (25 ml) at room temperature for 12 h. The reaction mixture was extracted with ether (20 ml) three times. Then, the organic layer was dried over anhydrous $MgSO_4$, and concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography using AcOEt–*n*-hexane (1 : 3) to afford **16** (597 mg, 62%) as a colorless oil. $[\alpha]_D$ −23.0° (*c*=1.01, MeOH). IR (neat): 1692 (C=O) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.04 (6H, s, $SiMe_2$), 0.93 (9H, s, Si^{t}Bu), 1.39, 1.49 (each 3H, s, CMe_2), 2.50—2.52 (1H, m, H-2), 3.09—3.12 (1H, m, H-6), 3.64—3.66 (1H, m, H-3), 3.75—3.82 (2H, m, H-7, H-7′), 3.81—3.83 (1H, m, H-1), 3.94—3.96 (1H, m, H-1′), 4.01—4.21 (2H, m, H-4, H-5), 5.04—5.21 (2H, m, $COOCH_2Ph$), 7.27—7.37 (5H, m, Ph). ^{13}C-NMR (CD_3OD) δ: −4.0 (2×q, $SiMe_2$), 20.6 (s, $SiCMe_3$), 25.4 (3×q, $SiCMe_3$), 26.7, 28.3 (2×s, 2×CMe), 57.9, 58.1 (2×d, C-6), 60.3, 60.7 (2×d, C-2), 63.9, 64.1 (2×t, C-1), 64.8, 65.1 (2×t, C-7), 73.1, 73.3 (2×d, C-3), 75.8, 76.2 (2×d, C-4), 81.5, 81.9 (d, C-5), 109.2, 111.4 (s, CMe_2), 127.0, 127.5, 127.9, 128.3, 128.5 (5×d, COOCHPh), 133.0, 133.4 (2×s, CPh), 148.2, 152.1 (2×s, C=O). *Anal.* Calcd for $C_{24}H_{39}NO_7Si$: C, 59.85; H, 8.16; N, 2.91. Found: C, 59.62; H, 8.11; N, 2.88.

***N*-Benzyloxycarbonyl-1,5-di-*O*-benzyl-7-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-2,6-dideoxy-2,6-imino-D-*glycero*-D-*talo*-heptitol (17)** As described for **9**, a mixture of compound **16** (480 mg, 1.0 mmol) and benzyl trichloroacetimidate (760mg, 3.0 mmol) in CH_2Cl_2–cyclohexane (1 : 1) (10 ml) was stirred at room temperature. The reaction mixture was stirred with TFMSA (15 mg, 0.1 mmol) at −10 °C under argon for 2 h and then at 0 °C for 24 h. The solution was concentrated to dryness, and the residue was chromatographed on silica gel with AcOEt–*n*-hexane (1 : 5) to give **17** (264 mg, 52%) as a white powder. $[\alpha]_D$ +2.3° (*c*=1.00, $CHCl_3$). IR(KBr): 1698 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.06 (6H, s, $SiMe_2$), 0.87 (9H, s, Si^{t}Bu), 1.32, 1.50 (each 3H, s, CMe_2), 3.63—3.69 (1H, m, H-6), 3.80—4.78 (8H, m, H-1, H-1′, H-2, H-3, H-4, H-5, H-6, H-7, H-7′), 4.50—4.66 (4H, m, 2×CH_2Ph), 5.06—5.11 (2H, m, $COOCH_2Ph$), 7.07—7.35 (15H, m, 3×Ph). ^{13}C-NMR ($CDCl_3$) δ: −5.6 (2×q, $SiMe_2$), 18.3 (s, $SiCMe_2$), 25.7, 25.8, 25.9 (3×q, $SiCMe_3$), 24.1, 30.2 (2×q, CMe2), 56.7 (d, C-6), 67.2, 67.9 (2×t, $COOCH_2Ph$), 72.6, 72.8 (2×t, CH_2Ph), 109.1 (s, CMe_2), 126.7, 126.8, 126.9, 127.0, 127.3, 127.4, 127.8, 128.1, 128.2, 128.7, 129.2, 129.3, 130.5 (15×d, CHPh), 136.1, 136.3, 137.8 (3×s, CPh), 162.1 (s, C=O). *Anal.* Calcd for $C_{38}H_{51}NO_7Si$: C, 68.95; H, 7.77; N, 2.12. Found: C, 68.77; H, 7.66; N, 2.01.

***N*-Benzyloxycarbonyl-1,5-di-*O*-benzyl-2,6-dideoxy-2,6-imino-D-*glycero*-D-*talo*-heptitol (18)** As described for **10**, compound **17** (330 mg, 0.5 mmol) was treated with trifluoroacetic acid–water (1 : 1) at room temperature for 3 h. The reaction mixture was evaporated *in vacuo*, and the residue was chromatographed on silica gel with CH_2Cl_2–MeOH (10 : 1) to afford **18** (131 mg, 52%) as a colorless oil. $[\alpha]_D$ −1.8° (*c*=0.88, MeOH). IR (neat): 3442 (br OH), 1692 (C=O) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.77—2.82 (2H, m, H-7, H-7′), 4.42—4.63 (4H, m, 2×CH_2Ph), 7.25—7.32 (15H, m, Ph). ^{13}C-NMR (CD_3OD) δ: 57.5 (d, C-6), 67.8, 68.4 (2×t, $COOCH_2Ph$), 72.5, 72.8 (2×t, CH_2Ph), 109.1 (s, CMe_2), 127.7, 127.9, 128.0, 128.2, 128.5, 128.6, 128.9 (15×d, CHPh), 163.0 (s, C=O). *Anal.* Calcd for $C_{29}H_{33}NO_7$: C, 68.62; H, 6.55; N, 2.76. Found: C, 68.22; H, 6.31; N, 2.77.

***N*-Benzyloxycarbonyl-7-*O*-*tert*-butyldimethylsilyl-1,5-di-*O*-benzyl-2,6-dideoxy-2,6-imino-D-*glycero*-D-*talo*-heptitol (19)** As described for **11**, imidazole (51 mg, 0.75 mmol) and TBDMSCl (90 mg, 0.6 mmol) were added to a stirred solution of **18** (254 mg, 0.5 mmol) in DMF (5 ml) at −40 °C under argon. The mixture was stirred at the same temperature for 2 h, then diluted with AcOEt (50 ml), and successively washed with AcOEt and water. The organic layer was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography using AcOEt–hexane (1 : 3) to afford **19** (140 mg, 45%) as a colorless oil. $[\alpha]_D$ −3.2° (*c*=0.51, MeOH). IR (neat): 3402 (br OH), 1689 (C=O) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 0.03 (6H, s, $SiMe_2$), 0.89 (9H, s, Si^{t}Bu), 4.51—4.82 (4H, m, 2×CH_2Ph), 5.18 (2H, s, $COOCH_2Ph$), 7.25—7.39 (15H, m, Ph). ^{13}C-NMR (CD_3OD) δ: −5.6 (2×q, $SiMe_2$), 18.1 (s, $SiCMe_3$), 25.7, 25.9, 26.0 (3×q, $SiCMe_3$), 67.0 (t, $COOCH_2Ph$), 72.5, 72.7 (2×t, CH_2Ph), 127.6, 127.8, 127.9, 128.0, 128.2, 128.5, 129.0 (15×d, 3×Ph). *Anal.* Calcd for $C_{35}H_{47}NO_7Si$: C, 67.60; H, 7.62; N, 2.25. Found: C, 67.21; H, 7.33; N, 2.31. FAB-MS *m/z*: 622 $(M+H)^+$.

Protected Glcα1,4βHMJ (24) As described for **22**, a catalytic amount of TFMSA was added to a solution of **19** (127 mg, 0.2 mmol) and **20** (136 mg, 0.2 mmol) in CH_2Cl_2 at 0 °C under argon. The reaction mixture was stirred at room temperature for 24 h, and adjusted to pH 7.0 with IRA-94S. The resin was filtered off, and the filtrate was concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 5) to give **24** (34 mg, 15%) as a colorless oil. $[\alpha]_D$ +11.2° (*c*=1.00, $CHCl_3$). IR (neat): 1656 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.11 (6H, s, $SiMe_2$), 0.74 (9H, s, Si^{t}Bu), 2.96—5.16 (30H, m), 6.00 (1H, d, $J_{1,2}=3.8$ Hz, 2H-1), 7.26—7.35 (35H, m, Ph). *Anal.* Calcd for $C_{69}H_{81}NO_{12}Si$: C, 72.41; H, 7.13; N, 1.22. Found: C, 72.11, H, 7.23; N, 1.31.

Glcα1,4βHMJ (5) As described for **3**, a solution of 1 N TBAF in THF (5 ml) was added to a stirred solution of **24** (100 mg, 0.09 mmol) at room temperature over 1 h. The mixture was evaporated *in vacuo*, and the residue was dissolved in MeOH (5 ml). A catalytic amount of palladium black was added to the solution, and the mixture was stirred at room temperature for 12 h. Then the resin was filtered off, and the filtrate was concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography with CH_2Cl_2–MeOH–H_2O (60 : 60 : 10) to afford **5** (14 mg, 45%) as a white powder. $[\alpha]_D$ +27.5° (*c*=0.18, MeOH). IR (KBr): 3400 (br OH, NH) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.51—2.82 (2H, m, 1H-2, 1H-6), 3.32 (1H, d, $J_{4,5}=9.6$ Hz, 1H-4), 3.48 (1H, t, $J_{4,3}=J_{4,5}=8.8$ Hz, 2H-4), 3.63 (1H, dd, $J_{2,1}=3.3$ Hz $J_{2,3}=8.9$ Hz, 2H-2), 3.78—3.92 (8H, m, 1H-1, 1H-1′, 1H-7, 1H-7′, 2H-3, 2H-5, 2H-6, 2H-6′), 3.96 (1H, d, $J=10.8$ Hz, 1H-5), 4.32 (1H, s, 1H-3), 5.15 (1H, s, 2H-1). FAB-MS *m/z*: 356 $(M+H)^+$.

Protected Manα1,4βHMJ (25) As described for **23**, was added a catalytic amount of TFMSA to a solution of compound **19** (124 mg, 0.2 mmol) and compound **21** (136 mg, 0.2 mmol) in CH_2Cl_2 at 0 °C under argon. The reaction mixture was stirred at room temperature for 24 h, and adjusted to pH 7.0 with IRA-94S. The resin was filtered off, and the filtrate was concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with AcOEt–*n*-hexane (1 : 5) to give **25** (11 mg, 5%) as a colorless oil. $[\alpha]_D$ +10.7° (*c*=0.10, $CHCl_3$). IR (neat): 1672 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: −0.01 (6H, s, $SiMe_2$), 0.86 (9H, s, Si^{t}Bu), 3.44—5.18 (31H, m), 7.15—7.37 (35H, m, Ph). *Anal.* Calcd for $C_{69}H_{81}NO_{12}Si$: C, 72.41; H, 7.13; N, 1.22. Found: C, 72.32, H, 7.33; N, 1.11.

Manα1,4βHMJ (6) As described for **4**, a solution of 1 N TBAF in THF (5 ml) was added to a stirred solution of **25** (100 mg, 0.09 mmol) at room temperature over 1 h. The mixture was evaporated *in vacuo*, and the residue was dissolved in MeOH (5 ml). A catalytic amount of palladium black was added to the solution, and the mixture was stirred at room temperature for 12 h. Then the resin was filtered off, and the filtrate was concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography with CH_2Cl_2–MeOH–H_2O (60 : 60 : 10) to afford **6** (14 mg, 35%) as a white powder. $[\alpha]_D$ +15.8° (*c*=0.22, MeOH). IR (KBr): 3420 (br OH, NH) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 2.48—2.73 (2H, m, 1H-2, 1H-6), 3.31 (1H, d, $J_{4,5}=9.5$ Hz, 1H-4), 3.71—3.94 (6H, m, 1H-1, 1H-1′, 1H-5, 1H-7, 1H-7′, 2H-3), 4.10 (1H, br s, 2H-2), 4.23—4.25 (1H, m, 1H-3), 5.15 (1H, s, 2H-1). FAB-MS *m/z*: 356 $(M+H)^+$.

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