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THE METHANOLYSIS OF SOME DERIVATIVES OF 2,3,4-TRI-*O*-BENZYL-α-D-GLUCOPYRANOSYL BROMIDE IN THE PRESENCE AND ABSENCE OF SILVER SALTS

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ABSTRACT

In contrast to reactions with high concentration, reactions of several derivatives of 2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide with low concentrations of methanol gave mainly the α-D-glucosides regardless of the structure of the C-6 substituent Methanolysis of the same α-D-glucosyl bromides or the corresponding chlorides in the presence of silver tetrafluoroborate or hexafluorophosphate at −78° gave mainly the β-D-glucosides The use of these silver salts led to side reactions, particularly when the glucosyl halide had an acyl blocking group at C-6 The side reactions were minimized when silver trifluoromethanesulfonate (triflate) was used The relative amounts of α- and β-D-glucosides produced in the presence of silver triflate depended on the structure of the C-6 substituent and the solvent polarity A rapid methanolysis of 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-α-D-glucopyranosyl bromide with silver triflate in ether at −78° gave a high proportion of the methyl α-D-glucoside

The results of direct methanolysis seem to be due to competitive methanolysis of the anomeric bromides and a "push-pull" mechanism is postulated in the presence of silver tetrafluoroborate or hexafluorophosphate Glucosyl triflate intermediates are proposed for the silver triflate-assisted methanolyses

INTRODUCTION

The solid-phase synthesis of oligosaccharides being developed in this laboratory[1–3] requires a glycoside-forming reaction which is both rapid and stereospecific The 6-*O*-acyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl halides are useful for the preparation of (1→6)-linked oligomers of D-glucose since the C-6 ester group is easily cleaved after each coupling step It is advantageous to use an excess of the glucosyl halide in the coupling steps since the alcohol functions are attached to a solid support and the excess glucosyl halide and products of side reactions are easily eliminated

Frechet and Schuerch[1] have shown that, in a series of 6-*O*-acyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromides, methanolysis with excess methanol in acetone is subject to steric control by C-6 substituents When 2,3,4-tri-*O*-benzyl-6-*O*-*p*-methoxybenzoyl-α-D-glucopyranosyl bromide was used over 90% of β-D-glucoside was obtained, whereas 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-α-D-glucopyranosyl bromide, as previously reported by Ishikawa and Fletcher[4], gave over 90% of α-D-glucoside When these two monomers were used in the solid-phase synthesis, however the coupling reactions were very slow and, according to the optical rotations of the products, the proportion of α- and β-D-linkages was the same no matter which of the two monomers was employed The exact proportion of α- and β-D-linkages in the products was not determined but the optical data suggest that the oligosaccharides were mostly α-D linked

In the solid-phase technique benzene was used as a solvent instead of acetone, and the hydroxyl groups were immobilized Although these variations could have affected the stereoselectivity of the reactions, the fact that the solid-phase coupling reactions were much slower than the solvolysis reactions suggests that the alcohol concentration was an important variable Several experiments were, therefore, carried out to determine the effect of the alcohol concentration of the stereochemistry of the methanolysis of some of the monomers Also, a new monomer—2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-α-D-glucopyranosyl bromide—was synthesized and its reaction with methanol was studied This monomer is interesting because the nitrogen atom, bonded directly to the carbonyl group, should be a better electron-donator than any of the *p*-substituted phenyl groups previously studied

Since the direct coupling reactions of the 2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromides were quite slow, the utility of using silver salts to increase the reaction rates was also explored Silver carbonate and silver oxide have been used quite extensively to increase reaction rates in Koenigs–Knorr reactions, but the yields are often low owing to hydrolysis of the glucosyl halide by the water formed in the reactions and to other side reactions Also, the reactions are somewhat unpredictable because they are performed under heterogeneous conditions[5,6] A number of silver salts of strong acids, such as silver perchlorate, silver nitrate, and silver tetrafluoroborate, which are soluble in many organic solvents, react rapidly with glycosyl halides The weakly nucleophilic anions in such silver salts are easily displaced from C-1 of the sugar if an intermediate ester or carbonium ion is formed Hickinbottom[7] has shown that silver nitrate can be used advantageously in an α-D-glucoside synthesis from 3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl chloride Silver perchlorate has been used along with silver carbonate, notably by Wolfrom and co-workers[8,9] Igarashi, Honma, and Irisawa[10,11] have shown that silver perchlorate converts various glycosyl chlorides into perchlorate esters which react rapidly with methanol at low temperatures Bredereck and co-workers[12] have employed both silver perchlorate and silver tetrafluoroborate in the reaction of sugar trityl ethers with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide.

We expected that highly reactive intermediates could be generated by treating the 2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl halides with silver tetrafluoroborate, hexafluorophosphate, or trifluoromethanesulfonate (triflate) Since the intermediates were expected to be highly reactive, the experiments were performed under anhydrous conditions at −78° The low-temperature procedure also minimized anomerization of the glucosides and other side-reactions produced by the strong acids formed in the reaction In some experiments, 2,6-di-*tert*-butylpyridine was used as an acid acceptor In this amine the nitrogen atom is blocked so effectively that it does not react with Lewis acids[13] Thus, it was not expected to react with any of the intermediates in the glucoside formation Methanol was used as the alcohol in the model reactions because the relative amounts of α- and β-D-glucosides produced could be conveniently determined by an n m r method[1]

RESULTS

The results of the direct methanolysis experiments together with some results obtained under solvolysis conditions by other investigators are given in Table I The results of the silver salt-assisted methanolyses are given in Table II The error in the α- to β-D-glucoside ratios is about ±5% or possibly less where a high proportion of one anomer is present The yields of glucosides, which were estimated by comparing the ratios of the aliphatic proton integrals to the aromatic proton integrals with theoretical ratios expected for the pure glucosides, may be in error by as much as ±20% In some cases it was possible to detect unreacted D-glucosyl chlorides in the products, whereas unreacted D-glucosyl bromides were probably hydrolyzed during the work-up of the reaction mixture Products of side-reactions or hydrolysis products were found in some cases, but no quantitative estimates of these materials were obtained

TABLE I

METHANOLYSIS OF SOME DERIVATIVES OF 2,3,4-TRI-*O*-BENZYL-α-D-GLUCOPYRANOSYL BROMIDE

Substituent at C-6	*Solvent*	*Methanol conc (mole/liter)*	*Methanol/bromide (moles/mole)*	*Ratio of D-glucosides (α β)*	*Reaction time (h)*	*Yield (%)*	*Ref*[a]
Acetyl	Acetone	18	390	7 13			1
Benzoyl	Acetone	18	390	4 21			1
Benzyl	Acetonitrile	0 4	4	4 1	24	100	T
	Acetonitrile[b]	0 12	1 5	93 7	60	50[c]	T
	Dichloromethane	2 2	67	9 11			4
p-Methoxy-benzoyl	Acetone	18	390	2 23			1
	Acetonitrile	0 4	4	23 2	60	100	T
	Acetonitrile[b]	0 10	1 5	47 3	60	42[c]	T
p-Nitro-benzoyl	Dichloromethane	2 2	73	24 1			4
Phenylcar-bamoyl	Acetonitrile	0 12	1 5	23 2	48	100[d]	T
	Ether	0 12	1 5	1 0	48	70[e]	T
	Methanol	22	760	11 89	24	100[d]	T

[a] T denotes this work [b] Lutidine used as an acceptor [c] Product contained impurities [d] Product crystallized spontaneously [e] Product contained unreacted glucosyl bromide

TABLE II

SILVER SALT ASSISTED METHANOLYSIS OF SOME DERIVATIVES OF 2,3,4-TRI *O* BENZYL α D GLUCOPYRANOSYL HALIDE AT −78°

No	*Substituent at C 6*	*Halogen*	*Silver salt*	*Solvent*	t_1[a] (*min*)	t_2[b] (*min*)	*Methanol/halide (moles/mole)*	*Yield* (%)	*Ratio of* D *glucosides* (*β α*)
1	Benzyl	Br	$AgPF_6$	Dichloromethane	15	15[c]	5	97	23 2
2		Br	$AgBF_4$	Dichloromethane	15	15[c]	5	96	93 7
3		Cl	$AgBF_4$	Dichloromethane	45	15[c]	1 3	0[d]	
4		Cl	$AgPF_6$	Dichloromethane	45	15[c]	1 3	37[d]	≈9 1
5		Cl	$AgBF_4$	Dichloromethane	15	15[c]	5	50[d]	≈9 1
6		Cl	$AgPF_6$	Ether	15	15[c]	1 3	100[e]	93 7
7		Cl	$AgBF_4$	Ether	15	15[c]	1 3	100[e]	47 3
8		Cl	$AgBF_4$	Ether[f]	1	30	1 3	88[e]	97 3
9		Cl	$AgSO_3$-CF_3	Ether	1	15	1 3	58	9 1
10		Cl	$AgSO_3$-CF_3	Ether[f]	1	15	1 3	60[g]	9 1
11		Cl	$AgSO_3$-CF_3	Ether	30	15	1 3	82	13 7
12		Br	$AgSO_3$-CF_3	Dichloromethane	1	30	1 3	60[h]	1 0
13		Br	$AgSO_3$-CF_3	Dichloromethane	30	30	1 3	67[h]	1 0
14		Br	$AgSO_3$-CF_3	Ether	1	30	1 3	70[h]	13 12
15		Cl	$AgSO_3$-CF_3	Dichloromethane	30	30	1 3	40[g]	1 0
16	*p*-Nitrobenzoyl	Br	$AgBF_4$	Dichloromethane	5	15[c]	5	88	49 1
17		Cl	$AgBF_4$	Ether	15	15[c]	1 3	low[i]	
18		Cl	$AgPF_6$	Ether	15	15[c]	1 3	low[i]	
19		Cl	$AgBF_4$	Ether	1	15	1 3	70[g]	24.1
20		Br	$AgPF_6$	Ether	1	30	1 3	40[i]	89 11
21		Cl	$AgPF_6$	Ether	1	30	1 3	33[g]	24 1
22		Br	$AgSO_3$-CF_3	Ether	1	30	1 3	96	3 7
23		Br	$AgSO_3$-CF_3	Ether[f]	1	30	1 3	68	7 13
24		Br	$AgSO_3$-CF_3	Ether[f]	30	30	1 3	77	27 73
25		Br	$AgSO_3$-CF_3	Dichloromethane	1	30	1 3	85	13 7
26		Br	$AgSO_3$-CF_3	Dichloromethane	30	30	1 3	58	63 37
27		Cl	$AgSO_3$-CF_3	Sulfur dioxide	30	30	1 3	33[h]	3 1
28	*p* Methoxybenzoyl	Br	$AgPF_6$	Dichloromethane	15	15	5	low[i]	
29		Br	$AgBF_4$	Dichloromethane	15	15	5	low[i]	
30		Cl	$AgPF_6$	Ether	1	15	1 3	35[g]	9 1
31		Cl	$AgBF_4$	Ether	1	60	1 3	65[g]	97 3
32		Br	$AgBF_4$	Ether	1	15	1 3	low[i]	
33		Br	$AgSO_3$-CF_3	Ether	1	15	1.3	90	3 2
34		Br	$AgSO_3$-CF_3	Dichloromethane	1	15	1 3	80	17 3
35		Br	$AgSO_3$-CF_3	Dichloromethane[f]	15	30	1 3	100	9 1
36		Br	$AgSO_3$-CF_3	Tetrachloromethane[f]	15	30	1 3	low	
37	Phenylcarbamoyl	Br	$AgSO_3$-CF_3	Ether	15	15	1 3	80	3 97
38		Br	$AgSO_3$-CF_3	Methanol–ether		15	≈500	100[e]	99 1

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[a] t_1, Time allowed before addition of methanol [b] t_2, Time allowed after addition of methanol [c] The reaction was allowed to reach 0° before termination [d] 1,6-Anhydro-2,3,4-tri-*O* benzyl-*β*-D-glucopyranose formed [e] Product crystallized [f] 2,6 Di-*tert* butylpyridine added [g] The starting material present [h] Hydrolysis products present [i] Unknown products formed [j] The reaction done at −20° [k] The reaction done at −50° with a special apparatus and filtration of silver chloride attempted before the methanol was added

Direct methanolysis experiments — The reaction of the derivatives of 2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl bromide with dilute methanol proved to be quite slow and it was necessary to use high-vacuum techniques to insure anhydrous conditions Most of the reactions were performed in acetonitrile because displacement of a bromide ion by an alcohol is expected to be faster in polar solvents[14]. The one reaction carried out in ether was still incomplete after 48 h The ratios of α- to β-D-glucosides produced in these reactions are strongly dependent on the methanol concentration Without exception, the glucosyl bromide derivatives, many of which gave high proportions of β-D-glucosides at high methanol concentrations, gave a high proportion of α-D-glucoside at low methanol concentrations According to these results the oligosaccharides prepared by Frechet and Schuerch[3] on a solid support may have been almost exclusively α-D linked

Silver salt-assisted methanolyses — Very good yields of the methyl glucosides were obtained from 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide and a five-fold excess of methanol in the presence of either silver tetrafluoroborate or hexafluorophosphate in dichloromethane The ratio of β- to α-D-glucoside was over 9 1 Similar treatment of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride gave much poorer yields and it appeared, from n m r and t l c data, that 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose was a major component of the reaction mixtures When ether was used as the solvent, the chloride was converted cleanly into the glucosides (Nos 6 and 7) Again over 90% β-D-glucoside was obtained A slight improvement in stereospecificity was observed in one experiment (No 8) in which 2,6-di-*tert*-butylpyridine was used as an acid acceptor In the other experiments, allowing the reaction mixtures to warm to 0° before termination may have caused a small amount of anomerization

With silver triflate, good yields of the methyl D-glucosides were realized from both 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide and 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride in either ether or dichloromethane (Nos 9–15) No trace of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose was found in any of these products, although 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose was detected in some cases This apparently resulted from the hydrolysis of the glucosyl halides or reactive intermediates either during work-up of the reaction mixtures or because of traces of water in the solvents In ether, 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide gave essentially a 1 1 mixture of α- and β-D-glucosides with silver triflate, but the results obtained with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride depended on the length of time allowed for the initial reaction of the chloride with the silver salt (Compare Nos 9 and 10 with No 11) The reason for this will be discussed later With silver triflate in dichloromethane, both the bromide and the chloride gave the β-D-glucoside and no trace of α-D-glucoside or 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose was found

The results obtained with the 6-*O*-acyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl halides in the presence of silver tetrafluoroborate or hexafluorophosphate were somewhat unpredictable (Nos 16–21 and 28–33) Little or no methyl D-glucoside could be obtained, unless the methanol was added after only a very short time had been allowed for the initial reaction between the glycosyl halide and the silver salt In many of these experiments only byproducts (which were not identified) were found In other cases, significant amounts of starting material were present All the reactions performed with silver tetrafluoroborate or hexafluorophosphate gave high proportions of β- to α-D-glucoside

Much better yields were obtained when silver triflate was used in the methanolysis of the 6-*O*-acyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl halides The dependence on the solvent of the stereoselectivity of the reactions was similar to that found with the tetrabenzyl analogs The 6-*O*-*p*-methoxybenzoyl-α-D-glucopyranosyl bromide derivative gave more β-D-glucoside than did the 6-*O*-*p*-nitrobenzoyl analog in both solvents The most promising result was obtained with 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-α-D-glucopyranosyl bromide, which gave a high proportion of α-D-glucoside with silver triflate in ether Interestingly, the same bromide gave a high proportion of β-D-glucoside when a large excess of methanol was used in either the direct or the silver triflate-assisted methanolysis

DISCUSSION

Direct methanolysis experiments — A rather simple explanation for the results of the direct methanolysis experiments may be advanced if one adopts Ishikawa and Fletcher's[4] scheme for the methanolysis of the 2-*O*-benzyl-α-D-glucopyranosyl bromide According to their scheme, the α-D-glucosides are formed from a small amount of β-D bromide which is in equilibrium with the α-D bromide and reacts much faster than the α-D bromide with methanol (with inversion at C-1) This process requires a constant supply of β-D bromide *via* anomerization of the α-D bromide At high concentrations of methanol, much of the α-D bromide may react directly with the alcohol (again with inversion at C-1), and the β-D-glucoside may be formed preferentially At low concentrations of methanol, the reaction of the α-D bromide with methanol is much slower This allows most of the α-D bromide to anomerize to the β-D bromide before reacting with methanol, and the α-D-glucoside is always the major product Ishikawa and Fletcher[4] have also shown that acceleration of the rate of methanolysis of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide by addition of sodium methoxide to methanol increased the yield of β-D-glucoside, whereas the increase of the rate of anomerization of the D-glucosyl bromide by addition of tetrabutylammonium bromide resulted in an increase in the yield of α-D-glucoside

In terms of this scheme, the steric control by C-6 substituents observed by Frechet and Schuerch[1] was probably due to variations in the rates of anomerization or methanolysis in the series of 6-*O*-acyl-2,3,4-tri-*O*-benzyl-D-glucopyranosyl bromides that they studied Their results of the solid-phase synthesis are also readily interpreted in terms of this scheme, since it has been demonstrated here that at the low alcohol concentrations, inherent in the solid-phase synthesis, all of the 2,3,4-tri-*O*-

benzyl-α-D-glucopyranosyl bromides are converted preferentially into α-D-glucosides. Judging from these results, it is not surprising that the stereoselectivity of glycoside formation is often unpredictably dependent on the structure of the glycosyl halides and the conditions employed in the reactions. Thus, participation by C-4 or C-6 substituents, which has also been postulated by Flowers[15,16] to account for the formation of α-glycosides from α-glycosyl halides, is probably not responsible for the variations observed here.

The reduced rate of methanolysis, at low concentrations of methanol, observed in these experiments may be due mainly to solvent effects. The rate of displacement of the bromide ion by an alcohol is expected to increase as the alcohol concentration increases, because the addition of the alcohol causes an increase in the polarity of the solvent. Either a unimolecular or a bimolecular displacement of bromide ion by an alcohol should be faster in polar solvents[14]. Thus, it is not possible to determine from these experiments whether the reactions are unimolecular or bimolecular.

Silver salt-assisted methanolyses. — Silver tetrafluoroborate and silver hexafluorophosphate are very reactive halogenophiles that promote rapid methanolysis of the D-glucosyl bromides and chlorides, even at −78°, with approximately equimolar amounts of methanol. In every case, these silver salts promote β-D-glucoside formation from the α-D-glucosyl halides, the expected result of attack by methanol on a silver-ion complex of the α-D-glucosyl halide. The formation of α-D-glucosides is much slower under these conditions, because the reactions are rapid compared to the rate of anomerization, and no bromide ion accumulates in the reaction mixture. When no alcohol is present, the silver salts convert the D-glucosyl halides to other products, which in the case of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride appears to be 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose. The 6-*O*-acyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl halides are more vulnerable to side reactions, but none of the products were identified. A number of other workers have found that glycosyl halides undergo predominant inversion of configuration upon reacting with alcohols in the presence of reactive, soluble silver salts[7–9]. Wulff *et al.*[6,17,18] have shown that 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, in the presence of such insoluble silver salts as silver carbonate, reacts with alcohols *via* a "push-pull" mechanism. Others[19,20] have shown that 2-octyl halides may react with soluble silver salts *via* a "push-pull" mechanism to give an inverted substitution product.

The best explanation for the variations in the configuration of the products obtained in the silver triflate-assisted methanolyses is that the glycosyl halides can react with the silver triflate and alcohol *via* the "push-pull" mechanism but, if enough time is allowed for the initial reaction between the glycosyl halide and the silver salt, the glycosyl halide is converted into a glycosyl triflate. Reaction *via* the "push-pull" mechanism gave mainly the β-D-glucoside, but the methanolysis of the triflate gave both the α -and β-D-glucoside in various amounts depending on the structure of the bromide and the polarity of the solvent. This appears to be the only reasonable explanation for the observation that 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride gave a 9:1 ratio of β- to α-D-glucoside when one min was allowed for the initial reaction and a 13 7 ratio when 30 min was allowed, whereas 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide, which is apparently converted more rapidly into the triflate, gave essentially a 1 1 mixture of α- and β-D-glucosides Also, 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-α-D-glucopyranosyl bromide gave a 3 97 ratio of β- to α-D-glucoside when methanol was added to the reaction mixture of the D-glucosyl bromide and silver triflate, but the same monomer gave a 99.1 ratio of β- to α-D-glucoside when methanol was present in a large excess at the time the D-glucosyl halide and silver salt were allowed to react

Most of the reactions that are presumed to go through a glycosyl triflate intermediate gave a nearly random mixture of α- and β-D-glucosides in ether and a predominance of the β-D-glucoside in dichloromethane Since the trifluoromethanesulfonate group is strongly electron-withdrawing, the glycosyl triflates may be α-D esters In dichloromethane, shielding by the departing triflate ion could be responsible for the formation of a predominance of β-D-glucoside, since ion-pair separation should be unfavorable in this poorly solvating solvent More research will be necessary to explain the variations in stereoselectivity in relation to the various C-6 substituents The reaction of the 6-*O*-(*N*-phenylcarbamoyl) monomer with silver triflate in ether is, in our experience, unique, for it gave a very high proportion of α-D-glucoside However under other conditions, the same compound gave a high proportion of β-D-glucoside In the latter respect its behavior is very similar to that of the other monomers studied

By use of reactions similar to some of the model reactions described here for the stereospecific, rapid synthesis of oligosaccharides appears to be quite feasible However, since the reactions are sensitive to subtle changes in the nature of the reactants and solvents, the conditions must be very carefully controlled Perhaps further research in this area will result in a better understanding of the stereoselectivity and in the discovery of even more useful monomers, electrophilic reagents, and reaction conditions

EXPERIMENTAL

General — N m r spectra were obtained with a Varian A-60-A spectrometer, chloroform-*d* containing tetramethylsilane as an internal reference was used as the solvent 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 Thin-layer chromatograms were developed with dichloromethane or dichloromethane–ether (*ca* 9 1) on 3 × 7 cm silica gel plates with plastic support and fluorescent indicator (J T Baker Chem Co)

Materials — Silver hexafluorophosphate (Ozark–Mahoning Co) and silver tetrafluoroborate (K & K Lab) were dried for several h *in vacuo* 2,6-Di-*tert*-butylpyridine (Willow Brook Labs) was dried over calcium hydride Spectro-grade methanol was dried by distillation from a magnesium methoxide solution Spectro-grade dichloromethane and spectro-grade ether were dried over calcium hydride

Preparation of the 2,3,4-tri-O-benzyl-α-D-glucopyranosyl halides — Two of the compounds — 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide and 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-α-D-glucopyranosyl bromide — have been reported by Ishikawa and Fletcher[4] Frechet and Schuerch[1] have described the preparation of 2,3,4-tri-*O*-benzyl-6-*O*-*p*-methoxybenzoyl-α-D-glucopyranosyl bromide and 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-α-D-glucopyranosyl chloride Optical rotations and n m r. spectra of these compounds, which were syrups, agreed well with the reported values except that 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-α-D-glucopyranosyl bromide had $[\alpha]_D^{25}$ +130° (*c* 1 8, dichloromethane) instead of +126 5° (This is probably due to the fact that the concentration reported here is g/ml of solution, whereas the concentration reported by Ishikawa and Fletcher[4] was g/ml of solvent)

*Preparation of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride* — A solution of 2,3,4,6-tetra-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-glucopyranose[21] (1 004 g, 1 475 mole) in dry dichloromethane (15 ml) was added to dry ether (10 ml) saturated with hydrogen chloride Hydrogen chloride was bubbled through the solution for 7 h, with precipitation of *p*-nitrobenzoic acid beginning after 0 5 h The mixture was kept overnight at 0°, and then the solvent was evaporated and replaced with fresh, dry dichloromethane (~5 ml) The *p*-nitrobenzoic acid was filtered off, washed with dichloromethane, dried, and weighed to give 241 5 mg (1 446 mmole, 99 2%) The solution of the chloride was passed through a small column of silica gel and the column was rinsed with dichloromethane The combined solutions were evaporated to give a colorless syrup which was homogeneous on t l c After being dried in a high vacuum, it had $[\alpha]_D^{25}$ +126° (*c* 4 0, benzene), the n m r spectrum contained a doublet centered at δ 6 12, $J_{1,2}$ 3 5 Hz, indicating that it was the α-D anomer Austin *et al*[21] reported $[\alpha]_D$ +66° (*c* 6 3, benzene) for 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride prepared from 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose with hydrogen chloride and $[\alpha]_D$ +95° (*c* 4 0, benzene) for the chloride prepared from 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose and thionyl chloride

*Preparation of 2,3,4-tri-*O*-benzyl-6-*O*-p-methoxybenzoyl-α-D-glucopyranosyl chloride* —2,3,4-Tri-*O*-benzyl-1,6-di-*O*-*p*-methoxybenzoyl-β-D-glucopyranose[1] (1 3 g) was suspended in 10 ml of dry ether saturated with hydrogen chloride and the mixture was kept for 3 days at 0° The diester gradually dissolved and *p*-methoxybenzoic acid began to precipitate The ether was evaporated and replaced by dichloromethane, (~5 ml) and the *p*-methoxybenzoic acid was filtered off The remaining solution was washed with cold, saturated, aqueous sodium hydrogen carbonate solution, dried (magnesium sulfate), and passed through a small silica gel column The column was washed with dichloromethane and the solution was evaporated to give a colorless syrup, homogeneous on t l c After drying in a high vacuum, it had $[\alpha]_D^{25}$ +99° (*c* 1 45, chloroform), the n m r spectrum contained a doublet centered at δ 6 13, $J_{1,2}$ 3 5 Hz, indicating that the α-D anomer had been obtained

*Preparation of 2,3,4-tri-*O*-benzyl-1,6-di-*O*-(*N*-phenylcarbamoyl)-β-D-glucopyranose* —2,3,4-Tri-*O*-benzyl-α-D-glucopyranose[22] (10 g, 22 2 mmoles) was dissolved in pyridine (50 ml) which had been dried over potassium hydroxide The solution was cooled to 0°, and phenyl isocyanate (5 2 ml, 5 8 g, 10% excess) was added The solution was stirred for 0 5 h at 0°, 0 5 h at room temperature, 0 5 h at 80°, and then it was cooled to 0° Methanol (5 ml) was added, and the solution was heated to 80°, cooled, and poured into water (500 ml) The product was extracted with chloroform, the extracts were dried (magnesium sulfate) and evaporated, and the residue was dissolved in excess warm benzene Upon cooling, 1 2 g of diphenylurea crystallized (m p ≈240°) The filtrate was evaporated, and the crystalline residue was recrystallized twice from ethanol–dichloromethane, once from methanol–dichloromethane, and once from benzene (4 5 g, 30%) The product, a voluminous solid, was homogeneous on t l c , m p 195–197°, $[\alpha]_D^{25}$ −12 8° (*c* 1 9, chloroform), the n m r spectrum contained a doublet centered at δ 5 72, $J_{1\ 2}$ 7 5 Hz, and two broad N-H proton peaks near δ 6 7

Anal Calc for $C_{41}H_{40}N_2O_8$ C, 71 50. H, 5 85, N, 4 07 Found C, 71 54, H, 5 62, N, 4 02

*Preparation of 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-α-*D*-glucopyranosyl bromide* — 2,3,4-Tri-*O*-benzyl-1,6-di-*O*-(*N*-phenylcarbamoyl)-β-D-glucopyranose (577 mg, 0 838 mmole) was dissolved in dry dichloromethane (15 ml) and hydrogen bromide was bubbled through the solution for 10 min, with anilinium hydrobromide beginning to precipitate after about 0 5 min The solution was kept for 10 min, and the solvent was evaporated and replaced by fresh, dry dichloromethane (10 ml) The anilinium salt was filtered off, washed with dichloromethane, and weighed (144 mg, 98 8%) The solution was concentrated at room temperature and the syrup which remained turned brown after being dried for several h *in vacuo*, no accurate optical rotation was obtained, the n m r spectrum of the material, which contains a doublet centered at δ 6 40, $J_{1\ 2}$ 3 5 Hz, and a broad N-H proton peak near δ 6 7, is consistent with the assigned structure

Direct methanolysis reactions–high vacuum techniques — The direct methanolysis reactions were performed in sealed tubes Solvents were distilled into the reaction tube through a breakseal from solvent tubes containing calcium hydride Methanol was distilled *in vacuo* from a solution of magnesium methoxide into small, calibrated tubes which were then sealed with a torch The methanol vials were put into a sidearm of the reaction vessel along with a magnetic hammer and the methanol was distilled into the reaction tube after breaking the vial

The assembled apparatus was connected to the vacuum line and an ether solution of the D-glucopyranosyl bromide (100–300 mg) was introduced through the open top The ether was evaporated in a stream of nitrogen, the top was sealed with a torch under nitrogen, and the bromide was dried for several h *in vacuo* Then the apparatus was melted off the vacuum line, the solvent (5 ml) and methanol were distilled into the reaction tube, and the sidearms were melted off The reagents were then mixed thoroughly and the tubes were kept at room temperature protected from light

The reactions were terminated by opening the tubes and concentrating the solutions to syrups The products were then dissolved in dichloromethane, and the solutions were washed with aqueous sodium hydrogen carbonate, then with water, and dried (magnesium sulfate) The solvent was distilled off and the syrups were dried *in vacuo* N m r spectra were obtained with 40–100-mg aliquots The relative amounts of α- and β-D-glucosides formed were determined by cutting out and weighing the 250-Hz sweep-width spectra of the methyl peaks Comparison of the integrals of the aliphatic region with those of the aromatic region gave a semiquantitative estimate of the purity of the methyl D-glucosides

Methanolysis reactions with silver salts — These reactions were performed in a small 2-necked flask which was dried *in vacuo* All reagents were added under a stream of nitrogen, and a positive pressure of nitrogen was maintained in the flask during the reactions The silver salt (a 20% molar excess) was dried in the flask for several h, the solvent (5 ml) was added, and the solution (or mixture) was cooled to −78° A solution of the D-glucopyranosyl halide (100–300 mg) in the same solvent was added, stirring was continued for several min (t_1 in Table II), a solution of methanol in the same solvent was added, and stirring was continued for several more min (t_2 in Table II) The reactions were terminated by shaking the mixtures with excess saturated sodium hydrogen carbonate In some cases the reactions were allowed to warm to ~0° before termination After the end of the reaction, the solutions were filtered through Celite to remove the silver halide and the organic layer was separated, washed with water, dried (magnesium sulfate), and concentrated to a syrup which was dried *in vacuo* N m r analyses similar to those just described were performed on 40–100-mg aliquots

In some cases the product crystallized Pure methyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside from one experiment was recrystallized from ethanol to give needles, m p 67 5–68 5°, $[\alpha]_D^{25}$ +12 2° (*c* 4 9, dioxane); lit [14] m p 68–69°, $[\alpha]_D$ +11° (*c* 5 0, dioxane)

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