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THE USE OF 1-*O*-SULFONYL-D-MANNOPYRANOSE DERIVATIVES IN α-D-MANNOPYRANOSIDE SYNTHESIS*

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ABSTRACT

Several 1-*O*-sulfonyl derivatives of D-mannopyranose having a nonparticipating benzyl ether group at C-2 and ester functions at C-6 and C-4 were synthesized from the corresponding D-mannopyranosyl chloride derivatives with silver sulfonates in acetonitrile The reaction of 1-*O*-sulfonyl-D-mannopyranose compounds with methanol in various solvents at room temperature gave high yields of glycosides with low degrees of stereoselectivity On the other hand, 1-*O*-sulfonyl-D-mannopyranose derivatives having an acyl participating-group at O-2 and benzyl ethers at C-3, C-4, and C-6 gave high yields and high stereoselectivity of α-D-mannopyranosides with primary and secondary alcohols in several solvents Model studies were carried out to determine the best combination of 2-*O*-acyl group, solvent, time, temperature, and 1-*O*-sulfonyl group to give high yields with high stereoselectivity The method has been used to prepare in good yields more complex glycosides, including perbenzylated methyl 2-*O*-(α-D-mannopyranosyl)-α-D-mannopyranoside

INTRODUCTION

A systematic study of glycoside-forming reactions undertaken in this laboratory[1–5] has shown that the steric outcome of reactions between equal amounts of a glycosyl derivative having a C-2 nonparticipating group and an alcohol can be controlled by a careful choice of C-1 leaving group, solvent, and substituents at C-4 and C-6 Both D-glucosyl and D-galactosyl derivatives have been investigated and conditions determined that give high degrees of stereoselectivity for α-D-glycoside in high yields This knowledge has been used to prepare α-D-(1→6)-linked glucose oligomers[6] and their protein conjugates[7] Recently, we have become interested in preparing a series of oligosaccharides containing both α-D-glucopyranosyl and α-D-mannopyranosyl residues for immunological testing Methods of preparing α-D-mannopyranosyl linkages usually involve the use of Koenigs–Knorr or orthoester

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reactions, in which the mannopyranosyl derivative has a participating group at C-2 Both of these reactions usually give high stereoselectivity, but often give low yields, sometimes due to side products with unreactive sugar alcohols We have found that the halide ion-catalyzed reaction of mannopyranosyl halides having a nonparticipating group at C-2 can also give mainly α-glycosides, however, the yields and reaction rates are low unless a large excess of glycosyl halide is used

In this report we have extended the investigation of these glycoside-forming reactions to D-mannopyranose derivatives having a 1-*O*-sulfonyl group and either a nonparticipating benzyl ether or a participating ester group at C-2

RESULTS AND DISCUSSION

1 6-Di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranose was prepared from methyl α-D-mannopyranoside by tritylation benzylation, detritylation, and acetolysis as described by Sondheimer Eby, and Schuerch[8] The acetyl groups were removed by transesterification to give 2 3,4-tri-*O*-benzyl-D-mannopyranose (**1**) The 1,6-di-*O*-(*N*-phenylcarbamoyl) derivative **2** was prepared by the method of Kronzer and Schuerch[1]

The 6-*O*-*p*-tolylsulfonyl derivative was prepared from 2,3,4-tri-*O*-benzyl-D-mannopyranose by treatment with *p*-toluenesulfonyl chloride in 2,6-dimethylpyridine The 1,6-di-*O*-substituted derivative was formed initially, but this compound was very reactive due to the nonparticipating benzyl group at O-2 Hydrolysis of the 1,6-di-*O*-tosyl derivative with water gave exclusively 2,3,4-tri-*O*-benzyl-6-*O*-tosyl-D-mannopyranose (**3**) Reaction with phenyl isocyanate in pyridine gave 2 3,4-tri-*O*-benzyl-1-*O*-(*N*-phenylcarbamoyl)-6-*O*-tosyl-α-D-mannopyranose (**4**)

2 3 4-Tri-*O*-(*p*-bromobenzyl)-1,6-di-*O*-(*N*-phenylcarbamoyl)-D-mannopyranose (**6**) was prepared from methyl 6-*O*-trityl-α-D-mannopyranoside by the same reaction sequence used to prepare the corresponding tribenzyl derivative **2** The purpose for preparing this compound was to see what influence the nonparticipating group has on the stereoselectivity of the glycoside-forming reaction

Synthesis of 1 4,6-tri-*O*-acetyl-2,3-di-*O*-benzyl-α-D-mannopyranose (**7**) was achieved through acetolysis of methyl 2,3-di-*O*-benzyl-α-D-mannopyranoside[9] The 6-substituted 1-*O*-(*N* phenylcarbamoyl) derivatives were converted into the glycosyl chloride derivatives with hydrogen chloride in dichloromethane as described previously[6,7] However, for 4,6-di-*O*-acetyl-2,3-di-*O*-benzyl-α-D-mannopyranosyl chloride (**8**) a solution of 20% dichloromethane in ether was found to be better for carrying out the displacement

The D-mannopyranosyl chlorides were used to prepare the corresponding D-mannopyranose -1-*O*-tosyl -*p*-bromophenylsulfonyl -2,2 2-trifluoroethylsulfonyl, and -trifluoromethylsulfonyl derivatives by reaction with the silver salt of the corresponding sulfonic acid in acetonitrile They were then treated with one equivalent of methanol, as described for the D-glucose and D-galactose derivatives[4–6]. The relative amounts of methyl α- and β-D-mannopyranosides were determined from ^{1}H-n m r

spectra of the reaction products The methoxyl group of the α-D anomer resonates at δ 3 25 and that of the β-D anomer at δ 3 45 for all of the methyl 2-*O*-benzyl or 2-*O*-*p*-bromobenzyl glycosides The yields in all cases were over 90%, as determined from the ^{1}H-n m r spectra[1] The results shown in Table I indicate that, in general, the nature of the C-6 substituent, C-1 leaving group, C-2 nonparticipating group, and the solvent

TABLE I

REACTION OF 6-SUBSTITUTED 2 3,4-TRI-*O*-BENZYL-D-MANNOPYRANOSE 1-SULFONATES AND RELATED DERIVATIVES WITH METHANOL[a]

Substituent at		*Leaving group at C-1*[b]	*Solvent*	*α Anomer (%)*
O-2 3,4	*O-6*			
Benzyl	*N*-Phenylcarbamoyl	Tosyloxy	Ether	43
			CH_3CN	37
			CH_2Cl_2	53
			Ether–Me_2SO[c]	40
			CH_3CN–Me_2SO[c]	40
			Ether–Et_3N[d]	33
			CH_3CN–Et_3N	44
		Brosyloxy	Ether	41
			CH_3CN	33
		Tresyloxy	Ether	43
			CH_3CN	73
		Triflyloxy[e]	Ether	40
			CH_2Cl_2	47
	p-Tolylsulfonyl	Tosyloxy	$(MeOCH_2)_2$	38
			CH_3CN	40
		Tresyloxy	$(MeOCH_2)_2$	40
			CH_3CN	36
p-Bromobenzyl	*N*-Phenylcarbamoyl	Tosyloxy	Ether	35
			CH_3CN	38
			CH_2Cl_2	40
4-Acetyl-2 3-di-benzyl	Acetyl	Tosyloxy	CH_3CN	46
			Ether	50

[a]Ratio of methanol to D-mannose derivative was 1 1 at room temperature for 16 h (conc 0 181 mol/l) [b]Abbreviations *p*-bromophenylsulfonyl brosyl 2 2 2-trifluoroethylsulfonyl tresyl and trifluoromethylsulfonyl triflyl [c]Ratio of Me_2SO to D-mannosyl derivative was 1 1 (m/m) [d]Ratio of triethylamine to D-mannosyl derivative was 1 1 (m/m) Reaction performed at −78 for 1 h

had very little effect on the stereoselectivity of the glycoside-forming reaction The results are similar to those obtained for the 6-substituted 2 3,4-tri-*O*-benzyl-D-galactosyl derivatives[4 5], which also showed only a small change in stereoselectivity with changes in solvent and leaving groups The one exception involves the use of the trifluoromethylsulfonyl group as the leaving group at low temperature In the case of D-galactose[5 6], the yields of methyl β-D-glycoside were quite high, while with D-mannose the yield of the β-D anomer was about 50%

TABLE II

1,2-DI-*O* ACYL 3,4,6 TRI-*O* BENZYL D-MANNOPYRANOSES

Comp	*Substituents at O-1 and O 2*	*N m r spectrum*[a]		*M p* (°)	$[\alpha]_D^b$ (°)	*Formula*	*Anal*[c]			
		Hα	*Hβ*				*C*	*H*	*Cl*	*N*
9	Dichloroacetyl	6 25		86–87[d]	+74 6	$C_{31}H_{30}Cl_4O_8$	55 38 55 60	4 49 4 32	21 12 20 97	
10	Acetyl	6 12	5 69	syrup	+15 5	$C_{31}H_{34}O_8$	69 64 69 64	6 41 6 35		
11	*p*-Nitrobenzoyl	6 58	6 18	amorphous	+4 6	$C_{41}H_{36}O_{12}N_2$	65 77 65 66	4 84 4 79		3 74 3 98
12	Benzoyl	6 48		115–116[d]	+30 4	$C_{41}H_{38}O_8$	74 80 74 64	5 8 5 56		
13	*p*-Methoxybenzoyl	6 51	6 08	syrup	−18	$C_{43}H_{42}O_{10}\ H_2O$	70 10 69 81	6 2 5 87		

[a]N m r spectrum indicates anomeric form, units of δ (p p m) [b]The measurements were taken at 20° on solutions in dichloromethane except for **12** which was dissolved in chloroform [c]Upper line, calculated value, lower line, experimental value [d]Crystallized from ether–hexane

3,4,6-Tri-*O*-benzyl-D-mannose[10] was acylated with various acylating agents to give the diester derivatives **9–13** These compounds, which in some cases were isolated as a mixture of α- and β-D anomers (Table II), were converted to the corresponding glycosyl halides by conventional methods[11] (Table III) The 1-*O*-tosyl-D-mannopyranose derivatives were prepared from the corresponding α-D-mannopyranosyl bromides or chlorides (**14–18**) by treatment with silver *p*-toluenesulfonate in acetonitrile at room temperature[3]

The glycosylation reactions were carried out in several solvents (Table IV), of which dichloromethane was found to provide the best yields In the model studies with methanol, the anomeric purity and the yield were estimated from ^{1}H-n m r and ^{13}C-n m r data In contrast to the 2-*O*-benzylglycosides the methoxyl group of the various methyl α-D-glycosides from **14–18** gave a signal that appeared between δ 3 31 and 3 41 (Tables IV and V) The methoxyl group signal of the β-D anomer appeared ~0 1 p p m downfield compared to the α-D anomer A similar change was observed also, in the ^{13}C-n m r spectrum, between C-1 α and C-1 β

Acetyl, benzoyl, and *p*-methoxybenzoyl residues were found to be effective participators as neighboring groups and led to *trans*-glycoside formation, however, reactions with the 2-*O*-benzoyl derivative gave products in highest purity and yield The efficacy of the 1-*O*-tosyl-2-*O*-benzoyl derivative was further demonstrated in the preparation of glycosides **28**, **29**, **30**, and **31**, usually in yields of over 90% of essentially pure product The yield of the glycosylation dropped to about 80% only in the reaction with an axial secondary hydroxyl group

The 2,2,2-trifluoroethylsulfonyl derivative obtained from **17** was significantly less stereoselective than the tosyl derivative on reaction with methanol at room temperature, and it showed the formation of an observable amount of a β-D-glycoside derivative However, at 0°, high stereoselectivity was also obtained with this more reactive leaving-group

Glycosidation reactions of 2-glycosyl derivatives with electronegative leaving-groups at C-1 and nonparticipating substituents at C-2 vary greatly in their stereoselectivity The stereoselectivity of the reaction can be interpreted on the basis of the

TABLE III

2-*O*-SUBSTITUTED 3,4 6-TRI-*O*-BENZYL-α-D-MANNOPYRANOSYL HALIDES

Comp	*Substituents at*		$[\alpha]_D^{20}$ (°)[a]	*N m r spectrum*[b]		
	C-2	*C-1*		H_2	$J_{1,2}$ (*Hz*)	*H-2*
14	Dichloroacetate	Br	+123	6 42	1 7	5 55
15	Acetate	Cl	+47	6 0	1 7	5 41
16	*p*-Nitrobenzoate	Br	+34 8	6 55	1 7	5 8
17	Benzoate	Cl	+30 5	6 21	1 7	5 72
18	*p*-Methoxybenzoate	Cl	+5 7	6 21	1 7	5 71

[a]Measured on solutions in dichloromethane [b]Units of δ (p p m)

TABLE IV

REACTION OF 2-*O*-ACYL-3,4 6-TRI-*O*-BENZYL-1-*O*-TOSYL-D-MANNOPYRANOSE WITH METHANOL[a]

Comp formed	*Substituent at C-2*	*Solvent*	*Total yield (%)*	*α Anomer (%)*	*^{1}H-N m r*			*^{13}C-N m r*	
					MeO_α	*MeO_β*	*H-2*	*C-1_α*	*C-1_β*
23	Dichloro-acetate	Ether	65	54	3 42	3 53	5 48	99 16	99 35
		CH_2CN	70	61					
24	Acetate	CH_2Cl_2	80	>98	3 31		5 37	98 95	
		Ether	75	>98					
25	*p*-Nitro-benzoate	CH_3CN	70	92	3 41	3 52	5 61	98 56	99 2
26	Benzoate	CH_3CN	75	>98					
		Ether	70	>98	3 33		5 61	98 9	
		CH_2Cl_2	95	>98					
27	*p*-Methoxy-benzoate	Ether	45	~98	3 36		6 62		
		CH_3CN	40	~98					

[a]2-*O*-Benzoyl-3 4,6-tri-*O*-benzyl-1-*O*-(2 2 2-trifluoroethylsulfonyl)-D-mannopyranose formed 60% of α- and 40% of β-D-glycosides at room temperature and essentially pure (>98%) α-D-glycoside at 0 Because of difficulty in measuring methanol the listed yields should be considered minimal In reactions carried out with a small excess of dry methanol the yields are usually essentially quantitative

TABLE V

GLYCOSIDES OF 2-*O*-BENZOYL-3,4,6-TRI-*O*-BENZYL-α-D-MANNOPYRANOSIDE

Comp	$[\alpha]_D^{20}$ (-)[a]	*Total yield (%)*	*α Anomer (%)*	*^{1}H-N m r*		*^{13}C-N m r*
				H_α	*H-2*	*C-1_α*
28	−3 1	90	>95	4 97	5 63	98 97
29	+1 5	90	> 95	5 15	5 60	95 97
30	+5 6	95	>98	4 95	5 60	97 68
31	−5 8	78–80	90	4 92	5 77	100 20

[a]Determined on solutions in dichloromethane

mechanism proposed by Rhind-Tutt and Vernon[12] The course of the reaction depends upon a competition between three possible processes (see Fig 1) direct β-glycosidation (reaction *2*), or anomerization of an α-tight ion-pair, followed immediately by a very rapid glycosidation (reactions *3* and *5*), or ion separation which leads to loss of steric control (reactions *6*, *7*, and *8*) In order to avoid ion separation, solvents of low dielectric constant are advantageous In these systems, the rate of reaction *2* is increased over that of reaction *3*, and β-glycoside formation is

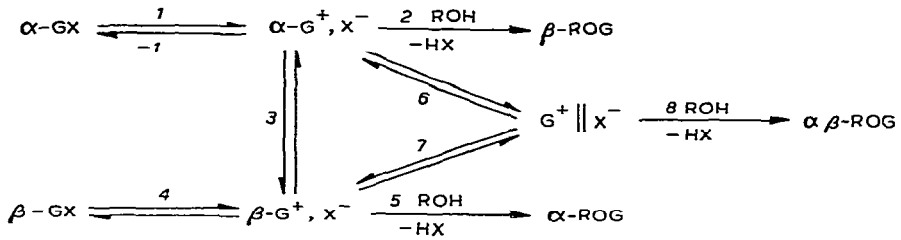


Fig 1 Mechanism of glycosidation modified according to Rhind-Tutt and Vernon[12]

enhanced by high concentrations of alcohol Reaction *3* and α-glycoside formation can also often be enhanced by proper selection of experimental conditions The halide-ion catalyzed α-glycosidation described by Lemieux *et al*[13] depends upon suppression of reaction *2* by low alcohol concentration and enhancement of ion-pair anomerization (reaction *3*) by nucleophilic attack of halide ion Glaudemans and Fletcher[14] have noted that increased halide-ion concentration can suppress the rate-determining ionization (reaction *1*) by a common-ion effect and thus offset any rate enhancement by reaction *3* The two factors that are required for high α-stereoselectivity (low alcohol and high halide-ion concentration) thus tend to produce a relatively slow reaction We have attempted to apply the halide ion-catalyzed method to 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl)-α-D-mannopyranosyl bromide Using the customary reaction conditions[12] with ~1 1 equiv of methanol in dichloromethane, we found that the reaction was stereoselective (~90% of α anomer) but at only 50% of completion after four days

Therefore, it appeared advisable to investigate some of the structural modifications of sugar derivatives that have been shown to alter, independently, rate and stereoselectivity of α-glycosidations These modifications have been reviewed elsewhere[15] In general, compounds having tightly bound leaving-groups, such as chloride or fluoride, tend to react by direct substitution rather than by ion anomerization or separation Thus, methanolysis of 2 3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl chloride produces nearly pure β-glycoside[12] However, the corresponding D-mannose derivative in methanol (dielectric constant ε 32 6) produced a mixture of glycosides containing 42% of β anomer[12] Rhind-Tutt and Vernon[12] ascribe this behavior to shielding by the axial C-2 substituent, which allows the ion pair to separate and C-1 to adopt a planar conformation before reaction The strain due to 1,3 interactions with the 2-axial group may be released and provide the driving force for the ionization and dissociation The same explanation probably accounts for the poor stereoselectivity of the reactions reported in Table I The reason for our selection of compounds with nonparticipating groups at C-2 is as follows

It has been observed in other systems[15] that 2-*O*-benzylglycosyl sulfonates tend to undergo glycosidation with more α-stereoselectivity if C-6 and C-4 are esterified rather than etherified This higher α-specificity appears to be the result of a sensitivity

to solvent that is less prominent with the fully etherified derivatives. Apparently, when an α ion-pair of appropriate reactivity is generated in a solvent of high donicity[15,16], the solvent can compete effectively with the alcohol and solvate the ion pair, thus reducing its reactivity[17] and providing time for anomerization. Thus, reaction *3* is favored over reaction *2*. In order to avoid dissociation (reaction *6*), the solvent must have a low dielectric constant. Ethers are inert solvents of high donicity and low dielectric constant and are thus especially suitable for α-glycosidation reactions.

The compounds reported in Table I should produce ion pairs of different reactivities since they have leaving groups of different electronegativities. They have ester functions at C-6 (and in one case C-4). The solvents include those of relatively high donicity and high dielectric constant[15] (acetonitrile), low donicity and low dielectric constant (dichloromethane), and two of high donicity and low dielectric constant (ethyl ether and dimethoxyethane). No clear trends and almost no significant variation in selectivity is apparent. The results give strong support to the interpretation of Rhind-Tutt and Vernon[12] that shielding by the C-2 axial substituent allows planarity of the D-mannosyl cation before reaction.

It, therefore, appeared to be necessary to select 2-*O*-acyl participating groups to ensure *trans*-1,2 α-stereoselectivity with D-mannose. Glycosyl halides having an acyl participating group at C-2 yield 1,2-*trans*-glycosides or orthoesters when allowed to react with alcohols under a variety of conditions (for a review, see Ref. 18). The orthoesters themselves can be caused to rearrange or react with alcohols to give 1,2-*trans*-glycosides. Thus, methods are available to give β-D-gluco-, β-D-galacto- and α-D-manno-pyranosides.

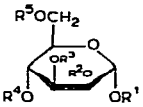
Per-*O*-acyl-D-mannopyranosyl bromides or chlorides have been widely used in the Koenigs–Knorr or orthoester reaction to give α-D-mannopyranosides of simple or reactive alcohols in good yields and stereoselectivity. However, when aglycons of low reactivity are used, yields are reduced and in some cases so is the stereoselectivity. The low yields seem to be due mainly to the low reactivity of peracyl derivatives, which provides time for side reactions to occur. The results of Wallace and Schroeder[19] and of Shaban and Jeanloz[20] indicate that D-glucopyranosyl halides having an acyl group at O-2 and ether functions (either benzyl or methyl) at O-3, O-4, and O-6 give high stereoselectivity in the synthesis of 1,2-*trans* glycosides and faster reaction rates than the corresponding peracylated derivatives. Hanessian and Banoub have activated peracylated glucopyranosyl halides using silver trifluoromethanesulfonate[21]. Good yields of β-D-glucopyranosides were obtained with good stereoselectivity in short reaction-times (4–8 h), although it is not clear whether the 1-*O*-trifluoromethylsulfonyl derivative is the intermediate or whether the reaction proceeds by silver-assisted abstraction of halide ion.

In the present work, partially etherified 2-*O*-acyl-α-D-mannopyranosyl bromides or chlorides (**14–18**) were converted into the corresponding 1-*O*-sulfonyl derivatives (**19–22**) by reaction with the appropriate silver sulfonate in acetonitrile solution. The silver halide was separated by filtration in an evacuated system. The acetonitrile

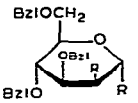
solution either was evaporated to dryness and the product dissolved in the desired solvent and treated with methanol, or was treated directly with methanol. (A number of D-gluco- and D-galacto-pyranosyl sulfonates have been shown previously to have the α configuration, but no attempt was made to characterize these D-mannosyl sulfonates). The glycosides formed were characterized by ^{1}H-n.m.r. spectroscopy. As shown in Table IV, the stereoselectivity of the glycoside-forming reaction is dependent on the electronic nature of the 2-*O*-acyl group. Dichloroacetyl and *p*-nitrobenzoyl groups are poorer participating groups and give lower degrees of stereoselectivity, as expected[14]. To the degree that participation is incomplete, an uncontrolled attack by an alcohol at C-1 gives both α- and β-glycosides. Acetyl, benzoyl, and *p*-methoxybenzoyl groups are good participating groups, and all gave very high stereoselectivity. However, the benzoyl group appears preferable because of ease of manipulation.

The choice of solvent had little effect on the stereoselectivity of reactions with compound **22**. Thus, participation of the benzoyl group was more rapid than, and preferred over, solvation of the cation by another molecule. However, the yield of glycoside was dependent on the solvent for reasons that are not clear. The best solvent was found to be dichloromethane, which dissolved all the D-mannopyranosyl derivatives and aglycons, and gave high yields and stereoselectivity. When the trifluoroethanesulfonate group was the leaving group, stereoselectivity was lost at room temperature but, at zero degree, the stereoselectivity was as high as that with the *p*-toluenesulfonate group. The best and most convenient choice of variables, therefore, included reaction at room temperature in dichloromethane with 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-*O*-*p*-tolylsulfonyl-D-mannopyranose (**22**). A series of α-D-mannopyranosides having various aglycons were synthesized under these conditions (Table V). The yields and stereoselectivity were very high but, in general, when the aglycon was of low reactivity or sterically hindered, the yield and stereoselectivity were somewhat decreased.

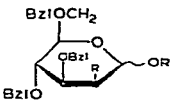
2-*O*-Benzoyl-3,4,6-tri-*O*-benzyl-1-*O*-*p*-tolylsulfonyl-D-mannopyranose (**22**) may exist as the α or β anomer, but the α form is presumably greatly preferred. In theory, *endo* and *exo* isomers of the acyloxonium *p*-toluenesulfonate may also exist. We have, however, not obtained adequate spectral evidence to determine which isomers exist or preponderate. There are four corresponding, tight-ion pairs, which may be present as reactive intermediates in glycosidation. However, the lack of sensitivity to the solvent, and the influence of nitro substitution of the benzoyl group on stereoselectivity (as shown by the reaction of **21**) strongly support the classical interpretation that an acyloxonium ion is the important intermediate in this glycosidation. It appears unlikely that this ion is converted to an orthoester and that the orthoester rearranges. A reaction between 0.7 mmol of **22** and 1.4 mmol of methanol in 2 ml of chloroform-*d* was followed by ^{1}H-n.m.r. spectral analysis at 25°. The reaction had progressed very far at the first reading, 15 min after mixing; no methoxyl proton characteristic of an orthoester could be seen. After 3 h, no change in the relative size of the peaks of free methanol (δ 3.40) and α-D-glycosidic methoxyl group (δ 3.46) was observed, and processing of the reaction mixture showed that the reaction had gone to



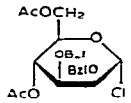
1 $R^1 = R^5 = H$ $R^2 = R^3 = R^4 = Bzl$
2 $R^1 = R^5 = PhNHCO$ $R^2 = R^3 = R^4 = Bzl$
3 $R^1 = H$ $R^2 = R^3 = R^4 = Bzl$ $R^5 = Ts$
4 $R^1 = PhNHCO$ $R^2 = R^3 = R^4 = Bzl$ $R^5 = Ts$
5 $R^1 = R^5 = H$ $R^2 = R^3 = R^4 = (p)BrC_6H_4CH_2$
6 $R^1 = R^5 = PhNHCO$ $R^2 = R^3 = R^4 = (p)BrC_6H_4CH_2$
7 $R^1 = R^4 = R^5 = Ac$ $R^2 = R^3 = Bzl$



9 R = R = Cl_2CHCO_2
10 R = R = AcO
11 R = R′ = $(p)NO_2C_6H_4CO_2$
12 R = R = BzO
13 R = R = $(p)MeOC_6H_4CO_2$
14 R = Br R = Cl_2CHCO_2
15 R = Cl R = AcO
16 R = Br R = $(p)NO_2C_6H_4CO_2$
17 R = Cl R = BzO
18 R = Cl R′ = $(p)MeOC_6H_4CO_2$



19 R = Ts R = Cl_2CHCO_2
20 R = Ts R = AcO
21 R = Ts R = $(p)NO_2C_6H_4CO_2$
22 R = Ts R = BzO
23 R = Me R = Cl_2CHCO_2
24 R = Me R = AcO
25 R = Me R = $(p)NO_2C_6H_4CO_2$
26 R = Me R = BzO
27 R = Me R = $(p)MeOC_6H_4CO$



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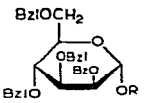
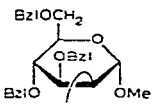


28 R = Me_2CHCH_2
29 R = cyclohexyl
30 R = $(p)TsNHC_6H_4CH_2CH_2$

31 R =



completion The rate of reaction appears greater than expected for an orthoester intermediate

When **17** was treated with silver trifluoromethanesulfonate and the product allowed to react with methanol 40% of β-glycoside was formed at room temperature whereas at zero degree the product was essentially pure α-glycoside Apparently, with the more reactive trifluoromethanesulfonate leaving-group, direct glycosidation with inversion can compete with rearrangement to the acyloxonium ion However the former reaction has the higher activation energy and can be eliminated by lowering the temperature This method of preparing *trans*-1,2-glycosides rapidly and in high yield is also useful for the preparation of *trans*-1 2-β-D-galactosides

EXPERIMENTAL

General — ^{1}H-N m r spectra were determined with a Varian A-60-A spectrometer on solutions in chloroform-*d* with tetramethylsilane as an internal standard Optical rotations were recorded with a Perkin–Elmer 141 polarimeter Melting points were determined with a 76-mm immersion thermometer Spectrograde dichloromethane, acetonitrile, diethyl ether, and 1 2-dimethoxyethane were dried over CaH_2 Silver *p*-toluenesulfonate (Eastman Organic Chemicals, Rochester, NY 14650), silver trifluoromethanesulfonate (Cationics, Inc Columbia, SC 29240), and silver *p* bromobenzenesulfonate (prepared from the sodium salt with silver nitrate) were dried under high vacuum before use

Silver 2,2,2-trifluoroethanesulfonate — 2,2,2-Trifluoroethanesulfonyl chloride (5 ml) was hydrolyzed with water at room temperature to the sulfonic acid and HCl The HCl was removed by azeotropic distillation with water, and the remaining sulfonic acid was treated with a silver nitrate solution A white precipitate formed, and was filtered off and dried The silver salt can be recrystallized from benzene

2,3,4-Tri-O-*benzyl*-D-*mannopyranose* (**1**) — 1,6-Di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-mannopyranose (16 g) was deacetylated with sodium ethoxide in ethanol The solution was neutralized with acetic acid and evaporated to a syrup The product was dissolved in dichloromethane and washed with water, dilute HCl, $NaHCO_3$ solution, water, dried (Na_2SO_4), and evaporated to a syrup T l c on silica gel with ether as eluent showed only one spot and ^{1}H-n m r showed 3 benzyl groups and 2 protons exchangeable with D_2O, (yield 13 g). $[\alpha]_D^{25}$ +45 0° (*c* 1, chloroform)

Anal Calc for $C_{27}H_{30}O_6$ C, 71 98, H, 6 71 Found C, 71 78, H, 6 67

2,3,4-Tri-O-*benzyl*-1,6-*di*-O-(N-*phenylcarbamoyl*)-D-*mannopyranose* (**2**) — 2 3,4-Tri-*O*-benzyl-D-mannopyranose (10 g) was converted into **2** according to the method used for the corresponding D-glucose derivative[1] The product was purified by column chromatography on alumina to give 13 g of **2** as a noncrystalline, glassy solid, $[\alpha]_D^{25}$ +17 4° (*c* 1, chloroform)

Anal Calc for $C_{41}H_{40}N_2O_8$ C, 71 59, H, 5 85, N, 4 07 Found C, 71 35 H, 5 80, N, 4 05

2,3,4-Tri-O-*benzyl*-6-O-p-*tolylsulfonyl*-D-*mannopyranose* (**3**) — 2,3,4-Tri-*O*-benzyl-D-mannopyranose (**1**) (3 0 g) was dissolved in dry 2,6-dimethylpyridine (20 ml) *p*-Toluenesulfonyl chloride (2 0 g) was added and the solution stirred overnight at room temperature Water (1 ml) was added to decompose the excess of chloride and to hydrolyze the tosyl group at O-1 After 4 h the solution was poured into water, and the suspension was extracted with dichloromethane The organic phase was washed with water dilute HCl $NaHCO_3$ solution, water, dried ($NaSO_4$), and evaporated to a syrup Chromatography on silicic acid gave **3** as a syrup (2 0 g), $[\alpha]_D^{25}$ +2 5° (*c* 1, chloroform) the ^{1}H-n m r spectrum showed 3 benzyl groups, one tosyl group, and one proton exchangeable with D_2O

2,3,4-Tri-O-*benzyl*-1-O-(N-*phenylcarbamoyl*)-6-O-p-*tolylsulfonyl*-α-D-*mannopyranose* (**4**) — 2,3,4-Tri-*O*-benzyl-6-*O*-*p*-tolylsulfonyl-D-mannopyranose (**3**) (2 0 g) was dissolved in dry pyridine (20 ml), and phenyl isocyanate (1 g) was added The reaction mixture was processed as described previously[1] The product crystallized from ether–petroleum ether to give 2 0 g (83%) of **4**, m p 154–155°, $[\alpha]_D^{25}$ +24 3° (*c* 1, acetone) The n m r spectrum showed 3 benzyl groups, 2 carbanilate groups, and a doublet at δ 6 05 ($J_{1,2}$ 1 5 Hz) characteristic of the α-D anomer

Anal Calc for $C_{41}H_{41}NO_9S$ C, 68 03 H, 5 71 N, 1 94 Found C, 68 59 H, 5 45, N, 1 85

2,3,4-Tri-O-(p-*bromobenzyl*)-D-*mannopyranose* (**5**) — Methyl 6 *O*-trityl-α-D-mannopyranoside (10 g) was dissolved in dry tetrahydrofuran (200 ml), and NaH (3 5 g) was added After the evolution of H_2 had ceased, a solution of *p*-bromobenzyl bromide (23 g) in dry tetrahydrofuran (100 ml) was added dropwise The mixture

was boiled under reflux for 4 h, and then the excess NaH was eliminated with methanol The solution was evaporated to give a syrup, water was added, and the organic compounds were extracted with dichloromethane The organic phase was washed with water, dried ($NaSO_4$), and evaporated to a syrup that would not crystallize The syrup was detritylated with HBr in glacial acetic acid, followed by acetolysis in acetic anhydride–H_2SO_4 for 3 h at room temperature The crude, noncrystalline 1,6-di-*O*-acetyl-2,3,4-tri-*O*-(*p*-bromobenzyl)-D-mannopyranose was deacetylated by transesterification in ethanol with sodium ethoxide to give **5**, which crystallized from chloroform–petroleum ether to give 7 0 g (45%), m p 168–171°, $[\alpha]_D^{25}$ −59 7° (*c* 1, dimethyl sulfoxide)

Anal Calc for $C_{27}H_{27}Br_3O_6$ C, 47 18, H, 3 96, Br, 34 89 Found C, 47 31, H, 4 17, Br, 35 43

2 3,4-Tri-O-(p-*bromobenzyl*)-*1,6-di*-O-(N-*phenylcarbamoyl*)-D-*mannopyranose* (**6**) — This compound was prepared from **5** by reaction with phenyl isocyanate in pyridine, as described for the corresponding glucose derivative[1] The product was purified on an alumina column to give **6** as a noncrystalline, glassy solid, $[\alpha]_D^{25}$ −3 18° (*c* 1, chloroform)

Anal Calc for $C_{41}H_{37}Br_3O_8N_2$ C, 53 21, H, 4 03, N, 3 03 Found C, 53 38, H, 4 11, N, 3 10

1,4,6-Tri-O-*acetyl-2 3-di*-O-*benzyl-α*-D-*mannopyranose* (**7**) — Methyl 2,3-di-*O*-benzyl-α-D-mannopyranoside[9] (4 g) was dissolved in acetic anhydride (10 ml) To this solution was added 8 ml of acetic anhydride containing 5 drops of conc H_2SO_4 The acetolysis was followed by ^{1}H-n m r and appeared complete after 10 min This reaction must be carefully monitored Processing of the acetolysis reaction by a procedure similar to that of **3** led to the isolation of a syrup in an almost quantitative yield, pure according to t l c Crystallization from ether at −5° gave **7**, m p 96–98° $[\alpha]_D^{20}$ +7 5° (*c* 4 39, dichloromethane)

Anal Calc for $C_{26}H_{30}O_9$ C, 64 18, H, 6 22 Found C, 63 54, H, 5 99

4,6-Di-O-*acetyl-2,3-di*-O-*benzyl-α*-D-*mannopyranosyl chloride* (**8**) — The tri-*O*-acetyl-di-*O*-benzyl derivative **7** (4 g) was dissolved in ether (80 ml) and dichloromethane (20 ml) Into this solution gaseous HCl was bubbled for 15 min The reaction flask was closed and kept overnight at room temperature After 20 h, t l c (3 2 ether–hexane) indicated that the reaction was completed The solution was concentrated under vacuum at room temperature The residue was dissolved in dichloromethane, and the solution was washed with cold sodium hydrogencarbonate solution and water The dried organic extract was evaporated under vacuum to give a syrupy residue, $[\alpha]_D^{20}$ +28 8° (*c* 4 7, dichloromethane), ^{1}H-n m r ($CDCl_3$) δ 7 3 (10 aromatic H), 6 1 (d, $J_{1,2}$ 1 8 Hz, H-1), 4 65 and 4 5 (4 H of 2 CH_2), and 1 98 (6 H of 2 Ac)

Preparation and glycosidation of 6-substituted-D mannopyranose derivatives with methanol — 6-Substituted 2,3,4-tri-*O*-(benzyl- or *p*-bromobenzyl)-1-*O*-(*N*-phenylcarbamoyl)-D-mannopyranoses were converted into the D-mannopyranosyl chlorides with HCl gas in dichloromethane as described for D-glucopyranosyl chloride

derivatives[7] The chlorides were treated immediately with the corresponding silver salt in acetonitrile to form the sulfonates, as described for D-glucosyl and D-galactosyl derivatives[3–5] The D-mannose 1-*p*-toluenesulfonate, 1-*p*-bromobenzenesulfonate, 1-(2,2,2-trifluoroethanesulfonate), and 1-trifluoromethanesulfonate were dissolved in the appropriate solvent, and the silver chloride formed was filtered off and the solution allowed to react with 1 equiv of methanol 4,6-Di-*O*-acetyl-2,3-di-*O*-benzyl-α-D-mannopyranosyl chloride was converted into the corresponding 1-*O*-tosyl derivative, which was allowed to react with methanol similarly All operations were performed on a high-vacuum rack, as described for the D-glucose derivatives[3] The mixtures were isolated and the crude product analyzed by ^{1}H-n m r , results are shown in Table I

*Preparation of 1,2-di-*O*-acyl-3,4,6-tri-*O*-benzyl-*D*-mannopyranose derivatives* (**9–13**) — The starting material for all syntheses of 2-*O* acyl derivatives was 3,4,6-tri-*O*-benzyl-D-mannopyranose, which was obtained as described by Franks and Montgomery[10] To a 10mM solution of 3,4,6-tri-*O*-benzyl-D-mannopyranose (**1**) in dry benzene (20 ml) containing a slight excess of 2,6-dimethylpyridine (for the preparation of **9** and **11**) or pyridine (for the preparation of **10, 12** and **13**) was added with cooling 2 2 equiv of the appropriate acyl chloride In most cases, a precipitate of hydrochloride formed immediately and the resulting suspension was stirred for 24 h at room temperature Afterwards, a few drops of water were added to destroy any unreacted chloride After stirring for an additional 30 min, the reaction mixture was treated several times with cold sodium hydrogencarbonate solution The organic extract was dried and concentrated under vacuum, and the residue was chromatographed on a short column of silica gel In all cases, yields of the diesters were nearly quantitative The products were composed generally of a mixture of anomers In some cases, it was possible to obtain the α-D anomer in a crystalline state (see Table II) The properties of the diester derivatives are listed in Table II

T l c analysis was performed with 3 2 (v/v) ether–hexane or 19 1 (v/v) dichloromethane–ether

*3,4,6-Tri-*O*-benzyl-2-*O*-p-nitrobenzoyl-α-D-mannopyranosyl bromide* (**16**) — Into a solution of **11** (1 8 g) in dichloromethane (20 ml) was bubbled gaseous HBr, *p*-nitrobenzoic acid started to separate after 2 min, and after 10 min the acid was filtered off The filtrate was concentrated under vacuum at room temperature The residue was dissolved in dichloromethane , and the solution was washed successively with cold sodium hydrogencarbonate solution and water The dry extract was concentrated under vacuum to give a syrupy product (1 5 g, 94%) The physical data are reported in Table II Chromatographic purification on either alumina or silica caused extensive decomposition Thus, the glycosyl halides were used without further purification

*3,4,6-Tri-*O*-benzyl-2-*O*-(dichloroacetyl)-α-D-mannopyranosyl bromide* (**14**) — The preparation of **14** was performed similarly to that of **16**, except that in this case the liberated acid was soluble in the reaction medium

*Preparation of 2-*O*-acyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride derivatives* (**15, 17, 18**) — The 10mM solution of the diester derivative in anhydrous ether

(100 ml) was saturated with HCl in the cold (5°), then the flask of the reaction was closed tightly with a stopcock After the solution had been kept for two days at room temperature, t l c on silica gel in 3 2 (v/v) ether–hexane indicated that the chlorination was almost complete Processing included washing with cold aqueous sodium hydrogencarbonate and water The products obtained were syrupy and could not be induced to crystallize

The chloride **15** was prepared by an alternative method 3,4,6-Tri-*O*-benzyl-D-mannopyranose (1 3 g) was dissolved in dry toluene (20 ml) Acetyl chloride (5 ml) was added, followed by 2 drops of pyridine, and the reaction mixture was stirred overnight at room temperature After 20 h, HCl was bubbled in for 3 min, and the reaction was allowed to continue for an additional 24 h at room temperature The processing was as just described The crude yield of the chlorination reaction was almost quantitative according to ^{1}H-n m r and t l c data

Reaction of 2-O-acyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl halide derivatives with methanol — The suitable halide dissolved in acetonitrile was allowed to react with silver *p*-toluenesulfonate (or trifluoroethanesulfonate) to form the corresponding sulfonyl derivative (**19–22**) Then, the acetonitrile was distilled off (except for the case where acetonitrile itself served as a medium for the reaction) The sulfonyl derivative was dissolved in the appropriate solvent, the silver chloride (or bromide)[1] formed was filtered off, and the solution was treated with 1 equiv of methanol All operations were performed on a high-vacuum rack as described for the D-glucose derivatives[1] The mixtures were isolated, and the crude product (**23–27**) was analyzed by ^{1}H-n m r Results are shown in Table IV

Methyl 2-O-benzoyl-3,4 6-tri-O-benzyl-α-D-mannopyranoside (**26**, α *anomer*) — The reaction of **22** was performed in dichloromethane as just mentioned The processing of the glycosidation mixture included washing of the organic extract with cold sodium hydrogencarbonate and thiosulfate solutions The syrupy residue obtained after evaporation of the organic solvent was pure according to ^{1}H-n m r and t l c data (3 2 v/v, ether–hexane) After eliminating traces of impurities (mainly silicone grease) by use of a short silica gel column, a solid material was obtained, which crystallized from ethanol–hexane at −10°, m p 76–78°, $[\alpha]_D^{20}$ −22° (*c* 1 1, dichloromethane)

Anal Calc for $C_{35}H_{36}O_7$ C, 73 92, H, 6 38 Found C, 73 94 H, 6 28

This compound (100 mg) was treated in abs methanol with a catalytic amount of sodium methoxide The product obtained was identical with a reference compound synthesized by the method of Franks and Montgomery[10] This result provided a chemical verification of the absence of any orthoester by-product among the glycosidation products

2-[p-Tosylamino)phenyl]ethyl 2-O-benzoyl-3,4,6-tri-O-benzyl-α-D-mannopyranoside (**30**) — This glycoside was obtained in a similar manner to **26** A glycosidation in dichloromethane starting from **17** (500 mg) and 253 mg of 2-[(*p*-tosylamino) phenyl]ethanol gave 690 mg (95%) of product, pure according to n m r and t l c criteria For an analytical sample, chromatography on alumina with elution with

mixtures of chloroform–ether (starting from a solution of 10% ether) gave 550 mg of **30** as a white amorphous solid, optical rotation and n m r data are reported in Table V

Anal Calc for $C_{49}H_{49}NO_9S$ C, 71 08, H, 5 96, S, 3 86 Found C, 71 17 H, 5 95, S, 4 04

Methyl 2-O-(2-O-benzoyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl)-3,4,6-tri-O-benzyl-α-D-mannopyranoside (**31**) — The glycosidation was carried out as described for **26** The chloride **17** (475 mg) and methyl 3,4,6-tri-*O*-benzyl-α D-mannopyranoside (415 mg) gave 650 mg (79%) of **31** The proportion of **31** estimated from n m r spectra and t l c appear to be ~90% of the total yield, optical rotation and n m r data are reported in Table V The β-D anomer (minor component) could not be isolated in a pure state

Anal Calc for $C_{62}H_{62}O_{12}$ C, 74 52, H, 6 25 Found C, 74 57 H, 6 34

Characterization of an analogous disaccharide derived from the condensation of 2 [(*p*-tosylamino)phenyl]ethyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**30**) with **22** showed no evidence of the β-D anomer

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