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Chemical Modification of Maltose. V.[1] A New Synthesis of 2-Acetamido-2-deoxy-4-O-α-D-glucopyranosyl-α-D-glucopyranose (N-Acetylmaltosamine)[2]

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Crystalline 2′,3,3′,4′,6′-penta-O-acetyl-1,6-anhydro-β-N-acetylmaltosamine (**10**) was prepared in 7 steps from 1,6: 2,3-di-anhydro-4-O-(4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranosyl)-β-D-mannopyranose (**3**) as follows: benzylation, azidolysis of the oxirane ring, detosylation, debenzylidenation, acetylation, reduction of the azido to an amino group with concomitant debenzylation, and acetylation. Acetolysis of the 1,6-anhydro-β-ring of 3-O-acetyl-1,6-anhydro-2-azido-2-deoxy-4-O-(2,4,6-tri-O-acetyl-3-O-benzyl-α-D-glucopyranosyl)-β-D-glucopyranose, which is the fifth intermediate in the synthesis of **10** from **3**, yielded an anomeric mixture of the corresponding hexaacetates (**12**). Catalytic reduction of **12** followed by acetylation gave an anomeric mixture of 1,2′,3,3′,4′,6,6′-hepta-O-acetyl-N-acetylmaltosamines (**13**). De-O-acetylation of **13** gave the title disaccharide **17**. The mp and $[\alpha]_D$ values of **17** were in fairly good agreement with those of N-acetylmaltosamine synthesized by Sinaÿ *et al.* [M.A.M. Nassr, J.-C. Jacquinet, and P. Sinaÿ, *Carbohydr. Res.*, **77**, 99 (1979)].

Keywords——synthesis; N-acetylmaltosamine; maltosan; 1,6-anhydro-β-N-acetylmaltosamine; azidolysis; detosylation; ^{1}H-NMR; ^{13}C-NMR

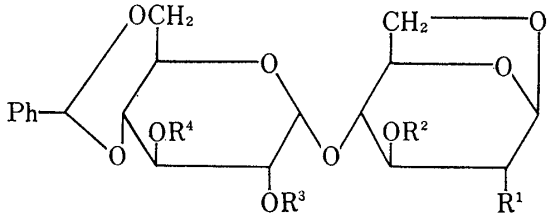
2-Amino-2-deoxy-4-O-α-D-glucopyranosyl-α-D-glucopyranose (maltosamine) was isolated by Wolfrom *et al.*[3] as crystalline hydrochloride from a hydrolyzate of carboxyl-reduced, partially desulfated heparin with hydrochloric acid. They also reported that it gave a crystalline N-acetyl derivative, 2-acetamido-2-deoxy-4-O-α-D-glucopyranosyl-α-D-glucopyranose (N-acetylmaltosamine). A chemical synthesis of maltosamine hydrochloride was subsequently achieved in the same laboratory.[4] However, the $[\alpha]_D$ value (+110°) reported[5] for the N-acetylmaltosamine synthesized enzymically is very different from the value (+87°→+39°) reported by Wolfrom *et al.*[3b] In order to clarify this discrepancy, Sinaÿ, and his co-workers[6] recently synthesized N-acetylmaltosamine by condensation of benzyl 2-acetamido-3,6-di-O-benzyl-2-deoxy-α-D-glucopyranoside with 2,3,4,6-tetra-O-benzyl-1-O-(N-methyl)acetamidoyl-β-D-glucopyranose, followed by removal of the protecting groups. The product thus obtained gave crystals having mp 205—207 °C (dec.) and $[\alpha]_D$ +111°→+93°. Therefore, they pointed out that the disaccharide described by Wolfrom *et al.* appeared to be not maltosamine, and that the structures of both the natural and the synthetic disaccharides required re-investigation. A new synthesis of the title disaccharide **17** from maltose by an unequivocal route was therefore investigated.

The starting material of this synthesis is 1,6: 2,3-dianhydro-4-O-(4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranosyl)-β-D-mannopyranose (**3**), which was prepared from 1,6-anhydro-4′,6′-O-benzylidene-β-maltose (**1**) in 61% yield in 2 steps, selective tosylation of **1** to yield 1,6-anhydro-4′,6′-O-benzylidene-2,2′-di-O-tosyl-β-maltose (**2**), and subsequent treatment of **2** with sodium methoxide.[1] The shortest route from **3** to a protected N-acetylmaltosamine must be as follows: 1) detosylation of **3**, 2) acetylation, 3) azidolysis of the oxirane ring, and 4) reduction of the azido to an amino group, followed by N-acetylation. Thus, detosylation of **3** was firstly attempted under several conditions, but the desired compound was obtained in only poor yield. The best yield of the detosylated product (16.1% as its crystalline acetate **4**) was obtained when compound **3** was treated with 2.5% sodium amalgam. Studies on this route were therefore abandoned and, as a next step, the following detour was investigated.

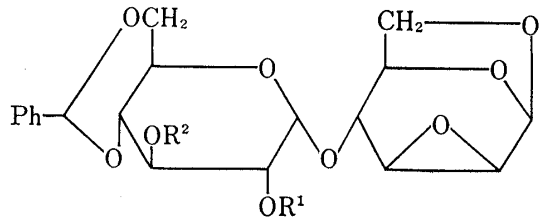
Benzylation of **3** with barium hydroxide, barium oxide, and benzyl bromide in N,N-dimethylformamide (DMF) gave the crystalline 3'-O-benzyl ether **5**, 1,6: 2,3-dianhydro-4-O-(3-O-benzyl-4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranosyl)-β-D-mannopyranose, in 85.1% yield. However, when benzylation of **3** was carried out with sodium hydride and benzyl bromide in DMF, 1,6: 2,3-dianhydro-4-O-(2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranosyl)-β-D-mannopyranose[1] was obtained as the major product in 51% yield, while **5** was isolated in only 23.1% yield. Therefore, preferential diepoxide formation proceeded under these conditions.

Azidolysis of **5** with sodium azide and ammonium chloride in aqueous hexamethylphosphoric triamide (HMPA) at 110 °C gave crystalline 1,6-anhydro-2-azido-2-deoxy-4-O-(3-O-benzyl-4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranosyl)-β-D-glucopyranose (**6**) in 85.1% yield. In the infrared (IR) spectrum of **6**, absorption maxima due to hydroxyl and azido groups could be observed at 3460 and 2120 cm^{-1}, respectively. In compound **5**, the 1,6-anhydrohexopyranose residue is rigidly fixed by the 1,6-anhydro ring. Epoxide attached to the rigid 1,6-anhydro system is known to undergo scission by nucleophiles, leading to predominantly *trans*-diaxial substitution according to the Fuerst–Plattner rule.[1,7] Thus, the oxirane ring in **5** undergoes scission by the azido anion, leading to the product having a D-gluco configuration.

In contrast to the case of **3**, as mentioned in the earlier part of this paper, detosylation of **6** proceeded smoothly upon refluxing of **6** in dioxane–methanol with potassium hydroxide solution to provide crystalline 1,6-anhydro-2-azido-2-deoxy-4-O-(3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranosyl)-β-D-glucopyranose (**7**) in 63.2% yield. The benzylidene acetal of **7** was then hydrolyzed with warm aqueous acetic acid to yield 1,6-anhydro-2-azido-2-deoxy-4-O-(3-O-benzyl-α-D-glucopyranosyl)-β-D-glucopyranose (**8**). Acetylation of **8** gave 3-O-acetyl-1,6-anhydro-2-azido-2-deoxy-4-O-(2,4,6-tri-O-acetyl-3-O-benzyl-α-D-glucopyranosyl)-β-D-glucopyranose (**9**).



1: R^1=OH, R^2=R^3=R^4=H
2: R^1=OTs, R^2=R^4=H, R^3=Ts
6: R^1=N_3, R^2=H, R^3=Ts, R^4=Bn
7: R^1=N_3, R^2=R^3=H, R^4=Bn



3: R^1=Ts, R^2=H
4: R^1=R^2=Ac
5: R^1=Ts, R^2=Bn

Ac=acetyl
Bn=benzyl
Ts=tosyl

Chart 1

The azido group of **9** was hydrogenated to an amino group with concomitant debenzylation of the C-3' position and, after acetylation, crystalline 2',3,3',4',6'-penta-O-acetyl-1,6-anhydro-β-N-acetylmaltosamine (**10**) was isolated in 70.3% yield. De-O-acetylation of **10** gave crystalline 1,6-anhydro-β-N-acetylmaltosamine (**11**) in 83.3% yield. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **11** measured in pyridine-d_5, two anomeric protons were observed. A singlet at 5.92 ppm was due to the anomeric proton of the 1,6-anhydro-β-sugar moiety, and a doublet at 5.56 ppm having a coupling constant of 4 Hz was assigned as that of the non-reducing D-glucose residue in maltose.

In the paper by Sinaÿ *et al.*,[6] **10** was synthesized as an amorphous powder by another route. However, the elemental composition for **10**, $C_{24}H_{33}NO_{15}$, was erroneously reported

as $C_{24}H_{33}NO_{14}$. They reported no ^{1}H-NMR spectral data for **10**, nor a preparation of **11**.

The carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum, in the Fourier transform mode with complete proton decoupling, of **11** was measured in pyridine-d_5 at room temperature. Tetramethylsilane (TMS) was used as a standard, and chemical shifts are given in ppm from TMS. The signals for anomeric carbons were assigned by selective proton decoupling of the corresponding anomeric protons, and those of other carbons were assigned as follows. Firstly, the signals for 1,6-anhydro-β-N-acetylglucosamine and 1,6-anhydro-β-maltose were assigned by comparison with literature values for methyl α-D-glucopyranoside,[8] methyl 2-acetamido-2-deoxy-α-D-glucopyranoside,[9] and 1,6-anhydro-β-D-glucopyranose.[10] Secondly, the signals for **11** were assigned by comparison with the observed values for 1,6-anhydro-β-N-acetylglucosamine and 1,6-anhydro-β-maltose mentioned above. The data are listed in Table I.

Table I. ^{13}C-NMR Chemical Shifts of 1,6-Anhydro-β-N-acetylmaltosamine (**11**) and Relevant Compounds: δ (ppm) from TMS in Pyridine-d_5

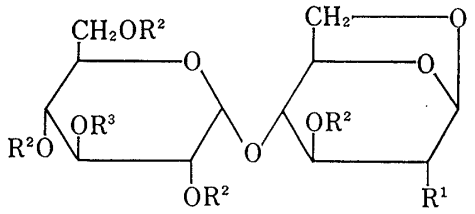
Compounds	α-D-Glucosyl moiety						1,6-Anhydrosugar moiety							NHCOCH$_3$	
	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	C-1	C-2	C-3	C-4	C-5	C-6	OCH$_3$	CO	CH$_3$
Methyl α-D-glucopyranoside	101.3 [101.2][a]	73.7 [73.7]	75.3 [75.3]	72.0 [72.0]	74.0 [73.9]	62.8 [62.7]							55.0 [55.0]		
Methyl 2-acetamido-2-deoxy-α-D-glucopyranoside	99.1[b]	54.5	72.5	70.8	72.0	61.4							56.0	175.1	22.8
1,6-Anhydro-β-D-glucopyranose							104.0	73.3	75.2	73.6	78.1	66.3			
1,6-Anhydro-β-D-N-acetylglucosamine							102.2	53.8	72.5	73.4	77.5	66.0		169.8	23.0
1,6-Anhydro-β-maltose	99.9	73.3	75.3	72.1	74.9	62.9	104.0	73.7	72.1	79.1	76.7	66.4			
1,6-Anhydro-β-N-acetylmaltosamine (**11**)	98.0	73.2	75.1	72.1	74.6	62.9	101.2	52.9	68.4	76.1	75.2	65.4		169.6	22.9

a) Data in brackets are those of Tori *et al.*, see Ref. 8.
b) Data measured in D_2O, see Ref. 9.

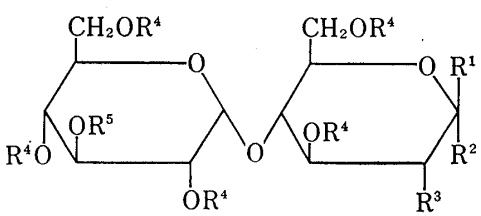
In order to prepare the title disaccharide, the 1,6-anhydro-β-ring of the aforementioned azido **9** was acetolyzed with a cold acetolysis mixture and the acetolyzate was chromatographed on a column of silica gel. The major fractions eluted contained an anomeric mixture of the hexaacetates **12**, 1,3,6-tri-O-acetyl-2-azido-2-deoxy-4-O-(2,4,6-tri-O-acetyl-3-O-benzyl-α-D-glucopyranosyl)-D-glucopyranoses, containing *ca.* 60% of the α-anomer. The content was estimated from the ratio of α-anomeric proton at C-1 in the ^{1}H-NMR spectrum of **12**.

Catalytic reduction of **12** in acetic acid with palladium black resulted in reduction of the azido to an amino group with concomitant debenzylation of the C-3′ benzyl group, and after acetylation, an anomeric mixture of 1,2′,3,3′,4′,6,6′-hepta-O-acetyl-N-acetylmaltosamines (**13**) was obtained in 77.1% yield. Each anomer was separated by column chromatography on silica gel: the α-anomer (**14**) was eluted faster than the β-anomer (**15**). However, when the reduction of **12** was carried out in methanol–ethyl acetate, preferential reduction of the azido to an amino group occurred and, after acetylation, an anomeric mixture of 1,2′,3,4′,6,6′-hexa-O-acetyl-3′-O-benzyl-N-acetylmaltosamines (**16**) was obtained as the major products (51.8%) with a small amount of **13** (29.3%).

De-O-acetylation of **13** afforded the title disaccharide **17** in 65.9% yield. The product was crystallized from ethanol as white needles having mp 198—201°C (dec.) and $[\alpha]_D$ +123.8° (2 min) →+91.9° (24 h). These values were approximately consistent with those [mp 205—207 °C (dec., softening at 175—177 °C) and $[\alpha]_D$ +113°→+98°] reported by Sinaÿ and his co-workers.[6]



8: $R^1=N_3$, $R^2=H$, $R^3=Bn$
9: $R^1=N_3$, $R^2=Ac$, $R^3=Bn$
10: $R^1=NHAc$, $R^2=R^3=Ac$
11: $R^1=NHAc$, $R^2=R^3=H$



12: R^1, $R^2=H$, OAc, $R^3=N_3$, $R^4=Ac$, $R^5=Bn$
13: R^1, $R^2=H$, OAc, $R^3=NHAc$, $R^4=R^5=Ac$
14: $R^1=H$, $R^2=OAc$, $R^3=NHAc$, $R^4=R^5=Ac$
15: $R^1=OAc$, $R^2=H$, $R^3=NHAc$, $R^4=R^5=Ac$
16: R^1, $R^2=H$, OAc, $R^3=NHAc$, $R^4=Ac$, $R^5=Bn$
17: $R^1=R^4=R^5=H$, $R^2=OH$, $R^3=NHAc$

Chart 2

Experimental

Instruments used and conditions for chromatography were the same as in part IV[1] unless otherwise indicated. Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60_{254} with the following solvent combinations (v/v): (A), CH_2Cl_2–acetone (9: 1); (B), CH_2Cl_2–acetone (5: 1); (C), benzene–ether (1: 3); (D), $CHCl_3$–MeOH (5: 1); (E), AcOEt–2-PrOH–H_2O (5: 7: 3).

1,6: 2, 3-Dianhydro-4-O-(2, 3-di-O-acetyl-4, 6-O-benzylidene-α-D-glucopyranosyl)-β-D-mannopyranose (4)——A 2.5% sodium amalgam (7.5 g) was added in small portions under stirring to an ice-cold solution of **3**[1] (750 mg, 1.37 mmol) in dioxane–MeOH (1: 4, 75 ml). After being stirred for 20 h below 10°C, the mixture was filtered, and the residue was washed with MeOH. The combined filtrate and washings were neutralized with AcOH in MeOH, and concentrated to a syrup, which was acetylated with Ac_2O (5 ml) and pyridine (5 ml) at room temperature overnight. The mixture was concentrated to dryness by repeated co-distillation with toluene. The residue was chromatographed on a column of silica gel with benzene–ether (6: 1). The major fraction eluted was crystallized from MeOH. Recrystallization from MeOH gave fine needles (105 mg, 16.1%), showing a purple color in the Ross test,[11] mp 222—224°C, $[\alpha]_D^{22}$ +67.1° ($c=1.12$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 2.07, 2.09 (6H, each s, OAc×2), 5.35 (1H, d, $J_{1',2'}=4$ Hz, H-1′, α-Glc), 5.49 (1H, s, C_6H_5CH), 5.68 (1H, d, $J_{1,2}=3$ Hz, H-1, β-Man). TLC: *Rf* 0.55 (solvent A), 0.39 (C). *Anal.* Calcd for $C_{23}H_{26}O_{11}$: C, 57.74; H, 5.48. Found: C, 57.29; H, 5.38.

1,6: 2,3-Dianhydro-4-O-(3-O-benzyl-4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranosyl)-β-D-mannopyranose (5)——Benzyl bromide (9 ml, 75.8 mmol) was added dropwise with stirring at 0° to an ice-cold suspension of **3** (3.1 g, 5.65 mmol), BaO (8.8 g, 57.4 mmol), and $Ba(OH)_2\cdot 8H_2O$ (3.5 g, 11.1 mmol) in dry DMF (90 ml). The mixture was stirred for 30 min at 0°C, then the container was taken from the ice-bath, and stirring was continued for 20 h at room temperature. The mixture was poured into ice–H_2O (300 ml) with the aid of CH_2Cl_2 (100 ml), stirred for 24 h, and then filtered. The filtrate was extracted with CH_2Cl_2 (2×80 ml), and the extracts were successively washed with H_2O, 10% HCl, H_2O, aq. $NaHCO_3$, and H_2O. Desiccation ($CaCl_2$) and removal of the solvent provided a syrup, which was crystallized from ether as white needles (2.32 g, 64.3%). More **5** (0.75 g, 20.8%) was obtained from the filtrate of crystallization after removal of the solvent followed by silica gel column chromatography with CH_2Cl_2 and CH_2Cl_2–acetone (50: 1): **3** was eluted with the latter. The overall yield of **5**, mp 154—156°C, $[\alpha]_D^{23}$ +14.7° ($c=1.09$, $CHCl_3$), reached 85.1%. IR ν_{max}^{KBr} cm^{-1}: 1595 (C=C of tosyl), 1365, 1175 (SO_2). ^{1}H-NMR ($CDCl_3$): 2.36 (3H, s, $C_6H_4CH_3$), 5.42 (1H, d, $J_{1',2'}=4$ Hz, H-1′, α-Glc), 5.52 (1H, s, C_6H_5CH), 5.68 (1H, d, $J_{1,2}=3.5$ Hz, H-1, β-Man), 7.12—7.48 (12H, m, aromatic protons), 7.76 (2H, d, $J=8$ Hz, aromatic protons *ortho* to SO_2). TLC: *Rf* 0.66 (solvent A), 0.58 (C). *Anal.* Calcd for $C_{33}H_{34}O_{11}S$: C, 62.06; H, 5.37. Found: C, 62.28; H, 5.41.

Benzylation of 3 with Sodium Hydride and Benzyl Bromide——Powdered NaH (10 mg, 0.42 mmol) was added in portions to an ice-cold solution of **3** (0.2 g, 0.36 mmol) in dry DMF (10 ml) and, a few min later, benzyl bromide (0.1 ml, 0.84 mmol) was added dropwise. The mixture was left overnight below 10°C, then MeOH (3 ml) was added to decompose excess benzyl bromide, and the mixture was concentrated under reduced pressure to a syrup. The syrup was treated with CH_2Cl_2 (2×20 ml) and the combined CH_2Cl_2 layers were washed with H_2O, and dried (Na_2SO_4). Removal of the solvent gave a syrup, which was chromatographed on a column of silica gel with benzene–ether (4: 1). From the earlier fractions, **5** (54 mg, 23.1%) was isolated. From the subsequent fractions, crystals (70 mg, 51%), mp 196—198°C, $[\alpha]_D^{23}$ +76.4° ($c=1$, $CHCl_3$), were obtained which were indistinguishable from authentic 1,6: 2,3-dianhydro-4-O-(2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranosyl)-β-D-mannopyranose[1] in terms of mp, $[\alpha]_D$, IR, and ^{1}H-NMR.

1,6-Anhydro-2-azido-2-deoxy-4-O-(3-O-benzyl-4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranosyl)-β-D-glucopyranose (6)——A mixture of **5** (1.32 g, 2.07 mmol), NaN_3 (1.32 g, 20.3 mmol), and NH_4Cl (260 mg, 4.86 mmol) in a mixture of HMPA (60 ml) and H_2O (6 ml) was heated in an oil bath at 110°C for 24 h. After

cooling to room temperature, the mixture was poured into ice–H_2O (300 ml) to precipitate crude **6**. The air-dried material was recrystallized from EtOH to afford white needles (1.20 g, 85.1%), mp 158—159°C, $[\alpha]_D^{18}$ −7.4° ($c=1$, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3460 (OH), 2120 (N_3), 1598 (C=C of tosyl), 1173 (SO_2). ^{1}H-NMR ($CDCl_3$): 2.37 (3H, s, $CH_3C_6H_4$), 7.13—7.43 (12H, m, aromatic protons), 7.79 (2H, d, $J=8$ Hz, aromatic protons *ortho* to SO_2). TLC: *Rf* 0.47 (solvent A), 0.44 (C). *Anal.* Calcd for $C_{33}H_{35}N_3O_{11}S$: C, 58.14; H, 5.19; N, 6.16. Found: C, 58.09; H, 5.08; N, 6.01.

1,6-Anhydro-2-azido-2-deoxy-4-O-(3-O-benzyl-4,6-O-benzylidene-α-D-glucopyranosyl)-β-D-glucopyranose (7)——A mixture of **6** (2.5 g, 3.67 mmol) dissolved in dioxane (50 ml), 8 N KOH (30 ml), and MeOH (60 ml) was gently heated under reflux for 3.5 h. The mixture was cooled at 0°C, neutralized with cold 2 N H_2SO_4, and concentrated to a sludgy residue, which was treated with CH_2Cl_2 (50 ml) and H_2O (20 ml) to effect dissolution. The organic later was separated, washed with H_2O (2×20 ml), and dried ($MgSO_4$). Removal of the solvent gave a solid, which was crystallized from EtOH to afford long needles (1.22 g, 63.2%), mp 135—136°C, $[\alpha]_D^{23}$ +37.7° ($c=1.03$, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3340 (OH), 2130 (N_3). TLC: *Rf* 0.15 (solvent A), 0.25 (B), 0.15 (C), 0.61 (D). *Anal.* Calcd for $C_{26}H_{29}N_3O_9$: C, 59.20; H, 5.54; N, 7.97. Found: C, 58.75; H, 5.59; N, 7.65.

1,6-Anhydro-2-azido-2-deoxy-4-O-(3-O-benzyl-α-D-glucopyranosyl)-β-D-glucopyranose (8)——A mixture of **7** (1.8 g, 3.41 mmol) in 80% (v/v) AcOH (50 ml) was warmed at 80°C for 2 h. After being concentrated to a syrup by repeated co-distillation with EtOH and toluene, the residue was chromatographed on a column of silica gel with $CHCl_3$–MeOH (10: 1). The major fraction eluted gave **8** as a hygroscopic amorphous powder (1.25 g, 83.3%), $[\alpha]_D^{22}$ +46.3° ($c=1.4$, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3360 (broad OH), 2100 (N_3). TLC: *Rf* 0.01 (solvent A), 0.02 (B), 0.02 (C), 0.36 (D), 0.71 (E). *Anal.* Calcd for $C_{19}H_{25}N_3O_9$: C, 51.93; H, 5.73; N, 9.56. Found: C, 51.89; H, 5.75; N, 9.11.

3-O-Acetyl-1,6-anhydro-2-azido-2-deoxy-4-O-(2,4,6-tri-O-acetyl-3-O-benzyl-α-D-glucopyranosyl)-β-D-glucopyranose (9)——Compound **8** (0.95 g, 2.16 mmol) was acetylated with Ac_2O (10 ml) and pyridine (10 ml) at 0°C as described for the preparation of **4**: the acetate was eluted from a column with CH_2Cl_2–acetone (50: 1). Removal of the solvent gave **9** (1.22 g, 93.1%) as a white amorphous powder, $[\alpha]_D^{20}$ +74.4° ($c=0.81$, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 2110 (N_3), 1740 (C=O). ^{1}H-NMR ($CDCl_3$): 1.92, 2.04, 2.09 (12H, all s, OAc×4), 5.32 (1H, d, $J_{1',2'}=4$ Hz, H-1′, α-Glc), 5.56 (1H, s, H-1, β-Glc), 7.26 (5H, s, aromatic protons of benzyl). TLC: *Rf* 0.50 (solvent A), 0.29 (C). *Anal.* Calcd for $C_{27}H_{33}N_3O_{13}$: C, 53.38; H, 5.48; N, 6.92. Found: C, 53.14; H, 5.40; N, 6.63.

2-Acetamido-3-O-acetyl-1,6-anhydro-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-β-D-glucopyranose (2′,3,3′,4′,6′-Penta-O-acetyl-1,6-anhydro-β-N-acetylmaltosamine) (10)——A solution of **9** (250 mg, 0.39 mmol) in AcOH (10 ml) was hydrogenated with a Pd catalyst at room temperature under atmospheric pressure for 20 h, the catalyst was freshly prepared from $PdCl_2$ (250 mg) according to the method of Schmidt and Staab.[12] After removal of the catalyst by filtration, the catalyst was washed with AcOH. The combined filtrate and washings were concentrated to a syrup, which was acetylated with Ac_2O (5 ml) and pyridine (5 ml). The mixture was treated as described for the preparation of **9** to afford **10** (150 mg, 70.3%): the solvent combination for elution was CH_2Cl_2–acetone (20: 1). Compound **10** was crystallized from EtOH as white prisms, mp 204—205°C, $[\alpha]_D^{23}$ +38.4° ($c=1.05$, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3420 (NHAc), 1760—1730 (C=O), 1675 (amide I), 1490 (amide II). ^{1}H-NMR ($CDCl_3$): 2.05, 2.07, 2.09, 2.11 (18H, all s, OAc×5, NAc), 6.19 (1H, d, $J=9$ Hz, NHAc, exchangeable with D_2O). TLC: *Rf* 0.15 (solvent A), 0.19 (B), 0.03 (C), 0.66 (D). *Anal.* Calcd for $C_{24}H_{33}NO_{15}$: C, 50.08; H, 5.78; N, 2.43. Found: C, 50.09; H, 5.79; N, 2.44. lit.[6] an amorphous powder, $[\alpha]_D^{20}$ +18° ($c=2$, $CHCl_3$).

2-Acetamido-1,6-anhydro-2-deoxy-4-O-α-D-glucopyranosyl-β-D-glucopyranose (1,6-Anhydro-β-N-acetylmaltosamine) (11)——A 0.5 N methanolic solution of MeONa (0.2 ml) was added to a suspension of **10** (110 mg, 0.19 mmol) in MeOH (10 ml), and the mixture was stirred at room temperature for 9 h under exclusion of moisture. The mixture was neutralized with Amberlite IR-120 (H^+) resin, filtered, and the filtrate was concentrated to dryness. The residue was crystallized from EtOH to give **11** (58 mg, 83.3%), as white prisms, mp 198—199°C, $[\alpha]_D^{23}$ +101° ($c=0.43$, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3480—3280 (OH, NH), 1625 (amide I), 1565 (amide II). ^{1}H-NMR (pyridine-d_5): 2.00 (3H, s, NAc), 5.56 (1H, d, $J_{1',2'}=4$ Hz, H-1′, α-Glc), 5.92 (1H, s, H-1, β-GlcNAc), 8.00 (1H, d, $J=8$ Hz, NH, exchangeable with D_2O). ^{13}C-NMR (pyridine-d_5): see Table I. TLC: *Rf* 0.41 (solvent E). *Anal.* Calcd for $C_{14}H_{23}NO_{10}$: C, 46.03; H, 6.35; N, 3.83. Found: C, 45.61; H, 6.38; N, 3.78.

1,3,6-Tri-O-acetyl-2-azido-2-deoxy-4-O-(2,4,6-tri-O-acetyl-3-O-benzyl-α-D-glucopyranosyl)-D-glucopyranoses (12)——Compound **9** (820 mg, 1.28 mmol) was added in small portions under stirring to an ice-cold acetolysis mixture [10 ml, H_2SO_4–Ac_2O–AcOH (1: 70: 30, v/v)] at 0°C, and the mixture was stirred for 2 h at 5°C. The solution was poured into ice–H_2O (30 ml) with stirring, and the mixture was stirred for 2 h. After neutralization with $NaHCO_3$, the whole was extracted with CH_2Cl_2 (30 ml×2), and the extracts were washed with H_2O. Desiccation (Na_2SO_4) and removal of the solvent gave a syrup, which was chromatographed on a column of silica gel with benzene–ether (2: 1) to yield **12** (868 mg, 95.6%) as a white powder, $[\alpha]_D^{25}$ +102.1° ($c=0.88$, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 2110 (N_3), 1730 (C=O). ^{1}H-NMR ($CDCl_3$): 1.93, 2.10, 2.11, 2.14, 2.23 (18H, all s, OAc×6), 6.26 (0.6H, d, $J_{1,2}=3.5$ Hz, α-anomeric proton of C-1), 7.27 (5H, s, aromatic protons of benzyl). TLC: *Rf* 0.57 (solvent A), 0.51 (B). *Anal.* Calcd for $C_{31}H_{39}N_3O_{16}$: C, 52.47;

H, 5.54; N, 5.92. Found: C, 52.60; H, 5.47; N, 5.86.

Anomeric Mixture of 2-Acetamido-1,3,6-tri-O-acetyl-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-D-glucopyranose (13)——Reduction of the azido group of **12** (350 mg, 0.51 mmol) in AcOH (35 ml) to an amino group with concomitant debenzylation was carried out as described for the preparation of **10**. The resulting syrupy amino sugar was acetylated with Ac_2O (10 ml) and pyridine (10 ml). After column chromatography with CH_2Cl_2–acetone (10: 1), **13** was obtained as an amorphous powder (268 mg, 77.9%).

2-Acetamido-1,3,6-tri-O-acetyl-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-α-D-glucopyranose (14)——The anomeric mixture (**13**, 260 mg) in CH_2Cl_2 (5 ml) was chromatographed on a column of silica gel with CH_2Cl_2–acetone (20: 1). From the earlier fractions, the α-anomer (**14**, 126 mg, 48.5%) was isolated as a white powder, $[\alpha]_D^{23}$ +121.4° (c=1.02, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3360 (NH), 1760—1725 (C=O), 1675 (amide I), 1520 (amide II). ^{1}H-NMR ($CDCl_3$): 1.92, 2.01, 2.03, 2.05, 2.10, 2.13, 2.23 (24H, all s, OAc×7, NAc), 5.50 (1H, d, $J_{1',2'}$=4 Hz, H-1′, α-Glc), 5.59 (1H, d, J=9 Hz, NH, exchangeable with D_2O), 6.10 (1H, d, $J_{1,2}$=3.5 Hz, H-1, α-GlcNAc). TLC: *Rf* 0.15 (solvent A), 0.21 (B), 0.02 (C), 0.66 (D). *Anal.* Calcd for $C_{28}H_{39}NO_{18}$: C, 49.63; H, 5.80; N, 2.07. Found: C, 49.04; H, 5.82; N, 2.04.

2-Acetamido-1,3,6-tri-O-acetyl-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-β-D-glucopyranose (15)——The β-anomer (**15**, 130 mg, 50%) was eluted in later fractions from the column chromatography of **13**. The product was crystallized from EtOH as a crystalline powder, mp 160—162°C, $[\alpha]_D^{25}$ +74.2° (c=1.07, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1760—1730 (C=O), 1660 (amide I), 1535 (amide II). ^{1}H-NMR ($CDCl_3$): 1.95, 2.04, 2.07, 2.08, 2.12, 2.16 (24H, all s, OAc×7, NAc), 5.48 (1H, d, $J_{1',2'}$=4 Hz, H-1′, α-Glc), 5.74 (1H, d, $J_{1,2}$=8 Hz, H-1, β-GlcNAc), 5.92 (1H, d, J=9 Hz, NH, exchangeable with D_2O). TLC: *Rf* 0.10 (solvent A), 0.16 (B), 0.02 (C), 0.64 (D). *Anal.* Calcd for $C_{28}H_{39}NO_{18}$: C, 49.63; H, 5.80; N, 2.07. Found: C, 49.47; H, 5.89; N, 2.14.

Anomeric Mixture of 2-Acetamido-1,3,6-tri-O-acetyl-2-deoxy-4-O-(2,4,6-tri-O-acetyl-3-O-benzyl-α-D-glucopyranosyl)-D-glucopyranose (16)——A solution of **12** (220 mg, 0.31 mmol) in a mixture of MeOH (10 ml) and AcOEt (5 ml) was reduced with a Pd catalyst for 3 h at room temperature under atmospheric pressure: the catalyst was freshly prepared[12] from $PdCl_2$ (220 mg). The catalyst was filtered off and washed with MeOH. The combined filtrate and washings were concentrated to a syrup, which was acetylated with Ac_2O (4 ml) and pyridine (4 ml). The mixture was treated as described for the preparation of **4**. Compound **16** (118 mg, 51.8%), $[\alpha]_D^{20}$ +94.1° (c=1.05, $CHCl_3$), was obtained as an amorphous powder from the earlier fractions of column chromatography with CH_2Cl_2–acetone (20: 1). IR ν_{max}^{Nujol} cm^{-1}: 3350 (NH), 1760—1730 (C=O), 1680 (amide I), 1525 (amide II). ^{1}H-NMR ($CDCl_3$): 1.92, 1.96, 2.04, 2.08, 2.11, 2.13, 2.24 (21H, all s, OAc×6, NAc), 5.53 (1H, d, $J_{1',2'}$=4 Hz, H-1′, α-Glc), 5.67 (1H, d, J=9 Hz, exchangeable with D_2O), 6.17 (0.5H, d, $J_{1,2}$=3.5 Hz, H-1, α-GlcNAc). TLC: *Rf* 0.18 (solvent A), 0.26 (B), 0.03 (C), 0.67 (D). *Anal.* Calcd for $C_{33}H_{43}NO_{17}$: C, 54.62; H, 5.92; N, 1.93. Found: C, 54.24; H, 5.96; N, 1.89.

Compound **13** (61 mg, 29.3%) was eluted in subsequent fractions.

2-Acetamido-2-deoxy-4-O-(α-D-glucopyranosyl)-α-D-glucopyranose (N-Acetylmaltosamine) (17)——De-O-acetylation of **13** (140 mg, 0.21 mmol) in MeOH (8 ml) with a 0.5 N methanolic solution of MeONa (0.2 ml) was carried out as described for the preparation of **11** to yield **17**. The product was crystallized from EtOH as white needles (53 mg, 65.9%), mp 198—201°C (dec.), $[\alpha]_D^{23}$ +121.8° (2 min)→+91.9° (24 h) (c=1.1, H_2O–MeOH, 19: 1, v/v). lit.[6] mp 175—177°C (softening), 205—207°C (dec.), $[\alpha]_D^{20}$ +111°→+93° (24 h) (c=0.8, H_2O–MeOH, 19: 1). IR ν_{max}^{KBr} cm^{-1}: 3340 (broad NH, OH), 1640 (amide I), 1550 (amide II). TLC: *Rf* 0.33 (solvent E). *Anal.* Calcd for $C_{14}H_{25}NO_{11}$: C, 43.86; H, 6.57; N, 3.65. Found: C, 44.08; H, 6.62; N, 3.41. Paper partition chromatography with BuOH–pyridine–H_2O (6: 4: 3, v/v): *Rf* 0.37 cf. 0.39 (Glc); 0.47 (GlcNAc); 0.26 (Mal).

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References and Notes

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