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CARBOHYDRATE RESEARCH

Note

Carbohydrate haptens: 4-nitrophenyl 2-acetamido-2-deoxy-β-D-glucopyranosyl-(1 → 6)-α-D-mannopyranosyl-(1 → 6)-β-D-mannopyranoside and a related trisaccharide *

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Several transformed cell lines show increased branching at the trimannosyl core of complex type Asn-linked oligosaccharides [2,3], and in particular increased β-D-Glc*p*NAc-(1 → 6)-α-D-Man*p*-(1 → 6)-β-D-Man*p*-linked antennae [4,5]. β-(1 → 6)-Branching has also been shown to correlate with the metastatic potential of certain tumor cells [4,6,7]. Consistent with these findings is the observation that Glc*p*NAc-transferase V, the enzyme that begins the (1 → 6)-linked antenna, was found to be elevated in transformed cells while other Glc*p*NAc-transferase activities remained unchanged [2]. In addition, it was shown that increased expression of β-(1 → 6)-branching has a strong correlation with the occurrence of breast carcinomas in a significant human population [5]. The trisaccharide carbohydrate unit mentioned above has also been reported [8] to occur as a part of the tetraantennary structure of human immunodeficiency virus (HIV) envelope glycoprotein gp-120.

In continuation of our studies on the synthesis of carbohydrate haptens [9,10], we herein report the synthesis of two trisaccharides, namely, β-D-Glc*p*NAc-(1 → 6)-α-D-Man*p*-(1 → 6)-β-D-Man*p*-$OC_6H_5NO_2$-4 (**9**) and β-D-Glc*p*NAc-(1 → 6)-α-

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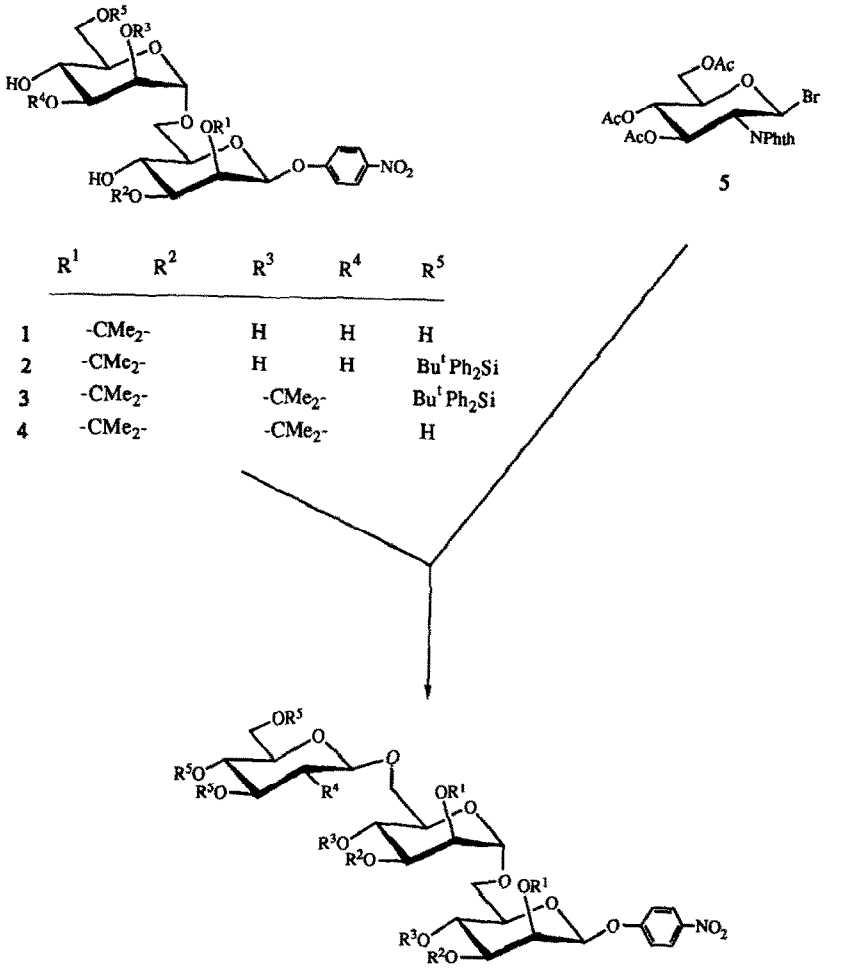


Scheme 1.

D-Man*p*-(1 → 6)-*β*-D-Glc*p*-$OC_6H_5NO_2$-4 (**14**). Such compounds can be employed as synthetic antigens after reduction of their nitro groups and subsequent coupling of their amino groups (as their diazonium salts) to a carrier protein [11]. Immunization of rabbits or mice with a glycoprotein antigen prepared from **9** should produce anti-**9** antibodies, whereas trisaccharide **14** is expected to be useful in inhibition studies of the antibodies.

Table 1
Selected ^{1}H and ^{13}C NMR data for protected disaccharides [a]

Nucleus [b]	Compound		
	2	3	4
H-1 ($J_{1,2}$)	5.54 (3)	5.55 (3.2)	5.59 (3)
H-1′ ($J_{1',2'}$)	4.59 (1.2)	4.78 (< 1)	4.78
$(CH_3)_2$	1.54, 1.37	1.58, 1.41	1.60, 1.42
		1.36, 1.09	1.37, 1.06
$(CH_3)_3$	0.96	1.0	
$C_6H_4-NO_2$ (^{3}J)	8.14 (9.0)	8.16 (9.0)	8.20 (9.0)
	7.08 (9.0)	7.08 (9.0)	7.13 (9.0)
C-1	95.13	95.22	95.02
C-1′	99.41	97.22	97.01
C-6	65.90	65.63	65.02
C-6′	64.79	64.36	62.52
$C(CH_3)_2$	25.57	27.75, 26.63	27.83, 26.63
		25.78, 25.51	25.66, 25.39
$C(CH_3)_2$	111.49	111.57, 109.57	111.35, 109.63
$C(CH_3)_3$	26.82	26.86	
$C(CH_3)_3$	19.19	19.23	
CNO_2	161.91	162.01	162.14
CO (phenolic)	142.39	142.44	142.34
Aromatic	135.60, 132.94	135.69, 135.63	125.67, 116.36
	132.86	133.07, 132.89	
	129.90, 127.83	129.90, 127.85	
	125.85, 116.26	127.81, 125.78	
		116.24	

[a] Spectra were recorded in $CDCl_3$ at 300 MHz (^{1}H) or 75.5 MHz (^{13}C).
[b] Locants: unprimed, β-D-Man*p*; single prime, α-D-Man*p*.

The synthesis of **9** (Scheme 1) began with a partially protected reducing end disaccharide, 4-nitrophenyl 2,3-*O*-isopropylidene-α-D-mannopyranosyl-(1 → 6)-β-D-mannopyranoside (**1**), available from previous work [12]. Compound **1** was treated with *tert*-butylchlorodiphenylsilane in *N*,*N*-dimethylformamide in the presence of imidazole to afford the 6′-*O*-silylated derivative **2** in 65% yield. This was converted in 91% yield into the 2′,3′-*O*-isopropylidine derivative **3** by treatment with 2,2-dimethoxypropane in acetone. Removal of the *tert*-butyldiphenylsilyl group of **3** was readily accomplished by treatment with tetrabutylammonium fluoride in oxolane to give **4** in almost quantitative yield. In the ^{1}H NMR spectrum of compounds **2**–**4**, the anomeric protons of β-D-mannosides showed an unusually large coupling constant of $J_{1,2} \sim 3$ Hz (Table 1). These anomalies are probably due to conformational changes forced by the 2,3-*O*-isopropylidene group and are consistent with the results recently reported by Kunz and co-workers [13,14] for somewhat related compounds.

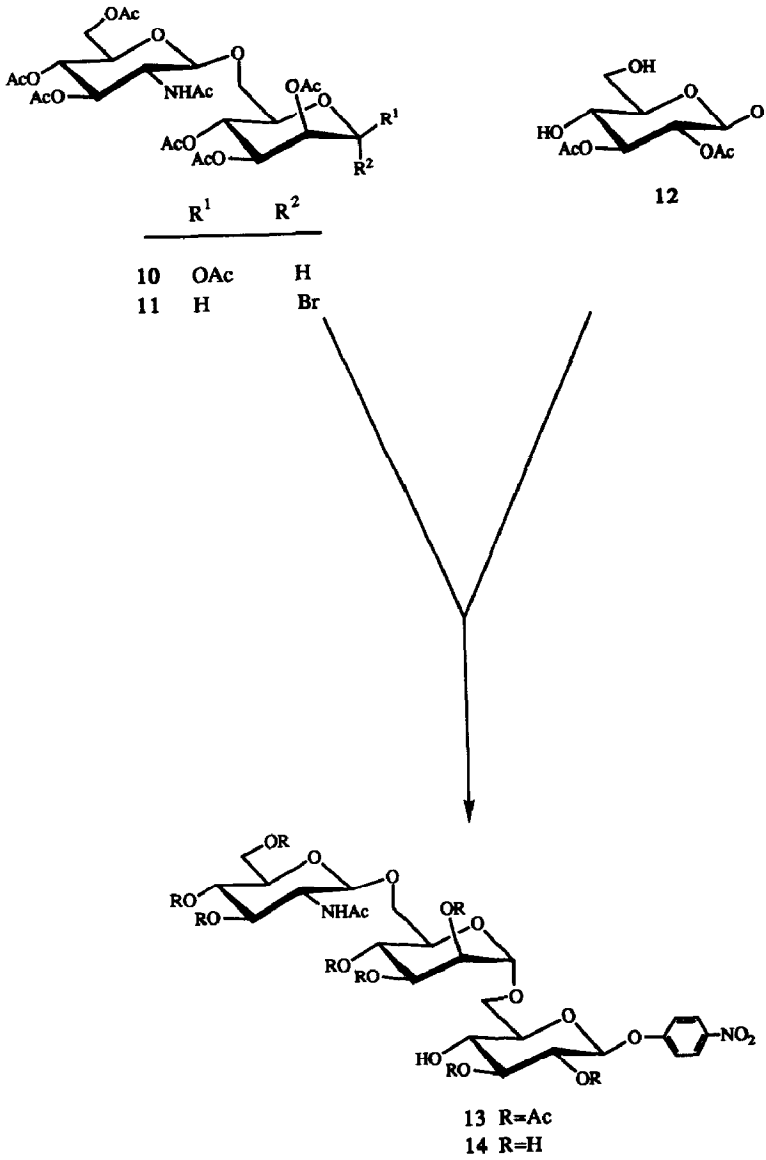
Condensation of **4** with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide [15] (**5**) in dichloromethane in the presence of silver trifluoromethanesulfonate, *sym*-collidine, and 4A molecular sieves, followed by the customary deacetylation–peracetylation sequence [16,17] of the resulting phthalim-

ido acetate (**6**), and column chromatographic purification, afforded in good yield, the fully protected trisaccharide **7**. *O*-Deacetylation of **7** in methanolic sodium methoxide, followed by cleavage of the acetal group of **8** with hot 60% aqueous acetic acid, furnished **9** in 56% yield. In the ^{1}H NMR spectrum of **9**, the anomeric proton signals were located at δ 5.53 (H-1), 4.48 (H-1″, $J_{1'',2''}$ 8.5 Hz), and 4.85 (H-1′, $J_{1',2'}$ 1.5 Hz). The characteristic coupling constants observed for the anomeric protons resolved the discrepancies noted for protected intermediates. In addition, in the ^{13}C NMR spectrum the resonance at δ 102.34 could reasonably be assigned to C-1′, whereas the signals at δ 99.64 and 104.25 were assigned to C-1 and C-1″, respectively. The downfield shift, for C-6 and C-6′, which resonated at δ 68.83 and 71.43, respectively, was evidence of glycosylation at these sites. Recently Hindsgaul's group [18] has reported the 8-methoxycarbonyloctyl glycoside of **9** as the intermediate in combined chemical and enzymatic synthesis of an acceptor for β-(1 → 3)-*N*-acetylglucosaminyltransferase (GlcNAcT-"i").

For the synthesis of trisaccharide **14**, glycosyl donor **11** was readily prepared (97%) from the known disaccharide [19] **10** by treatment with HBr in glacial acetic acid (Scheme 2). Glocosylation of diol [16] **12** with bromide **11**, promoted by silver trifluoromethanesulfonate (triflate) and *sym*-collidine, gave the partially protected trisaccharide **13** (56%) from which acetyl groups were removed by Zemplén transesterification to afford the trisaccharide **14** (68%). The ^{1}H and ^{13}C NMR spectra of both **13** and **14** contained signals supporting their structures (see Table 2).

1. Experimental

General methods.—Optical rotations were measured at 22 ± 2°C with a Perkin–Elmer 241 polarimeter. TLC was conducted on aluminum sheets, precoated with 0.2-mm layers of Silica Gel 60F-254 (E. Merck). The compounds were located by UV light and/or by charring with 5% H_2SO_4. Column chromatography was performed on silica gel (Baker Analyzed, 60–200 mesh). The following solvent systems (v/v) were used for chromatography: *A*, 3:2 $CHCl_3$–acetone; *B*, 4:1 $CHCl_3$–acetone; *C*, 9:1 $CHCl_3$–MeOH; *D*, 4:1 EtOAc–hexane; *E*, 13:6:1 $CHCl_3$–MeOH–H_2O; *F*, 5:4:1 $CHCl_3$–MeOH–H_2O; *G* 99:1 $CHCl_3$–MeOH; *H*, 66:1 $CHCl_3$–MeOH; and *I*, 19:1 $CHCl_3$–MeOH. ^{1}H NMR spectra were recorded either at 90 MHz (Varian EM-390) or 300 MHz (Bruker AM300) for solutions in $CDCl_3$ (internal Me_4Si, δ 0) or D_2O (internal acetone, δ 2.225). ^{13}C NMR spectra were recorded either at 75.5 MHz (Bruker AM300) or at 100.6 MHz (Bruker AM400) for solutions in $CDCl_3$ (internal Me_4Si, δ 0) or D_2O (external Me_4Si, δ 0). Only partial NMR data are reported, as the other data were in accord with the overall proposed structures. The assignments of ^{13}C chemical shifts are tentative. FAB mass spectra were obtained using an AEI MS-9 instrument with Xe as the bombarding gas and 5:1 1,4-dithiothreitol:1,4-dithioerythritol as matrix. Unless otherwise indicated, all reactions were carried out at ambient temperature. Solutions were dried with Na_2SO_4 and concentrated at 40–50°C/2 kPa. Elemental



Scheme 2.

analyses were performed by Robertson Laboratory, 29 Samson Ave., Madison, New Jersey 08940 (USA).

4-Nitrophenyl 6-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-α-D-mannopyranosyl-(1 → 6)-β-D-mannopyranoside (**2**).—To a stirred solution of compound [12] **1** (2.1 g, 4.17 mmol), and imidazole (0.92 g, 13.5 mmol), in DMF (42 mL) was added *tert*-butylchlorodiphenylsilane (1.9 g, 6.9 mmol), and stirring was continued for 4 h

Table 2
Selected ^{1}H and ^{13}C NMR data for protected and unprotected trisaccharides [a]

Nucleus [b]	Compound		
	9	**18**	**19**
H-1 ($J_{1,2}$)	5.53	n.d. [c]	5.31(7)
H-1′ ($J_{1',2'}$)	4.85(1.5)	4.85(< 1)	4.83
H-1″ ($J_{1'',2''}$)	4.48(8.5)	n.d.	4.49(8.5)
NAc	2.01	1.82	2.03
OAc		1.90, 1.96, 2.02, 2.03 2.04, 2.08, 2.14, 2.17	
C_6H_4-NO_2 (^{3}J)	8.27(9.0) 7.20(9.0)	8.27(9.0) 7.12(9.0)	8.27(9.0) 7.24(9.0)
C-1	99.64	98.14	101.97
C-1′	102.34	96.63	102.40
C-1″	104.25	101.95	104.24
C-2″	58.30	53.82	58.33
C-6	68.83	66.10	68.47
C-6′	71.43	68.41	71.45
C-6″	63.57	61.93	63.57
$COCH_3$	177.32	171.28, 171.11, 170.72 170.52, 170.31, 169.92 169.50, 169.27	177.30
$COCH_3$	25.03	23.14, 20.90, 20.78 20.70, 20.61	25.05
CNO_2	164.22	161.42	164.37
CO (phenolic)	145.22	143.17	145.38
Aromatic	128.93, 119.06	126.10, 116.65	128.96, 119.23

[a] Spectra were recorded at 300 MHz (^{1}H in $CDCl_3$ for **18** and D_2O for **9** and **19**), 75.5 MHz (^{13}C in $CDCl_3$ for **16**) and 100.6 MHz (^{13}C in D_2O for **9** and **19**).
[b] Locants: unprimed, β-D-Man*p* or β-D-Glc*p*; single prime, α-D-Man*p*, double prime, β-D-Glc*p*NAc.
[c] Not determined due to spectral overlap.

at room temperature. The mixture was then poured into ice–water and extracted with $CHCl_3$. The $CHCl_3$ solution was successively washed with water, satd $NaHCO_3$, and water, dried, and concentrated, and the residue was applied to a column of silica gel and eluted with a solvent gradient consisting of 0–25% acetone in $CHCl_3$. On concentration, fractions corresponding to the product afforded **2** (2.02 g, 65%) as an amorphous solid; $[\alpha]_D - 71°$ (*c* 1.0, $CHCl_3$); R_f 0.31 (solvent *A*). NMR data are presented in Table 1. Anal. Calcd for $C_{37}H_{47}NO_{13}Si$: C, 59.90; H, 6.39; N, 1.89. Found: C, 59.52; H, 6.27; N, 1.81.

*4-Nitrophenyl 6-*O*-tert-butyldiphenylsilyl-2,3-*O*-isopropylidene-α-*D*-mannopyranosyl-(1 → 6)-2,3-*O*-isopropylidene-β-*D*-mannopyranoside* (**3**).—To a solution of **2** (2 g, 2.7 mmol) in dry acetone (50 mL) were added 2,2-dimethoxypropane (50 mL, 0.41 mol) and 4-toluenesulfonic acid monohydrate (0.2 g, 1.1 mmol). The mixture was stirred for 6 h at room temperature, made neutral by the dropwise addition of Et_3N, and then concentrated. The residue was purified on a column of silica gel with $CHCl_3$ as the eluent to give **3** (1.92 g, 91%) as an amorphous solid $[\alpha]_D - 83°$ (*c* 1.1, $CHCl_3$); R_f 0.52 (solvent *B*). NMR data are presented in Table 1. Anal.

Calcd for $C_{40}H_{51}NO_{13}Si$: C, 61.44; H, 6.57; N, 1.79. Found: C, 61.36; H, 6.47; N, 1.52.

4-Nitrophenyl 2,3-O-isopropylidene-α-D-mannopyranosyl-(1 → 6)-2,3-O-isopropylidene-β-D-mannopyranoside (**4**).—A solution of **3** (1.9 g, 2.43 mmol) in dry oxolane (45 mL) was treated with a M solution of tetrabutylammonium fluoride in oxolane (5.5 mL, 5.5 mmol), and the stirring was continued for 7 h at room temperature. The mixture was concentrated to dryness, and the residue was purified on a column of silica gel with a solvent gradient consisting of 0–5% MeOH in $CHCl_3$ to afford **4** (1.31 g, 99%) as an amorphous solid; $[\alpha]_D$ − 101° (*c* 0.8, $CHCl_3$); R_f 0.44 (solvent *C*). NMR data are presented in Table 1. Anal. Calcd for $C_{24}H_{33}NO_{13}$: C, 53.04; H, 6.12; N, 2.58 Found: C, 53.33; H, 6.11; N, 2.32.

4-Nitrophenyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl-(1 → 6)-4-O-acetyl-2,3-O-isopropylidene-α-D-mannopyranosyl-(1 → 6)-4-O-acetyl-2,3-O-isopropylidene-β-D-mannopyranoside (**7**).—A mixture of compound **4** (0.28 g, 0.52 mmol), silver trifluoromethanesulfonate (0.2 g, 0.78 mmol) *sym*-collidine (0.08 g, 0.69 mmol), and 4A molecular sieves (0.4 g) in CH_2Cl_2 (10 mL), protected from light and moisture, was stirred for 30 min at room temperature in an atmosphere of dry N_2. A solution of glycosyl bromide [15] **5** (0.35 g, 0.7 mmol) in CH_2Cl_2 (10 mL) was added dropwise, with stirring, during 20 min, and the stirring was continued for an additional 3 h. Additional portions of silver trifluoromethanesulfonate (0.1 g, 0.39 mmol) and *sym*-collidine (0.08 g, 0.66 mmol) were added, followed by the dropwise addition of a solution of bromide **5** (0.18 g, 0.36 mmol) in CH_2Cl_2 (8 mL), and the stirring was continued for an additional 20 h. TLC (solvent *C*) then revealed the presence of a major product, migrating faster than **4**, some slower and some faster migrating impurities (presumably, due to decomposition of **5**), were also revealed by TLC. The mixture was diluted with an equal volume of CH_2Cl_2, and the solids were filtered off (a bed of Celite), and washed with CH_2Cl_2. The filtrate and washings were combined, successively washed with ice-cold water, cold 3% aq HCl, cold satd $NaHCO_3$, and water, dried, and concentrated to a small volume. The concentrate was applied to a column of silica gel and eluted with a solvent gradient consisting of 50–66% EtOAc in hexane. On concentration, fractions corresponding to the major product afforded **6** (0.3 g, 61%) as a foamy solid that was contaminated (TLC solvent *D*) with some slow migrating impurities. This material was used without purification in the next step.

A solution of crude **6** (0.29 g, 0.3 mmol) in a mixture of EtOH (10 mL) and hydrazine hydrate (2 mL) was boiled for 3 h under N_2. The mixture was then concentrated to dryness to give a residue that was dissolved in pyridine (10 mL) and Ac_2O (5 mL) and heated for 30 min at 90°C. The Ac_2O and pyridine were evaporated under diminished pressure, and the residue was dissolved in $CHCl_3$, successively washed with water, aq $NaHCO_3$, and water, dried, and concentrated. The residue was applied to a column of silica gel and eluted with a solvent gradient consisting of 40–70% EtOAc in hexane. On concentration, the fractions corresponding to the product gave a solid which was dissolved in CH_2Cl_2.

Addition of ether–hexane caused the precipitation of **7** (0.2 g, 69%); $[\alpha]_D$ − 51° (*c* 0.5, $CHCl_3$); R_f 0.13 (solvent *D*); ^1H NMR (90 MHz, $CDCl_3$): δ 8.17 and 7.12 (d, 2 H each, $^3J \sim 9$ Hz, arom), 6.04 (d, 1 H, $J_{2,NH} \sim 8$ Hz, NH), 2.14, 2.07, 2.05, 2.02, and 2.0 (s, 3 H each, 5 OAc), 1.84 (s, 3 H, NAc), and 1.58–1.14 (cluster of s, 12 H, 2 CMe_2). Anal. Calcd for $C_{42}H_{56}N_2O_{23}$: C, 52.72; H, 5.90; N, 2.93. Found: C, 52.39; H, 5.75; N, 2.61.

*4-Nitrophenyl 2-acetamido-2-deoxy-β-*D*-glucopyranosyl-(1 → 6)-2,3-*O*-isopropylidene-α-*D*-mannopyranosyl-(1 → 6)-2,3-*O*-isopropylidene-β-*D*-mannopyranoside* (**8**).—Compound **7** (0.18 g, 0.19 mmol) in 20 mM methanolic NaOMe (33 mL) was stirred overnight at room temperature. The base was neutralized with Amberlite IR-120 (H^+) cation-exchange resin. The resin was filtered off (Celite bed) and thoroughly washed with MeOH, and the filtrate and washings were combined and concentrated to give **8** (0.11 g, 78%) as an amorphous solid; $[\alpha]_D$ − 67° (*c* 0.3, MeOH); R_f 0.53 (solvent *E*); ^1H NMR (90 MHz, CD_3OD): δ 8.20 and 7.18 (d, 2 H each, $^3J \sim 9$Hz, arom), 5.64 (d, 1 H, $J_{1,2} \sim 3$ Hz, H-1), 1.95 (s, 3 H, NAc), and 1.55, 1.39, 1.36, and 1.08 (s, 3 H each, 2 CMe_2). Anal. Calcd for $C_{32}H_{46}N_2O_{18}$: C, 51.47; H, 6.21; N, 3.75. Found: C, 51.12; H, 6.52; N, 3.49.

*4-Nitrophenyl 2-acetamido-2-deoxy-β-*D*-glucopyranosyl-(1 → 6)-O-α-*D*-mannopyranosyl-(1 → 6)-β-*D*-mannopyranoside* (**9**).—Compound **8** (0.09 g, 0.12 mmol) in 60% aq AcOH (20 mL) was stirred for 1.5 h at 60°C. The AcOH was then evaporated, and several portions of toluene were added to and evaporated from the residue, which was then applied to a column of silica gel. Elution with a solvent gradient consisting of 10–30% MeOH in $CHCl_3$, followed by solvent *E* and concentration of the fractions corresponding to the major product, gave **9** (0.045 g, 56%) as an amorphous solid; $[\alpha]_D$ − 28° (*c* 0.4, H_2O); R_f 0.46 (solvent *F*). FABMS: *m/z* 667 [0.3%, $(M + 1)^+$] and 689 [0.2%, $(M + Na)^+$]. NMR data are presented in Table 2. Anal. Calcd for $C_{26}H_{38}N_2O_{18} \cdot 1.5H_2O$: C 45.02; H, 5.96; N, 4.04 Found: C, 45.10; H, 5.62; N, 3.65.

*4-Nitrophenyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl-(1 → 6)-2,3,4-tri-*O*-acetyl-α-*D*-mannopyranosyl-(1 → 6)-2,3-di-*O*-acetyl-β-*D*-gluco-pyranoside* (**13**).—To a cold (0°C, bath), stirred solution of disaccharide [19] **10** (3 g, 4.43 mmol) in CH_2Cl_2 (33 mL) was added a 31% solution of HBr in glacial AcOH (7.5 mL), and stirring was continued for 12 h at 0°C. The mixture was then poured into ice–water and extracted with CH_2Cl_2, successively washed with cold water, cold satd $NaHCO_3$, and cold water, dried and concentrated to give 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl-(1 → 6)-2,3,4-tri-*O*-acetyl-α-D-mannopyranosyl bromide (**11**) as an amorphous solid (3 g, 97%); $[\alpha]_D$ +56.9° (*c* 1.3, $CHCl_3$); R_f 0.3 (solvent *B*); ^1H NMR (90 MHz, $CDCl_3$): δ 6.30 (s, 1 H, H-1), and 2.17–1.99 (cluster of s, 21 H, 6 OAc and NAc).

A solution of the glycosyl bromide **11** (1 g, 1.43 mmol) in CH_2Cl_2 (30 mL) was added at 0°C to a stirred mixture of 4-nitrophenyl 2,3-di-*O*-acetyl-β-D-gluco-pyranoside [16] (**12**, 0.37 g, 0.95 mmol), *sym*-collidine (0.17 mL, 1.28 mmol), silver trifluoromethanesulfonate (0.37 g, 1.43 mmol), and pulverized 4A molecular sieves (1.0 g) in CH_2Cl_2 (20 mL). After 5 h the mixture was allowed to warm to room

temperature and stirred for an additional 16 h. The mixture was diluted with CH_2Cl_2 (200 mL) and filtered (Celite), the solids were washed with CH_2Cl_2 (100 mL), and the combined filtrate was concentrated. Chromatography ($CHCl_3 \rightarrow$ solvent $G \rightarrow H$) furnished the amorphous trisaccharide **13** (0.54 g, 56%); $[\alpha]_D$ – 16.9° (*c* 1.0, $CHCl_3$); R_f 0.4 (solvent *I*). NMR data are presented in Table 2. Anal. Calcd for $C_{42}H_{54}N_2O_{26}$: C, 50.30; H, 5.43; N, 2.79. Found: C, 50.49; H, 5.57; N, 2.67.

*4-Nitrophenyl 2-acetamido-2-deoxy-β-*D*-glucopyranosyl-(1 → 2)-*O*-α-*D*-mannopyranosyl-(1 → 6)-β-*D*-glucopyranoside* (**14**).—Deacetylation of **13** (0.20 g, 0.2 mmol), as described for **7** (to give **8**) gave after chromatography (solvent *E*) the amorphous trisaccharide **19** (0.09 g, 67.7%); $[\alpha]_D$ – 57.5° (*c* 0.7, H_2O); R_f 0.4 (solvent *F*). FABMS: *m/z* 667 [8.3%, $(M + 1)^+$] and 689 [1.4%, $(M + Na)^+$]. NMR data are presented in Table 2. Anal. Calcd for $C_{26}H_{38}N_2O_{18}$: C, 46.85; H, 5.75; N, 4.20. Found: C, 46.60; H, 5.91; N, 3.95.

Acknowledgments

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