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SYNTHESIS OF A SUBSTITUTED 2,6-DIOXABICYCLO[3.1.1]HEPTANE, 1,3-ANHYDRO-2,4,6-TRI-*O*-BENZYL-β-D-GLUCOPYRANOSE*

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ABSTRACT

1,3-Anhydro-2,4,6-tri-*O*-benzyl-β-D-glucopyranose has been synthesized by ring closure of 2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl chloride *via* two reaction sequences. The preferable method has allyl 3-*O*-allyl-D-glucopyranoside as key intermediate. This appears to be the first example of an anhydro sugar derivative with the 2,6-dioxabicyclo[3.1.1]heptane skeleton.

INTRODUCTION

Although the polymerization of bicyclic acetals to produce stereoregular polysaccharides or related polyacetals has been widely investigated[1–6], no synthesis of a bicyclic glycopyranose derivative having the 2,6-dioxabicyclo[3.1.1]heptane skeleton has been reported. Stereospecific polymerization of such a 1,3-anhydro-β-glycopyranose with ring opening and inversion at the anomeric center would form a (1→3)-α-glycopyranan. Sequences of this linkage and configuration are of interest, as they are prominent features of polysaccharides from bacteria, yeast, fungi, and lichens[7]. We now report the preparation of the first example of this class of bicyclic acetal, 1,3-anhydro-2,4,6-tri-*O*-benzyl-β-D-glucopyranose (**8**).

RESULTS AND DISCUSSION

Many bicyclic acetals have been synthesized by ring closures of the SN2 type involving a hydroxyl group and a leaving group in a trans relationship on two different carbon atoms. Recent examples from this laboratory include the syntheses of 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose[2] and 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose[8].

Compound **8** was synthesized by reaction of an equatorial, O-3 oxide ion with C-1 bearing an axial leaving-group. The conformational requirement for this reaction

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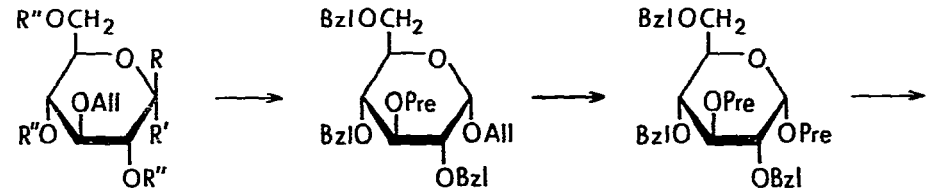
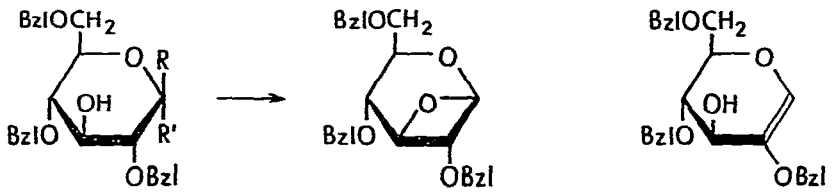
appears to be readily met. If C-2 drops below the plane of the ring, the ring adopts an appropriate skew conformation with C-6 in a quasi-equatorial position. The energy requirements for the molecule to adopt this position should not be high and, in this position, the steric relationship of groups is nearly ideal for ring closure.



1 R = R" = H, R' = OH
2 R' = R" = H, R = OH
3 R = H, R' = All, R" = Bzl

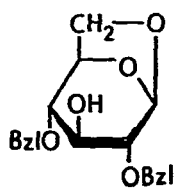
4 5



6 R, R' = OH, H
7 R' = Cl, R = H

8 9

All = Allyl
Pre = 1-Propenyl



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Our first attempted synthesis began with the preparation of methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside by partial benzylation of methyl α-D-glucopyranoside[9]. Acid hydrolysis of the glycoside gave a tri-*O*-benzyl-D-glucopyranose fraction (37%) which was separated by chromatography on silica gel. Chromatography of the fraction on poly(vinyl acetate) in toluene gave, in a 3 : 1 ratio, essentially pure, syrupy 2,4,6-tri-*O*-benzyl-α,β-D-glucopyranose (**6**) and crystalline 2,3,6-tri-*O*-benzyl-D-glucopyranose of correct m.p. Compound **6** was treated with hydrogen chloride in diethyl ether to give the glycosyl chloride **7**. Ring closure was effected by heating **7** at reflux temperature with potassium *tert*-butoxide in tetrahydrofuran for 16 h. The crude product was separated into two fractions by chromatography on poly(vinyl acetate) in toluene. The first fraction (42%) was found by ^{1}H-n.m.r. spectrometry to contain about 91% of the desired anhydro sugar derivative **8**, and *tert*-butyl 2,4,6-tri-*O*-benzyl-D-glucopyranoside (9%). The second fraction (58%) was unsaturated and was identified as 1,5-anhydro-2,4,6-tri-*O*-benzyl-D-*arabino*-hex-1-enitol (**9**).

For the preparation of larger quantities of **8**, purification of crude **6** was attempted by conversion to the di-*p*-nitrobenzoate and crystallization[9]. The di-*p*-nitrobenzoate obtained agreed generally in m.p. and specific rotation with the literature values, but removal of the *p*-nitrobenzoate groups with sodium methoxide in methanol failed to give pure **6**, so the di-*p*-nitrobenzoate was allowed to react with hydrogen chloride in dichloromethane to form the corresponding glycosyl chloride. Reaction of this compound with sodium ethoxide in ethanol gave a mixture containing 17% of the desired 1,3-anhydro compound **8**, which could be separated from ethyl 2,4,6-tri-*O*-benzyl-D-glucopyranoside and other products by chromatography on poly(vinyl acetate) in toluene.

The contamination of **6** with at least one isomer made the preparation of pure **8** rather difficult by this route and resulted in low yields. To avoid this problem, another sequence of reactions was, therefore, selected. This sequence gave superior results in spite of the complication that rearrangement of the allyl groups occurs under conditions milder than expected, and frequently an equilibrium seems to be established rather than complete conversion to propenyl groups. This complication has not been a serious problem in related syntheses in this laboratory.

Crystalline 3-*O*-allyl-D-glucopyranose was prepared by allylation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[10], followed by hydrolysis[11]. Allylation by the Fischer method[12] gave a fraction containing allyl 3-*O*-allyl-D-glucopyranoside which was readily separated by preparative liquid chromatography (p.l.c.) from small amounts of apparently dimeric impurities. Analytical liquid chromatography (a.l.c.) allowed separation of the fraction into the α-D anomer **1** (66%) and the β-D anomer **2** (34%), which were identified by ^{13}C- and ^{1}H-n.m.r. spectroscopy. No glucofuranosyl derivatives were detected.

Benzylation of the anomeric mixture with sodium hydride in *N*,*N*-dimethylformamide gave a crystalline main fraction and some partially benzylated material, which were readily separated by p.l.c. into a major fraction that was fully benzylated and a minor product that was dibenzylated. The main product was separated into allyl 2,4,6-tri-*O*-benzyl-3-*O*-(1-propenyl)-α-D-glucopyranoside (**4**) in crystalline form and a mother liquor containing an anomeric mixture of compounds having 1-*O*-propenyl and 3-*O*-allyl groups. The partially benzylated by-products included an inseparable, highly crystalline mixture identified by ^{13}C-n.m.r. spectroscopy as allyl 3-*O*-allyl-2,4-di-*O*-benzyl- and allyl 2,4-di-*O*-benzyl-3-*O*-(1-propenyl)-α-D-glucopyranoside.

Benzylation of the mixture of **1** and **2** with powdered potassium hydroxide in toluene, on the other hand, was complete, but rearrangement of the allyl group still took place to form mixtures of **3**, **4**, and **5**. The proportions varied widely, depending on minor differences in reaction conditions. The main product **4** was isolated by crystallization, and **5** could be separated by l.c. of the mother liquor. Isomerization of allyl groups has been reported only by use of potassium *tert*-butoxide in dimethyl sulfoxide[13], or tris(triphenylphosphine)rhodium(II) chloride[14], so this complication was unexpected. Our experience indicates that isomerization

under benzylation conditions is unusual, and that rearrangement is not specifically related to the type (axial or equatorial) or position of the allyl group, but that the 3-*O*-allyl group on a glucopyranose ring seems to be most readily isomerized.

Conversion of **4** to crystalline **5** was most readily accomplished with potassium *tert*-butoxide in toluene at reflux. Hydrolysis of **5** with a small amount of hydrochloric acid in 1,4-dioxane[15] gave 2,4,6-tri-*O*-benzyl-D-glucopyranose (**6**). Treatment of **6** with hydrogen chloride in ether by the method of Micheel and Kreutzer[16] gave the desired 2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl chloride (**7**) essentially quantitatively.

Ring-closure experiments were carried out under various conditions. When **7** was treated with a weak base such as triethylamine or anhydrous ammonia, no reaction took place. With potassium *tert*-butoxide in tetrahydrofuran, the principal by-product was the glucal **9** produced by trans elimination of hydrogen chloride from C-1 and C-2. Both ring closure and elimination occurred on treatment of **7** with potassium *tert*-butoxide in 18-Crown-6–benzene or sodium hydroxide in tetrahydrofuran, with the ratio of product to by-product varying with reaction conditions. When the chloride and base were mixed in cold tetrahydrofuran and brought to reflux temperature, the yield of **8** was considerably lower than when a butoxide suspension or solution was added dropwise to a refluxing solution of **7** in tetrahydrofuran. Since **9** is presumably formed from the favored $^4C_1$ (D) conformation, and the anhydro sugar **8** from a skew conformation, the higher temperature of reaction throughout the period of the latter experiments may be the significant variable favoring anhydro-ring formation. Although the reactions with potassium *tert*-butoxide gave relatively pure compounds, small amounts of glucoside were formed which were difficult to separate from **8**.

Treatment of **7** with freshly prepared silver carbonate in the presence of molecular sieves in refluxing benzene gave a low yield (36%) of **8** together with disaccharides (**6**) and 1,6-anhydro-2,4-di-*O*-benzyl-β-D-glucopyranose (**10**). Glucal **9** was not formed, however, in contrast to the results of a similar reaction of 3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl bromide[17].

The desired anhydro compound **8** could not be prepared directly from glucal **9** by heating at reflux temperature with *p*-toluenesulfonic acid in benzene, although 6,8-dioxabicyclo[3.2.1]octane was so prepared from 3,4-dihydro-2-hydroxymethyl-2*H*-pyran[18]. Presumably, the 1,3-anhydro ring (if formed) may be too sensitive to acid conditions.

The highest yield of **8** was obtained by reaction of **7** with sodium hydride in refluxing tetrahydrofuran. The formation of **9** was reduced, no glycoside could be produced, and the two products could be separated satisfactorily. The purity of **8** was established by a.l.c. and gel-permeation chromatography, by the absence of both a carbonyl absorption peak in the i.r. spectrum and obvious, extraneous signals in the ^{1}H- and ^{13}C-n.m.r. data, and by correct chemical analysis.

In the skeletal structure of **8**, the bonds linking C-1, C-2, C-3, C-4, and O-3 and O-5 are fixed and rigid, and thus only C-5 is capable of conformational motion. The two conformers possible can be described in terms of the shape of the two six-

membered rings which include C-5. In one case, the molecule comprises a 1,3-dioxane ring in a boat conformation and a pyranose ring in the $^1C_4$ (D) conformation, with C-6 being axial. In the second possible conformation, the molecule has a 1,3-dioxane ring in a chair conformation with C-6 being equatorial, and a pyranose ring in a boat conformation. The less-hindered position of C-6 should favor the second conformation.

The anomeric-peak position in the ^{13}C-n.m.r. spectrum was consistent with the assigned structure **8**, for the anomeric-carbon resonance was observed at 106.14 p.p.m., ~5 p.p.m. lower-field than the C-1 signal of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose. This chemical-shift difference parallels[19] that between oxetane (72.8 p.p.m.) and tetrahydrofuran (68.6 p.p.m.).

The anomeric-proton resonance appeared at δ 5.48 as a triplet, demonstrating the presence of vicinal (1,2) and long-range coupling with coupling constants ~4 Hz. In the preferred conformation just described, the dihedral angle between the anomeric C–H bond and the C-5–H bond is near the minimum range (~90°) of the Karplus relationship, and the probability of a coupling constant of $J_{1,5} \simeq 4$ Hz is virtually nil. In contrast, there is considerable evidence that a value of $J_{1,3} \simeq 4$ Hz is reasonable. Although the corresponding long-range coupling of oxetane itself is reported[20] to be <1 Hz, in saturated systems the largest four-bond couplings have been observed for protons separated in a planar, zig-zag or W arrangement[21,22] (*cf.* Coxon's value of $J_{2,4}$ 2.45 Hz for 3-*O*-benzoyl-1,2,4-*O*-benzylidyne-α-D-ribopyranose[23]). Theoretical studies of the conformation and substituent dependence of long-range, proton-coupling constants have confirmed and explained the relationship[24]. In 1,3-anhydro sugars, the arrangement of H-1 and -3 approaches the planar, zig-zag form more closely than in oxetane itself. In addition, very large values for four-bond, long-range couplings have been observed for bicyclo[1.1.0]butane (^4J 10 Hz) (ref. 25), bicyclo-[1.1.1]pentane (^4J 10, 18 Hz) (refs. 25, 26), bicyclo[2.1.1]hexane (^4J 6.7 ~8.1 Hz) (refs. 27–29), and bicyclo[2.2.1]heptane (^4J 1.5, 3 ~4 Hz) (refs. 30, 31). It is noteworthy that the long-range coupling found for the substituted dioxabicyclo[3.1.1]-heptane derivative **8** ($^4J_{1,3}$ 4 Hz) is intermediate between that of oxetane ($^4J_{2,4}$ <1.0 Hz) and that of bicyclo[2.1.1]hexane (^4J 6.7 ~8.1 Hz), and on the basis of this evidence we propose the assignment $^3J_{1,2} \simeq {}^4J_{1,3} \simeq 4$ Hz.

EXPERIMENTAL

General. — N.m.r. spectra were recorded with a Varian XL100-15 spectrometer, in Fourier-transform mode, or with a Varian A-60-A spectrometer, for solutions in chloroform-*d*, with tetramethylsilane (Me_4Si) as internal standard. Chemical shifts are expressed in p.p.m. down field from the internal Me_4Si absorption. Optical rotations were determined with a Perkin–Elmer model 141 polarimeter for solutions in a 1-dm, jacketed cell. Melting points were determined with a Mel-Temp apparatus. High-pressure liquid chromatography (l.c.) was performed with a Glenco septumless injector (model SV-3), a Glenco pump (model HPLPS-1), and a Waters differential refractometer R-401. Pure ethyl acetate or ethyl acetate–hexane in a silica gel column

(Whatman, Partisil M9 10/25) was used at a flow rate of 8 mL/min. Preparative liquid chromatography (p.l.c.) was performed with a Waters Prep-500 (ethyl acetate–hexane). Volume ratios of solvents are indicated. Stainless-steel columns (61 cm × 1.9 cm outside diameter) packed with Styragel (200 Å, Waters Assoc., Milford, Mass., 01757) for gel-permeation separations, or with poly(vinyl acetate) (Fractogel PVA 6000, EM Laboratories Inc., Elmsford, NY 10523) for partition chromatography were used at a toluene flow-rate of 3 mL/min, with use of a Glenco pump, model HPLPS-1. To separate dibenzyl ether from 1-propenyl 2,4,6-tri-*O*-benzyl-3-*O*-(1-propenyl)-α-D-glucopyranoside (**5**), a preparative gel permeation chromatography was set up; it used a copper column (2 cm × 66 cm) packed with a mixture of Bio-Beads S-X12 (Bio-Rad Laboratories, Richmond, Calif., 94804) and Styragel 100 A, and toluene as a solvent.

*Allyl 3-*O*-allyl-α-* (**1**) *and -β-*D*-glucopyranoside* (**2**). — 3-*O*-Allyl-D-glucopyranose (54 g, m.p. 126–128°) was prepared by hydrolysis of 3-*O*-allyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (78.5 g) in refluxing dilute sulfuric acid (3 g in 360 mL). Allyl alcohol (132 mL) containing hydrogen chloride (3 g) was poured over 3-*O*-allyl-D-glucopyranose and heated to less than reflux temperature. After much of the solid had dissolved, the mixture was stirred for a few hours at room temperature, then brought to reflux for 0.5 h. The temperature was lowered to 62° by addition of 150 mL of allyl alcohol. The reaction mixture was stirred overnight at 64–65°, and again boiled under reflux for ~3 h. The mixture was treated with ammonia gas and concentrated to dryness (*cf.* ref. 12).

Purification was achieved by p.l.c. with ethyl acetate as eluent. The faster-moving, major fraction (~90%) was separated from dimeric material, and was then analyzed by l.c. (ethyl acetate). Fractionation gave two well-separated peaks. ^{1}H- and ^{13}C-N.m.r., and optical rotation indicated that the faster-moving peak at count 16 (~34%) corresponded to the β-D anomer and the slower-moving peak at count 18 (~66%) to the α-D anomer.

Compound **1**. Syrup, $[\alpha]_D^{25}$ + 138.9° (*c* 1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 6.4–5.6 (m, 2 H, -CH=), 5.55–5.05 (m, 4 H, $=CH_2$), and 4.09 (s, 1 H, anomeric); ^{13}C-n.m.r. ($CDCl_3$): 135.55 (C-3, allyl -CH=), 133.90 (C-1, allyl -CH=), 118.03 (C-1, allyl $=CH_2$), 117.23 (C-3, allyl $=CH_2$), 97.92 (C-1), 82.17 (C-3), 73.93, 72.34 and 71.81 (C-2, C-4, C-5), 69.75 and 68.57 (OCH_2), and 61.69 (C-6) p.p.m.

Compound **2**. Syrup, $[\alpha]_D^{25}$ −31.9° (*c* 1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 6.4–5.6 (m, 2 H, -CH=), and 5.6–5.05 (m, 4 H, $=CH_2$); ^{13}C-n.m.r. ($CDCl_3$); 135.49 (C-3, allyl -CH=), 134.08 (C-1, allyl -CH=), 118.10 (C-1, allyl $=CH_2$), 117.32 (C-3, allyl $=CH_2$), 102.12 (C-1), 83.77 (C-3), 75.65, 74.01 and 73.91 (C-2, C-4, C-5), 70.50 and 69.79 (OCH_2), and 62.01 (C-6) p.p.m.

Anal. Calc. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.21; H, 7.73.

Direct allyl glucosidation of 3-*O*-allyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was attempted according to the method of Cunningham *et al.*[32], but without success.

*Allyl 2,4,6-tri-*O*-benzyl-3-*O*-(1-propenyl)-α-D-glucopyranoside* (**4**). — (*a*). In

a 1-L, three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a condenser connected to a drying tube, allyl 3-*O*-allyl-α,β-D-glucopyranoside (13.0 g, 50 mmol, mixture of **1** and **2**) was dissolved in dry *N*,*N*-dimethylformamide (200 mL). Sodium hydride (8.1 g, 190 mmol, 57% in mineral oil) in *N*,*N*-dimethylformamide (100 mL) was slowly added through the condenser into the vigorously stirred solution at ~100°. After stirring for 1 h at 100°, benzyl chloride (19 mL, 165 mmol) was added dropwise to the solution. Since the reaction was very slow, sodium hydride (2 g) in *N*,*N*-dimethylformamide and benzyl chloride (5 mL) were added seven times, and the temperature was raised to about 120°. After 67 h, methanol was added to the reaction mixture, followed by addition of water. The products were extracted with dichloromethane and washed with water. The brown organic phase was concentrated and steam-distilled twice in a cyclone apparatus, and then the products were extracted with dichloromethane. The organic layer was dried (anhydrous magnesium sulfate). Crude yield, ~24 g.

The products were fractionated with Prep-500 (1:1, v/v ethyl acetate–hexane). The faster-moving, major fraction was concentrated to a syrup, to which hexane was added, and the solution was kept in a refrigerator overnight. Crystals of **4** were collected and washed with cold petroleum ether and recrystallized from absolute ether–petroleum ether. Liquid chromatography showed a single, sharp peak at count 7 (1:2, v/v, ethyl acetate–hexane) of compound **4**, m.p. 80–82°, $[\alpha]_D^{25}$ + 25.7° (*c* 1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 6.5–6.25 (q of d, 1 H, J_{cis} 6 Hz, $J_{H\alpha,CH_3}$ 1.7 Hz, OCH=), 6.2–5.65 (m, 2 H, allyl -CH=), and 5.5–5.1 (m, 2 H, $=CH_2$); ^{13}C-n.m.r. ($CDCl_3$): 147.49 (OCH=), 138.60, 138.40, 138.29 (aromatic C-1), 128.46, 128.09, 127.84 (aromatic), 133.94 (allyl =CH-), 117.96 (allyl $=CH_2$), 98.77 (=CH-), 96.18 (C-1), 84.75 (C-3), 78.33, 72.18, 70.14, 74.90, 73.62, 73.27, and 68.35 (C-2, C-4, C-5, OCH_2), 68.64 (C-6), and 9.31 (CH_3) p.p.m.

Anal. Calc. for $C_{33}H_{38}O_6$: C, 74.69; H, 7.22. Found: C, 74.55; H, 7.14.

^{1}H-N.m.r. data of the compound showed allyl as well as methyl signals (~1:1 molar ratio), indicating that one of the allyl groups was rearranged to a 1-propenyl group during the benzylation reaction. In order to know which allyl group was rearranged, acid hydrolysis was carried out according to Gent and Gigg[15]. ^{13}C-N.m.r. data of the syrupy product showed only a single, anomeric-carbon absorption at 95.77 p.p.m., due to a glucosidic linkage, revealing that only the allyl group on O-3 was isomerized during the benzylation reaction. ^{13}C-Signals due to only one isomer of the propenyl groups were observed, and the examination of the coupling constant (~6 Hz) of the olefinic protons revealed that the allyl group was rearranged exclusively to the cis 1-propenyl group. This is not surprising, since studies on cis–trans equilibria of various propenyl ethers have shown that bulkier alkoxy groups stabilize the cis relative to the trans isomers[33].

The slower-moving, by-product fraction was concentrated to a syrup, which crystallized at room temperature. The crystals were washed with petroleum ether, and then with cold ether, m.p. 112–113°, $[\alpha]_D^{25}$ +47.7° (*c* 1, chloroform).

Anal. Calc. for $C_{26}H_{32}O_6$: C, 70.89; H, 7.32. Found: C, 70.87; H, 7.24.

^{1}H- and ^{13}C-N.m.r. spectroscopy, and l.c. revealed that the by-product was a mixture of allyl 3-*O*-allyl-2,4-di-*O*-benzyl-α-D-glucopyranoside and allyl 2,4-di-*O*-benzyl-3-*O*-(1-propenyl)-α-D-glycopyranoside.

(*b*). Allyl 3-*O*-allyl-D-glucopyranoside (**2**) (20.3 g) and then toluene (150 mL) were introduced into a 500-mL, three-necked flask equipped with a dropping funnel, a mechanical stirrer, and a condenser connected to a drying tube. Powdered potassium hydroxide (60 g, 85%) was added with vigorous stirring. The mixture was kept at reflux temperature with stirring, and benzyl chloride (90 mL) was added dropwise over 3 h. The reaction was continued for 4.5 h, water was added, and the products were extracted with toluene and washed with water. The organic layer was concentrated to a syrup. After steam-distillation in the presence of sodium hydrogencarbonate, the products were extracted with chloroform, and washed with water. The organic phase was dried (anhydrous magnesium sulfate) and concentrated to a syrup. In contrast to the results of method (*a*), no partially benzylated products were detected by liquid chromatography (1:2, v/v, ethyl acetate–hexane).

The syrup was found to contain allyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (**3**), allyl 2,4,6-tri-*O*-benzyl-3-*O*-(1-propenyl)-α-D-glucopyranoside (**4**), and dibenzyl ether in molar proportion ~17:62:21. The syrup was seeded with crystalline **4** and slowly crystallized. The crystals were washed with cold petroleum ether and recrystallized from ether–petroleum ether, m.p. 72–74°, $[\alpha]_D^{25}$ +20.0° (*c* 1, chloroform). The crystals were found to be contaminated with a small amount of **5**. ^{13}C-N.m.r. spectroscopy showed the same compounds in the mother liquor.

*1-Propenyl 2,4,6-tri-*O*-benzyl-3-*O*-(1-propenyl)-α-D-glucopyranoside* (**5**). — Crystalline **4** (5.50 g) was dissolved in toluene (50 mL) to which potassium *tert*-butoxide (5 g) was added. The mixture was stirred at reflux temperature for 23 h. Water was added, and the product was extracted with toluene and washed with water. The organic layer was dried (anhydrous magnesium sulfate) and concentrated to dryness. Compound **5** was crystallized from absolute ether–petroleum ether (yield 3.1 g), m.p. 59–60°, $[\alpha]_D^{25}$ + 2.5° (*c* 1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 6.5–6.25 (q of d, 1 H, J_{cis} 6, $J_{H\alpha,CH_3}$ 1.7 Hz, OCH= on C-3), 6.2–5.95 (q of d, 1 H, J_{cis} 6, $J_{H\alpha,CH_3}$ 1.7 Hz, OCH= on C-1), 1.69 (d of d, 3 H, $J_{CH_3,H\beta}$ 7, $J_{CH_3,H\alpha}$ 1.7 Hz, CH_3 on C-3), and 1.60 (d of d, 3 H, $J_{CH_3,H\beta}$ 7, $J_{CH_3,H\alpha}$ 1.7 Hz, CH_3 on C-1); ^{13}C-N.m.r. ($CDCl_3$): 147.46 (OCH= on C-3), 142.27 (OCH- on C-1), 138.44, 138.35, 138.16 (aromatic C-1), 128.50, 128.15, 127.93 (aromatic), 104.67 (=CH- on C-1), 99.04 (=CH- on C-3), 97.68 (C-1), 84.63 (C-3), 78.08, 76.95, and 70.69 (C-2, C-4, C-5) 75.05, 73.63, 73.31 (OCH_2), 68.40 (C-6), 9.52 (CH_3 on C-1), and 9.34 (CH_3 on C-3) p.p.m.

Anal. Calc. for $C_{33}H_{38}O_6$: C, 74.69; H, 7.22. Found: C, 74.61; H, 7.21.

*2,4,6-Tri-*O*-benzyl-D-glucopyranose* (**6**). — Crystalline **5** (3.05 g, 5.75 mmol) was dissolved in 1,4-dioxane (20 mL), to which ~M hydrochloric acid (1.5 mL) was added. The mixture was stirred at reflux for 2 h. After the solution was concentrated to a syrup, aqueous sodium hydrogencarbonate was added and the product was extracted with chloroform, washed with water, and dried (anhydrous magnesium

sulfate). The organic phase was concentrated to a syrup, which very slowly crystallized on being kept at room temperature (crude yield 3.1 g). Crystallization proved not to be a practical method of purification because of the tendency of **6** to revert to syrup. It was, therefore, subjected to a.l.c. and p.l.c. on silica gel with (1 : 1, v/v, ethyl acetate–hexane) as solvent. Two peaks corresponding to β- and α-D anomers were isolated and distinguished by mutarotation and optical activity measurements; $[\alpha]_D^{25}$ + 55.1° (*c* 1, chloroform, equilibrium value); ^{13}C-n.m.r. ($CDCl_3$) (α anomer): δ 90.84 (C-1), 74.66 (C-3), and 69.01 (C-6); (β anomer) 97.28 (C-1), 76.70 (C-3), and 69.25 (C-6) p.p.m.

Anal. Calc. for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 71.82; H, 6.79.

*2,4,6-Tri-*O*-benzyl-α-D-glucopyranosyl chloride*[16] (**7**). — The diol **6** (3.8 g, 8.4 mmol) was dissolved in absolute ether (50 mL). Under nitrogen flow, the solution was saturated with hydrogen chloride for 20 min at 0°. The flask was tightly stoppered and the solution was allowed to return to room temperature; then the solution was stirred overnight at room temperature. Nitrogen gas was bubbled into the solution to remove hydrogen chloride. The solution was concentrated to a syrup, diluted with dichloromethane, and evaporated. Addition and evaporation of the solvent was repeated several times, and the final solution was passed through a small column containing three layers of activated charcoal, silicic acid, and Celite, respectively. The solution was concentrated to a syrup (yield ~100%).

The chloride **7** did not crystallize, although ^{1}H-n.m.r. spectrometry and liquid chromatography in 1 : 2 (v/v) ethyl acetate–hexane showed that it was highly pure. It also was stable enough to survive a temperature of 100° and treatments with water and silica gel: $[\alpha]_D^{25}$ + 113.6° (*c* 1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): 6.09 (d, 1 H, J_{vic} 3.6 Hz, anomeric) and 2.80 (broad, 1 H, OH): ^{13}C-n.m.r. ($CDCl_3$): δ 138.50, 137.95, 137.45 (aromatic C-1), 128.71, 128.56, 128.21, 128.01, 127.86 (aromatic), 92.77 (C-1) 79.39, 76.27, 74.74, 73.16, 73.47, 73.16, and 72.58 (C-2, C-3, C-4, C-5, OCH_2), and 67.97 (C-6) p.p.m.

Anal. Calc. for $C_{27}H_{29}ClO_5$: C, 69.15; H, 6.23; Cl, 7.56. Found: C, 69.27; H, 6.45; Cl, 7.74.

*1,3-Anhydro-2,4,6-tri-*O*-benzyl-β-D-glucopyranose* (**8**). — The chloride **7** (0.73 g, 1.5 mmol) was dissolved in tetrahydrofuran (50 mL), to which sodium hydride (0.33 g, 57% in mineral oil, 7.9 mmol) was added. The mixture was stirred at reflux temperature for 2 h while the reaction was being monitored by t.l.c., liquid chromatography (1 : 2, v/v, ethyl acetate–hexane), and ^{1}H-n.m.r. spectrometry. The precipitate formed was filtered off, and the clear, colorless solution was concentrated to dryness. By ^{1}H-n.m.r. spectroscopy, the ratio of the desired compound **8** to the by-product **9** was estimated to be 87/13. Diol, glucopyranoside, and disaccharide were not detected by l.c. (1 : 2, v/v, ethyl acetate–hexane), gel permeation chromatography (Styragel 200 A, toluene), or ^{1}H-n.m.r. spectroscopy. The products were fractionated by l.c. (1 : 2, v/v, ethyl acetate–hexane). After fractionation, the recovery of **8** was ~73%. Compound **8** was stable to heat at 100° and to silica gel chromatography. However, storage of the purified compound in ethanol in the refrigerator resulted in ethyl glucoside formation. Compound **8** did not crystallize, $[\alpha]_D^{25}$ + 58.0° (*c* 1,

chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 5.48 (t, 1 H, $^3J_{1,2} \simeq {}^4J_{1,3} \simeq 4$ Hz, anomeric); ^{13}C-n.m.r. ($CDCl_3$): 138.50, 138.31, 137.60 (aromatic C-1), 128.46, 127.89, 127.61 (aromatic), 106.14 (C-1), 80.94 (C-3), and 76.48, 74.78, 73.24, 72.64, 72.31, 71.48 (C-2, C-4, C-5, C-6, OCH_2) p.p.m.

Anal. Calc. for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 74.64; H, 6.69.

The by-product glucal (**9**) was crystallized from ether-petroleum ether, m.p. 60–62°, $[\alpha]_D^{25}$ + 52.2° (*c* 1, chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 6.28 (s, 1 H, anomeric) and 2.74 (d, 1 H, hydroxyl); ^{13}C-n.m.r. ($CDCl_3$): 139.33 (C-2), 138.53, 138.21, 137.06 (aromatic C-1), 128.70, 128.55, 128.25, 128.05, 127.86, 127.28 (aromatic and C-1), 76.93, 76.52, 73.66, 73.30, 71.27, 70.31 (C-3, C-4, C-5, OCH_2), and 68.99 (C-6) p.p.m.

Anal. Calc. for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 75.53; H, 6.60.

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