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PREPARATION OF A GLYCOSYL DONOR SUITABLE FOR SYNTHESIS OF GLYCOPROTEIN "CORE" OLIGOSACCHARIDES*

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ABSTRACT

2-*O*-Acetyl-3-*O*-allyl-4-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-D-glucopyranosyl chloride (**14**), a glycosyl donor suitable for synthesis of oligosaccharides corresponding to the N-glycoprotein saccharide "core", was synthesized by an efficient, six-stage route from 3,4,6-tri-*O*-acetyl-1,2-*O*-[1-(*exo*-ethoxy)ethylidene]-α-D-glucopyranose. Silver triflate-promoted coupling of **14** with benzyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside gave a protected β-D-(1→4)-linked disaccharide in 38% yield, but a major side-reaction also occurred. When the *tert*-butyldiphenylsilyl group was quantitatively removed from **14** prior to the coupling reaction, and replaced afterwards, the yield in the glycosidation was increased to 55%, and major side-products were avoided.

INTRODUCTION

The pentasaccharide **1** occurs in the "core" saccharide region of the N-glycoproteins[1] and in the "lipid intermediates" involved in their biosynthesis[2]. The synthesis of **1** is important for the study of the structure and biosynthesis of the N-glycoproteins. Such a synthesis is difficult because of the presence of a β-D-mannosyl residue and two (1→4)-linkages to 2-acetamido-2-deoxy-D-glucopyranosyl residues. In this laboratory, the synthesis of the "core" trisaccharide β-D-Man*p*-(1→4)-β-D-Glc*p*NAc-(1→4)-D-Glc*p*NAc has been successfully achieved by two alternative routes[3,4], both of which depend on the initial synthesis of a D-glucosyl "donor", which is the precursor of the β-D-mannopyranosyl residue. Thus, after coupling with a 2-acetamido-2-deoxy-D-glucose or di-*N*-acetylchitobiose residue, epimerization is effected at C-2 of the β-D-glucosyl residue, by a sequence of *O*-

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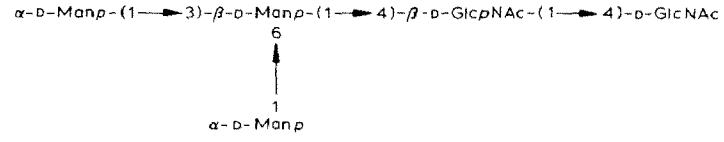
deacetylation, oxidation, and highly stereoselective reduction. These steps all give high yields, and this synthetic route has the advantage that the coupling reaction is stereospecific, so that no α-D-mannopyranosyl derivative is formed.



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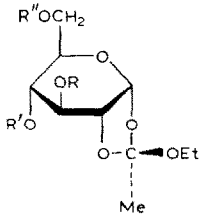
To extend this synthetic approach to **1**, and the corresponding tetrasaccharides containing either (1→3)- or (1→6)-linked α-D-mannopyranosyl residues, it is necessary to prepare a D-glucosyl "donor" having strict requirements for its protective groups. Thus, O-2 must be protected by an acyl group, so that neighboring-group participation in the Koenigs–Knorr reaction will specifically provide a β-D-glucopyranosyl (and hence a β-D-mannopyranosyl) group, O-3 and O-6 must have "temporary" protective groups[5], and O-4 a "persistent" protective group. Furthermore, the groups at O-3 and O-6 should be independently removable, so that they can be selectively substituted with isotopically labeled α-D-mannopyranosyl residues, for the resulting synthetic compounds to be used as exogenous D-mannosyl acceptors in biosynthetic experiments[6].

Because, in our scheme to construct the pentasaccharide **1**, the D-glucosyl "donor" **14** will be the central unit to which the other sugar residues will be attached, it is essential that the compound be easily prepared, in good overall-yield. In this paper, an efficient synthesis of **14** is reported. Previously, **14** had been obtained by a different, longer route[7].

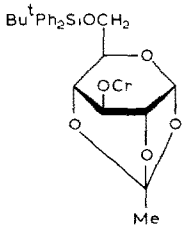
RESULTS AND DISCUSSION

Orthoesters are generally prepared from 2-*O*-acylglycosyl halides and may be readily converted back into the halides by treatment with an acid, such as hydrobromic acid[8], or a trimethylsilyl halide[9]. An orthoester may, therefore, be considered as a protected form of a glycosyl halide and, as such, meets the requirement for a precursor to the D-glucosyl "donor" just described. The simultaneous protection of O-1 and O-2 facilitates the introduction, in the required order, of the substituents at the other positions.

3,4,6-Tri-*O*-acetyl-1,2-*O*-[1-(*exo*-ethoxy)ethylidene]-α-D-glucopyranose[10] (**2**) was deacetylated by treatment with triethylamine to give **3**. To selectively block OH-6, the *tert*-butyldiphenylsilyl (Bu^tPh_2Si) group[11] was chosen, instead of the traditional trityl group, because of the relative ease of preparation of the required compound in high yield, its greater stability under mild acid conditions, and the ease and convenience with which the Bu^tPh_2Si group may be removed under mild,



2 R = R′ = R″ = Ac
3 R = R′ = R″ = H
4 R = R′ = H, R″ = Bu^tPh_2Si
5 R = All, R′ = H, R″ = Bu^tPh_2Si
6 R = R′ = All, R″ = Bu^tPh_2Si
7 R = Cr, R′ = H, R″ = Bu^tPh_2Si
8 R = All, R′ = Bn, R″ = Bu^tPh_2Si
9 R = All, R′ = R″ = Bn
10 R = All, R′ = Bn, R″ = Ac



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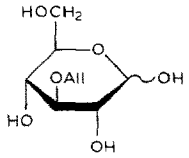

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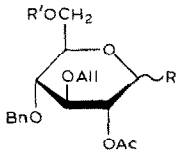


13 R = OH, R′ = Bu^tPh_2Si
14 R = Cl, R′ = Bu^tPh_2Si
15 R = OMe(β), R′ = Bu^tPh_2Si
16 R = Br, R′ = Ac

All = $CH_2{=}CH{-}CH_2$

Cr = $CH_3{-}CH{=}CH{-}CH_2$

Bu^tPh_2Si = $(CH_3)_3C{-}Si(C_6H_5)_2$

neutral conditions that do not affect other protective groups. When **3** was treated with *tert*-butylchlorodiphenylsilane in the presence of imidazole or pyridine, t.l.c. indicated the occurrence of a major side-reaction, possibly involving polymerization, as well as the desired formation of **4** in low yield. Therefore, **3** was converted into the bis(tributyl)stannylene derivative[12], which, when treated with *tert*-butylchlorodiphenylsilane in the presence of tetrabutylammonium bromide[13], gave a high yield of **4**. For the selective introduction of an allyl group at O-3 of **4**, the compound was briefly treated with an excess of allyl bromide in the presence of silver oxide[14] to give **5**. Prolonged treatment lead to the formation of the 3,4-di-*O*-allyl derivative **6**. The position of allylation in **5** was confirmed by chemical conversion. Thus, mild acid hydrolysis of **5**, followed by deacetylation and removal of the Bu^tPh_2Si group, gave a compound identical with 3-*O*-allyl-D-glucose (**12**) obtained by acid hydrolysis of 3-*O*-allyl-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose[15]. In an attempt to prepare the 3-*O*-(2-butenyl) analog, **5** was treated with crotyl bromide and silver oxide, but, instead of the expected compound **7**, the tricyclic orthoester **11** was obtained. Presumably, steric bulk of the combined 6-*O*-*tert*-

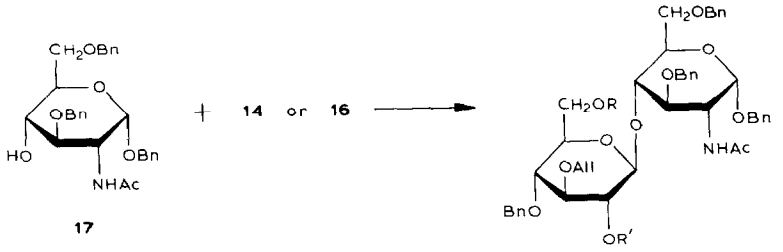
butyldiphenylsilyl and 3-*O*-(2-butenyl) groups caused a subtle conformational change that allowed transesterification to occur between OH-4 and the ethoxy group of the orthoester. In the case of the 3-*O*-allyl compound **5**, the lack of a methyl group in the substituent was presumably sufficient to avoid this conformational shift.

Benzylation of OH-4 of **5** was achieved by treatment with benzyl bromide in the presence of barium oxide and barium hydroxide. Unexpectedly, isomerization of the ethoxyethylidene group also occurred, and the 4-*O*-benzyl compound **8** was obtained as a mixture of two isomers, whose ratio, as determined by ^{1}H-n.m.r., was 3:2 (*exo*:*endo*). A by-product of this reaction, which migrated more slowly than **8** on t.l.c., was shown to be the 3-*O*-allyl-4,6-di-*O*-benzyl compound **9**. Formation of **9** showed that the Bu^{t}Ph$_2$Si group is not completely stable to mild basic treatment.

When compound **8** was treated with hydrogen bromide in acetic acid[8], or with bromotrimethylsilane[9], t.l.c. showed that the Bu^{t}Ph$_2$Si group was cleaved off, and the allyl group was brominated. Therefore **8** was converted into the OH-1 compound **13** by treatment with a cation-exchange resin, and **13** was converted into the desired glycosyl chloride **14** by either the triphenylphosphine–carbon tetrachloride method[16], or by using the Vilsmeier reagent, chloromethylenedimethylammonium chloride[17]. In previous applications of this reagent to carbohydrates[18], short reaction-times were sufficient for the complete conversion of OH-1 compounds into glycosyl chlorides. However, for the preparation of **14** from **13**, overnight stirring at room temperature, or stirring at elevated temperatures for 3–4 h, was necessary. This result prompted us to test the reactivity of **14** by conversion into its methyl glycoside **15**, by treatment with methanol and a mixture of mercuric bromide and mercuric cyanide. Compound **15** was shown to be the expected β-D anomer by observing the optical rotation and ^{1}H-n.m.r. spectrum, but the yield was only fair.

During the formation of **15**, a side-reaction occurred in which the Bu^{t}Ph$_2$Si group was removed. The product of this reaction was not fully characterized, but the i.r. and n.m.r. spectra indicated that the Bu^{t}Ph$_2$Si group had been removed. The unexpected lability of the Bu^{t}Ph$_2$Si group[11] during a benzylation, and in a modified Koenigs–Knorr reaction, requires that caution must be exercised when this group is employed for protection in carbohydrate synthesis. It is noteworthy that such unexpected lability was also observed[19] recently in the closely related *tert*-butyldimethylsilyl group.

In order to demonstrate its usefulness as a glycosyl donor, **14** was coupled with the readily available "aglycon" benzyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside[3] (**17**). The condensation of **14** with **17** was attempted under various conditions using silver triflate as promotor. By following t.l.c. it was determined that yields of condensation product were very low when either 1,1,3,3-tetramethylurea or 2,4,6-trimethylpyridine were present. The best result was obtained when the reaction was carried out in dichloromethane containing silver



18 R = R′ = Ac
19 R = Bu^tPh_2Si, R′ = Ac
20 R = Bu^tPh_2Si, R′ = H

triflate and molecular sieve at 4°. Under these conditions, the disaccharide **19** was isolated in 38% yield, together with a major side-product which was not the α anomer (23%), and unreacted starting compounds **14** and **17**. The ^{1}H-n.m.r. spectrum (500 MHz) of **19** showed a doublet at δ 4.96 for H-1 ($J_{1,2}$ 3.7 Hz) and a doublet at δ 4.48 for H-1′ ($J_{1',2'}$ 8.4 Hz), which is consistent with a β-D-(1→4)-disaccharide linkage and an α-D linkage at the reducing end. The identity of the side-product is under investigation.

In order to improve the yield in the coupling reaction and minimize side-reactions, an alternative route was investigated, in which the Bu^tPh_2Si group was removed from O-6 of the donor and replaced after the condensation. This approach had the advantage that the more-reactive glycosyl bromide could be employed. Thus, **8** was treated with M tetrabutylammonium fluoride in oxolane followed by acetylation to give the 6-*O*-acetyl derivative **10**. Compound **10** was readily converted into bromide **16** by treatment with hydrogen bromide in dichloromethane, and **16** was condensed with **17** under essentially the same conditions as those for the preparation of **19**. The reaction gave the desired disaccharide **18** in 55% yield. The ^{1}H-n.m.r. (500 MHz) spectrum showed the H-1 signal at δ 4.92 as a doublet ($J_{1,2}$ 3.7 Hz) and H-1′ at δ 4.47 ($J_{1',2'}$ 8.4 Hz); these are similar to the resonances observed in compound **19**. This improved yield warrants the almost quantitative extra steps of replacing the Bu^tPh_2Si by the acetate group.

To restore the selectivity between O-3 and O-6, the Bu^tPh_2Si group was reintroduced at O-6 by deacetylation and treatment of the product with *tert*-butyldiphenylchlorosilane to give **20** in 70% overall yield. *O*-Deacetylation of **19** gave a product identical with **20**.

EXPERIMENTAL

General methods. — Melting points were determined with a Mettler FP2 hot-stage equipped with a microscope, and correspond to "corrected melting points". Optical rotations were determined in 1-dm, semimicro tubes with a Perkin–Elmer No. 141 polarimeter. I.r. spectra were recorded with a Perkin–Elmer spec-

trophotometer, Model 237. ^{1}H-N.m.r. spectra were recorded at 500 MHz with a Bruker WM-500 spectrometer, unless otherwise specified, with chloroform-*d* as the solvent (containing 1% of tetramethylsilane as the internal standard). Evaporations were conducted *in vacuo*, with the bath temperature kept <30°. Dichloromethane was dried by distillation from phosphorus pentaoxide, and addition of 3A molecular sieve (No. M-9882, Sigma Chemical Co., St. Louis, MO 63178). *N,N*-Dimethylformamide was dried by addition of 4A molecular sieve (Sigma). The microanalyses were performed by Dr. W. Manser, CH-8704 Herrliberg, Zurich, Switzerland, and by Galbraith Laboratories Inc., Knoxville, TN 37821.

Chromatographic methods. — T.l.c. and preparative t.l.c. were performed on precoated plates of silica gel, 0.25-mm thick (E. Merck AG, Darmstadt, Germany); for t.l.c., the plates supplied were cut to a length of 6 cm before use, but otherwise were used without pretreatment. All proportions of solvents are v/v. Preparative-layer chromatography was performed on precoated Silica Gel F254 PLC plates, 2-mm thick (Merck), or on precoated plates of Silica Gel F254, 0.5-mm thick (Merck). The spray reagent, unless otherwise stated, was 1:1:18 anisaldehyde–sulfuric acid–ethanol[20], and the plates were heated to 125°. Unsaturation was detected by spraying with a solution of 1% potassium permanganate in 2% aqueous sodium hydrogencarbonate. Column chromatography was performed on silica gel (0.05–0.2 mm, 70–325 mesh, Merck). Solvent systems used for chromatography were: *A*, 2:1 hexane–ethyl acetate; *B*, 1:1 hexane–ethyl acetate; *C*, 20:1 chloroform–methanol; and *D*, 30:1 chloroform–methanol, unless otherwise specified. When plates were eluted more than once, they were dried in a stream of air for at least 30 min between each elution.

*1,2-*O*-[1-(*exo*-Ethoxy)ethylidene]-α-*D*-glucopyranose* (**3**). — 3,4,6-Tri-*O*-acetyl-1,2-*O*-[1-(*exo*-ethoxy)ethylidene]-α-D-glucopyranose[10] (12 g, 0.32 mol) was deacetylated by stirring with triethylamine (25 mL) in anhydrous methanol (4 mL) at room temperature overnight. The solution was evaporated to a syrup, which could be used for the next step without purification. However, to the best of our knowledge, this compound has not been fully characterized. Therefore, the syrup was applied to a column of silica gel and eluted with 5:1 chloroform–methanol containing 1% triethylamine. Evaporation of the solvent gave a yellow syrup (7 g, 88%), $[\alpha]_D^{28}$ +44° (*c* 0.47, chloroform); R_F 0.49 (5:1 chloroform–methanol).

Anal. Calc. for $C_{10}H_{18}O_7 \cdot 0.5\ H_2O$: C, 46.33; H, 7.39; O, 46.28. Found: C, 46.76; H, 7.01; O, 46.46.

*6-*O*-(tert-Butyldiphenylsilyl)-1,2-*O*-[1-(exo-ethoxy)ethylidene]-α-*D*-glucopyranose* (**4**). — Crude syrupy **3** (derived from 10 g of triacetyl orthoester **2**) was dissolved in toluene (200 mL). Bis(tributyl)tin oxide (20 g) was added and the solution boiled under reflux for 3 h with continuous removal of water. The solution was then evaporated to as dry as possible. The concentrate was treated with *tert*-butylchlorodiphenylsilane (10 mL) and tetrabutylammonium bromide (10.5 g). After being stirred for 24 h at room temperature, the solution was purified by medium-pressure (0.2 MPa) preparative-liquid chromatography (Jobin Yvon

Chromatospac Prep 10; 1:1 hexane–ethyl acetate with 1% triethylamine) to obtain compound **4** (11.3 g, 87%), $[\alpha]_D^{28}$ +13° (*c* 1.24, chloroform); R_F 0.23 (solvent *B*); ν_{max}^{film} 3440 (br.), 3050, 2975, 2940, 2860, 1475, 1460, 1425, 1380, 1250, 1100 (br.), 950, 900, 825, 730, and 680 cm^{-1}; ^{1}H-n.m.r.: δ 5.84 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1), 4.37 (t, 1 H, $J_{2,3}$ 5.5 Hz, H-2), 3.60 (q, 2 H, OCH_2CH_3), 2.89 (br., 2 H, 2 OH), 1.69 (s, 3 H, C-Me), 1.18 (t, 3 H, OCH_2CH_3), and 1.05 (s, 9 H, CMe_3).

Anal. Calc. for $C_{26}H_{36}O_7Si$: C, 63.91; H, 7.42. Found: C, 63.61; H, 7.50.

*3-O-Allyl-6-O-(*tert*-butyldiphenylsilyl)-1,2-O-[1-(*exo*-ethoxy)ethylidene]-α-*D*-glucopyranose* (**5**). — To a solution of **4** (2 g, 4.1 mmol) and allyl bromide (3 mL) in *N,N*-dimethylformamide (10 mL) was added silver oxide (6 g), portionwise with cooling, over a period of 1 h. The suspension was stirred for 4 h at room temperature, or until t.l.c. (solvent *A*) showed the conversion of **4** into a major product having R_F 0.67. The suspension was diluted with chloroform and filtered through Celite. The filtrate was evaporated *in vacuo* to a solid mass, which was taken up in methanol and filtered again through Celite to remove the insoluble, yellowish silver bromide. The filtrate was evaporated and purified on a column of silica gel (solvent *B*, containing 1% of triethylamine) to give **5** (1.6 g, 74%) as a syrup, $[\alpha]_D^{26}$ +11° (*c* 0.15, chloroform); ν_{max}^{film} 3475, 3075, 3060, 2950, 2900, 2860, 1875, 1460, 1360, 1250, 1120 (br.), 950, 920, 825, 730, and 680 cm^{-1}; ^{1}H-n.m.r.: δ 7.80–7.30 (m, 10 H, 2 Ph), 5.76 (d, 1 H, $J_{1,2}$ 5.5 Hz, H-1), 3.58 (q, 2 H, OCH_2CH_3), 1.69 (s, 3 H, CMe), 1.19 (t, 3 H, OCH_2CH_3), and 1.06 (s, 9 H, CMe_3).

Anal. Calc. for $C_{29}H_{40}O_9Si$: C, 65.88; H, 7.63. Found: C, 65.72; H, 7.45.

When the reaction of **4** with allyl bromide and silver oxide was allowed to proceed for periods >4 h, t.l.c. showed the formation of **6**, R_F 0.83. After processing as described for **5**, compound **6** (0.85 g, 40%) was isolated as a syrup, $[\alpha]_D^{26}$ +25° (*c* 4.1, chloroform).

3-O-Allyl-D-glucose (**12**). — To confirm that the substitution had taken place at O-3, **5** was converted into **12** by the following procedure: compound **5** (20 mg) in 95% ethanol was stirred with cation-exchange resin (H^+) for 15 min at room temperature. The resin was filtered off and the filtrate evaporated to a syrup, which was deacetylated with 0.5% sodium methoxide in dry methanol (0.1 mL). After 4 h, the solution was neutralized with cation-exchange resin (pyridinium$^+$), the suspension filtered, and the filtrate evaporated to give a syrup. Finally, removal of the Bu^tPh_2Si group was effected by treating the syrup with M tetrabutylammonium fluoride in oxolane (0.15 mL). The solution was stirred for 4 h at room temperature when t.l.c. (5:1 chloroform–methanol) showed one spot (R_F 0.4) that gave a positive reaction with the potassium permangate spray and was not fluorescent under u.v. light. This product was identical, according to t.l.c. in 5:1 chloroform–methanol (multiple development) and in 1:1 diethyl ether–petroleum ether, to compound **12** obtained by acid hydrolysis of 3-*O*-allyl-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose[14] with IR-120 (H^+) resin suspended in 80% aqueous ethanol and kept for 3 h at 90°.

*3-O-(2-Butenyl)-6-O-(*tert*-butyldiphenylsilyl)-1,2,4-O-orthoacetyl-α-D-gluco-*

pyranose (**11**). — To a mixture of **4** (0.2 g, 0.4 mmol), crotyl bromide (0.45 mL), and *N,N*-dimethylformamide (2 mL) was added silver oxide (0.6 g) with cooling, and the mixture was stirred overnight at room temperature. Filtration (Celite) and evaporation of solvent gave a syrup that was purified on a column of silica gel with 5:1 hexane–ethyl acetate containing 1% triethylamine as eluent. The product (**11**) was collected as a colorless syrup (0.30 g, 85%), $[\alpha]_D^{24}$ +24° (*c* 0.17, chloroform); R_F 0.44 (4:1 hexane–ethyl acetate); ν_{max}^{film} 2950, 2875, 1475, 1450, 1410, 1305, 1110 (br.), 1000, 995, 875, 850, 825, 725, and 700 cm^{-1}; ^{1}H-n.m.r.: (250 MHz, performed on a Bruker 250 MHz instrument): δ 7.67–7.35 (m, 10 H, 2 Ph), 5.73 (d, 1 H, $J_{1,2}$ 4.78 Hz, H-1), 5.60, 5.37 (m, 2 H, -CH=CH_2), 1.66 (s, 3 H, CH_3), 1.64 (br. d, CH=CHCH_3), and 1.06 (s, 9 H, CMe_3).

Anal. Calc. for $C_{28}H_{36}O_6Si \cdot 0.5\ H_2O$: C, 66.51; H, 7.38. Found: C, 66.53; H, 7.51.

*3-O-Allyl-4-O-benzyl-6-O-(*tert*-butyldiphenylsilyl)-1,2-O-(ethoxyethylidene)-α-*D*-glucopyranose* (**8**). — A mixture of **5** (3.1 g, 5.9 mmol), benzyl bromide (2 mL), barium oxide (2 g), barium hydroxide octahydrate (0.5 g), and *N,N*-dimethylformamide (20 mL) was stirred overnight at room temperature, when t.l.c. (3:1 hexane–ethyl acetate) showed the formation of two products (R_F 0.72 and 0.67). The mixture was filtered (Celite), and the residue washed with *N,N*-dimethylformamide and chloroform. The filtrates were combined and evaporated. A solution of the residue in chloroform was applied to a column of silica gel, and eluted with 5:1 hexane–ethyl acetate containing 1% triethylamine. Evaporation of solvent gave a colorless syrup (3.0 g, 82%), $[\alpha]_D^{26}$ +28° (*c* 0.13, chloroform); ν_{max}^{film} 3080, 2950, 2060, 1500, 1438, 1415, 1390, 1370, 1255, 1120 (br.), and 820 cm^{-1}; the ^{1}H-n.m.r. spectrum showed the product to be a 3:2 mixture of *exo* and *endo* isomers: δ 5.85 (d, 1 H, $J_{1,2}$ 5 Hz, H-1), 5.47, 5.34 (m, 2 H, CH=CH_2), 1.65 and 1.54 (s, 3 H, OCH_2CH_3), 1.06, 1.01 (s, 9 H, CMe_3 of *exo*- and *endo*-isomers). The *exo*-isomer later crystallized from the mixture. However, no attempt was made to recrystallize it.

Anal. Calc. for $C_{36}H_{46}O_7Si$: C, 69.87; H, 7.49. Found: C, 69.92; H, 7.05.

A slower moving by-product **9** (R_F 0.55) was also isolated from this reaction (480 mg, 10%). The ^{1}H-n.m.r. and i.r. spectra showed the absence of Bu^tPh_2Si groups and the presence of two benzyl groups.

*2-O-Acetyl-3-O-allyl-4-O-benzyl-6-O-(*tert*-butyldiphenylsilyl)-α- and -β-*D*-glucopyranose* (**13**). — Compound **8** (0.1 g, 0.16 mmol) was dissolved in 95% ethanol (5 mL) and treated with cation-exchange resin (200–400 mesh, H^+). The mixture was stirred for 15 min at room temperature when t.l.c. (solvent *A*) showed the complete hydrolysis of **8** into two products (R_F 0.35, 0.24, α- and β-D anomers, respectively). The mixture was filtered and evaporated to give syrupy **13**, which was purified by preparative-layer chromatography (solvent *D*); **13** was located on the plate by viewing under u.v. light, and by spraying a narrow zone with (*a*) the potassium permanganate, and (*b*) the anisaldehyde spray-reagents. Extraction was performed by scraping off the silica gel from the plate and stirring overnight with

chloroform, filtration, and evaporation. The α- and β-D anomers were well resolved and were extracted separately to give α anomer (75 mg) and β anomer (slower-moving spot, 23 mg) (overall yield 98 mg, 95%), $[\alpha]_D^{26}$ +42° (*c* 0.85, chloroform) and +35° (*c* 1.92 chloroform) for α- and β-D anomer, respectively; ν_{max}^{film} 3400 (br.), 3070, 2950, 2860, 1750, 1600, 1590, 1580, 1500, 1460, 1430, 1370, 1240, 1100 (br.), 925, 825, 725, and 680 cm^{-1}.

Anal. Calc. for $C_{34}H_{42}O_7Si$: C, 69.12; H, 7.17. Found: C, 69.00; H, 7.14.

*2-O-Acetyl-3-O-allyl-4-O-benzyl-6-O-(*tert*-butyldiphenylsilyl)-D-glucopyranosyl chloride* (**14**). — A solution of **13** (0.1 g, 0.17 mmol) in dry dichloromethane was treated with chloromethylenedimethylammonium chloride, prepared freshly from 0.25 mL each of *N,N*-dimethylformamide and thionyl chloride[16]. The solution was stirred at room temperature overnight, diluted with dry toluene, and filtered through Florisil. Evaporation of the filtrate gave **14** as a syrup (80 mg, 78%) (R_F 0.80; solvent *A*) which was used immediately for glycosylation without further purification.

*Methyl 2-O-acetyl-3-O-allyl-4-O-benzyl-6-O-(*tert*-butyldiphenylsilyl)-β-D-glucopyranoside* (**15**). — The chloride **14** was converted into the methyl glycoside by the following procedure. A mixture of **14** (70 mg, 0.11 mmol), mercuric cyanide (80 mg), mercuric bromide (90 mg), and anhydrous methanol (10 mL) in dichloromethane was stirred overnight at room temperature. T.l.c. (solvent *A*) indicated the formation of two major products (R_F 0.72 and 0.63). The mixture was filtered and the filtrate evaporated to give a syrup that was purified by preparative-layer chromatography (solvent *A*). The faster-moving band containing **14** was located as described for compound **13**. The compound was extracted by scraping off the silica gel from the plate and stirring overnight with 5:1 chloroform–methanol to give syrupy **15**, yield 30 mg (43%), $[\alpha]_D^{28}$ −11° (*c* 0.1, chloroform); ν_{max}^{film} 2940, 2860, (C-H), 1750, 1400, 1430, 1375, 1230, 1100 (br.), 825, 730, and 700 cm^{-1}; ^{1}H-n.m.r.: δ 5.02 (m, 2 H, CH=CH_2), 4.95 (d, 1 H, $J_{1,2}$ 7 Hz, H-1), 4.36 (d, 2 H, C$H_2C_6H_5$), 3.47 (s, 3 H, OMe), 2.05 (s, 3 H, COCH_3), and 1.02 (s, 9 H, CMe_3).

Anal. Calc. for $C_{35}H_{44}O_7Si$: C, 69.51; H, 7.33. Found: C, 69.45; H, 7.50.

The product showing R_F 0.63 (17.5 mg, 25%) had ν_{max}^{film} 2950, 2260, 1750, 1475, 1390, 1250, and 1100 cm^{-1}; ^{1}H-n.m.r.: δ 7.40 (5 H, Ph), 3.51 (3 H, OMe), and 2.09 (3 H, OAc).

6-O-Acetyl-3-O-allyl-4-O-benzyl-1,2-O-[1-ethoxyethylidene]-α-D-glucopyranose (**10**). — This compound was prepared from **8** in two steps. Thus, **8** (1 g, 1.62 mmol), which was a mixture of *endo* and *exo* isomers, was treated with M tetrabutylammonium fluoride in oxolane (3.5 mL). The solution was stirred at room temperature for 4 h, the solvent evaporated, and the residue, after being dried, was treated with acetic anhydride–pyridine overnight. Evaporation by repeated addition and removal of toluene gave a syrup, which was purified by column chromatography on silica gel (4:1 hexane–ethyl acetate with 1% triethylamine) to give **10** as syrup (0.55 g, 81%), $[\alpha]_D^{28}$ +47° (*c* 0.24, chloroform); ν_{max}^{film} 2975, 2950 (C-H), 1730 (OAc), 1100 (C-O-C), 760, and 740 cm^{-1} (Ph); ^{1}H-n.m.r. (60 MHz) δ 7.42 (m, 5

H, Ph), 3.65 (q, 2 H, OCH_2CH_3), 2.02 (s, 3 H, Ac), 1.70 (s, 3 H, C-CH_3), and 1.20 (t, 3 H, OCH_2CH_3).

Anal. Calc. for $C_{22}H_{30}O_8$: C, 62.54; H, 7.16; O, 30.30. Found: C, 62.54; H, 7.19; O, 30.25.

2,6-Di-O-acetyl-3-O-allyl-4-O-benzyl-D-glucopyranosyl bromide (**16**). — Compound **10** (0.42 g, 0.99 mmol) was dissolved in dichloromethane (4 mL) and cooled to 0° in an ice–water bath. A 32% solution of hydrogen bromide in acetic acid (1 mL) was then quickly added. The solution was stirred at 0° for 30 min, whereupon t.l.c. (solvent *A*) showed the formation of bromide **16** (R_F 0.62). The mixture was processed immediately by diluting with dichloromethane and washing, successively, with ice–water, cold aqueous sodium hydrogencarbonate, and ice–water. The organic portion was dried ($MgSO_4$) and evaporated to a syrup (0.39 g, 90%), which was used immediately without purification.

Benzyl 2-acetamido-3,6-di-O-benzyl-2-deoxy-4-O-(2,6-di-O-acetyl-3-O-allyl-4-O-benzyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**18**). — To a mixture containing compound[3] **17** (0.365 g, 0.74 mmol), silver triflate (0.305 g, 1.19 mmol), 4A molecular sieve, and dichloromethane (8 mL) was added **16** [prepared from 0.73 g of **10**] at −70° under nitrogen. The solution was kept in the dark and allowed to warm up gradually to room temperature while stirring was continued for 48 h. The mixture was filtered through Celite and the filtrate evaporated to a syrupy product, which was purified by preparative-layer chromatography (solvent *C*) to give **18** as an amorphous glass (0.352 g, 55%), R_F 0.54 (solvent *C*), $[\alpha]_D^{26}$ +75° (*c* 0.1, chloroform); ν_{max}^{film} 3300 (NH), 3025, 2925, 2875 (C-H), 1750 (OAc), 1650 (amide I), 1550 (amide II), 1150–1000 (C-O-C), 760, and 685 cm^{-1} (Ph); ^{1}H-n.m.r.: δ 5.87 (m, 1 H, OCH_2-C*H*=CH_2), 5.25 [dd, 1 H, *J* 17.2 Hz, -C*H*=CH_2 (t)], 5.16 [dd, 1 H, *J* 10.4 Hz, -C*H*=CH_2 (c)], 5.08 (d, 1 H, $J_{2,NH}$ 8.6 Hz, NH), 4.92 (t, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.47 (d, 1 H, $J_{1',2'}$ 8.4 Hz, H-1'), 4.24 (ddd, 1 H, H-2), 2.01, 1.85 (s, 3 H, OAc), and 1.70 (s, 3 H, NAc).

Anal. Calc. for $C_{49}H_{57}NO_{13}$: C, 67.81; H, 6.62; N, 1.61; O, 23.96. Found: C, 67.54; H, 6.60; N, 1.68; O, 24.07.

*Benzyl 2-acetamido-4-O-(2-O-acetyl-3-O-allyl-4-O-benzyl-6-O-*tert*-butyldiphenylsilyl-β-D-glucopyranosyl)-3,6-di-O-benzyl-2-deoxy-α-D-glucopyranoside* (**19**). — A mixture of compound[3] **17** (0.1 g, 0.19 mmol), silver triflate (0.1 g), molecular sieve 4A, and dichloromethane (2 mL) was cooled to −70° and a solution of chloride **14** (0.175 g, 0.21 mmol) in dichloromethane (2 mL) was then added. The reaction was allowed to warm up gradually to 4°, and kept at that temperature for 48 h, whereupon t.l.c. (solvent *B*) indicated the formation of two products (R_F 0.62, 0.45). The solution was processed as described for the preparation of **18**, and the resulting mixture was subjected to preparative-layer chromatography (solvent *B*) to give **19** (R_F 0.62) as a syrup (0.08 g, 38%), $[\alpha]_D^{29}$ +73° (*c* 0.58, chloroform); ν_{max}^{film} 3440 (NH), 3050, 2900 (C-H), 1750 (OAc), 1675 (amide I), 1550 (amide II), 1200–1000 (C-O-C), 780, and 700 cm^{-1} (Ph); ^{1}H-n.m.r. data: δ 7.71–7.26 (m, 30 H, Ph), 5.87 (m, 1 H, -CH_2-C*H*=CH_2), 5.74 [dd, 1 H, *J* 17.2 Hz, -C*H*=CH_2 (t)], 5.15

[dd, 1 H, J 10.4 Hz, -C*H*=CH_2 (c)], 5.03 (d, 1 H, $J_{2,NH}$ 8.6 Hz, NH), 4.96 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 4.95 (dd, 1 H, $J_{2',3'}$ 7.6 Hz, H-2') 4.48 (d, 1 H, $J_{1',2'}$ 8.4 Hz, H-1'), 4.26, 4.09 (dd, 1 H, -OCH_AH_BCH=CH_2), 4.16 (ddd, 1 H, $J_{2,3}$ 10.5 Hz, H-2), 4.06 (t, 1 H, $J_{3,4} = J_{4,5}$ = 9.2 Hz, H-4), 3.65 (m, 1 H, H-5), 3.57 (dd, 1 H, H-3), 2.02 (s, 3 H, OAc), 1.69 (s, 3 H, NAc), and 0.99 (s, 9 H, *tert*-butyl).

Anal. Calc. for $C_{63}H_{73}NO_{12}Si$: C, 71.09; H, 6.91; N, 1.32. Found: C, 70.84; H, 7.00; N, 1.23.

The slower moving by-product was isolated as a syrup (0.05 g, 23%). According to the n.m.r. spectrum, i.r. spectrum and elemental analysis, it was not the α-linked anomer, but rather a positional isomer of **19**.

*Benzyl 2-acetamido-4-*O*-(3-*O*-allyl-4-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-β-*D*-glucopyranosyl)-3,6-di-*O*-benzyl-2-deoxy-α-*D*-glucopyranoside* (**20**). — *Method A.* Compound **18** (205 mg, 0.74 mmol) was dissolved in 1:2 dichloromethane–methanol (4.8 mL). The solution was treated with 5% sodium methoxide (0.5 mL) and kept at room temperature for 24 h. Neutralization (AG 50W-X8 cation-exchange resin, pyridinium$^+$), followed by filtration and evaporation of the solvent, gave a white solid, which was first dried and then treated with *tert*-butylchlorodiphenylsilane (0.07 mL), imidazole (33 mg), and *N,N*-dimethylformamide (2 mL). The solution was stirred overnight at room temperature. Purification by chromatography on a column of silica gel (solvent *B*) gave **20** as a syrup (160 mg, 70%), $[\alpha]_D^{19}$ +85° (*c* 0.31, chloroform), R_F 0.40 (solvent *B*); ν_{max}^{film} 3440 (OH), 3300 (NH), 3050, 2950 (CH), 1650 (amide I), 1505 (amide II), 1200–1000 (C-O-C), 725, and 700 cm^{-1} (Ph); ^{1}H-n.m.r. (60 MHz) data: δ 7.60–7.35 (m, 30 H, Ph), 5.10 (d, 1 H, NH), 1.75 (s, 3 H, NAc), and 1.00 (s, 9 H, *tert*-butyl).

Anal. Calc. for $C_{61}H_{71}NO_{11}Si$: C, 71.67; H, 7.00; N, 1.37. Found: C, 71.72; H, 7.17; N, 1.26.

Method B. Compound **19** (50 mg, 0.05 mmol) was deacetylated as described in Method A to give **20** (44 mg, 92%), with identical properties.

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