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THE USE OF 1-*O*-TOSYL-D-GLUCOPYRANOSE DERIVATIVES IN α-D-GLUCOSIDE SYNTHESIS

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ABSTRACT

1-*O*-Tosyl-D-glucopyranose derivatives having a nonparticipating benzyl group at O-2 have been shown to react rapidly in various solvents with low concentrations of alcohols, either methanol or methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside. The stereospecificity of the glucoside-forming reaction could be varied from 80% of β to 100% of α anomer by changing the solvent or modifying the substituents on the 1-*O*-tosyl-D-glucopyranose derivative. 2,3,4-Tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-1-*O*-tosyl-α-D-glucopyranose in diethyl ether gave a high yield of α-D-glucoside. Kinetic measurements of reaction with various alcohols (methanol, 2-propanol, and cyclohexanol) show a high rate even at low concentrations of alcohol, and give some insight into the reaction mechanism. The high rate and stereoselectivity of their reaction suggest that the 1-*O*-tosyl-D-glucopyranose derivatives may be used as reagents for oligosaccharide synthesis.

INTRODUCTION

Several methods[1–16] are available for the preparation of α-glycosides using glycosyl compounds with nonparticipating groups at C-2. In most cases, glycosyl chlorides or bromides are used, but large concentrations of alcohol or of metal salts are needed to increase the rate of reaction. The use of positively charged leaving groups (ammonium, phosphonium, or sulfonium salts) also give high yields of α-glycosides[13,14], but again a large excess of alcohol is needed to obtain high yields. Several disaccharide syntheses have been attempted using positively charged leaving groups, but either these have given low yields of product[17] or reaction did not occur at all[18]. These results are understandable in terms of the proposed mechanism[14]. Glycosyl iodides have been shown to react much more rapidly than the corresponding glycosyl bromides and the faster rates permit the use of lower concentrations[16] of alcohol. In fact, alcohol to iodide ratios near 1:1, in some cases, have given high yields of glycosides in less than 24 hours, and the use of low concentrations of alcohol also favored the formation of α-glycosides, as has been shown previously for the glucopyranosyl bromides[2].

In 1929, Helferich and Gootz[19] prepared 2,3,4,6-tetra-*O*-acetyl-1-*O*-tosyl-D-glucopyranose by heating at reflux 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with silver *p*-toluenesulfonate in diethyl ether. The product did not crystallize and it decomposed rapidly. No attempt was made to allow this 1-*O*-tosyl-D-glucopyranose derivative to react with an alcohol. Since that time, the D-glucopyranosyl *p*-toluenesulfonates seem to have received no attention. Kronzer and Schuerch[2] have, however, investigated the reaction of glucopyranosyl trifluoromethanesulfonates with alcohols. The glucopyranosyl trifluoromethanesulfonates were found to be extremely reactive, giving high yields of glucoside at low concentrations of alcohol and at low temperature (−78°) in 30 minutes or less. At higher temperatures, the glucopyranosyl trifluoromethanesulfonates either reacted with the solvent or decomposed and gave a mixture of undesired products.

We chose to investigate the reaction of 1-*O*-tosyl-D-glucopyranose derivatives containing the nonparticipating benzyl group at O-2 with various alcohols. The *p*-toluenesulfonate group, as a leaving group, is intermediate in reactivity between the iodide and the trifluoromethanesulfonate groups and it was, therefore, expected that these derivatives should react faster with low concentrations of alcohol than the corresponding glycosyl iodides and that low temperatures could be avoided. Furthermore, the *p*-toluenesulfonate anion is known to be a poor nucleophile so that anomerization of the D-glucopyranosyl *p*-toluenesulfonate by attack of the *p*-toluenesulfonate anion should be minimized. The anomerization by nucleophilic anion of both glycosyl halides[2,5,20] and glycosyl compounds with positively charged leaving groups[14] has been postulated to cause a decrease in the stereoselectivity of the glycoside-forming reaction.

In this article, we report on the synthesis of several 1-*O*-tosyl-D-glucopyranose derivatives and their reaction with two alcohols, methanol and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside in various solvents. The kinetics of the glucoside-forming reaction involving two *p*-toluenesulfonate derivatives and several alcohols, methanol, 2-propanol, and cyclohexanol, in diethyl ether are also described.

RESULTS

The 1-*O*-tosyl-D-glucopyranose derivatives were prepared from the corresponding α-D-glucopyranosyl bromides or chlorides by allowing them to react with silver *p*-toluenesulfonate in acetonitrile at room temperature. Acetonitrile was used as a solvent since it dissolves both the silver salt and the glucosyl halides readily, and it is known to increase the rate of reaction between the *p*-toluenesulfonate anion and an alkyl halide[21]. Since the 1-*O*-tosyl-D-glucopyranose derivatives were found to hydrolyze very rapidly, high-vacuum techniques were used to exclude moisture from the system. All additions and transfers were carried out *in vacuo* or under an atmosphere of dry nitrogen.

The specific rotations of two of the 1-*O*-tosyl-D-glucopyranose derivatives, 2,3,4,6-tetra-*O*-benzyl- and 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl), were about

+60° and +72°, respectively, in diethyl ether. The values of the rotations can probably be considered accurate only within five percent, since they are based on the starting weight of the glucosyl bromide used, and some losses in transferring the compounds are possible. The high positive rotations indicated, nevertheless, that the *p*-toluenesulfonates were largely present as the α-anomers. This observation was confirmed by the n.m.r. spectra of these compounds since each 1-*p*-toluenesulfonate in diethyl ether showed a characteristic doublet at δ 6.1 with a coupling constant ($J_{1,2}$ 3.5 Hz) characteristic of the β-anomeric proton. 2,3,4-Tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-1-*O*-tosyl-D-glucopyranose also had a small doublet at δ 5.5 ($J_{1,2}$ 8.0 Hz), which corresponded to the anomeric proton of the β-anomer and amounted to about 15% of the total 1-*O*-tosyl-D-glucopyranose present. In contrast, 2,3,4,6-tetra-*O*-benzyl-1-*O*-tosyl-D-glucopyranose showed no absorption for the β-anomer. Both glucopyranosyl *p*-toluenesulfonates decomposed over a few hours in the sealed n.m.r. tubes to give dark-colored solutions that showed no absorptions for the anomeric protons at either δ 6.1 or δ 5.5

TABLE I

REACTION OF 2,3,4,6-TETRA-*O*-BENZYL-1-*O*-TOSYL-α-D-GLUCOPYRANOSE WITH METHYL 2,3,4-TRI-*O*-BENZYL-α-D-GLUCOPYRANOSIDE IN VARIOUS SOLVENTS[a]

Solvent	*Total yield* (%)	*α-Anomer* (%)
Acetonitrile	75	38
Acetonitrile	60	49[b]
Acetonitrile	80	43[c]
Acetonitrile	70	37[d]
Dichloromethane	62	38
Carbon tetrachloride	69	38
Acetone	75	21
Toluene	82	40
Benzene	76	41
Tetrahydrofuran	67	50
1,4-Dioxane	70	34
Dimethoxyethane	83	35
Ethyl ether	70	63
Ethyl ether	60	61[b]
Ethyl ether	77	40[d]

[a]Ratio of alcohol to 1-*p*-toluenesulfonate derivative: 1:1. Conc. of alcohol: 0.35 mmole in 4.0 ml of solvent. Conditions: room temperature for 16 h. [b]2,6-Lutidine added as acid acceptor. [c]Excess of pyridinium *p*-toluenesulfonate added: 4 moles. [d]Conditions: 0° for 4 days.

The results of reaction of 2,3,4,6-tetra-*O*-benzyl-1-*O*-tosyl-α-D-glucopyranose with an alcohol, methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside, in various solvents are shown in Table I. This crystalline monosaccharide alcohol was chosen since it is a good starting point for a model of oligosaccharide synthesis. The two possible compounds that can be formed by the reaction are either methyl 2,3,4,2′,3′,4′,6′-

hepta-*O*-benzyl-α-isomaltoside[22] or methyl 2,3,4,2′,3′,4′,6′-hepta-*O*-benzyl-α-gentiobioside[22] which have specific rotations of +59° and +17.4°, respectively, in chloroform. These heptabenzyl disaccharides were also easily separated from the starting materials or any by-products by column chromatography on silicic acid with dichloromethane as eluting solvent. The pure disaccharide fraction was weighed to determine the yield of reaction. The relative amounts of α and β disaccharide formed could be calculated from the specific rotation of the fraction ($[\alpha]^{25}_{D,obs}$) according to the following equation: $\alpha\ (\%) = ([\alpha]^{25}_{D,obs} - 17.4°) \cdot (59° - 17.4°)^{-1} \cdot 100$.

The yields in most of the reactions were high, but the stereoselectivity was dependent on the solvent used. The nonether solvents gave products that contained more β isomer (gentiobioside), whereas the ether solvents gave products containing more α isomer (isomaltoside). Diethyl ether gave the highest percentage of α product. The results also showed that the ratio of α to β products formed was relatively independent of the temperature, the addition of a salt (pyridinium *p*-toluenesulfonate), or the use of an acid acceptor, such as 2,6-lutidine.

TABLE II

REACTION OF 6-*O*-SUBSTITUTED 2,3,4-TRI-*O*-BENZYL-1-*O*-TOSYL-D-GLUCOPYRANOSE WITH METHANOL IN VARIOUS SOLVENTS[a]

6-Substituent	*Solvent*	*α-Anomer* (%)
O-Benzyl	Acetonitrile	60
O-Benzyl	Ethyl ether	81
O-Benzyl	Butyl ether	54
O-Benzyl	Isopropyl ether	57
O-Benzyl	Methyl ether	71
O-Benzyl	1,4-Dioxane	69
O-Benzyl	Acetone	37
N-Ethylcarbamate	Acetonitrile	70
N-Ethylcarbamate	Ethyl ether	85
N-Phenylcarbamate	Acetonitrile	80
N-Phenylcarbamate	Ethyl ether	100[b]
p-Methoxybenzoate	Acetonitrile	80
p-Methoxybenzoate	Ethyl ether	90

[a]At room temperature for 16 h; conc. of alcohol: 0.35 mmole in 4 ml solvent; ratio of alcohol to 1-*p*-toluenesulfonate derivative: 1:1. [b]Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside also used as the alcohol to give an 80% yield of the disaccharide methyl 2,3,4,2′,3′,4′-hexa-*O*-benzyl-6′-*O*-(*N*-phenylcarbamoyl)-α-isomaltoside, m.p. 123–124°, $[\alpha]^{25}_{D}$ +61.6° (*c* 1, chloroform).

The reaction of various 6-*O*-substituted 2,3,4-tri-*O*-benzyl-1-*O*-tosyl-D-glucopyranose with methanol in several solvents is shown in Table II. The ratios of α- to β-glucosides formed were determined from the n.m.r. spectrum of the crude product by measuring the areas of the methoxyl peaks, as previously described[12]. In most cases, reaction with methanol gave a higher proportion of α-glucoside than did reaction with the sugar derivative listed in Table I. The replacement of the 6-*O*-benzyl group

TABLE III

KINETIC MEASUREMENTS OF RATES OF REACTION BETWEEN DIFFERENT D-GLUCOPYRANOSE 1-*p*-TOLUENESULFONATE DERIVATIVES AND VARIOUS ALCOHOLS AT 25° IN DIETHYL ETHER

1-O-Tosyl-D-glucopyranose	*Alcohol*	[*Substrate*] M	[*Alcohol*] M	[*Alcohol*]/[*Substrate*]	$K \times 10^3$ (min^{-1})	$t_{1/2}$ (*min*)
2,3,4-Tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-	Methanol	0.033	0.033	1:1	3.57	194
			0.166	5:1	6.56	106
			0.332	10:1	10.9	64
			1.66	50:1	40.6	17
	2-Propanol	0.037	0.037	1:1	2.90	239
			0.184	5:1	11.4	61
			0.368	10:1	42.7	16
			1.84	50:1	56.4	12
	Cyclohexanol	0.033	0.033	1:1	1.80	376
			0.164	5:1	6.68	104
			0.327	10:1	16.4	42
			1.64	50:1	74.9	9
2,3,4,6-Tetra-*O*-benzyl-	Methanol	0.031	0.031	1:1	.93	745
			0.151	5:1	2.54	273
			0.314	10:1	4.60	151
			1.51	50:1	31.5	22
	2-Propanol	0.036	0.036	1:1	.57	1230
			0.182	5:1	1.37	505
			0.364	10:1	4.19	165
			1.82	50:1	27.5	25

with an ester or carbamate group resulted in increasing the yield of α-glucosides. The *N*-phenylcarbamate group was unique since it apparently gave 100% of α-glucoside with diethyl ether as the solvent. This stereoselectivity was not changed when methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside was the alcohol. In all cases, a similar effect of solvent on the stereoselectivity of the reactions was observed. In every case, diethyl ether gave the highest proportion of α-glucosides.

1-*O*-Tosyl-D-glucopyranose derivatives prepared from either 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide or tetra-*O*-benzoyl-α-D-glucopyranosyl bromide were stable for considerably longer periods than the etherified *p*-toluenesulfonates. Reactions of fully esterified glucopyranosyl *p*-toluenesulfonates with methanol were, however, slow and resulted in a mixture of products which, by n.m.r. analysis, appeared to include methyl α- and β-D-glucosides, orthoesters, and the starting 1-*p*-toluenesulfonate. The fact, that the fully esterified glucopyranosyl *p*-toluenesulfonates survived the treatment, which included washing with water and sodium hydrogen carbonate solutions, indicates the relative stability of these compounds and their slow reaction rates. Thus, fully acetylated or benzoylated glucopyranosyl *p*-toluenesulfonates will probably not be particularly useful for oligosaccharide or glucoside synthesis.

The rates of reaction of the two D-glucopyranosyl *p*-toluenesulfonates with several alcohols at various concentrations in diethyl ether were determined polarimetrically. From a plot of rotation versus time, the pseudo first-order rate constants (K) could be determined using the classical polarimetric expression: $K=(t)^{-1}\cdot \ln(\alpha_0-\alpha_\infty)\cdot(\alpha_t-\alpha_\infty)^{-1}$. The half-time ($t_{1/2}$) was determined from the rate constant $t_{1/2}$ using the equation $t_{1/2}=\ln 2/K$. The results of these measurements are given in Table III. In all cases, the 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-1-*O*-tosyl-D-glucopyranose reacted faster than the tetra-*O*-benzyl derivative. At the lowest alcohol concentrations (1:1), the rates of reaction decrease as the alcohol becomes more sterically hindered. However, at higher alcohol concentrations the rates are about the same for the various alcohols. This effect has not been observed for either the glycosyl halides[12] or the sugar derivatives having positively charged leaving groups[14]. The fact, that hindered alcohols do not give slower rates at the higher concentrations suggests that the reactions are not of S_N2 type. Furthermore, no linear, second-order relationships were found when the classical second-order rate expression $K=(t)^{-1}\cdot(b-a)^{-1}\cdot\ln a(b-x)\cdot[b(a-x)]^{-1}$ was applied. The lack of clear dependence of the reaction rate on the structure of the alcohol and the lack of second-order kinetics indicate that the reactions are more S_N1-like in character.

DISCUSSION

The results of the reactions of etherified α-D-glucopyranosyl *p*-toluenesulfonates with alcohols can be explained on the basis of the following reaction scheme, which is similar to the one postulated by Rhind-Tutt and Vernon[20] and by Ishikawa and Fletcher[5] for the reaction of glucosyl halides with alcohol:

$$\alpha\text{-D-Glc}p\text{-1-Ts} \rightleftharpoons \alpha\text{-D-Glc}p^{+}, \mathrm{Ts}^{-} \xrightarrow[\mathrm{ROH}]{(3)} \beta\text{-D-glucopyranoside}$$

$$(1) \uparrow\downarrow (2)$$

$$\beta\text{-D-Glc}p\text{-1-Ts} \rightleftharpoons \beta\text{-D-Glc}p^{+}, \mathrm{Ts}^{-} \xrightarrow[\mathrm{ROH}]{(4)} \alpha\text{-D-glucopyranoside}$$

Because of the low nucleophilicity of the *p*-toluenesulfonate anion, inversion is assumed to proceed directly on a tight ion-pair within a solvent cage, rather than by an S_N2-like attack by anion. The failure of the glycosidation reaction to obey second-order kinetics suggests the intermediary of a cation and the presence of interchanging, tight ion-pairs is suggested by the variable stereochemical results obtained under different reaction conditions. A number of previous studies have shown that β-glycosyl derivatives with electronegative leaving groups at C-1 are more reactive than the corresponding α-anomers, so one can confidently predict that reaction (*4*) is faster than reaction (*3*). At low concentrations of alcohol, the glycosidation reaction of bromides with methanol leads predominantly to an α-D-glucoside[2]. Greater preference for α-glycosidation at low concentrations of alcohol is also observed with *p*-toluenesulfonates, since the α_∞ observed for high concentration of alcohol was lower than that observed for the low concentrations of alcohol in the kinetic experiments. The lower α_∞ indicates that more β-D-glucoside was formed. Therefore, under these conditions, reaction (*1*) must be faster than reaction (*3*), and reaction (*1*) coupled to (*4*) must also be faster than (*3*).

It is extremely difficult to interpret the influence of solvent on stereochemical results, since these effects are determined by the influence on the relative rates of reactions (*1*), (*2*), (*3*), and (*4*), and no clear trends can be discerned, even between such diverse solvents as benzene, carbon tetrachloride, acetone, and acetonitrile. However, ether solvents very clearly influence glycosidation toward the α-anomer. We are tempted to suggest that perhaps the β-anomer of a *p*-toluenesulfonate in ether solution takes on the characteristics of an incipient oxonium ion. Such an ion species would stabilize the β ion relative to the α ion, because of the reverse anomeric effect[13,14,23,24], that is, it would inhibit reaction (*2*) relative to reaction (*1*). This oxonium ion would probably not decrease the reaction rate of (*4*), since trialkyloxonium ions are known to be extremely rapid alkylating agents, and thus would favor α-glycosidation as do other onium salts[13,14].

Finally, this equilibrium can be used to explain the very striking increase in the α-stereoselectivity of the glycosidation reaction due to the presence of a 6-*O*-(*N*-phenylcarbamoyl) group in the D-glucopyranosyl *p*-toluenesulfonate molecule. A similar influence has been observed[2] on the reaction of the corresponding trifluoromethanesulfonates with methanol. The influence of various substituents on the steric course of glycosidation reactions has been observed before[2,5,6,12,25] and has frequently been ascribed to participation by functional groups at C-4 or C-6[6,12,25]. The mechanisms of the proposed participation are not completely satisfactory,

however, especially since they do not explain the sensitivity of the stereoselectivity to alcohol concentration. In this system, and probably others, it is easy to visualize that a substituent at C-6 might influence the looseness or tightness of the α-ion pair and lower the activation energy of reaction (*1*) relative to reaction (*3*). Such an effect would favor α-glycosidation. If, in addition, the reaction is carried out in ether, the enhanced stabilization of the β ion [incipient onium ion (?)] would decrease the rate of reaction (*2*) relative to reaction (*1*). In fact, this stabilization almost certainly occurs, because the nuclear magnetic resonance spectrum of 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-1-*O*-tosyl-D-glucopyranose in ether shows the presence of about 15% of the β-anomer, whereas none is present in acetonitrile. However, less stabilization of the β ion must occur in the case of 2,3,4,6-tetra-*O*-benzyl-1-*O*-tosyl-D-glucopyranose, since no β isomer was observed in ether. Whether the influence of the C-6 substituent is transmitted *via* the covalent bond structure or through the surrounding medium, we do not wish to speculate at this time.

In general, the rates of glycosidation observed (Table III) agree with the stereochemical results. That is, reactions of 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-1-*O*-tosyl-D-glucopyranose proceed faster than the corresponding reactions of the tetra-*O*-benzyl derivative, and, as would therefore be expected, the yield of α-glucoside tends to be higher for the 6-*O*-(*N*-phenylcarbamoyl) derivative. This relationship between a faster rate and higher yields of α-glycoside again indicates that reaction (*1*) must be faster than reaction (*3*), and that reaction (*1*) coupled to reaction (*4*) must be also faster than reaction (*3*).

2,3,4-Tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-1-*O*-tosyl-D-glucopyranose in ether holds considerable promise for the synthesis of α-glucosides. This compound reacts rapidly enough with primary alcohols to permit the use of nearly equivalent quantities of reactants, the yields and the stereoselectivity are high, and side reactions are minimal.

EXPERIMENTAL

General. — N.m.r. spectra were determined on a Varian A-60-A spectrometer with chloroform-*d* as the solvent and tetramethylsilane as internal standard. Optical rotations were determined with a Perkin–Elmer model 141 polarimeter with jacketed 1-dm cells kept at 25° by circulating water from a constant temperature bath. All melting points are uncorrected.

Materials. — Spectrograde dichloromethane and acetonitrile were dried over calcium hydride. Diethyl ether was stored over sodium wire. Methanol was dried by distillation over magnesium. Silver *p*-toluenesulfonate (Eastman Organic Chem., Rochester, N.Y. 14650) was dried under high vacuum before use. 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranose (Pfanstiehl Lab. Inc., Waukegan, Ill. 60085) was used as received. 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl bromide was prepared by the method of Ishikawa and Fletcher[5].

Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside. — This compound was prepared by a modification of the procedure described by Hixson[22]. Methyl 6-*O*-trityl-α-

D-glucopyranoside (10.9 g) was dissolved in dry *p*-dioxane (38 ml), and potassium hydroxide powder (55 g) was added. The mixture was stirred and heated on a steam-bath. Benzyl chloride (40 ml) was added, the first 15 ml in one portion, and then the remainder drop-wise over a period of 3 h. During this time, the mixture gelled and then became fluid. The solution was stirred overnight and then poured into water (100 ml). The product was extracted with chloroform, and the organic phase was washed, evaporated, and distilled with steam. The nonvolatile product was dissolved in chloroform and the solution was washed, dried over magensium sulfate, and evaporated to a syrup. To a solution of this syrup in glacial acetic acid (50 ml), cooled to *ca.* 5°, was added hydrobromic acid in glacial acetic acid (6.7 ml, 30% hydrobromic acid). The solution was stirred for 30 sec and then filtered to remove the precipitated trityl bromide. The filtrate was poured into ice–water (200 ml), and the product was extracted with chloroform. The solution was washed, neutralized, dried, decolorized, and evaporated to a syrup. The product was crystallized from a mixture of ether and naphtha solvent (b.p. 60–100°) as white needles (3.2 g, 30%), m.p. 66.5–67°, $[\alpha]_D^{25}$ +23.5° (*c* 1, chloroform); lit.[22]: $[\alpha]_D^{25}$ +26.3° (*c* 1.63, chloroform). The yield could be increased by chromatography of the mother liquor on a silicic acid column and crystallizing the purified product from ether–petroleum ether. Total yield: 5.7 g (53%).

Anal. Calc. for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.28; H, 6.87.

*2,3,4-Tri-*O*-benzyl-1,6-di-*O*-(N-phenylcarbamoyl)-α- and β-*D*-glucopyranose.* — These compounds were prepared by the method of Kronzer and Schuerch[2]. The crude product was dissolved in ether, and petroleum ether added until the solution was cloudy. The α-anomer crystallized first (yield 22%), m.p. 141–144° $[\alpha]_D^{25}$ +50.4° (*c* 1, chloroform); n.m.r. data: δ 6.4 (d, $J_{1,2}$ 3.5 Hz, H-1 of α-anomer), 6.7 and 7.0 (2 s, 2 p, N–H). The mother liquor was dissolved in acetone and ethanol added to give the β-anomer as a voluminous solid, dried under vacuum (yield 52%), m.p. 194–198°, $[\alpha]_D^{25}$ −12.6° (*c* 1, chloroform); lit.[2]: m.p. 195–197°, $[\alpha]_D^{25}$ −12.8° (*c* 1.9, chloroform).

*2,3,4-Tri-*O*-benzyl-1,6-di-*O*-(N-ethylcarbamoyl)-α- and β-*D*-glucopyranose.* — 2,3,4-Tri-*O*-benzyl-D-glucopyranose[26] (4.5 g) was dissolved in dry pyridine (15 ml). Ethyl isocyanate (4 ml) was added and the mixture stirred overnight. Water was added slowly to destroy the excess isocyanate and the solution poured into water (400 ml). The white precipitate was filtered off and washed with water, and then heated at reflux in water for 3 h to dissolve any 1,3-diethylurea The crude solid, after filtration and drying (7.0 g), was recrystallized from hot ethanol (150 ml) to give white needles (3.5 g), m.p. 184–186°, $[\alpha]_D^{25}$ −6.8° (*c* 1, chloroform); n.m.r. data: δ 5.6 (d, $J_{1,2}$ 7.5 Hz, H-1 of β-anomer) and 1.1 (Me of 2 Et). The mother liquor was evaporated to a syrup which crystallized from diethyl ether–petroleum ether as small needles (2.1; g a total yield 95%), m.p. 125–130°, $[\alpha]_D^{25}$ +41.4° (*c* 1, chloroform); n.m.r. data: δ 6.25 (d, $J_{1,2}$ 3.5 Hz, H-1, α-anomer), 1.1 and 1.05 (2t Me of 2 Et).

Anal. Calc. for $C_{33}H_{40}N_2O_8$: C, 66.88; H, 6.80; N, 4.73. Found (α-anomer): C, 66.69; H, 6.73; N, 4.81; (β-anomer): C, 66.84; H, 6.77; N, 4.68.

Preparation and glycosidation of 6-O-substituted 2,3,4-tri-O-benzyl-1-O-tosyl-D-glucopyranoses. — 6-*O*-(*N*-Phenyl- and *N*-ethylcarbamoyl) derivatives of 2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide were prepared from the corresponding 1,6-di-*O*-substituted compounds by the method of Kronzer and Schuerch[2]; 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-ethylcarbamoyl)-α-D-glucopyranosyl bromide had $[\alpha]_D^{25}$ +100° (*c* 1, chloroform). 2,3,4-Tri-*O*-benzyl-6-*O*-(*p*-methoxybenzoyl)-α-D-glucopyranosyl bromide was prepared by the method of Fréchet and Schuerch[12]. These derivatives were allowed to react with silver *p*-toluenesulfonate on a high-vacuum rack in a reaction vessel that had two chambers separated by a fritted glass filter. D-Glucopyranosyl *p*-toluenesulfonate was formed in one of the chambers *in vacuo*, and then filtered into the other chamber through the fritted glass filter, in order to remove the precipitated silver bromide. Chilling the receiver provided suction. Both chambers could be opened for addition or removal of reagents or products. All additions or removals were carried out under an atmosphere of dry nitrogen.

A weighed amount of silver *p*-toluenesulfonate was placed into the reaction vessel and dried under high vaccum for 2 h. 2,3,4-Tri-*O*-benzyl-6-*O*-substituted α-D-glucopyranosyl bromide was added to the silver salt as a solution in diethyl ether. The vessel was sealed and the solvent removed by distillation under high vacuum. Acetonitrile was then distilled into the vessel and the contents stirred to dissolve the silver *p*-toluenesulfonate and the glucosyl bromide. Silver bromide precipitated almost immediately. After stirring for 15 min, the solvent was distilled off under high vacuum and the solvent to be used for the glycosidation reaction was distilled in. After stirring, the *p*-toluenesulfonate mixture was filtered to remove the silver bromide. The solution was then either allowed to react with the alcohol or removed for analysis. 2,3,4-Tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-1-*O*-tosyl-D-glucopyranose had $[\alpha]_D^{25}$ +72° (*c* 2.4, diethyl ether); n.m.r. data: δ 6.8 (N–H), 6.1 (d, $J_{1,2}$ 3.5 Hz, H-1 of α-anomer), and 5.5 (d, $J_{1,2}$ 8.0 Hz, H-1 of β-anomer).2,3,4,6-Tetra-*O*-benzyl-1-*O*-tosyl-D-glucopyranose had $[\alpha]_D^{25}$ +60° (*c* 2.2, diethyl ether); n.m.r. datum: δ 6.1 (d, $J_{1,2}$ 3.5 Hz, H-1 of α-anomer). Both 1-*p*-toluenesulfonates showed no peak in the n.m.r. spectrum for the anomeric proton after being kept for 1 day.

For reaction of D-glucopyranosyl *p*-toluenesulfonate derivatives with alcohols, a solution of D-glucopyranosyl *p*-toluenesulfonate (0.4 mmole) in 4 ml of solvent was prepared, as previously described. The solution was filtered directly into an attached tube containing either methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (167 mg, 0.35 mmole) or methanol (15 μl, 0.32 mmole). The mixture was stirred and allowed to stand in the dark for 16 h. Dichloromethane (25 ml) was then added, and the solution washed with sodium hydrogen carbonate solution, water, and saturated sodium chloride solution. The organic phase was dried over magnesium sulfate and evaporated to a syrup. After reactions using methanol as the alcohol, the n.m.r. spectrum of the crude syrup was recorded. The relative amounts of α- and β-glucosides were determined from the peak areas of the methoxyl resonances, as described previously[12]. For reactions in which methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside was the alcohol, the crude syrup was chromatographed on a column of silicic acid

with dichloromethane as eluting solvent. The disaccharide fraction was evaporated and the yield determined by weighing the syrup. The syrup in every case chromatographed as a single spot on a silica gel t.l.c. plate developed with 9:1 benzene–ether. The n.m.r. spectrum of the syrup showed a ratio of aromatic to benzyl and ring to methoxyl protons to be 35:28:3, which indicates a methyl heptabenzyl disaccharide. The ratio of α to β disaccharide could not be determined from the n.m.r. spectrum, since the anomeric protons could not be distinguished. No other impurities were present, as indicated by the n.m.r. spectrum. The ratio of α- to β-anomer was determined from the specific rotation of the syrup, since the rotations of the two disaccharides that could be formed, namely methyl heptabenzyl-α-isomaltoside and methyl heptabenzyl-α-gentiobioside, are known.

Kinetic measurements. — The rates of the glucoside-forming reaction with various alcohols and glucopyranosyl *p*-toluenesulfonate derivatives were determined polarimetrically as a function of time in 1-dm cells kept at 25°. A 5.0-ml stock solution in diethyl ether of the glucopyranosyl *p*-toluenesulfonate was prepared from a known weight of the glucopyranosyl bromide ($\approx$ 0.5 mmole) according to the method just described. It was assumed that the reaction of the bromide with silver *p*-toluenesulfonate went to completion and that all transfers were quantitative. A stock solution of the alcohol (methanol, 2-propanol, or cyclohexanol, 5.0 ml) was prepared in diethyl ether (0.1 mmole alcohol/ml). Into a 3.0-ml volumetric flask was added an aliquot (1.0 ml) of the 1-*p*-toluenesulfonate solution. The desired volume of the alcohol stock solution was added with a microliter syringe and the flask was brought to volume by adding diethyl ether and the time of mixing was noted. The mixture was then transferred to the 1-dm polarimeter cell and the change in optical rotation recorded until a constant value was observed. The volume of alcohol solution that was added was calculated so that the molar ratios of alcohol to 1-*p*-toluenesulfonate would be 1:1, 5:1, 10:1, and 50:1. The rates of reaction could be determined from a plot of optical rotation versus time.

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