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THE SYNTHESIS AND PROPERTIES OF BENZYLATED OXAZOLINES DERIVED FROM 2-ACETAMIDO-2-DEOXY-D-GLUCOSE*

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ABSTRACT

2-Methyl-(2-acetamido-3,4,6-tri-*O*-benzyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline, 2-methyl-(2-acetamido-6-*O*-acetyl-3,4-di-*O*-benzyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline, and 2-methyl-(2-acetamido-4-*O*-acetyl-3,6-di-*O*-benzyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline were synthesized from the allyl 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranosides, and from the 3,4-di-*O*-benzyl or 3,6-di-*O*-benzyl analogs, respectively, both the α and β anomer being used in each case. The preparation of allyl 2-acetamido-3,4,6-tri-*O*-benzyl- and 3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside is also described. Treatment of the tri-*O*-benzyl oxazoline with dibenzyl phosphate gave a pentabenzylglycosyl phosphate, from which all the benzyl groups were removed by catalytic hydrogenation, giving 2-acetamido-2-deoxy-α-D-glucopyranosyl phosphate. The corresponding β anomer was not detectable. Treatment of the 3,4-, or 3,6-, di-*O*-benzyl oxazoline with allyl 2-acetamido-3,4-di-*O*-benzyl-α-D-glucopyranoside readily gave disaccharide products from which the protecting groups were removed, to give the (1→6)-linked isomer of di-*N*-acetylchitobiose. Under both acidic and basic conditions, this isomer was less stable than the (1→4)-linked compound.

Attempts to employ the 3,6-di-*O*-benzyl oxazoline for the formation of (1→4)-linked disaccharides, by treatment with either anomer of allyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-D-glucopyranoside, were not very successful, presumably owing to hindrance by the bulky benzyl groups.

INTRODUCTION

The synthetic applications of per-*O*-acetyl[1,2-*d*]oxazolines derived from 2-acetamido-2-deoxyhexoses are well known. They include the stereospecific prepara-

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tion of 1,2-*trans*-glycosides (including di- and tri-saccharides)[1,2], 1,2-*trans*-glycosyl phosphates derived from 2-acetamido-2-deoxy-D-mannose[3], and 1,2-*cis*-glycosyl phosphates derived from 2-acetamido-2-deoxy-D-glucose and di-*N*-acetylchitobiose[4,5]. However, the preparation and use of carbohydrate oxazolines bearing such substituents as benzyl groups has not been described. The availability of partially benzylated oxazolines having an *O*-acetyl group in the position not substituted by benzyl groups might be expected to extend significantly the synthetic utility of these compounds. For example, by reaction of one of them with an alcoholic component to give a glycoside or disaccharide, or treatment with dibenzyl phosphate to give a glycosyl phosphate[5], a new compound would be obtained having an *O*-acetyl group as well as benzyl substituents; then, the *O*-acetyl group could be selectively removed, making available a single hydroxyl group for linkage of a further sugar residue. In this paper are described the preparation and reactions of the 3,6- and 3,4-di- and 3,4,6-tri-*O*-benzyl oxazolines derived from 2-acetamido-2-deoxy-D-glucose.

RESULTS AND DISCUSSION

Gent and Gigg[6] introduced the concept of "temporary" and "persistent" protective groups in carbohydrate synthesis. Generally, the temporary groups are allyl (or 2-butenyl) groups, and the persistent groups are benzyl ethers. The same approach was employed in this investigation of benzylated oxazolines.

Allyl 2-acetamido-3,4,6-tri-*O*-benzyl-, 3,4-di-*O*-benzyl-, and 3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranosides (**1**, **2**, and **3**, respectively), prepared according to Warren and Jeanloz[2], were converted into the 1-propenyl glycosides **4**, **5**, and **6**, respectively, by treatment with potassium *tert*-butoxide in dimethyl sulfoxide[7]. Hydrolysis with mercuric chloride[8] gave 2-acetamido-3,4,6-tri-*O*-benzyl-, 3,4-di-*O*-benzyl-, and 3,6-di-*O*-benzyl-2-deoxy-D-glucopyranose (**7**, **8**, and **9**, respectively), which were converted into the corresponding glycosyl chlorides **10**, **11**, and **12** by treatment with acetyl chloride[9]. This reagent was not redistilled before use, because this would have eliminated the trace of hydrogen chloride therein that is necessary to catalyze the glycosyl chloride formation[10]. The required oxazolines **13**, **14**, and **15** were readily obtained from the corresponding, very unstable glycosyl chlorides, without prior purification of these, by chloride ion catalysis[11] in the presence of a base (sodium hydrogencarbonate). The compounds obtained (**13**, **14**, and **15**) showed one major spot on thin-layer chromatograms; they contained traces of benzyl acetate, due to partial acetolysis of benzyl groups by acetyl chloride. However, the oxazolines were suitable for glycosylation reactions without purification.

Compound **10** was also prepared by an alternative method (treatment of **7** with triphenylphosphine and carbon tetrachloride[12]) that avoided the acetolysis problem. Unfortunately, the by-product triphenylphosphine oxide (showing a typical spot in t.l.c.) was difficult to remove from the oxazoline **13** (and its derivatives) when **10** was obtained in this way, so that acetyl chloride remained the reagent of choice.

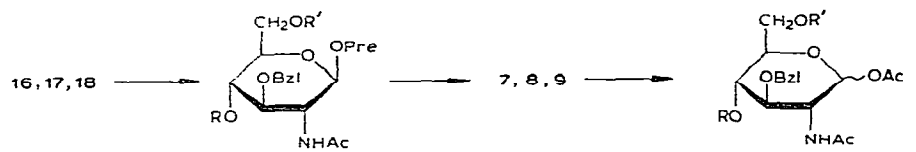
Although the benzylated oxazolines are unstable, they could to a considerable

All = $CH_2CH{=}CH_2$, Pre = $CH{=}CH{-}CH_3$

extent be purified by preparative t.l.c., to afford samples for spectroscopic and polarimetric examination and elementary analysis. The compounds were also characterized by conversion into the corresponding allyl β-D-glycosides, by treatment with dry allyl alcohol and *p*-toluenesulfonic acid, followed, in the case of the two di-*O*-benzyl derivatives, by *O*-deacetylation. Thus, **13**, **14**, and **15** gave compounds **16**, **17**, and **18**, respectively, these products being identified by comparison with standards.

Allyl 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**16**) was prepared by benzylation of **19** (ref. 13) with benzyl bromide and potassium hydroxide in *N*,*N*-dimethylformamide. The 3,4-di-*O*-benzyl derivative **17** had been synthesized by Shaban *et al.*[14]; it was also obtained, together with the 3,6-di-*O*-benzyl compound **18**, by partial benzylation of allyl 2-acetamido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside[14] (**20**). This was performed by two methods: in the first, **20** was briefly treated with ~1 mol. equiv. of benzyl bromide in the presence of sodium hydroxide, and the products (**17** and **18**) were separated by preparative layer-chromatography; in the second, the base was a mixture of barium oxide and hydroxide, and **20** was slowly converted into a mixture of **17** and **18**, from which **18** was purified by column chromatography. In both cases, the 3,6-di-*O*-benzyl compound **18** was preponderant, and only when sodium hydroxide was the base was an appreciable proportion of the product the 3,4-di-*O*-benzyl derivative **17**.

The allyl β-D-glycosides **16**, **17**, and **18** were also the alternative starting-materials for the synthesis of the corresponding oxazolines **13**, **14**, and **15**. In each case, the isomerization of the allyl into a 1-propenyl group was again achieved with potassium *tert*-butoxide[7] rather than with chlorotris(triphenylphosphine)rhodium[15], owing to the potential problem of unwanted hydrogenation with this catalyst[2,16]. It was also possible to replace dimethyl sulfoxide with *N*,*N*-dimethylformamide as the solvent for this reaction, thus avoiding offensive odors. The identities of the 1-propenyl glycosides **22**, **23**, and **24** were confirmed by their i.r. and n.m.r. spectra, and



22 R = R' = Bzl
23 R = Bzl, R' = H
24 R = H, R' = Bzl

25 R = R' = Bzl
26 R = Bzl, R' = Ac
27 R = Ac, R' = Bzl

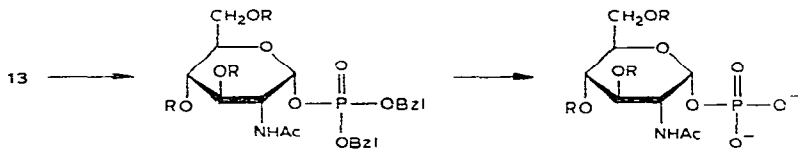
their ease of hydrolysis with dilute hydrochloric acid (to convert **22** into **7**) or with mercuric chloride (to convert **23** and **24** into **8** and **9**, respectively), after which, further conversion into the corresponding glycosyl chlorides **10**, **11**, and **12**, and hence into the corresponding oxazolines **13**, **14**, and **15**, was as described for the α series.

When the reducing derivatives **7**, **8**, and **9** were obtained from the α-D-glycosides **4**, **5**, and **6**, respectively, the main product was the α-D anomer. However, when the

starting materials were the β-D-glycosides **22**, **23**, and **24**, a mixture of anomers always resulted. In this instance, further characterization of **7**, **8**, and **9** was performed, by their conversion into the corresponding crystalline acetates **25**, **26**, and **27**.

One of the most important synthetic uses for oxazolines derived from 2-acetamido-2-deoxy-D-glucose (or di-*N*-acetylchitobiose) is their stereospecific conversion into α-D-glycosyl phosphates[4,5]. This is best done by treatment with dibenzyl phosphate, followed by hydrogenolysis of the benzyl groups from the phosphate group. If these steps were performed with an oxazoline having benzyl ether substituents, it is apparent that both types of benzyl groups could be removed in one step. Such a procedure would be advantageous for the synthesis of tri- or oligo-saccharide phosphates *via* oxazoline intermediates[2,5].

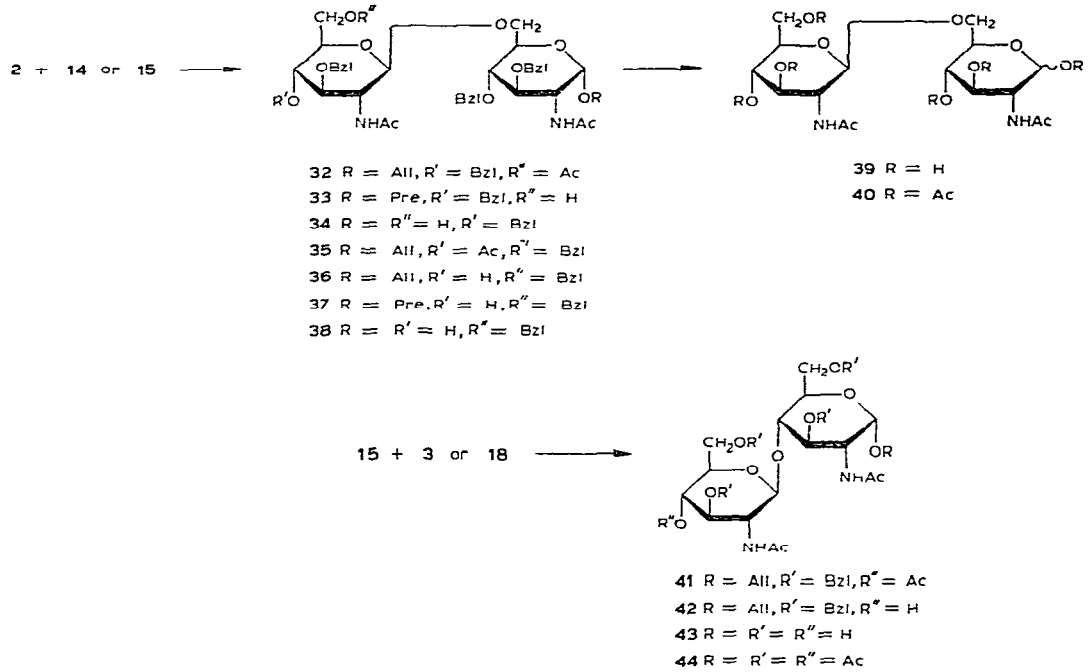
The mechanism of the formation of α-D-glycosyl phosphates from per-*O*-acetyl oxazolines is uncertain, because the products, in the case of the 2-amino-2-deoxy-D-glucose derivatives, would have been expected to have the β-D configuration[4,5]. It was important, therefore, to determine whether or not this unusual stereospecificity would be conserved when the oxazoline was substituted with benzyl groups. When **13** was kept overnight at room temperature with a small excess of dibenzyl phosphate in dry 1,2-dichloroethane, it was efficiently converted, as shown by t.l.c., into a single, phosphate-containing compound. However, this product was very unstable and, unlike[5] the per-*O*-acetyl derivative **29**, could not be purified by chromatography. Therefore, it was hydrogenated directly, and the product, consisting of **30** and unphosphorylated materials, was acetylated to give 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl phosphate (**31**), purified by preparative layer-chromatography. T.l.c. of unpurified **30** and **31** gave no indication of the β-D anomer. Compound **31** also had an n.m.r. spectrum identical with that of a sample prepared by the phosphoric acid procedure[17], and its α-D configuration was further confirmed by the value of the optical rotation.



28 R = Bzl
29 R = Ac

30 R = H
31 R = Ac

A further, potentially important, property of the benzylated oxazolines is their ability to glycosylate derivatives of 2-acetamido-2-deoxy-D-glucose having a single, unprotected hydroxyl group. This was investigated with **2**, **3** (ref. 2), and **18**. When a mixture of **14** and **2** was dissolved in dry dichloroethane and treated with anhydrous *p*-toluenesulfonic acid[2], a good yield of the (1→6)-linked disaccharide **32** was readily obtained. The behavior of the 3,6-di-*O*-benzyl oxazoline **15** was similar, and it gave **35**.



Compounds **32** and **35** were converted, by treatment with potassium *tert*-butoxide in dimethyl sulfoxide[7], into the *O*-deacetylated 1-propenyl glycosides **33** and **37**, respectively, which were hydrolyzed with mercuric chloride[8] to give **34** and **38**. Catalytic hydrogenolysis of the benzyl groups of **34** and **38** gave, as expected, the same product **39**, an isomer[18] of di-*N*-acetylchitobiose[19] (**43**). The (1→6)- and (1→4)-linked disaccharides (**39** and **43**, respectively) were readily distinguished from each other by t.l.c., by paper chromatography, or by their behavior when treated with hot, dilute hydrochloric acid, the (1→6)-linked compound **39** being the much more easily hydrolyzed[20]. When amorphous **39** was acetylated with acetic anhydride–pyridine, it gave the crystalline octaacetate **40** having properties similar to those previously reported[21]. However, it was not possible to purify **39** by conversion into **40**, recrystallization, and *O*-deacetylation, because **39** was not sufficiently stable, as shown by t.l.c., to the mild, alkaline conditions necessary for saponification; **43** could, however, be obtained by *O*-deacetylation of octaacetylchitobiose[19], and t.l.c. indicated only minor degradation.

As an alternative to concomitant *O*-deacetylation and allyl-group isomerization, **35** was *O*-deacetylated to give **36**. This compound will be useful for the synthesis of *O*-β-D-mannopyranosyl-(1→4)-*O*-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1→6)-2-acetamido-2-deoxy-D-glucose, the (1→6)-linked isomer of the "core" trisaccharide of *N*-glycoproteins[22] and thus an isomer of the structure probably present in the "lipid intermediates" of glycoprotein biosynthesis[23].

In attempts to synthesize a (1→4)-linked disaccharide, the 3,6-di-*O*-benzyl oxazoline **15** was treated with the α and β anomers of allyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-D-glucopyranoside (**3** and **18**, respectively) under conditions similar to those successfully employed for the synthesis of **35**. With the α-D anomer **3**, the very low yield of the desired compound **42**, and recovery of most of **3** unchanged, showed that the reaction to form **41** was severely hindered by the presence of benzyl groups in both **3** and **15**. When **3** was replaced by the β anomer **18**, the reaction took a different course, and **18** was not recovered, as shown by t.l.c. However, when the reaction mixture was carefully processed, a "product" was isolated that appeared to be the 4-*O*-acetyl derivative **21** of **18**. This conclusion was confirmed by the preparation of **21** from **18**, and by comparison of **21** with the compound obtained from the reaction of **15** with **18**. Thus, intermolecular transesterification had occurred, instead of the expected nucleophilic attack by the 4-hydroxyl group of **18** on C-1 of the oxazoline **15**.

EXPERIMENTAL

General methods. — Melting points were determined on 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 spectrophotometer, Model 237. N.m.r. spectra were recorded at 60 MHz with a Varian T-60 spectrometer, with deuterium oxide as the solvent and sodium 4,4-dimethyl-4-silapentane-1-sulfonate as the internal standard, or with chloroform-*d* as the solvent, containing 1% of tetramethylsilane as the internal standard. The cation-exchange resin used was AG 50 W-X 8 (200–400 mesh, Bio-Rad Laboratories, Richmond, CA); in all cases, the amount of resin used was in at least a two-fold excess over the quantity necessary to effect complete ion-exchange. Evaporations were, unless otherwise stated, conducted *in vacuo* with the bath temperature kept below 30°. Dichloromethane and 1,2-dichloroethane were dried by addition of molecular sieve (type 5A, Grade 522, 8–12 mesh, Fisher Scientific Co., FairLawn, NJ). Other solvents were dried (where stated) by treatment with molecular sieve followed by the addition of calcium hydride (in lump form Fisher). The microanalyses were performed by Dr. W. Manser, Zurich, Switzerland, and by Galbraith Laboratories Inc., Knoxville, TN.

Chromatographic methods. — T.l.c. and preparative t.l.c. were performed on precoated plates of Silica Gel G, 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 they were used without pretreatment. All proportions of solvents are v/v. Preparative layer-chromatography was performed on precoated Silica Gel PLC plates, 2 mm thick (Merck), or on precoated plates of Silica Gel F 254, 0.5 mm thick (Merck). The solvent system used for t.l.c. and preparative layer-chromatography was 10:1 chloroform–methanol, unless stated otherwise. The spray reagent, unless otherwise stated, was 1:1:18 anisaldehyde–sulfuric acid–ethanol[24], and the plates were

heated to 125°. Unsaturation was detected with a 1% solution of potassium permanganate in 2% sodium carbonate solution. Phosphate groups were detected with the spray reagent described by Dittmer and Lester[25]. When plates were eluted more than once, they were dried in air between each elution. Column chromatography was performed on Silica gel (0.05–0.2 mm, 70–325 mesh; Merck).

*1-Propenyl 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-α-*D*-glucopyranoside* (**4**). — A solution of[2] **1** (0.6 g) in anhydrous dimethyl sulfoxide (10 ml) was treated with potassium *tert*-butoxide (2.2 g), and the mixture was kept for 3 h at 55° in a stoppered tube. After being cooled, the mixture was diluted with a large excess of water, and three extractions with ether (~100 ml), followed by drying ($MgSO_4$) and evaporation, gave crude **4**. The product was purified by preparative layer-chromatography using 3 PLC plates (20 × 20 cm) (two elutions). After detection of **4** ($KMnO_4$ spray), the silica gel was removed from the plate, and stirred overnight with 5:1 chloroform–methanol to extract the product. Filtration (Celite) and evaporation gave solid **4** (0.58 g, 97%), which was pure according to t.l.c. (R_F 0.85). Crystallization from aqueous ethanol gave crystals, m.p. 138–139°, $[\alpha]_D^{20}$ +101° (*c* 1.7, chloroform); i.r. spectrum indistinguishable from that[2] of **1**.

Anal. Calc. for $C_{32}H_{37}NO_6$: C, 72.29; H, 7.01; N, 2.64; O, 18.06. Found: C, 72.32; H, 7.08; H, 2.60; O, 18.17.

*2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-*D*-glucopyranose* (**7**). — (*a*) *From* **4**. A solution of **4** (not recrystallized, 0.5 g) in 5:1 acetone–water (10 ml) was treated with $HgCl_2$ (1.25 g). After a few min, crystals of **7** began to appear. After 15 min, the separation of **7** from the reaction mixture was completed by the addition of a large excess of water, and cooling for 2 h at 4°. The product was filtered off, washed with water, and dried *in vacuo* over P_2O_5, to give **7** (0.37 g, 80%), a mixture of anomers according to t.l.c. (α anomer preponderant, R_F 0.56). For further characterization, see (*b*).

(*b*) *From* **16**. To a solution of **16** (0.27 g) in chloroform (10 ml) was added 2M HCl solution (5 ml), followed by methanol until a homogeneous phase was obtained. The mixture was stirred for 4 h at room temperature. Chloroform (100 ml) was added to the mixture, and the organic layer was separated, successively washed with water (2 × 25 ml), saturated $NaHCO_3$ solution (2 × 25 ml), and water (3 × 25 ml), and dried (Na_2SO_4). Evaporation of the solvent gave a residue which crystallized from dichloromethane to give **4** (0.2 g, 81%), m.p. 216-219°, $[\alpha]_D^{22}$ +8.5° (no mutarotation; *c* 3.0, chloroform); ν_{max}^{KBr} 3425, 3280, 1650, 1560, 740, and 680 cm^{-1}; R_F 0.46 (9:1 chloroform–ethanol).

Anal. Calc. for $C_{29}H_{33}NO_6$: C, 70.86; H, 6.77; N, 2.85; O, 19.53. Found: C, 70.68; H, 6.82; N, 2.81; O, 19.67.

*2-Acetamido-1-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-*D*-glucopyranose* (**25**). — Compound **7** (50 mg) in pyridine (3 ml) was treated with acetic anhydride (5 ml) for 16 h at room temperature. The mixture was evaporated, and the residue dried by several additions and distillations of toluene. Chromatography on a column of silica gel with 19:1 chloroform–ethanol gave **25** (47 mg, 86%), which could not be crystal-

lized. An analytical sample was prepared by precipitation from an ether solution by addition of pentane; $[\alpha]_D^{22}$ +46° (*c* 3.45, chloroform); ν_{max}^{KBr} 3280, 1750, 1650, 1545, 735, and 680 cm^{-1}; R_F 0.28 (19:1 chloroform–ethanol).

Anal. Calc. for $C_{31}H_{35}NO_7$: C, 69.78; H, 6.61; N, 2.63; O, 20.99. Found: C, 69.70; H, 6.62; N, 2.64; O, 21.10.

*2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-α-*D*-glucopyranosyl chloride* (**10**). — (*a*). Compound **7** (0.2 g) was dissolved in acetyl chloride (5 ml, not redistilled[10]), and the solution was kept for 16 h at room temperature in a stoppered tube. The mixture was evaporated, and dried by five additions and evaporations of toluene (4 ml), to give **10** as a highly unstable compound which was used without prior purification for the preparation of the oxazoline **13**.

(*b*). A solution of **7** (50 mg) in a mixture of dichloromethane (2 ml) and carbon tetrachloride (1 ml) was treated with triphenylphosphine (20 mg), and stirred for 4 h at room temperature. The progress of the reaction was monitored by t.l.c. (19:1 chloroform–ethanol), which revealed the gradual transformation of **7** into the faster-moving glycosyl chloride **10**. The mixture was evaporated, and the residue used, without further purification, for the synthesis of **13**.

*2-Methyl-(2-acetamido-3,4,6-tri-*O*-benzyl-1,2-dideoxy-α-*D*-glucopyrano)-[2,1-*d*]-2-oxazoline* (**13**). — Compound **10** (from 0.2 g of **7**) in dry acetonitrile (10 ml) was treated with tetraethylammonium chloride (80 mg) and anhydrous $NaHCO_3$ (80 mg), and the mixture was stirred for 1 h at room temperature. Evaporation gave a residue to which dichloromethane (70 ml) and water (30 ml) were added. The organic layer was separated, washed with water (2 × 25 ml), and dried (K_2CO_3). Evaporation gave 0.11 g (56% based on **7**) of **13**, which showed a minor, slow-moving by-product in t.l.c.; n.m.r. (chloroform-*d*): δ 2.09 (s, 3 H, CH_3 of oxazoline), 2.05, 2.14 (shoulders of main peak, $NHCOCH_3$, $OCOCH_3$ respectively, indicating contamination by a minor component having *O*- and *N*-acetyl groups), 3.34 (s, 3 H), 4.1 (d, 1 H, *J* 3 Hz), 4.61 and 4.66 (2 s, 6 H, CH_2 of $CH_2C_6H_5$), 6.12 (d, anomeric H, $J_{1',2'}$ 7.5 Hz), 7.36, 7.41, and 7.47 (3 s, 15 H, aromatic). An analytical sample was prepared by chromatography on a 2-mm thick plate, with 19:1 chloroform–ethanol containing 0.3% of triethylamine as the eluent. The product crystallized from dichloromethane–pentane, m.p. 192–194° (dec.), $[\alpha]_D^{22}$ +50° (*c* 1.4, chloroform); ν_{max}^{KBr} 1670 (C=N), 725, and 680 cm^{-1}; R_F 0.51 (19:1 chloroform–ethanol), R_F 0.9 (10:1 chloroform–methanol).

Anal. Calc. for $C_{29}H_{31}NO_5 \cdot 1.5H_2O$: C, 69.58; H, 6.85; N, 2.80. Found: C, 69.43; H, 6.96; N, 2.59.

*1-Propenyl 2-acetamido-3,4-di-*O*-benzyl-2-deoxy-α-*D*-glucopyranoside* (**5**). — A solution of[2] **2** (0.1 g) in dry dimethyl sulfoxide (2 ml) was treated with potassium *tert*-butoxide (0.2 g), and the mixture was kept for 5 h at 50° in a stoppered tube. After being cooled, the mixture was diluted with a large excess of water, and extracted with ether (3 × 25 ml). The ether layers were combined, washed with saturated aq. KCl, and dried ($MgSO_4$). Evaporation gave **5** (0.1 g, 100%) as a solid suitable for conversion into **8** without additional purification.

Crystallization of **5** from aq. methanol gave needles, m.p. 137–139°, $[\alpha]_D^{20}$ +100

(*c* 1.4, 5:1 chloroform–methanol); R_F 0.46; i.r. spectrum identical with that[2] of compound **5**.

Anal. Calc. for $C_{25}H_{31}NO_6$: C, 67.97; H, 7.09; N, 3.17; O, 21.74. Found: C, 67.94; H, 7.17; N, 3.07; O, 21.94.

*2-Acetamido-3,4-di-*O*-benzyl-2-deoxy-α-*D*-glucopyranose.* — A solution of **5** (0.1 g, not recrystallized) in 5:1 acetone–water (2 ml) was treated with $HgCl_2$ (0.25 g). This mixture was kept for 15 min at room temperature, when t.l.c. showed that all of the **5** (R_F 0.46) had been converted into **8**, a mixture of α and β anomers with the α compound (R_F 0.3) preponderant. The mixture was diluted with a large excess of chloroform, and the resulting solution washed twice with 50% aq. KI, dried ($MgSO_4$), and evaporated to give **8** (80 mg, 85%).

Crystallization from ether–methanol gave the anomer of **8** as plates, m.p. 162–166°, $[\alpha]_D^{20}$ +35° (*c* 1.15, 5:1 chloroform–methanol), $[\alpha]_D^{20}$ +32° after being kept overnight at room temperature; t.l.c. R_F 0.3 (α anomer); after mutarotation, ratio of α to β ~10:1.

Anal. Calc. for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49; O, 23.92. Found: C, 65.56; H, 6.95; N, 3.41; O, 24.00.

*2-Acetamido-3,4-di-*O*-benzyl-2-deoxy-*D*-glucopyranose* (**8**). — To a solution of **23** (0.4 g) in 9:1 acetone–water (25 ml) were added $HgCl_2$ (0.4 g) and yellow HgO (0.4 g), and the mixture was stirred for 30 min at room temperature. The inorganic residue was filtered off (Celite), and washed with hot acetone, and the filtrate and washings were combined, and evaporated to dryness. Chromatography on a column of silica gel, eluting first with chloroform (to remove the mercuric salts), and then with 9:1 chloroform–ethanol, gave 0.26 g (71%) of **8**. It crystallized from methanol–ether, m.p. 187–188°, and had the same properties as a sample prepared by a different procedure[14].

*2-Acetamido-1,6-di-*O*-acetyl-3,4-di-*O*-benzyl-2-deoxy-*D*-glucopyranose* (**26**). — A solution of **8** (41 mg) in dry pyridine (3 ml) was treated with acetic anhydride (3 ml) for 16 h at room temperature. The mixture was evaporated, and the residue was dried by repeated addition and distillation of toluene. Crystallization from dichloromethane–ether–pentane gave 42 mg (84%) of **26**, m.p. 146–147°, $[\alpha]_D^{22}$ +52° (*c* 4.4, chloroform); ν_{max}^{KBr} 3300, 1740, 1725, 1655, 1545, 740, and 680 cm^{-1}; R_F 0.28 (19:1 chloroform–ethanol).

Anal. Calc. for $C_{26}H_{31}NO_8$: C, 64.32; H, 6.44; N, 2.89; O, 26.36. Found: C, 64.32; H, 6.45; N, 2.84; O, 26.54.

*2-Acetamido-6-*O*-acetyl-3,4-di-*O*-benzyl-2-deoxy-α-*D*-glucopyranosyl chloride* (**11**). — Compound **8** (0.2 g) was suspended in acetyl chloride (10 ml), and stirred for 16 h at room temperature. The mixture was evaporated, and the residue was dried by several additions and distillations of toluene. In t.l.c., the glycosyl chloride **11** appeared as the major, faster-moving spot (R_F 0.35; 19:1 chloroform–ethanol), contaminated with some minor, slow moving by-products. The glycosyl chloride was used, without further purification, in the synthesis of the oxazoline **14**.

*2-Methyl-(2-acetamido-6-*O*-acetyl-3,4-di-*O*-benzyl-1,2-dideoxy-α-*D*-glucopyrano)-*

[*2,1*-d]-*2-oxazoline* (**14**). — A solution of **11** (from 73 mg of **8**) in dry acetonitrile (5 ml) was treated with dry $NaHCO_3$ (50 mg) and tetraethylammonium chloride (50 mg). The mixture was stirred for 3 h at room temperature, when t.l.c. showed the formation of almost pure **14** (R_F 0.80), together with a minor by-product (R_F 0.60). A large excess of dichloromethane was added, and the resulting solution was washed three times with water (1–2 ml), dried ($NaHCO_3$), and evaporated to give **14**, suitable for glycosylation without purification.

For characterization, **14** was purified by preparative t.l.c. on 2 plates (20 × 20 cm) using 10:1:0.1 chloroform–methanol–pyridine as the eluent. The band containing **14** was located by cutting a narrow strip from each plate and spraying with the anisaldehyde reagent, but it could also be observed from its faint u.v. fluorescence (it migrated just behind a narrow band giving an intense, u.v. fluorescence, which was a contaminant in the original preparation). The silica gel was removed from the plate, and product **14** was extracted from it by stirring overnight with 5:1 chloroform–methanol containing a trace of pyridine. Filtration and evaporation gave amorphous **14** (61 mg, 80% based on **8**), $[\alpha]_D^{20}$ +35° (*c* 1.4, dichloromethane); ν_{max}^{film} 3310, 3030, 3020, 2965, 1745, 1670 (C=N), 1500, 1450, 1375 (broad), 1320, 1235 (v. broad), 925, 735, and 685 cm^{-1}.

Anal. Calc. for $C_{24}H_{27}NO_6 \cdot 0.5H_2O$: C, 66.34; H, 6.49; N, 3.22; O, 23.96. Found: C, 66.49; H, 6.69; N, 3.10; O, 23.80.

*1-Propenyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-*D*-glucopyranoside* (**6**). — A solution of[2] **3** (0.1 g) in anhydrous dimethyl sulfoxide (2 ml) was treated with potassium *tert*-butoxide (0.2 g), and the mixture was kept for 5 h at 50° in a stoppered tube. A small portion of the brown mixture was removed, treated with water, and extracted with ether, and examination of the ether extract by t.l.c. showed the formation of a single product. Although the R_F value (0.68) was almost the same as that of the starting compound **3**, the spot showed no purple coloration diagnostic of an allyl ether[2]. Therefore, the reaction mixture was diluted with a large excess of water, and three extractions with ether (~20 ml), followed by drying ($MgSO_4$) and evaporation, gave **6** as a solid (0.1 g, 100%).

For characterization purposes, a portion was recrystallized from methanol–ether, to give needles, m.p. 99.5–103°, $[\alpha]_D^{20}$ +100° (*c* 1.2, chloroform); ν_{max}^{KBr} 3350, 3300, 3040, 2910, 2860, 1650, 1550, 1450, 1375, 1350, 1320, 1250, 1120, 1070, 1050, 1030, 735, and 690 cm^{-1}.

Anal. Calc. for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.17; O, 21.74. Found: C, 67.99; H, 7.08; N, 3.13; O, 21.84.

*2-Acetamido-3,6-di-*O*-benzyl-2-deoxy-*D*-glucopyranose* (**9**). — (*A*). A solution of **6** (0.1 g, not recrystallized) in 5:1 acetone–water (2 ml) was treated with $HgCl_2$ (0.25 g). The mixture was stirred for 15 min at room temperature, when t.l.c. showed complete conversion of **6** (R_F 0.68) into **9** (R_F 0.47). This t.l.c. also showed that **9** was mainly the α anomer (ratio of α to β ~10:1). The reaction mixture was diluted with a large excess of chloroform, and the resulting solution was washed twice with 50% aq. KI solution (10 ml), dried ($MgSO_4$), and evaporated, to give solid **9** (72 mg, 76.5%).

This product was suitable for synthetic purposes without further purification.

(*B*). For characterization, the β anomer was prepared from **24**. A solution of **24** (0.22 g) in 9:1 acetone–water (25 ml) was stirred with $HgCl_2$ (0.2 g) and yellow HgO (0.2 g) for 30 min at room temperature. The mixture was filtered (Celite), and the inorganic residue was washed with hot acetone (50 ml). The filtrate and washings were combined and evaporated, and the residue was chromatographed on a column of silica gel. The column was first eluted with chloroform (which removed the mercuric salts), and then with 19:1 chloroform–ethanol to give 0.135 g (67%) of **9**. It crystallized from methanol–ether, m.p. 162–163°, $[\alpha]_D^{22}$ +48° (no mutarotation; *c* 1.34, methanol): ν_{max}^{KBr} 3420, 3300, 1650, 1550, 740, and 690 cm^{-1}; R_F 0.35 (9:1 chloroform–ethanol).

Anal. Calc. for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49; O, 23.91. Found: C, 65.68; H, 6.85; N, 3.50; O, 23.94.

*2-Acetamido-1,4-di-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-*D*-glucopyranose* (**27**). — Compound **9** (25 mg) in dry pyridine (2 ml) was treated with acetic anhydride (2 ml) for 16 h at room temperature. The mixture was evaporated, and the residue dried by several additions and distillations of toluene. Crystallization from dichloromethane–ether–pentane gave 27 mg (88%) of **27**, m.p. 112–114°, $[\alpha]_D^{22}$ +3° (*c* 1.0, chloroform); ν_{max}^{KBr} 3300, 1735, 1745, 1650, 1545, 730, and 690 cm^{-1}; R_F 0.33 (19:1 chloroform–ethanol).

Anal. Calc. for $C_{26}H_{31}NO_8$: C, 64.32; H, 6.44; N, 2.89; O, 26.36. Found: C, 64.39; H, 6.47; N, 2.94; O, 26.48.

*2-Acetamido-4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-α-*D*-glucopyranosyl chloride* (**12**). — Compound **9** (72 mg, not crystallized) was dried by repeated additions and evaporations of toluene (2 ml), and then dissolved in acetyl chloride (3 ml, not redistilled)[10]. The mixture was kept overnight at room temperature in a stoppered flask, diluted with toluene, and evaporated (oil pump, CO_2–acetone trap). After five additions and evaporations of toluene (2 ml), the residue, consisting of the glycosyl chloride **12** plus some benzyl acetate (odor), was employed, without purification, for the preparation of the oxazoline **15**; t.l.c. (19:1 chloroform–ethanol) showed **12** as the major product (R_F 0.42), contaminated with minor by-products having lower R_F values.

*2-Methyl-(2-acetamido-4-*O*-acetyl-3,6-di-*O*-benzyl-1,2-dideoxy-α-*D*-glucopyrano)-[2,1-*d*]-2-oxazoline* (**15**). — The crude glycosyl chloride **12** (from 72 mg of **9**) was dissolved in dry acetonitrile (2 ml), and treated with dry $NaHCO_3$ (50 mg) and tetraethylammonium chloride (50 mg; Aldrich). The mixture was stirred for 3 h at room temperature, when t.l.c. showed the formation of a major product (**15**, R_F 0.83) and a minor product, R_F 0.70, most probably the 1,4-di-*O*-acetyl derivative arising from the presence of traces of acetic anhydride in the reagent[10]. The reaction mixture was diluted with a large excess of dichloromethane, and the resulting solution was washed three times with water (1–2 ml), dried ($NaHCO_3$), and evaporated, to yield amorphous **15**, suitable for glycosylation without further purification.

For characterization, **15** was purified by preparative t.l.c. by the same method as previously described for **14**, to give amorphous **15** (50 mg, 65%), $[\alpha]_D^{22}$ +9°

(*c* 1.15, dichloromethane); ν_{max}^{film} 3060, 3040, 2930, 2870, 1740, 1670 (C=N), 1500, 1455, 1375, 1320, 1235, 1100, 1040, 945, 730, and 690 cm^{-1}.

Anal. Calc. for $C_{24}H_{27}NO_6 \cdot 0.5CH_3OH$: C, 66.64; H, 6.63; N, 3.17. Found: C, 66.95; H, 7.32; N, 2.90.

Owing to the great instability of **15**, it was not possible to obtain more-accurate results for the elementary analyses.

Allyl 2-acetamido-3,4,6-tri-O-benzyl-2-deoxy-β-D-glucopyranoside (**16**). — (*A*). To a solution of allyl 2-acetamido-2-deoxy-β-D-glucopyranoside[13] (**19**, 1.3 g) in dry *N*,*N*-dimethylformamide (50 ml) were added benzyl bromide (2.5 g) and powdered KOH (4 g), and the mixture was stirred for 16 h at room temperature. The solvent was removed by co-distillation with *p*-xylene. To the gummy residue were added water (100 ml) and dichloromethane (200 ml), and the organic layer was successively washed with water (3 × 50 ml), 2M HCl (2 × 25 ml), and water (2 × 50 ml), and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was chromatographed on a column of silica gel. Elution with 19:1 chloroform–ethanol gave 2.1 g (78%) of **16**, which crystallized from dichloromethane–ether, m.p. 150–151°, $[\alpha]_D^{22}$ +21° (*c* 1.0, chloroform); ν_{max}^{KBr} 3280, 1650, 1560, and 685 cm^{-1}; n.m.r. (chloroform-*d*): δ 7.36 (m, 15 H, 3 Ph) and 1.83 (s, 3 H, $NHCOCH_3$); R_F 0.44 (19:1 chloroform–ethanol).

Anal. Calc. for $C_{32}H_{37}NO_6$: C, 72.29; H, 7.01; N, 2.64; O, 18.06. Found: C, 72.31; H, 7.06; N, 2.64; O, 18.03.

(*B*). A solution of **13** (0.1 g) in dry allyl alcohol (5 ml) was treated with anhydrous *p*-toluenesulfonic acid (~10 mg), and the mixture was heated for 2 h at 80 with stirring. The mixture was cooled to room temperature, treated with pyridine (2 ml), and evaporated. Crystallization of the residue from dichloromethane–ether gave 56 mg (53%) of **16**, m.p., and mixed m.p. with the compound described under (*A*), 150°.

1-Propenyl 2-acetamido-3,4,6-tri-O-benzyl-2-deoxy-β-D-glucopyranoside (**22**). — A solution of **16** (0.53 g) in dry *N*,*N*-dimethylformamide (7 ml) was treated with potassium *tert*-butoxide under dry nitrogen for 2 h at 80–85°. The mixture was diluted with water (25 ml), and the precipitated product was filtered off, washed with water, and dried. T.l.c. of the product showed complete isomerization of **16** to **22**. Crystallization from dichloromethane–ether gave 0.46 g (86%) of **22**, m.p. 156–158°, $[\alpha]_D^{22}$ +10° (*c* 3.0, chloroform): ν_{max}^{KBr} 3280, 1670 (1-propenyl), 1650, 1550, 750, 725, and 680 cm^{-1}; n.m.r. (chloroform-*d*): δ 7.50 (m, 15 H, 3 Ph), 1.83 (s, 3 H, $NHCOCH_3$), and 1.53 (d, 3 H, –O–CH=CH–CH_3, $J_{1',2'}$ 8 Hz); R_F 0.61 (19:1 chloroform–ethanol).

Anal. Calc. for $C_{32}H_{37}NO_6$: C, 72.29; H, 7.01; N, 2.64; O, 18.06. Found: C, 72.27; H, 6.82; N, 2.61; O, 17.98.

Allyl 2-acetamido-3,4-di-O-benzyl-2-deoxy-β-D-glucopyranoside (**17**). — (*A*). A solution of allyl 2-acetamido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside[14] (**20**, 0.125 g) in dry *N*,*N*-dimethylformamide (2 ml) was treated with benzyl bromide (60 mg) and powdered NaOH (60 mg). The mixture was stirred for 12 min at room temperature, when t.l.c. showed the conversion of **20** into a mixture of the 3,4-di-*O*-benzyl

derivative **17** (R_F 0.39) and the 3,6-di-*O*-benzyl derivative **18** (R_F 0.50), together with a small proportion of the 3,4,6-tri-*O*-benzyl derivative **16** (higher R_F value). The reaction was stopped by the addition of methanol (0.5 ml) and toluene (50 ml). The resulting mixture was filtered (Celite), and evaporated, and residual *N*,*N*-dimethylformamide was removed by repeated additions and evaporations of toluene; then, the residue was subjected to preparative layer-chromatography on two 2-mm plates (20 × 20 cm) (3 elutions). The bands containing **17** and **18** were located with the $KMnO_4$ spray reagent, and the products were extracted from the silica gel by stirring overnight with 2:1 chloroform–methanol. Filtration (Celite), and evaporation, gave **17** (61 mg, 39%), which cochromatographed in t.l.c. with an authentic sample[14]. Compound **18** was also obtained by this procedure.

(*B*). Compound **14** (purified by t.l.c., 15 mg) was treated with dry allyl alcohol (0.5 ml) and enough *p*-toluenesulfonic acid (a solution in dry toluene containing ~0.7 mg in 100 µl, prepared according to Warren and Jeanloz[2]) to give pH 4 (pH paper). The mixture was stirred for 1 h at 50° in a stoppered tube, cooled, and treated with pyridine (0.1 ml). Evaporation (nitrogen), followed by two additions and evaporations of toluene (0.5 ml), gave a residue which was triturated with 1:1 ether–hexane. The crystalline product (R_F 0.71) was isolated by centrifugation, washed twice with 1:1 ether–hexane, and then *O*-deacetylated by treatment with 3% sodium methoxide in methanol. After 1 h at room temperature, t.l.c. showed a single product **17** (R_F 0.39) which cochromatographed in t.l.c. with an authentic sample[14]. The solution was treated with cation-exchange resin (pyridinium$^+$); the resin was filtered off and washed with methanol, and the combined filtrates were evaporated to yield a solid (8 mg, 56%) which was recrystallized from methanol–ether–hexane, m.p. 200–203°. Crystallization of a sample of **17** prepared by method (*A*) gave m.p. 203–205°, and the mixed m.p. was undepressed.

*1-Propenyl 2-acetamido-3,4-di-*O*-benzyl-2-deoxy-β-*D*-glucopyranoside* (**23**). — Allyl 2-acetamido-3,4-di-*O*-benzyl-β-D-glucopyranoside[14] (**17**, 0.44 g) in dry *N*,*N*-dimethylformamide (3 ml) was stirred under nitrogen with potassium *tert*-butoxide (0.4 g) for 2 h at 80°. The mixture was diluted with water (25 ml), and the precipitated product was filtered off, washed with water, and dried. Crystallization from methanol gave 0.38 g (82%) of **23**, m.p. 216–218°, $[\alpha]_D^{22}$ −12° (*c* 1.8, chloroform); ν_{max}^{KBr} 3500, 3295, 1670 (1-propenyl), 1650, 1550, 740, and 680 cm^{-1}; n.m.r. (chloroform-*d*): δ 7.43 (m, 10 H, 2 Ph), 1.90 (s, 3 H, NHCOCH_3), and 1.60 (d, 3 H, –O–CH=CH–CH_3); R_F 0.29 (19:1 chloroform–ethanol) and 0.52 (9:1 chloroform–ethanol).

Anal. Calc. for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.17; O, 21.74. Found: C, 67.57; H, 6.96; N, 3.21; O, 22.20.

*Allyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-*D*-glucopyranoside* (**18**). — (*A*). A solution of allyl 2-acetamido-3-*O*-benzyl-2-deoxy-β-D-glucopyranoside[14] (**20**, 1.76 g) in dry *N*,*N*-dimethylformamide (15 ml) was treated with benzyl bromide (1.2 g), powdered BaO (2 g), and powdered $Ba(OH)_2 \cdot 8H_2O$ (0.54 g), and stirred for 4.5 h at room temperature. The mixture was diluted with chloroform (100 ml), filtered (Celite), and the inorganic residue was washed with hot chloroform (100 ml). The filtrate and

washings were combined and evaporated, and the residue was dried by several additions and distillations of *p*-xylene. T.l.c. of the product showed the presence of **18**, with **17** and **16** as minor by-products. Chromatography on a column of silica gel with 19:1 chloroform–ethanol gave 1.39 g (63%) of **18**, which crystallized from dichloromethane–ether, m.p. 145–146°, $[\alpha]_D^{22}$ −10° (*c* 1.8, chloroform); ν_{max}^{KBr} 3420, 3260, 1650, 1555, 725, and 680 cm^{-1}; R_F 0.28 (19:1 chloroform–ethanol) and 0.50 (9:1 chloroform–ethanol).

Anal. Calc. for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.17; O, 21.74. Found: C, 67.94; H, 7.07; N, 3.17; O, 21.78.

(*B*). Compound **18** was also prepared by partial benzylation of **20** [0.125 g; see preparation of **17**, method (*A*)]. Separation from **18** by preparative layer-chromatography (2-mm thick plate) gave **18** (79 mg, 50%), pure according to t.l.c. and cochromatography with the product obtained by method (*A*). Recrystallization from ether–methanol gave material having m.p. 143–146°, undepressed on admixture with product from (*A*).

(*C*). Compound **15** (prepared from 20 mg of **3**, and used without purification) was treated with dry allyl alcohol (1 ml) and *p*-toluenesulfonic acid, as described for the preparation of the corresponding 3,4-di-*O*-benzyl compound from the oxazoline **14** [see preparation of **17**, method (*B*)]. The reaction mixture was processed, and the product *O*-deacetylated, to give **18** (14 mg, 70%), pure according to t.l.c. (two elutions) and cochromatography with the products obtained by methods (*A*) and (*B*). Recrystallization from ether–methanol gave material having m.p. 143–147°, m.p. on admixture with the product from (*A*), or (*B*), 145–147°.

*Allyl 2-acetamido-4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-β-*D*-glucopyranoside* (**21**). — Compound **18** (23 mg) was treated with 1:2 acetic anhydride–pyridine (0.5 ml), and the mixture was kept overnight at room temperature, treated with water (0.5 ml), and evaporated. Two additions and evaporations of toluene (0.5 ml) gave **21** as a solid (25 mg, 100%), pure according to t.l.c. (10:1 chloroform–methanol, or 20:1 chloroform–methanol, 2 elutions), and having an R_F value much higher than that of **18**. Crystallization from methanol–ether–hexane gave material having m.p. 145–147°, $[\alpha]_D^{20}$ +10° (*c* 0.4, chloroform); ν_{max}^{KBr} 3280, 2875, 1745, 1650, 1550, 1500, 1455, 1375, 1370, 1320, 1250, 1220, 1150, 1125, 1070, 995, 730, and 685 cm^{-1}.

Anal. Calc. for $C_{27}H_{33}NO_7$: C, 67.07; H, 6.88; N, 2.90; O, 23.16. Found: C, 67.07; H, 6.91; N, 2.85; O, 23.06.

*1-Propenyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-*D*-glucopyranoside* (**24**). — A solution of **18** (0.44 g) in dry *N*,*N*-dimethylformamide (8 ml) was treated with potassium *tert*-butoxide (0.5 g) under dry nitrogen for 2 h at 80°. The mixture was diluted with water (30 ml), and the precipitated product was filtered off, washed with water, and dried. It crystallized from methanol to give 0.36 g (81%) of **24**, m.p. 150–152°, $[\alpha]_D^{22}$ −6° (*c* 1.7, chloroform); ν_{max}^{KBr} 3440, 3280, 1670 (1-propenyl), 1650, 1550, 745, and 680 cm^{-1}; n.m.r. (chloroform-*d*): δ 7.47 (m, 10 H, 2 Ph), 1.97 (s, 3 H, $NHCOCH_3$), and 1.60 (d, 3 H, $-O-CH=CH-CH_3$, $J_{1',2'}$ 7 Hz); R_F 0.32 (19:1 chloroform–ethanol) and 0.53 (9:1 chloroform–ethanol).

Anal. Calc. for $C_{25}H_{31}NO_6$: C, 68.01; H, 7.08; N, 3.17; O, 21.74. Found: C, 67.92; H, 6.92; N, 3.09; O, 21.94.

*2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-α-*D*-glucopyranosyl (dibenzyl phosphate)* (**28**). — A solution of **13** (derived from 0.1 g of **1**, without chromatographic purification) in dry 1,2-dichloroethane (1 ml) was treated with dibenzyl phosphate (75 mg, Aldrich), and the mixture was kept overnight at room temperature in a stoppered tube. T.l.c. showed the formation of **28** as the major product (R_F 0.54, phosphate reagent), and minor by-products (anisaldehyde reagent). This crude preparation was used for conversion into **30** and **31**. In an attempt to purify **28**, the reaction mixture was chromatographed on a 0.50-mm plate (10 × 10 cm). The band containing **28** was located by u.v. light, and the product was extracted from the silica gel with 2:1 chloroform–methanol by stirring for 15 min. Filtration, and evaporation, gave **28**, but t.l.c. showed that some decomposition had already occurred, giving additional spots having R_F 0.1 (phosphate) and 0.5 (anisaldehyde).

*2-Acetamido-2-deoxy-α-*D*-glucopyranosyl phosphate* (**30**). — A solution of the crude preparation of **28** in 1,2-dichloroethane (1 ml) was diluted with methanol (7 ml), and hydrogenolyzed at 2 atm. for 2 h over 10% palladium-on-charcoal (25 mg, Fluka). The catalyst was filtered off, washed with methanol, and replaced by a new batch. The hydrogenolysis was continued for 3.5 h, when t.l.c. (10:10:3 chloroform–methanol–water) showed the formation of a single, major product (R_F 0.36, giving a positive reaction with the phosphate and anisaldehyde spray-reagents), and minor products having higher R_F (anisaldehyde) or an R_F of 0 (phosphate). The reaction solution was made neutral with pyridine (0.2–0.3 ml), the catalyst was filtered off, and washed with methanol, and the combined filtrates were evaporated to yield **30** (pyridinium form). This product cochromatographed in t.l.c. (10:10:3 chloroform–methanol–water and 6:3:1 2-propanol–1.5M NH_4OH–water) with an authentic sample of 2-acetamido-2-deoxy-α-D-glucopyranosyl phosphate[17]. When applied to the plates along with a mixture of the α-D and β-D anomers[17], it co-chromatographed with the α-D anomer only.

*2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-*D*-glucopyranosyl phosphate* (**31**). — Compound **30** (pyridinium form, without purification) was treated with 1:2 acetic anhydride–pyridine (0.3 ml), and the mixture was stirred until a clear solution resulted, and then kept overnight at room temperature. After the addition of water (0.2 ml), evaporation, followed by two additions and evaporations of toluene (0.3 ml), gave a residue shown by t.l.c. (60:35:6 chloroform–methanol–water) to contain a major product **31** (R_F 0.24, phosphate and anisaldehyde spray-reagents) and minor contaminants. The product was purified by preparative layer-chromatography (0.50-mm plate, 20 × 20 cm) with 10:10:3 chloroform–methanol–water as the eluent. Compound **31** was located with the phosphate spray-reagent, and extracted from the silica gel by stirring overnight with the same solvent mixture as was used for the elution. Filtration (Celite) and evaporation gave a residue that was extracted with 5:1 chloroform–methanol. Filtration of the resulting extract, and evaporation, gave **31** (22 mg, 25% based on **13**: pyridinium form), pure according to t.l.c. in 60:35:6 chloroform–

methanol–water (R_F 0.24) and 10:10:3 chloroform–methanol–water (R_F 0.70). In both solvent-systems, the product cochromatographed with a sample of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl phosphate prepared by a different procedure[17], but in neither system was there a spot corresponding to the β-D anomer. Compound **31** was converted into the sodium salt by dissolution in water, and slow passage through a large excess of cation-exchange resin (Na^+). The column eluate was evaporated, and the product was dried by repeated additions and evaporations of toluene, giving **31** (20 mg, Na salt), $[\alpha]_D^{20}$ +55° (*c* 2, 1:1 methanol–water). The sample previously prepared by chromatographic separation of the α-D and β-D anomers[17] had $[\alpha]_D^{20}$ +49°, but the n.m.r. spectra, in D_2O, of the samples of **31** prepared by the two routes were identical.

Allyl 2-acetamido-6-O-(2-acetamido-6-O-acetyl-3,4-di-O-benzyl-2-deoxy-β-D-glucopyranosyl)-3,4-di-O-benzyl-2-deoxy-α-D-glucopyranoside (**32**). — A mixture of **14** (derived from 0.13 g of **2**, without purification) and **2** (40 mg) was dissolved in anhydrous 1,2-dichloroethane (1.3 ml), and the resulting solution was treated with enough *p*-toluenesulfonic acid in toluene[2] to give pH 4 (pH paper). The mixture was stirred in a stoppered tube for 3 h at 80°, cooled, treated with ether (8 ml), and kept for 2–3 h at 4°. The precipitated product was isolated by centrifugation, and washed three times with ether. Crystallization from chloroform–ethanol gave **32** (36 mg, 39% based on **2**), m.p. 285–288°, $[\alpha]_D^{20}$ +54° (*c* 1.0, 5:1 chloroform–methanol): ν_{max}^{KBr} 3280, 3090, 3065, 3040, 2910, 2880, 1745, 1650, 1550, 1455, 1375, 1325, 1250, 1125, 1070, 950, 925, 735, and 685 cm^{-1}; R_F 0.68.

Anal. Calc. for $C_{49}H_{58}N_2O_{12}$: C, 67.87; H, 6.76; N, 3.23; O, 22.14. Found: C, 67.87; H, 6.74; N, 3.19; O, 22.34.

1-Propenyl 2-acetamido-6-O-(2-acetamido-3,4-di-O-benzyl-2-deoxy-β-D-glucopyranosyl)-3,4-di-O-benzyl-2-deoxy-α-D-glucopyranoside (**33**). — A solution of **32** (30 mg) in dry dimethyl sulfoxide (1 ml) was treated with potassium *tert*-butoxide (60 mg), and the mixture was stirred for 6 h at 60°, when t.l.c. no longer showed the presence of an allyl ether[2]. The reaction mixture was diluted with a large excess of water, and kept for 2–3 h at 4°. The precipitated product **33** was isolated by centrifugation, and washed four times with water. It was used for the preparation of **34** without purification.

2-Acetamido-6-O-(2-acetamido-3,4-di-O-benzyl-2-deoxy-β-D-glucopyranosyl)-3,4-di-O-benzyl-2-deoxy-α-D-glucopyranose (**34**). — Compound **33** (from 30 mg of **32**, without drying) was suspended in acetone (5 ml), and treated with $HgCl_2$ (0.1 g). The mixture was stirred until a clear solution was obtained, and then kept for 15 min at room temperature, when t.l.c. showed complete conversion of **33** (R_F 0.68) into **34** (R_F 0.44). After evaporation of most of the acetone (nitrogen), the semi-solid residue was treated with water (12 ml), and the precipitation of **34** was completed overnight at 4°. The solid product was isolated by centrifugation, washed four times with water, and dried by (*a*) passage of nitrogen, and (*b*) high vacuum over P_2O_5, to give **34** (26 mg), pure according to t.l.c. (anisaldehyde), but containing traces of $HgCl_2$ according to t.l.c. (u.v. irradiation). Crystallization from methanol gave **34** (21 mg,

72% based on **32**), m.p. 226–226.5°, $[\alpha]_D^{22}$ +26° (*c* 1.2, 5:1 chloroform–methanol; unchanged after 15 h); ν_{max}^{KBr} 3280, 3045, 2930, 2885, 1650, 1550, 1455, 1375, 1365, 1320, 1220, 1120, 1070, 1030, 730, and 690 cm^{-1}.

Anal. Calc. for $C_{44}H_{52}N_2O_{11}$: C, 67.33; H, 6.68; N, 3.57; O, 22.43. Found: C, 67.17; H, 6.73; N, 3.48; O, 22.58.

Although mutarotation of **34** was not observed by polarimetry, t.l.c. of the chloroform–methanol solution after measurement of the $[\alpha]_D$ showed the formation of 5–10% of the β-D anomer.

2-Acetamido-6-O-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-D-glucopyranose[18] (**39**). — (*A*) A solution of **34** (15 mg) in methanol (2 ml) was treated with 10% palladium-on-charcoal (15 mg; Fluka) and hydrogenolyzed at 2 atm. for 3 h, when t.l.c. showed total disappearance of **34**, and formation of a single, major product (**39**) giving a double spot (α and β anomers, mean R_F 0.50, 10:10:3 chloroform–methanol–water), or a single spot (R_F 0.4, 6:3:1 2-propanol–15M NH_4OH–water). For comparison, di-*N*-acetylchitobiose[19] (**43**) also gave a double spot (mean R_F 0.58, 10:10:3 chloroform–methanol–water) and no separation of anomers in 6:3:1 2-propanol–15M NH_4OH–water (R_F 0.52). The catalyst was filtered off, and washed with 1:1 methanol–water, the combined filtrates were evaporated (nitrogen), and the amorphous residue was dried *in vacuo* over P_2O_5. Compounds **39** and **43** were also compared in hydrolysis studies (see later) and by paper chromatography on Whatman No. 1 paper in 6:4:3 butanol–pyridine–water for 28 h at 72°. Compounds **39** and **43** were detected by spraying the dried paper with propanolic sodium hydroxide, and viewing under u.v. light[26]. Compound **39** had $R_{di\text{-}N\text{-}acetylchitobiose}$ 0.72, with no separation of anomers.

(*B*). Compound **38** (33 mg) was hydrogenolyzed as described for **34**, giving a product which cochromatographed in t.l.c. (in all solvent systems tested) with the compound obtained from **34**.

2-Acetamido-6-O-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-1,3,4-tri-O-acetyl-2-deoxy-D-glucopyranose (**40**). — (*A*). Compound **39** (from 15 mg of **34**) was treated with 1:2 acetic anhydride–pyridine (0.3 ml). The mixture was stirred overnight at room temperature, treated with water (0.2 ml), and evaporated (nitrogen). After two additions and evaporations of toluene (0.2 ml), the residue was crystallized from ether–methanol to give **40** (11 mg, 85% based on **34**), m.p. 225–227°, pure according to t.l.c. (R_F 0.50) which did not show a double spot, indicating that **40** was obtained as a single anomer, probably α (see *O*-deacetylation studies). Compound **40** was not separated by t.l.c. from octaacetylchitobiose[19] (**44**), but the two isomeric disaccharide derivatives separated slightly when the chromatogram was eluted twice with 20:1 chloroform–methanol [R_F 0.29, β-D-(1→4)-linked compound; R_F 0.28, β-D-(1→6)-linked compound]. Crystallization from ethanol gave **40**, m.p. 227–229°, $[\alpha]_D^{20}$ +17° (*c* 1.1, 5:1 chloroform–methanol); ν_{max}^{KBr} 3330, 2950, 1745, 1660, 1430, 1375, 1150, 1125, 1075, 1050, and 940 cm^{-1}.

Anal. Calc. for $C_{28}H_{40}N_2O_{17}$: C, 49.71; H, 5.96; N, 4.14. Found: C, 49.37; H, 5.94; N, 4.06.

This compound was synthesized by Wang and Tai[21]; m.p. 236–238° (hot water), $[\alpha]_D^{16}$ +12°.

(*B*). The product of hydrogenolysis of **38** (33 mg) was treated with 1:2 acetic anhydride–pyridine (0.5 ml), and the mixture processed as in method (*A*), to give **40** (17 mg, 60% based on **38**), identical, according to t.l.c. and mixed m.p., with the compound obtained from **34**.

*Allyl 2-acetamido-6-O-(2-acetamido-4-O-acetyl-3,6-di-O-benzyl-2-deoxy-β-*D*-glucopyranosyl)-3,4-di-O-benzyl-2-deoxy-α-*D*-glucopyranoside* (**35**). — A mixture of **15** (derived from 0.125 g of **3**, without chromatographic purification) and **2** (40 mg) was dissolved in anhydrous 1,2-dichloroethane (2 ml), and the resulting solution was treated with a solution of dry *p*-toluenesulfonic acid in toluene (containing ~0.7 mg in 100 µl of toluene, prepared as described by Warren and Jeanloz[2]) to give pH ~4 (pH paper). The mixture was stirred in a stoppered tube for 2.5 h at 80° (oil bath), cooled, and diluted to ~12 ml with ether to complete the precipitation of solid **35**. After being kept for several h at 4°, the solid was collected by centrifugation, and washed twice with ether. T.l.c. showed that this product contained one major component (**35**, R_F 0.60), whereas the mother liquors contained almost all of the unchanged **2** (R_F 0.46) together with by-products from the oxazoline **15**. Recrystallization of the solid from ethanol–ether gave **35** (27 mg, 34% based on **2**), m.p. 280–283°, $[\alpha]_D^{20}$ +60° (*c* 1.2, pyridine); ν_{max}^{KBr} 3300, 3100, 3065, 3040, 2720, 2885, 1745, 1650, 1550, 1450, 1375, 1230, 1125, 1060, 730, and 685 cm^{-1}.

Anal. Calc. for $C_{49}H_{58}N_2O_{12}$: C, 67.87; H, 6.76; N, 3.23; O, 22.14. Found: C, 67.85; H, 6.81; N, 3.30; O, 22.30.

*1-Propenyl 2-acetamido-6-O-(2-acetamido-3,6-di-O-benzyl-2-deoxy-β-*D*-glucopyranosyl)-3,4-di-O-benzyl-α-*D*-glucopyranoside* (**37**). — A solution of **35** (87 mg) in dry dimethyl sulfoxide (5 ml) was treated with potassium *tert*-butoxide (0.2 g), and the mixture was stirred overnight at 45° in a stoppered tube, diluted with water (20 ml), and kept for 2–3 h at 4°. The precipitated product (**37**) was collected by centrifugation, washed four times with water, and used for the preparation of **38** without purification.

*2-Acetamido-6-O-(2-acetamido-3,6-di-O-benzyl-2-deoxy-β-*D*-glucopyranosyl)-3,4-di-O-benzyl-*D*-glucopyranose* (**38**). — Compound **37** (from 87 mg of **35**, without drying) was suspended in acetone (15 ml), and treated with $HgCl_2$ (0.25 g). The mixture was stirred until a clear solution resulted, and then kept for 15 min at room temperature, when t.l.c. showed the complete conversion of **37** (R_F 0.44) into **38** (R_F 0.36). After evaporation of most of the acetone (nitrogen), the semi-solid residue was treated with water (20 ml), and the resulting suspension kept for several h at 4°. The solid product was filtered off, washed with water, and dried (*a*) by passage of nitrogen, and (*b*) in high vacuum over P_2O_5, to give **38** (65 mg, 82.5% based on **35**), pure according to t.l.c., which showed the presence of both anomers (ratio ~10:1; R_F of the β anomer slightly lower that that of the α anomer).

For characterization purposes, a sample was crystallized from aqueous ethanol, m.p. 215–216°, $[\alpha]_D^{20}$ +22° (*c* 1.0, 2:1 chloroform–methanol); ν_{max}^{KBr} 3300,

3065, 3040, 2985, 1650, 1550, 1500, 1455, 1375, 1320, 1125, 1065, 1030, 730, and 690 cm^{-1}.

Anal. Calc. for $C_{44}H_{52}N_2O_{11}$: C, 67.33; H, 6.68; N, 3.57; O, 22.43. Found: C, 67.25; H, 6.75; N, 3.54; O, 22.53.

Allyl 2-acetamido-6-O-(2-acetamido-3,6-di-O-benzyl-2-deoxy-β-D-glucopyranosyl)-3,4-di-O-benzyl-α-D-glucopyranoside (**36**). — Compound **35** (55 mg) was treated with equal volumes of chloroform and 3% sodium methoxide in methanol until the pH of the resulting solution showed that a good excess of the base was present (pH paper). The reaction mixture was kept for 2.5 h at room temperature, when t.l.c. (10:1 chloroform–methanol) showed that all of the starting material **35** (R_F 0.60) had been converted into **38** (R_F 0.44). After treatment with cation-exchange resin (pyridinium$^+$) to remove Na ions, the resin was filtered off, and washed with 2:1 chloroform–methanol, and the combined filtrates were evaporated to give a solid which was recrystallized from ethanol–ether, to give **38** (50 mg, 94%), m.p. 257–260°, $[\alpha]_D^{20}$ +42° (*c* 1.0, 2:1 chloroform–methanol); ν_{max}^{KBr} 3430, 3290, 3095, 3055, 3040, 2910, 2875, 1650, 1550, 1500, 1455, 1375, 1365, 1320, 1220, 1125, 1065, 1030, 950, 925, 730, and 685 cm^{-1}.

Anal. Calc. for $C_{47}H_{56}N_2O_{11}$: C, 68.42; H, 6.84; N, 3.40; O, 21.33. Found: C, 68.19; H, 6.86; N, 3.34; O, 21.61.

Attempted O-deacetylation of **40**. — Compound **40** (1 mg) was treated with 3% sodium methoxide in methanol until an excess of the base was present (pH paper). The mixture was kept at room temperature, and examined by t.l.c. in 10:10:3 chloroform–methanol–water. After 40 min, the presence of at least two compounds was indicated, that having the lower R_F (the major product) migrating in the position of **39** (R_F 0.50). The greatest proportion of this product (presumably the free disaccharide **39**) was obtained after 80–120 min, when it accounted for ~60% of the product. It consisted mainly of the α anomer, an indication that **40** had the α configuration at C-1. After 4 h, the proportion of the compound with the higher R_F (0.65) had increased distinctly, and, after 15 h, this was the major product. T.l.c. in 6:3:1 2-propanol–15M NH_4OH–water, or in 60:35:6 chloroform–methanol–water (2 elutions) showed that this compound was not 2-acetamido-2-deoxy-D-glucose. When octaacetylchitobiose (**44**) was treated similarly, the main product corresponded to authentic di-*N*-acetylchitobiose (**43**).

Treatment of compound **39** *and di-N-acetylchitobiose*[19] (**43**) *with dilute acid.* — Each compound (1 mg) was treated with 0.01M HCl (100 μl), and the mixture kept at 93° in a stoppered tube; hydrolysis was monitored by t.l.c. in 10:10:3 chloroform–methanol–water. After 5 min, a trace of **39** had been converted into 2-acetamido-2-deoxy-D-glucose, and, after 15 min, this proportion had increased to ~5%, while **43** was unaffected. After 45 min, at least 50% of **39** had been hydrolyzed or *N*-deacetylated, while **43** showed only traces of degradation. When the treatment was performed for 140 min, **39** was almost totally degraded, the main products being 2-amino-2-deoxy-D-glucose and 2-acetamido-2-deoxy-D-glucose, while ~25% of **43** remained unchanged. These results confirmed the findings of Walker and Jeanloz[20] that these

compounds are more acid-labile when they contain a (1→6)- rather than a (1→4)-linkage.

Attempted synthesis of (1→4)-linked disaccharide derivatives from **15**. — (*A*). *From* **3**. A mixture of **15** (from 0.16 g of **3**, without purification) and **3** (50 mg) was dissolved in dry 1,2-dichloroethane (2 ml) and acidified with a solution of anhydrous *p*-toluenesulfonic acid in toluene[2] until pH 4 was reached. The mixture was stirred in a stoppered tube for 3 h at 80°, when t.l.c. showed that most of the **3** was unchanged (R_F 0.68), but a small proportion had been converted into a new compound, **41**, having a slightly higher R_F value. After neutralization of the acid with pyridine (0.1 ml), **3** and **41** were separated from other products by preparative layer-chromatography on a plate (20 × 20 cm × 2 mm thick) in 20:1 chloroform–methanol (2 elutions). The compounds were detected with the $KMnO_4$ reagent, and extracted from the silica gel by stirring overnight with 2:1 chloroform–methanol, filtration (Celite), and evaporation. The residue was treated with an excess of a solution of 3% sodium methoxide in methanol, and the mixture kept at room temperature until t.l.c. showed no further change. This treatment converted **41** into **42** (R_F 0.57), which was separated from **3** by preparative t.l.c. on two plates (20 × 20 cm), eluting twice with 20:1 chloroform–methanol. Compounds **3** and **42** were detected with the $KMnO_4$ reagent, and extracted from the silica gel as just described. Evaporation of the extract of the upper band gave unchanged **3** (39 mg), whereas evaporation of the extract from the lower band gave a residue that was triturated with 1:1 ether–hexane, to give **42** (3.5 mg; 3.5% based on total **3**, 16% based on **3** used up), m.p. 215–218 (dec.): insufficient material for further characterization.

Anal. Calc. for $C_{47}H_{56}N_2O_{11} \cdot 1.5H_2O$: C, 66.27; H, 6.98; N, 3.29. Found: C, 66.20; H, 6.60; N, 3.24.

(*B*). *From* **18**. A mixture of **15** (from 0.30 g of **3**) and **18** (50 mg) was dissolved in dry 1,2-dichloroethane (3 ml), and treated with *p*-toluenesulfonic acid as described in (*A*). Examination of the reaction mixture by t.l.c. showed that almost all of the **18** (R_F 0.50) had been converted into a single product (R_F 0.70). This compound was isolated by two-stage, preparative t.l.c. on (*a*) four 0.50-mm plates in 10:1 chloroform–methanol, and (*b*) 0.25-mm plates in 20:1 chloroform–methanol (2 elutions). In each case, the compound (R_F 0.70) was located with the $KMnO_4$ reagent, and extracted from the silica gel with 5:1 chloroform–methanol, followed by filtration (Celite), and evaporation. This gave a residue that was triturated with 1:1 ether–hexane, to give crystals (16 mg), m.p. 135–140°, having an i.r. spectrum showing an intense *O*-acetyl absorption (1745 cm^{-1}). Therefore, a sample was *O*-deacetylated by treatment with a solution of 3% sodium methoxide in methanol for 30 min at room temperature. T.l.c. of the resulting product showed that it cochromatographed with **18**. Therefore, the material having R_F 0.70, m.p. 135–140°, was compared in t.l.c. with the 4-*O*-acetyl compound **21**, and was found to cochromatograph with it in both 10:1 and 20:1 chloroform–methanol (2 elutions); the i.r. spectra were also identical, and the m.p. was undepressed on admixture with **21**. As this compound was apparently not a disaccharide, its synthesis and characterization were not pursued further.

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