THE SYNTHESIS OF 1-O-ACYL-ALDOSES

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements for the degree of Master of Science

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May 1975

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ABSTRACT

The synthesis of alkali labile glycosides was envisaged from two different routes. One of these involved 2,3,4,6-tetra-O-benzyl-1-O-trifluoromethanesulfonyl-β-D-glucopyranose as an intermediate, to be substituted at C-1 with nucleophiles such as salts of organic acids. However, the trifluoromethanesulfonyloxy group proved itself to be a poorer leaving group at C-1 than expected, and gave low yields of substitution products. By contrast, when gluco- and manno-1,2-(orthoesters) were reacted with acetic, propanoic, pivalic, cyclohexanecarboxylic, benzoic or picolinic acid the corresponding glycosyl ester was formed readily in good yield. The scope and stereochemistry of this orthoester reaction were studied.

RESUME

Deux approches différentes ont été envisagées pour la synthèse de glycosides-esters instables en milieu alcalin. Une de ces approches implique le 2,3,4,6-tétra-O-benzyl-1-O-trifluorométhanesulfonyl-β-D-glucopyranose, en tant qu'intermédiaire, pour être ensuite substitué à C-1 avec des nucléophiles comme des sels d'acides organiques. Le groupe trifluorométhanesulfonyloxy, qui d'ordinaire est un bon groupe partant, se montra à C-1 peu réactif envers la substitution. Cenpendant, lorsque les orthoesters gluco- ou manno- réagirent avec l'acide acétique, propanoique, cyclohexanecarboxylique, benzoique ou picolinique les glycosyls ester correspondants furent formés facilement avec de bons rendements. L'étendue et la stéréochimie de la réaction orthoester furent étudiées.

ACKNOWLEDGMENTS

The author wishes to express his sincere gratitude to Professor A.S. Perlin for his expert guidance and invaluable assistance with every aspect of the present work.

Special appreciation is extended to Drs. N. Cyr, R.G.S. Ritchie and S.S. Bhattacharjee for suggestions and helpful discussions.

Thanks are also due to Mr. R. Simoneau for running the p.m.r. spectra and to Mrs. C. Ewan for typing the manuscript.

Financial support from "Ministère de l'éducation du Québec", McGill University and the Pulp and Paper Research Institute of Canada is also gratefully acknowledged.

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List of Abbreviations

Ac:	acetyl (CH_3CO-)
Bz:	benzoyl (C_6H_5CO-)
c:	concentration in g/100 ml
c.m.r.:	carbon-13 magnetic resonance
DMF:	dimethylformamide
DMSO:	dimethylsulfoxide
d:	doublet
HMPA:	hexamethylphosphoramide
hr.:	hour
Hz:	Hertz
J:	Nuclear spin-spin coupling constant (measured splitting in Hz)
lit.;	literature
m:	multiplet
Me:	methyl
m.p.:	melting point
n.m.r.:	nuclear magnetic resonance
p.m.r.:	proton magnetic resonance
p.p.m.:	parts per million
PY:	pyridine
q:	quartet
RT:	room temperature
t:	triplet
TMS:	tetramethylsilane
Δ	heat

δ	chemical shift (in parts per million downfield from TMS)
$\emptyset$	phenyl (C_6H_5-)

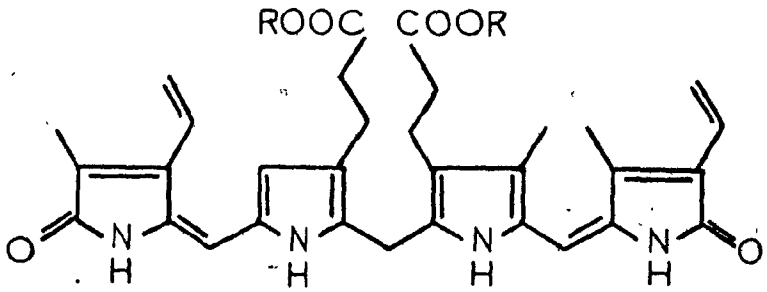
Cast of Molecules

CHAPTER I

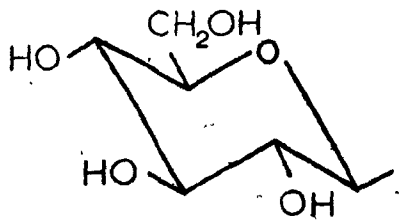
INTRODUCTION

1.1 Why synthesize 1-O-acyl aldoses?

This study originated in attempts to synthesize 1-O-acyl aldoses, particularly carbohydrate conjugates of bilirubin, although there are also a number of other naturally occurring carbohydrate esters of this type (1). Most bilirubin conjugates are thought to be glycosyl esters, probably having the β-D-gluco configuration:



R=CARBOHYDRATE i.e.



Bilirubin conjugation is a detoxication mechanism for the body. Conjugation means the synthetic union of one compound with another. It is a detoxication mechanism by which harmful chemicals are transformed by enzymes and thus rendered less toxic and more easily eliminated by the body.

Bilirubin arises from the metabolic breakdown of haemoglobin and other porphyrin compounds (2). Although it is only sparingly soluble in aqueous solutions at physiological pH, it is transformed by enzymes into the water soluble carbohydrate derivatives. The conjugates thus formed can be eliminated in bile or in urine.

Impaired or inadequate conjugation of bilirubin can lead to its

accumulation, as in certain forms of jaundice. Hydrolysis of the bilirubin conjugates in the gall bladder may play an important role in the formation of gall stones (3). Hence, a knowledge of the structure of naturally occurring bilirubin derivatives is of considerable importance.

"Work with bilirubin and its conjugates is notoriously difficult" says Dr. Heirwegh (4), a leading authority in the bilirubin field. Bilirubin conjugation appears to be a complex process involving a variety of monosaccharides and disaccharides. Recent work shows a structural complexity, hitherto unsuspected (5, and references therein). The chemistry and structure of those conjugates is still not fully understood.

In the conjugates these mono- or disaccharides are likely linked to the bilirubin through an acyl type of glycosidic bond. As the work with the naturally occurring conjugates is "notoriously difficult", and because of the indirect and often speculative evidence used in the structure elucidation of bilirubin conjugates, direct comparison with synthesized compounds would be invaluable.

Enzyme synthesis have been performed (6-9) but they have not provided sufficient quantities to permit extensive identification and comparison with naturally occurring conjugates. Thus, the absence of synthetic model compounds appears to be a major obstacle in the complete structure elucidation of the conjugates.

Since the key to the synthesis of these conjugates is the formation of a glycosyl ester linkage, it was the goal of this study to devise suitable methods for the synthesis of glycosides of this type.

1.2 Synthetic routes

Four possible routes to the synthesis of 1-O-acyl aldoses were considered, and two have so far been examined.

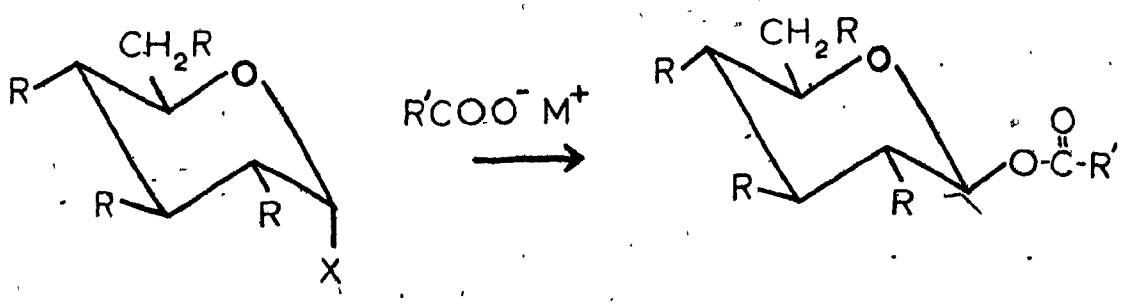
Route A. A reaction between a glycosyl halide and a metal salt of a carboxylic acid (which could be bilirubin) is a well known method (10,11). Of course, easily removable blocking groups are required on the glycosyl halide. However, depending upon the nature of R varying degrees of inversion and retention may take place so that the desired anomeric configuration cannot necessarily be assured.

Route B. Another route could involve the reaction of a carbohydrate with an acyl halide (12). Two problems make this method unattractive. Since free sugars can mutarotate, this method also would presumably not be stereoselective and lead to the synthesis of α and β ester glycosides. Secondly the nature of R' is important. For example it might be difficult to form the acyl halide of bilirubin, because of the lactam-lactim function which would obviously interfere in the formation of the acyl halide. Also, the bilirubin molecule is so unstable that it would not likely resist the reaction conditions needed for the formation of the bilirubin acyl halide.

Route C. Another approach, which is a variant of route A is to place a good leaving group at C-1 on a suitably protected carbohydrate; then displace this leaving group with a nucleophilic aglycone, thus forming the glycosidic linkage.

Route D. This consists of forming a cyclic orthoester, and subsequently opening it with a carboxylic acid to form the glycosyl ester linkage.

ROUTE A



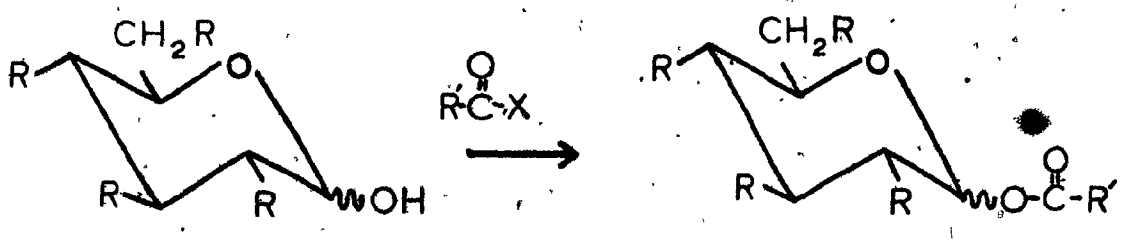
R = Suitable protecting group.

R' = Appropriate group, possibly bilirubin.

M = Metal, possibly silver.

X = Halide.

ROUTE B

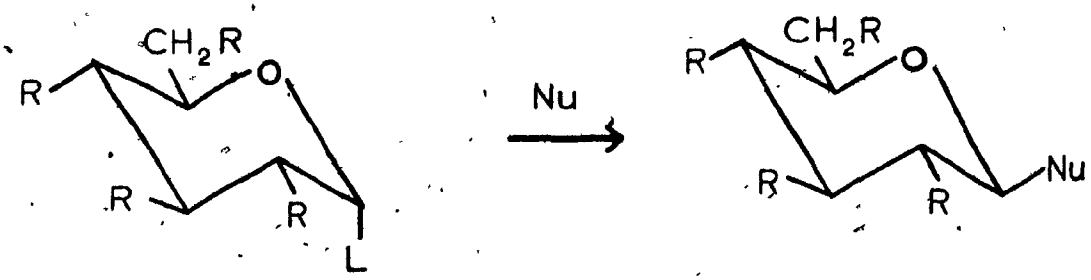


R = Protecting group.

R' = Suitable group (possibly bilirubin?)

X = Halide.

ROUTE C

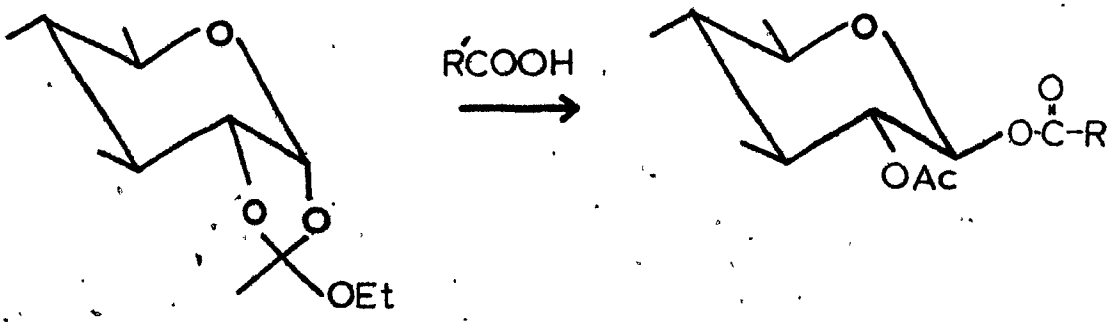


L : a good leaving group.

Nu : a nucleophile (e.g., bilirubin sodium salt).

R : a suitable protecting group.

ROUTE D



R' : appropriate group, possibly bilirubin

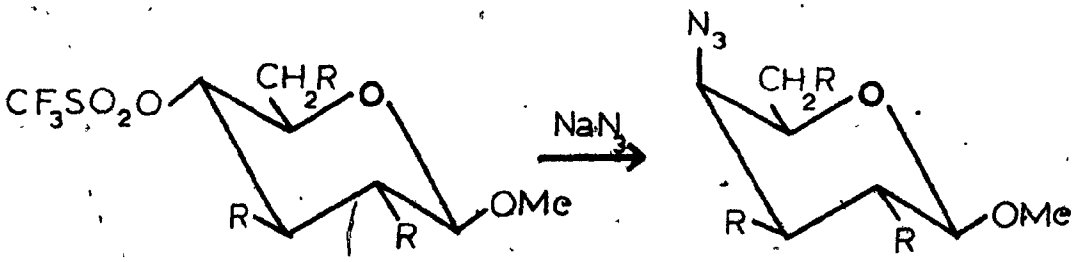
Routes C and D form the basis of the studies described below.

CHAPTER 2

THE TRIFLATE ROUTE

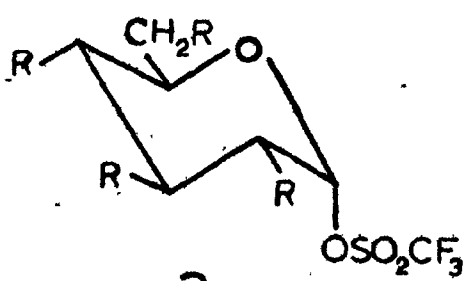
2.1 The synthon

In exploring the possible synthesis of 1-O-acyl aldoses via route C (see section 1.2) an attractive choice as a leaving group appeared to be the trifluoromethanesulfonyloxy (triflyl) group. The use of trifluoromethanesulfonates (triflates) in facile S_N reactions is well documented (13-16), and Maradufu and Perlin (17) have shown that triflyl derivatives of carbohydrates are useful in S_N2 reactions at secondary positions. Thus, methyl 2,3,6-tri-O-benzoyl-4-O-triflyl-β-D-gluco-pyranoside (1) with azide anion easily gave the expected galacto azide (2).



R= $O_2C\emptyset$ 1 2

It was not known, however, if such a facile nucleophilic substitution would occur at the anomeric carbon. The synthon would thus have to be a 1-triflate. Benzyl ethers, being easily cleaved by catalytic hydrogenation (18), under mild pH conditions, were chosen as protecting groups for the rest of the molecule. Accordingly, the synthon chosen was 2,3,4,6-tetra-O-benzyl-1-O-triflyl-α-D-glucopyranose (3):



R= $OCH_2\emptyset$ 3

Through displacement with inversion this compound should afford a β-D-glucopyranosyl ester.

2.2 Synthesis of the triflate

The sequence used for the synthesis of the synthon is described in Figure 1.

Methyl α-D-glucopyranoside (4) is transformed into methyl 2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside (5) and subsequently hydrolysed to form 2,3,4,6-tetra-O-benzyl-α-D-glucose (6) using the method of Perrine and coworkers (19).

Compound 6 was dissolved in pyridine, and a 1.5 fold excess of trifluoromethanesulfonic anhydride was added. After twenty minutes the reaction mixture was quenched with water, the product was extracted into chloroform, and was subsequently crystallized. It was expected that this compound would be 2,3,4,6-tetra-O-benzyl-1-O-triflyl-α-D-glucopyranose (3). However, the p.m.r. spectrum (Fig. 2) showed the anomeric proton to be a doublet with a J_{12} = 8.5 Hz. The dihedral angle between H_1 and H_2 in α-D-glucopyranose is ca 60°; using the Karplus curve (20) or empirical observations (21) one predicts J_{12} to be of the order of 2-3.5 Hz. In β-D-glucopyranose the dihedral angle is ca 180°, thus one predicts J's to be of the order of 8-9 Hz. This strongly indicated that the crystalline material was 2,3,4,6-tetra-O-benzyl-1-O-triflyl-β-D-glucopyranose (7). Also no anomeric proton peak corresponding to that of the α-anomer (3) was detected in the spectrum of the crude mixture. Compound 7 had a negative optical rotation (-20.1°), which confirmed that it is the β-anomer (7). This β-triflate (7) was analytically pure, and when kept in a desiccator at room temperature, was stable for months.

Although this synthesis of a β-triflate (7) from an α-sugar was unexpected, its formation may be rationalized by the following scheme:

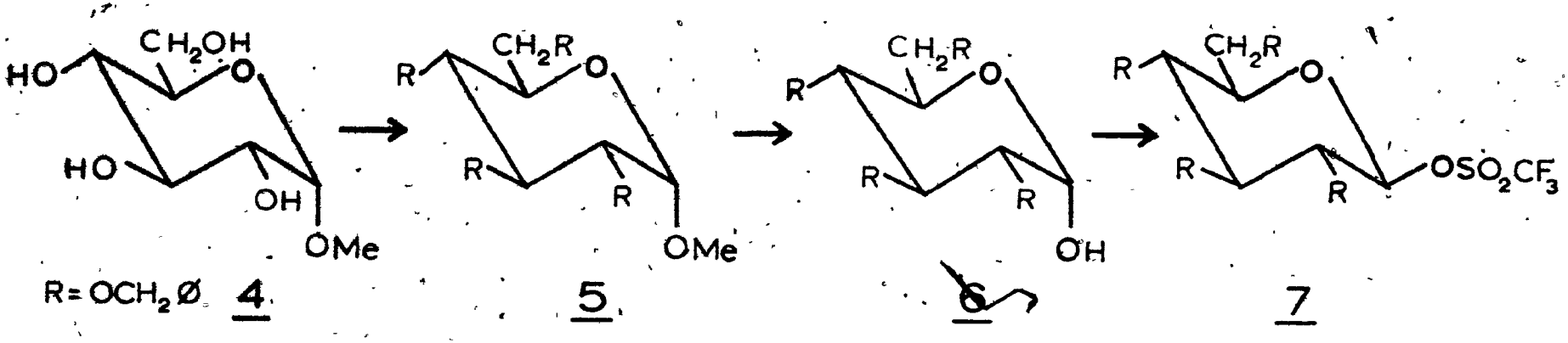
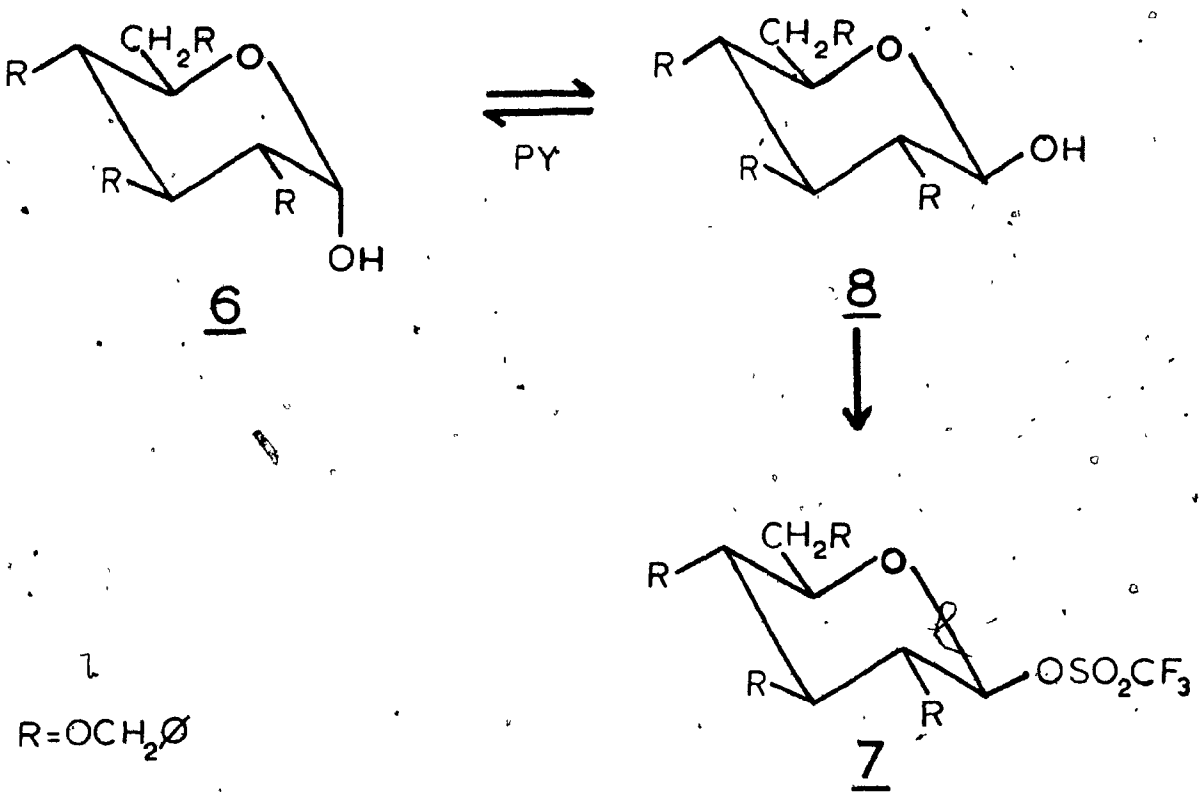


FIG. 1 Synthesis of 2,3,4,6-tetra-O-benzyl-1-O-triflyl-β-D-glucopyranose (7).



In the first step 6 mutarotates in the presence of pyridine to give some 2,3,4,6-tetra-O-benzyl-β-D-glucose (8). The latter then reacts with triflic anhydride to give 7.

Table 1 shows that the integral for H-1 of 6 in pyridine is smaller than in a solvent that does not (such as chloroform used for the initial spectrum (Fig. 2)) normally favor mutarotation. This indicates that there might normally be some β-sugar (8) formed when the α-sugar (6) is dissolved in pyridine. If the rate of triflation of 8 is faster than that of 6, the β-triflate (7) would thus be the kinetically-favored product. This does not rule out the possible formation of some α-triflate (3), but it could not be detected, and only the crystalline β-anomeric derivative (7) was isolated.

TABLE 1

Integral of H-1 for 2,3,4,6-tetra-O-benzyl-α-D-glucose in various solvents

Solvent*	Integral**
Chloroform	.9
DMSO	.8
Pyridine	.4

* All deuterated solvents.

** Relative to overall integral for the protons in the region 3 to 9 p.p.m.

Peculiarities of the p.m.r. of the β-triflate (7). The low field signals at 7.7, 8.3 and 8.7δ (see Fig. 2) are somewhat deshielded when compared to the benzyl aromatic signals of 6 (see Fig. 3) at 7.3δ. They probably arise from benzyl protons deshielded by a neighbouring group. Carbonyls are known to have magnetic anisotropies that can cause deshielding (22). By analogy the trifluoromethanesulfonyl group may also have anisotropic magnetic properties. Molecular models show that benzyl groups at C2 or C6 may be close enough to be influenced by the magnetic properties of the triflyl group. Furthermore, of all the benzyl derivatives synthesized for this study only the β-triflate (7) had the low field signals, which corroborates the hypothesis that the low field signals arise from protons deshielded by the triflyl group.

2.3 Reactions of the triflate (7)

When the β-triflate in DMF was heated at 100° with an excess of sodium acetate, an orange oil was obtained which consisted largely of unreacted starting material. There was no indication from the p.m.r. spectrum that this oil contained 1-O-acetyl derivatives.

With sodium benzoate as the nucleophile under these conditions, 7 gave a crystalline product (14% yield of purified material) which was characterized as 1-O-benzoyl-2,3,4,6-tetra-O-benzyl-β-D-glucopyranose (10). The β-anomeric designation is based on the large value (8 Hz) for $J_{1,2}$. No significant improvement in yield was effected by varying reaction times, nor by using HMPA as the solvent. In all instances decomposition was evident from the development of color, and prolonged reaction periods simply intensified the extent of side reactions.

FIG. 2. P.m.r. of 2,3,4,6-tetra-O-benzyl-1-O-trifly1-β-D-glucopyranose (7).

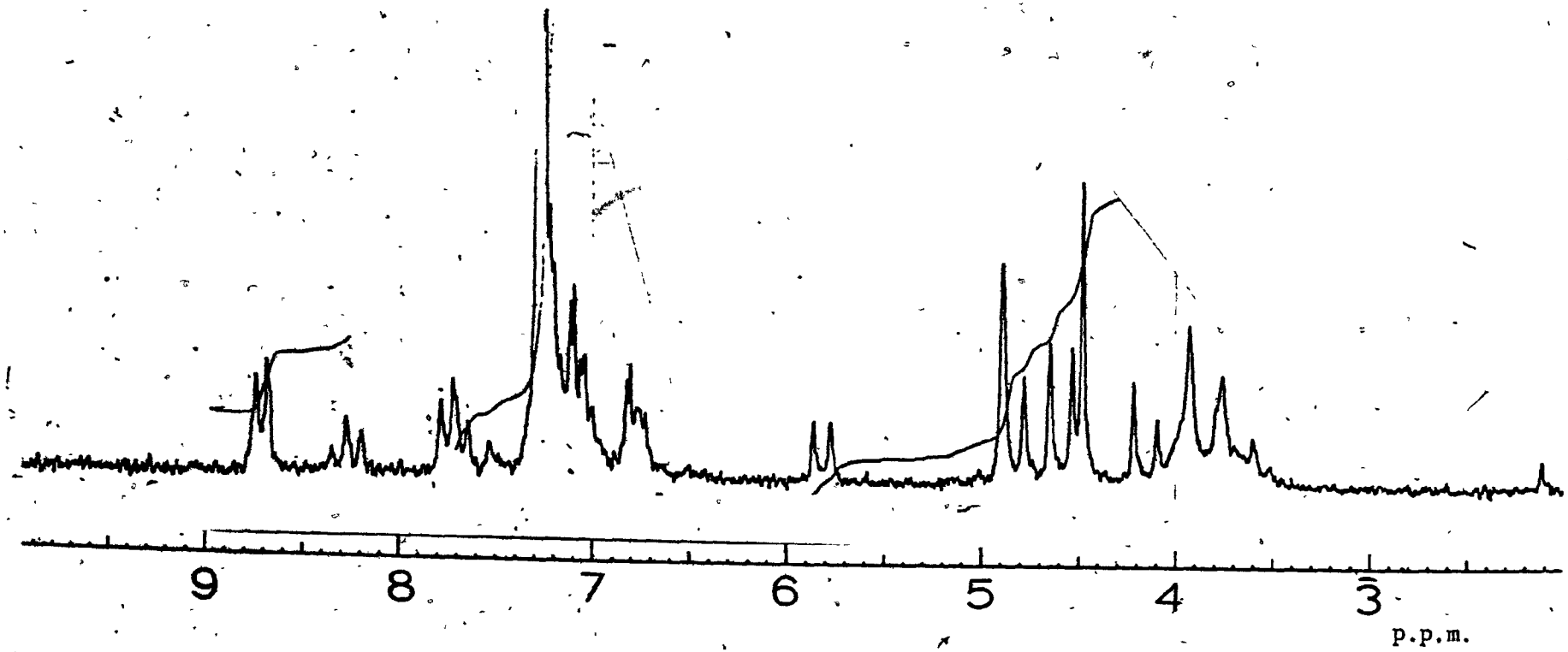
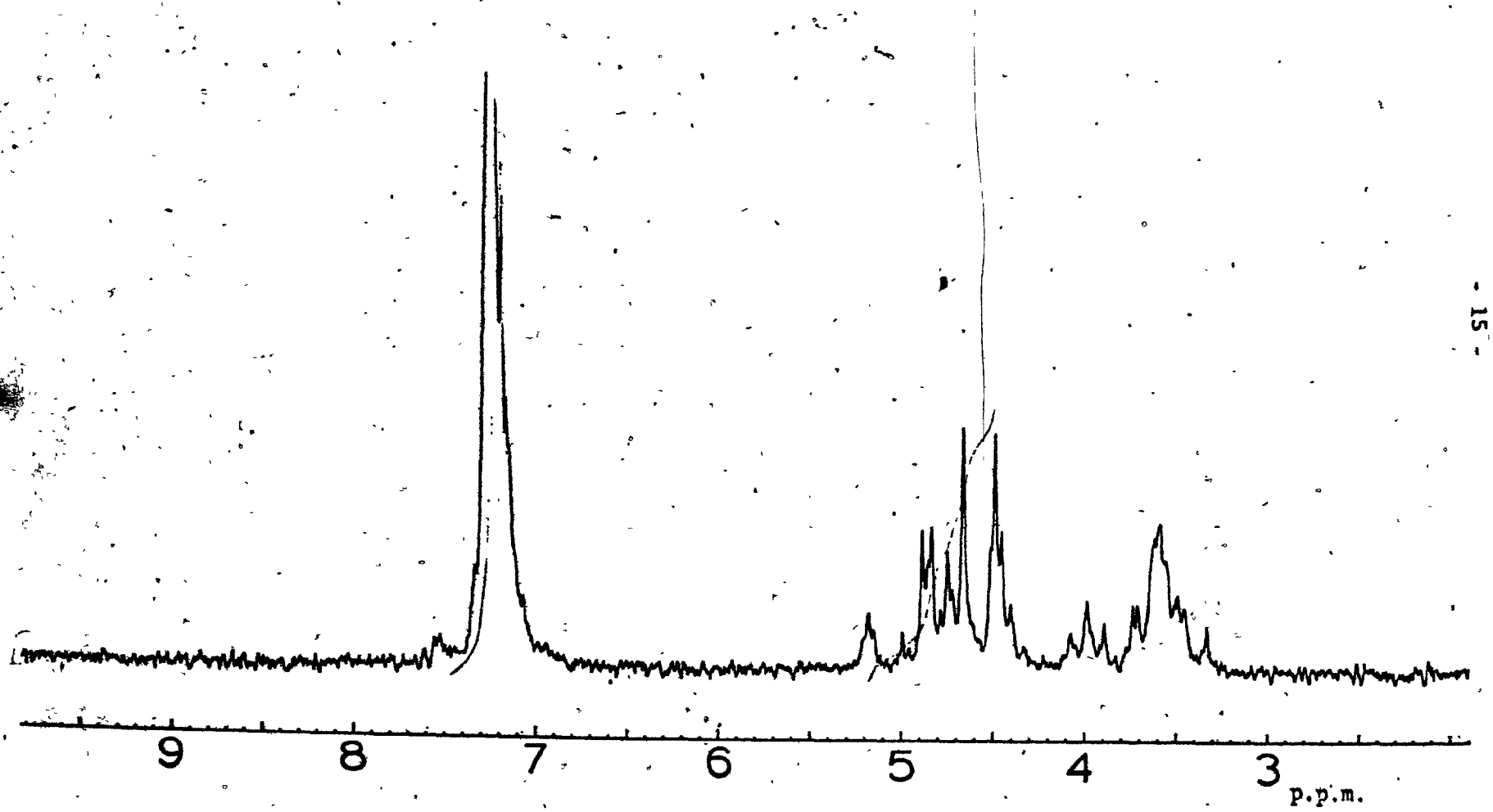
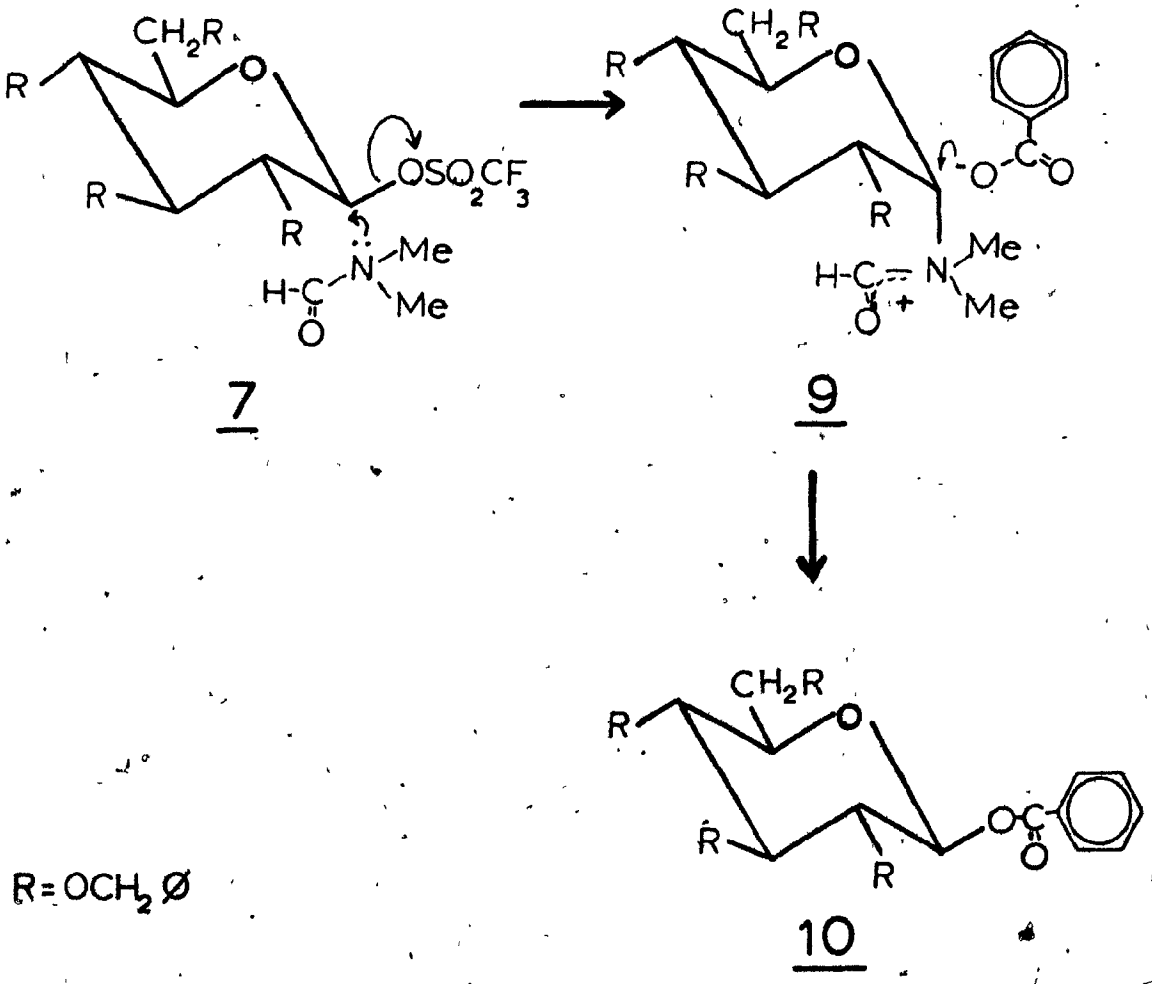


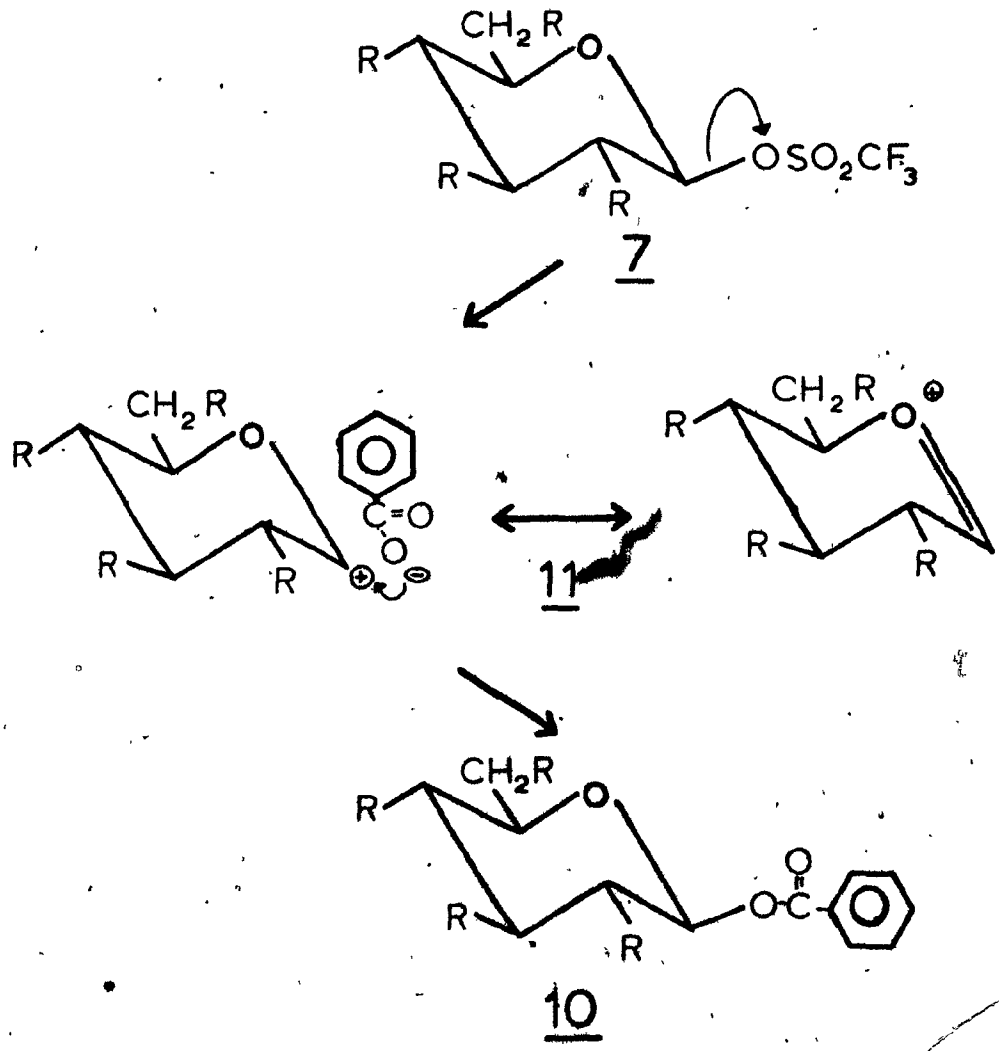
FIG. 3 P.m.r. of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (6).



Various pathways may be envisaged for the formation of the β-benzoate (10) from the β-triflate (7). For example, attack by the solvent may yield an intermediate (9) having the α-configuration. Subsequent nucleophilic substitution by the benzoate anion then leads to double inversion with overall retention of configuration (Pathway 1).



Another mechanism (Pathway 2) may be postulated in which a carbonium ion is formed at C-1 (11), then β-attack by the benzoate anion would form the β-benzoate (10):



R=OCH$_2$Ø

It also appears possible that neighbouring group participation by the benzyl group could be involved in such an S_N1 reaction (23).

The triflate (7) was also found to be unreactive towards methanol,

and gave decomposition products with sodium methoxide. No evidence of methyl glucoside formation was obtained from any of the crude reaction products.

The results of the reactions of nucleophiles with the β-triflate (7) are summarized in Table 2. It becomes evident that the β-triflyl group at C-1 is a rather poor leaving group. When a nucleophilic displacement occurs, a low yield of product is obtained. It is of interest to note that, apparently, when displacement occurs it does so with retention of configuration.

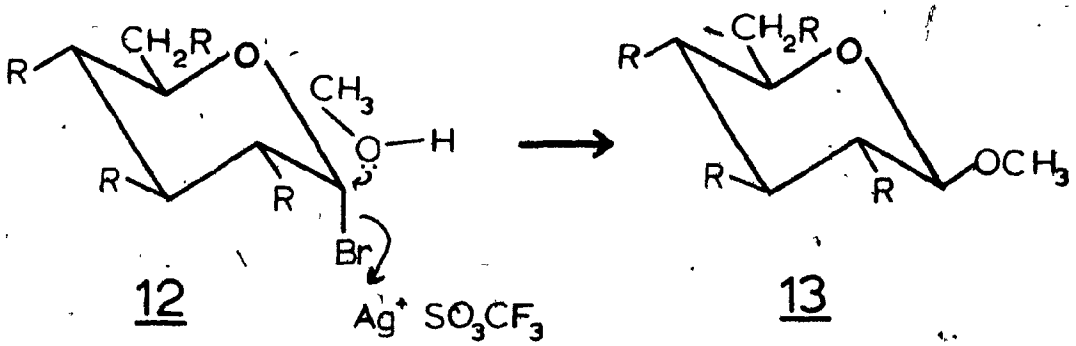
TABLE 2

Reactions of 2,3,4,6-tetra-O-benzyl-1-O-triflyl-β-D-glucopyranose (7)

Nucleophile	Result	Yield
CH_3OH	No Reaction	
CH_3ONa	Decomposition	
CH_3COONa	"	
Sodium Benzoate	2,3,4,6-Tetra-O-benzyl-1-O-benzoyl β-D-glucopyranose (10)	14%

During the course of our studies with trifluoromethanesulfonates, and coincident with a preliminary report of the current findings (presented at the 42e Congrès, A.C.F.A.S., Quebec (24)), Kronzer and Schuerch (25) published a study of the methanolysis of 2,3,4-tri-O-benzyl-α-D-glucopyranosyl bromide in the presence of the silver salt of triflic acid. In the belief that the carbohydrate silver trifluoromethanesulfonates would be highly reactive intermediates, Kronzer and Schuerch performed their

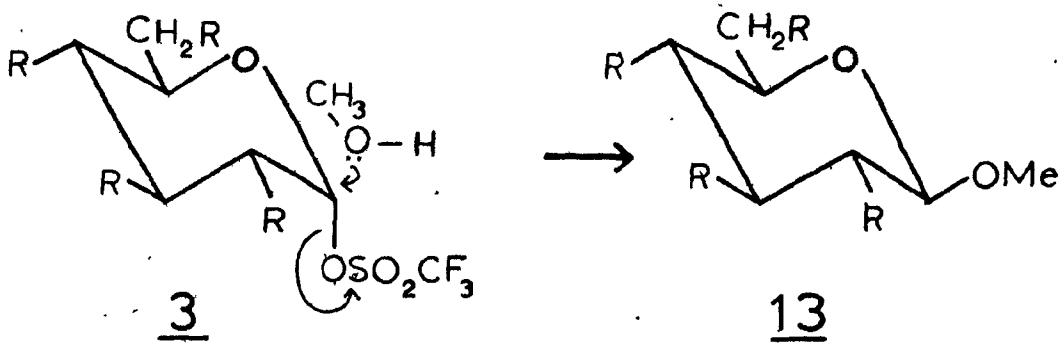
methanolyses under anhydrous conditions at -78°. They obtained methyl glycosides from the methanolysis of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl bromide (12) in the presence of silver triflate; when the solvent was dichloromethane, they only obtained the β methyl glycoside (13), and they found a 1:1 ratio of α to β when the solvent was ether. They rationalized their findings by postulating that glycosyl halides react with the silver triflate and alcohol via the push-pull mechanism (26,27). This gives rise mainly to the β-glycoside:



12 13

R = $OCH_2Ø$

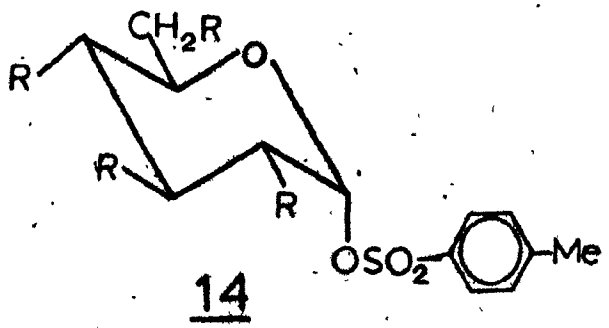
But they also postulate that if enough time is allowed for the reaction between the glycoside halide and the silver salt, the glycosyl halide is transformed into the glycosyl triflate. Since the trifluoromethanesulfonate is strongly electron withdrawing they believe that the glycosyl triflates may be α-D esters because of the anomeric effect. The preponderance of the β-glucoside, in dichloromethane, is explained by the shielding of the departing triflate ion, since ion-pair separation is unfavorable in the poorly solvating solvent:



3 13

R= $OCH_2\emptyset$

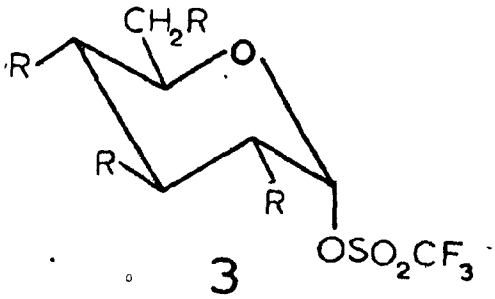
Hence, Kronzer and Schuerch proposed the possible existence of a highly reactive α-D-gluco triflate (3), as an intermediate in the formation of 13. More recently Eby and Schuerch (28) used an analogous reaction to prepare a 1-O-tosyl derivative, which was probably mainly the α-anomer (14). This compound, which was not isolated in pure form, decomposed rapidly at room temperature, as does the product described as the α-triflate (3). Furthermore, experiments with 1-O-sulfonyl glucopyranose derivatives were carried out under high vacuum techniques because the compounds were found to hydrolyze rapidly. Such behaviour is in marked contrast to the high stability of the crystalline β-triflate (7), and parallels the extraordinary difference between the two anomeric forms in their response towards methanolysis.



14

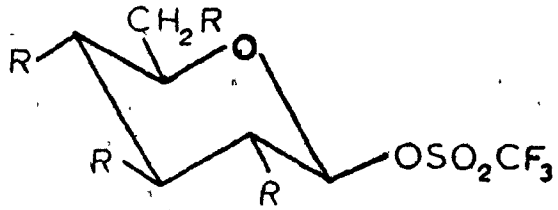
Room Temperature

⟶ RAPID DECOMPOSITION



3

Room Temperature → RAPID DECOMPOSITION



7

R = $OCH_2Ø$

Room Temperature → STABLE

At present, we cannot advance a rational mechanistic basis to account for rate differences of this magnitude in S_N reaction rates of anomeric pairs.

2.4 Resume

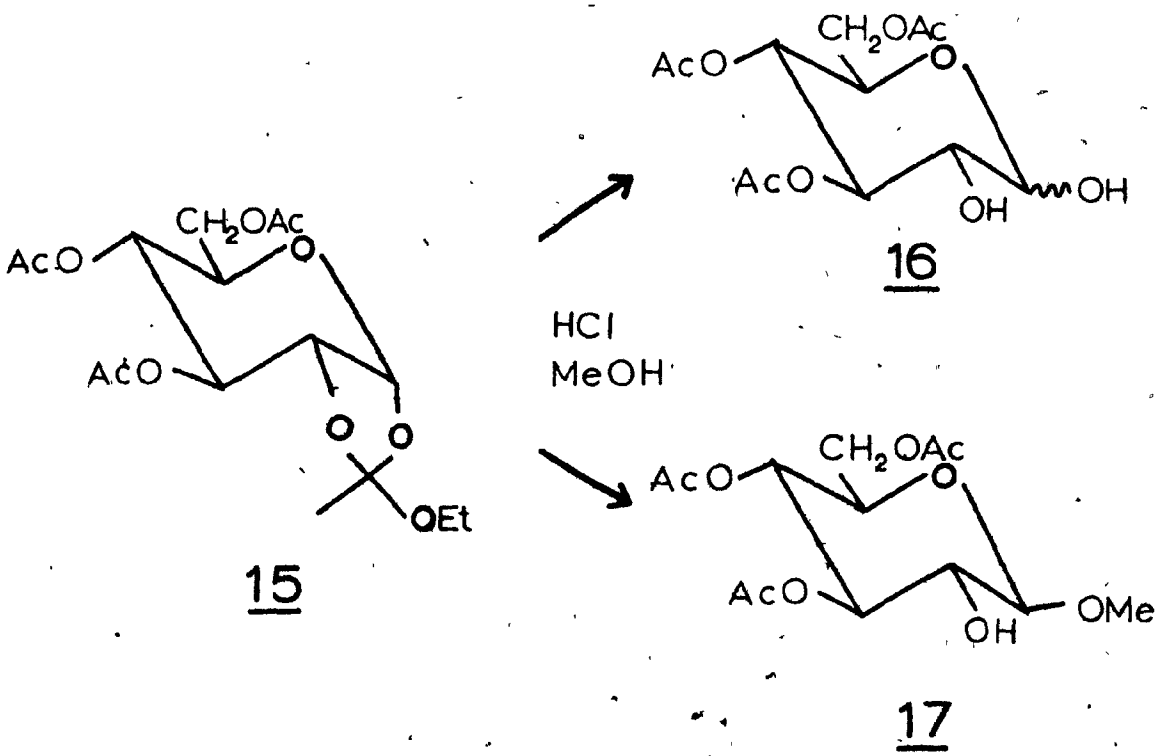
Our objective in these studies was to synthesize a 1-O-triflyl-D-glucopyranose in the hope that it would be a molecule highly reactive towards nucleophiles and thus form glycosides in good yield. 2,3,4,6-Tetra-O-benzyl-1-O-triflyl-β-D-glucopyranose (7) was synthesized. It proved to be a rather stable molecule, which gave only low yields of substitution products. These results are at variance with the literature, in which highly unstable triflate intermediates (not isolated) have been described.

CHAPTER 3

SYNTHESIS OF 1-O-ACYL ALDOSES BY THE ORTHOESTER METHOD

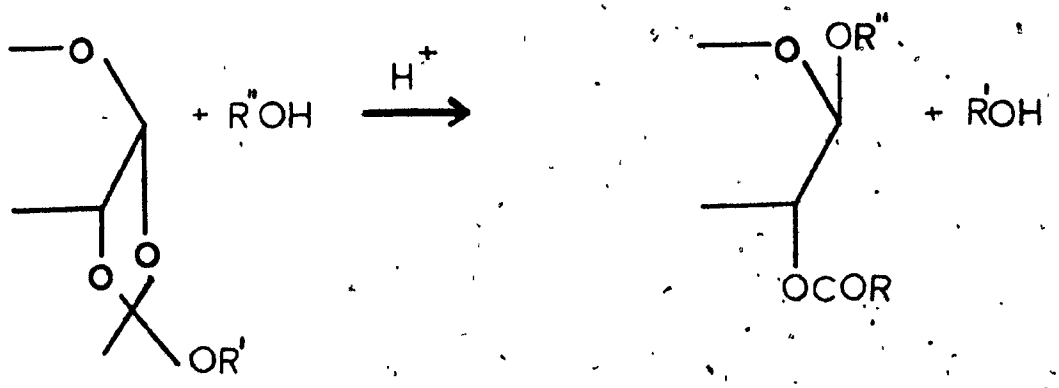
3.1 Introductory remarks

Dale (29) first observed that a small yield of methyl 2,3,4,6-tetra-O-acetyl-β-D-mannoside could be obtained in small yield when 3,4,6-tri-O-acetyl-β-D-mannose 1,2-(methyl orthoacetate) was treated with cold methanolic hydrogen chloride. Perlin (30) studied this reaction and the methanolysis of other orthoacetates. He found that several concurrent reactions appeared to take place in methanol initiated by protonation at different positions on the orthoester ring. For example, 3,4,6-tri-O-acetyl-α-D-glucopyranose 1,2-(ethyl orthoacetate)* (15) yielded 3,4,6-tri-O-acetyl-D-glucose (16) and methyl 3,4,6-tri-O-acetyl-β-D-glucopyranoside (17).



*Although these compounds are traditionally described as orthoesters an alternative nomenclature for compounds such as 15 and 27 is 3,4,6-tri-O-acetyl-α-D-glucose 1,2-(1'-exoethoxyethylidene) and 3,4,6-tri-O-acetyl-β-D-mannose 1,2-(1'exoethoxyethylidene). It should be noted that since there is an extra chiral center in the ethylidene ring, the exo-endo nomenclature is introduced.

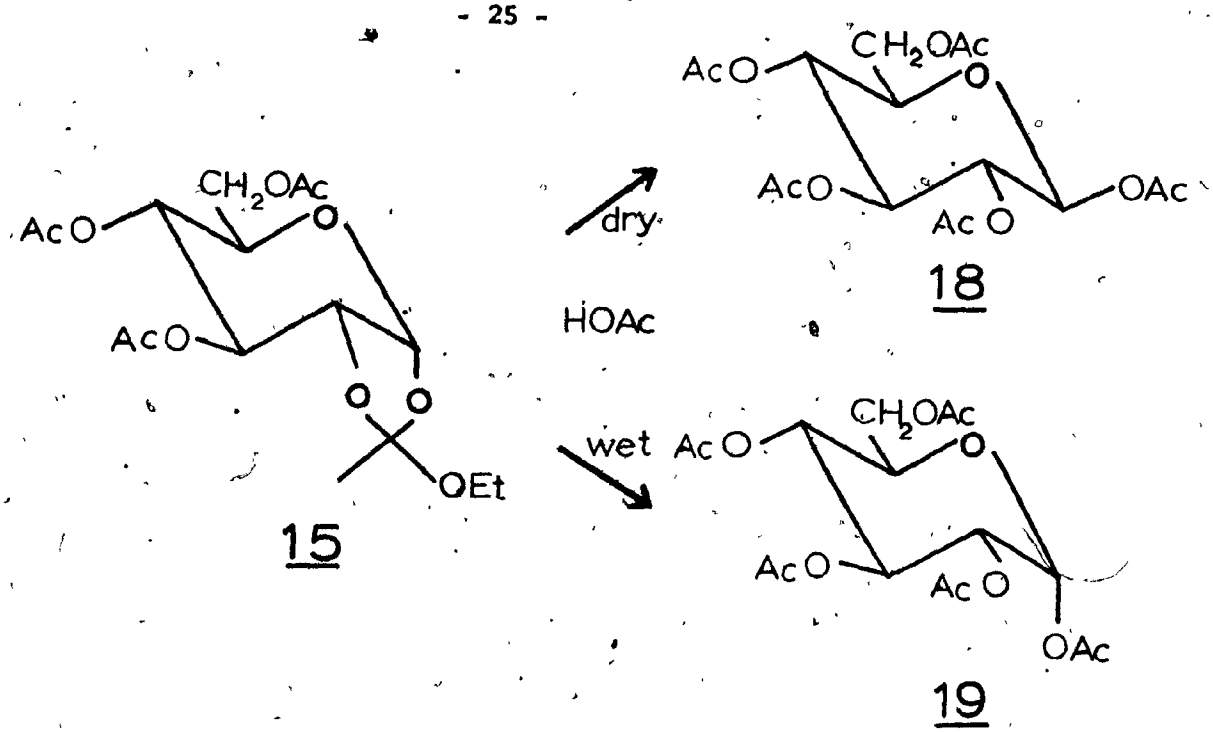
This was the synthesis of a glycoside from an orthoester. If the methanol was replaced by a carbohydrate alcohol suitably protected, a disaccharide could be synthesized. Repetition of the process leads to the formation of oligosaccharides. This is the so-called "orthoester method" for the synthesis of oligosaccharides developed by Kochetkov and coworkers (31 and references therein):



R = CH_3, ph R' = Me, Et, tBu R" = Carbohydrate Residue

Fig. 4. Orthoester + Alcohol = Glycoside.

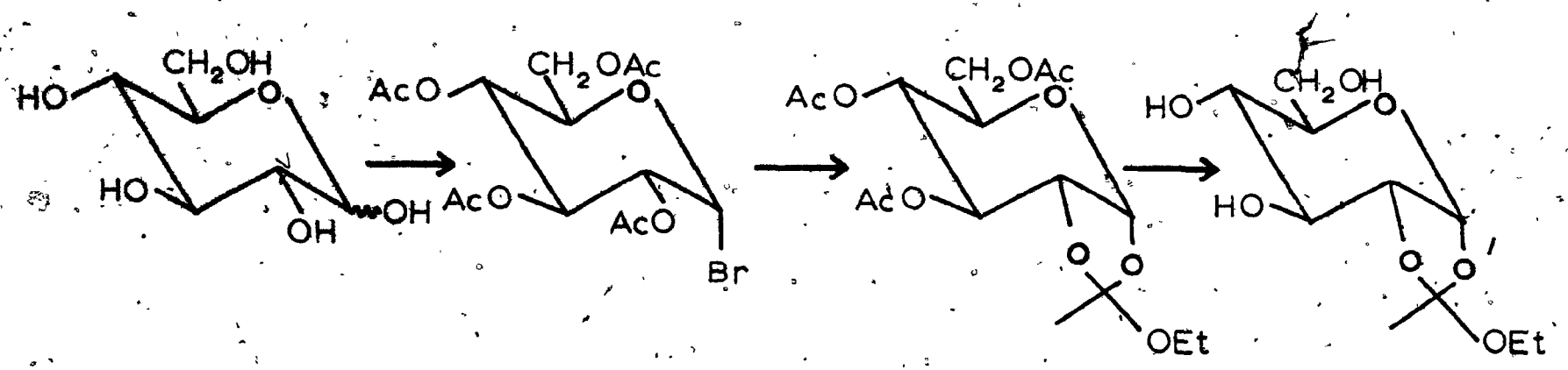
A glycosyl ester should be formed analogously by reacting a carboxylic acid with an orthoester. Thus, Lemieux and Cipera (32) had treated 3,4,6-tri-O-acetyl-D-glucose 1,2-(ethyl orthoester) (15) with concentrated acetic acid. With dry acetic acid they obtained 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose (18) and with wet acetic acid they obtained 1,2,3,4,6-penta-O-acetyl-α-D-glucopyranose (19):



In the current study, the general applicability of this reaction, its stereospecificity, and related questions have been examined.

3.2 Preparation of the orthoesters

The route, as depicted in Figure 5, involves the reaction of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide with ethanol in the presence of s-collidine, as described by Lemieux and Morgan (33). The reaction probably involves an intermediary 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl bromide (23) (see Fig. 6) and, by participation of OAc-2 allows the formation of the acetoxonium ion (24), which, with ethanol yields 3,4,6-tri-O-acetyl-α-D-glucopyranose 1,2-(ethyl orthoacetate) (15) (34). α-D-Glucose 1,2-(ethyl orthoacetate)(22) was prepared from 15 by catalytic deacetylation with barium methoxide.



20 21 15 22

FIG. 5 Synthesis of the gluco orthoesters.

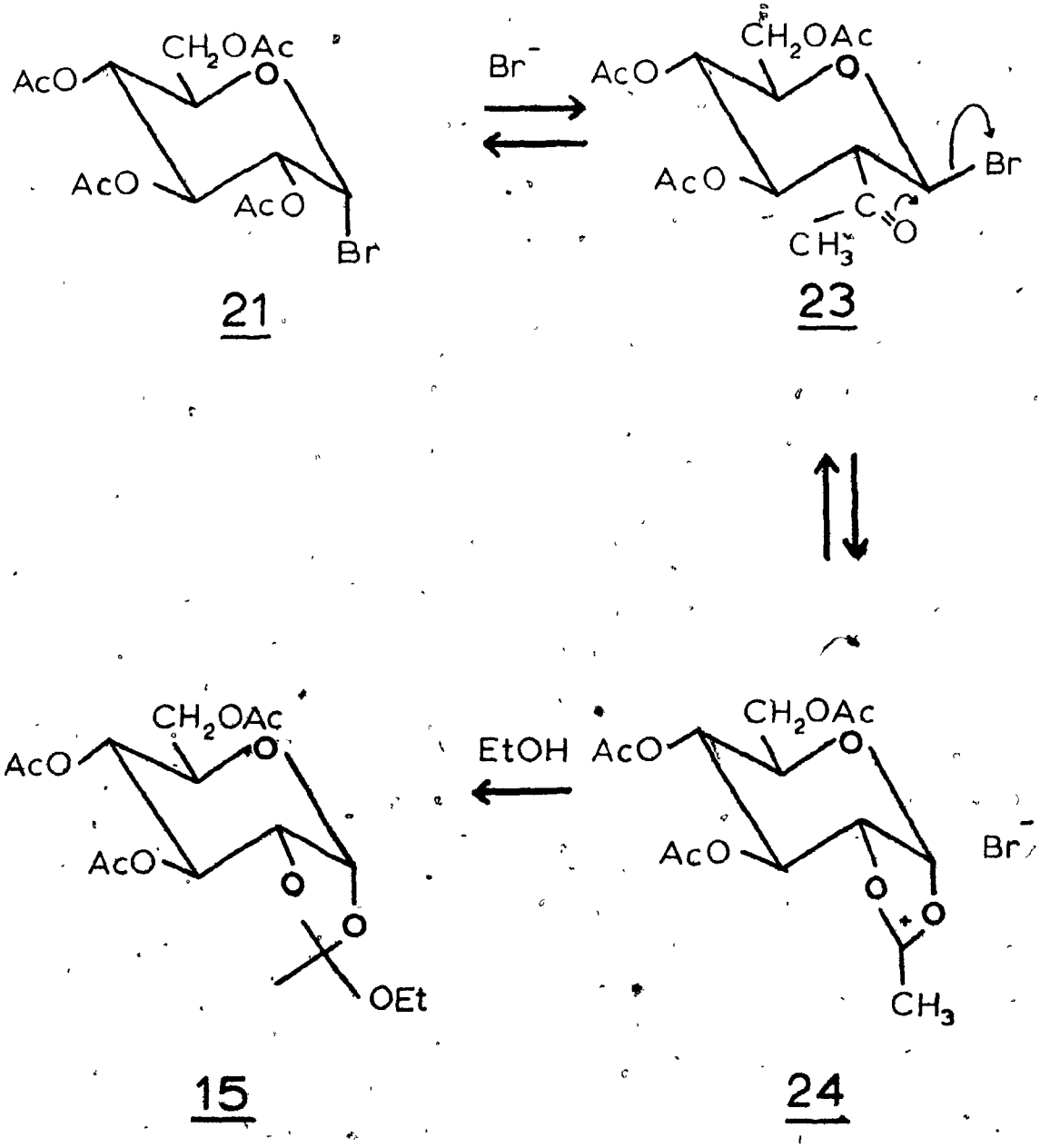


FIG. 6 Intermediates in the formation of 3,4,6-tri-O-acetyl-α-D-glucopyranose 1,2-(ethyl orthoacetate) (15).

3,4,6-Tri-O-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate)* (30) was prepared from 2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl bromide and methanol in 2,6-lutidine (35). Participation of OAc-2 permits the formation of the cyclic acetoxonium ion (24) intermediate which, with methanol, yields the orthoester.

3.3 The orthoester reaction

A The general reaction

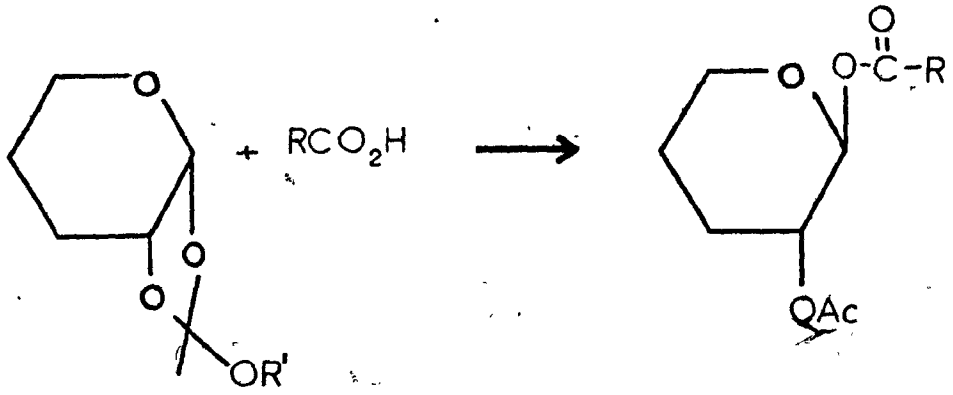


Fig. 7 Orthoester + carboxylic acid = ester glycoside

In order to use this reaction as a general synthetic route to 1-O-acyl aldoses, it appeared necessary to select a suitable solvent and to employ stoichiometric proportions of the reactants. Following preliminary experiments, the procedure adopted was to dissolve the orthoester in dry dioxane and then introduce a 1.5 (and up to 10) fold excess of the carboxylic acid. Several carboxylic acids were tested under these conditions, which resulted in the synthesis of a variety of 1-O-acyl aldoses:

* cf. footnote p. 23

B Scope of the reaction

i) Influence of the carboxylic acid on the reaction.

Acetic acid. Lemieux and Cipera (32) had reacted tri-O-acetyl-α-D-glucose 1,2-(ethyl orthoacetate) (15) with concentrated acetic acid, and obtained α- or β- (or mixtures) glucose pentaacetate depending upon the dryness of the acetic acid used. By using a 10 fold* excess of acetic acid in dry dioxane, 15 gave a syrup which by t.l.c. chromatography and p.m.r. spectroscopy, appeared to consist almost entirely of β-D-glucose pentaacetate (18). The latter was subsequently isolated and characterized by crystallization. It may be noted that there has been inversion at C-1 in this reaction.

Propanoic acid. The orthoester (15) was similarly treated with propanoic acid in dioxane to give a crystalline 2,3,4,6-tetra-O-acetyl-1-O-propanoyl-β-D-glucopyranose (25) (49% yield).

The fact that the reaction works well with acetic and propanoic acids indicates that aliphatic carboxylic acids in general can be used to form the corresponding 1-O-acyl aldoses.

Pivalic acid. (2,2-dimethylpropanoic acid). 2,3,4,6-Tetra-O-acetyl-1-O-(2,2-dimethylpropanoyl)-β-D-glucopyranose (26) was obtained as a crystalline material (34% yield) from the reaction of 15 with pivalic acid (1.8 molar equivalents).

Cyclohexanecarboxylic acid. Compound 15 was mixed with cyclohexanecarboxylic acid in dioxane and were left to react for 1 hr at room temperature. A 66% yield of 2,3,4,6-tetra-O-acetyl-1-O-(cyclohexylmethanoyl)-β-D-glucopyranose

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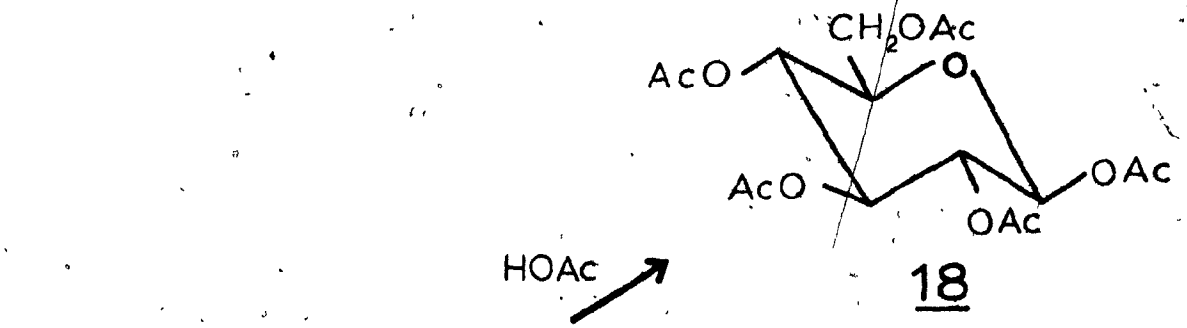
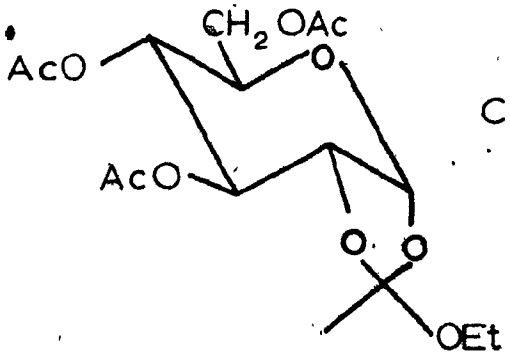
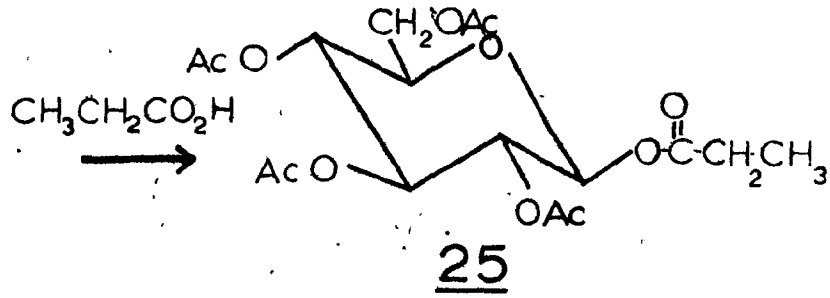
*Acetic acid is somewhat anomalous, requiring a large excess of acid to initiate the reaction.


CH2OAc
AcO
AcO
OAc
OAc
HOAc

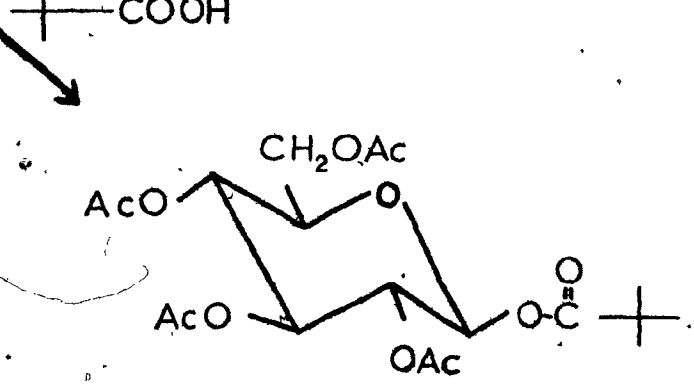
18


CH2OAc
AcO
AcO
O
O
OEt

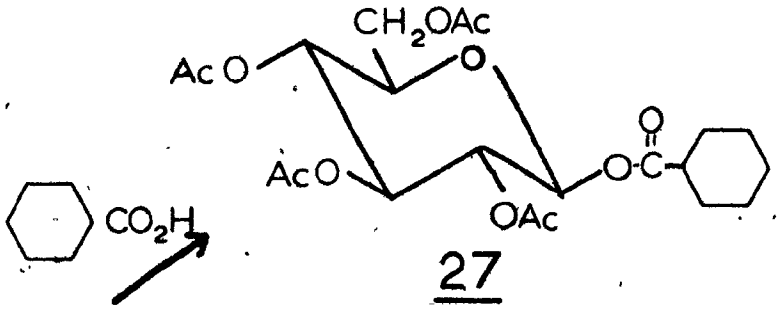
15


CH3CH2CO2H
CH2OAc
Ac O
Ac O
OAc
O
O-C-CH2CH3

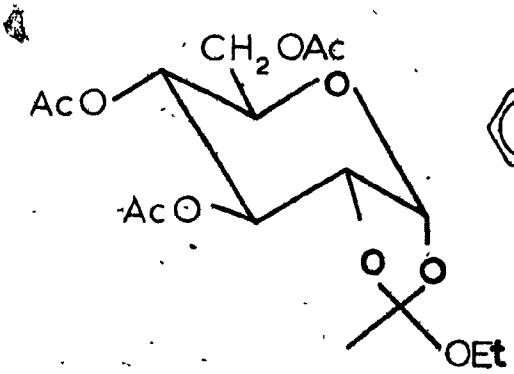
25


COOH
CH2OAc
AcO
AcO
OAc
O
O-C

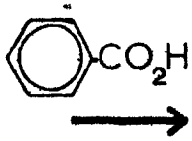
26

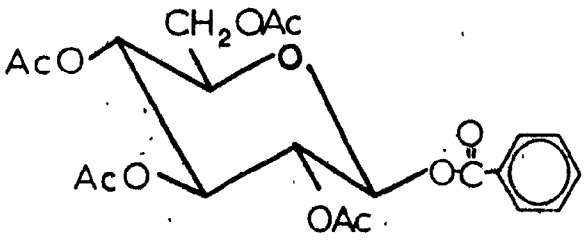

CH2OAc
AcO
AcO
OAc
O
O
CO2H

27

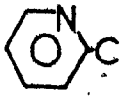

CH2OAc
AcO
AcO
O
O
OEt

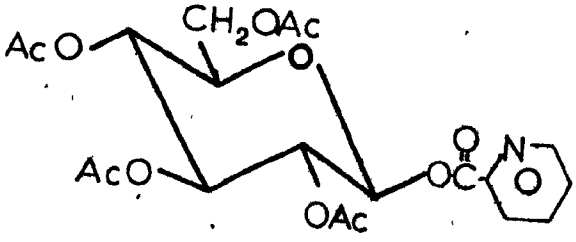
15


CO2H


CH2OAc
AcO
AcO
OAc
O

28


N
O
CO2H


CH2OAc
AcO
AcO
OAc
O
N
O

29

(27) was obtained from this reaction by using a 3 fold excess of the acid.

Severson, Bohm and Seaforth (12) have obtained a product described as 27 from the reaction of cyclohexanecarbonyl acid chloride with 2,3,4,6-tetra-O-acetyl-D-glucose in a 3 day reaction. Although these authors deliberately started with the β-anomer of the D-glucose tetra-acetate, since the reaction was carried out in pyridine it is likely that both anomers were present (cf section 2.2).

Benzoic acid. With 15, this acid (3 equivalents) gave 2,3,4,6-tri-O-acetyl-1-O-benzoyl-β-D-glucopyranose (28, 51% yield).

Picolinic acid. The product of 15 with picolinic acid (4 equiv.) is the new crystalline compound 2,3,4,6-tetra-O-acetyl-1-O-picolyl-β-D-glucopyranose (29). Picolinic acid was chosen as a model compound with characteristics close to those of bilirubin.

Table 3 lists the carboxylic acids used in the orthoester reaction. All of these, including simple aliphatic, bulky branched, bulky cyclic and aromatic acids worked well. This implies that the reaction is, indeed, a general one for the synthesis of 1-O-acyl-β-aldoses in the gluco series.

ii) Influence of the orthoester configuration on the reaction.

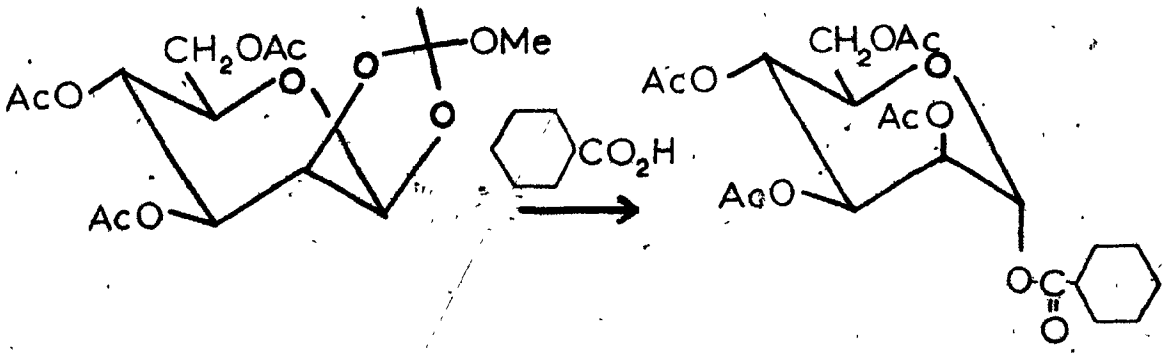
It is apparent from the reactions of 15 with acids, that the gluco configuration makes for a smooth, stereospecific synthesis of 1-O-acyl-β-aldoses in the orthoester reaction. However, when tri-O-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (30) was treated (as for 15) with cyclohexanecarboxylic acid for 2 hrs at room temperature, no reaction occurred. By contrast, after 3 hrs at 100°, 2,3,4,6-tetra-O-acetyl-1-O-(cyclohexylmethanoyl)-α-D-mannopyranose was obtained in 63% yield (31); (the crude product showed only one anomer by p.m.r. spectroscopy).

TABLE 3

The orthoester reaction: carboxylic acids used with 15

Acid	Yield*	Product
Acetic	28%	18
Propanoic	49%	25
2,2-Dimethylpropanoic	34%	26
Cyclohexanecarboxylic	66%	27
Benzoic	51%	28
Picolinic	25%	29

*Of the pure, crystalline, product

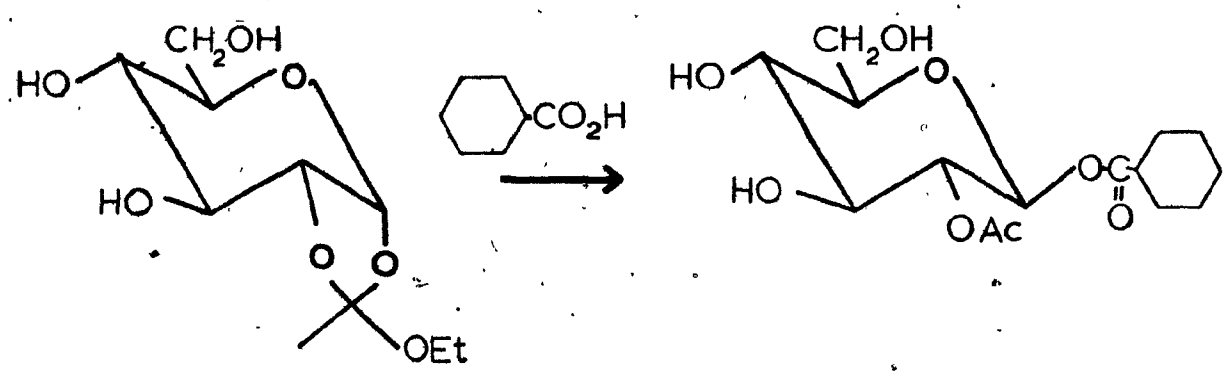


30 31

Hence the gluco and manno isomers have been used successfully. In both instances, the anomeric configuration is inverted so that the manno orthoester forms an α-mannosyl ester, as expected.

iii) Influence of hydroxyl groups in the carbohydrate moiety on the orthoester reaction.

As noted previously alcohols in the presence of acid, can react with orthoesters to form glycosides (cf. Fig. 4, 30-31). Hence it appeared possible that if an attempt were made to react an orthoester containing free hydroxyl groups with a carboxylic acid, the orthoester might react with itself to form a disaccharide, rather than the glycosyl ester. Accordingly, α-D-glucose 1,2-(ethyl orthoacetate) (22) was treated with cyclohexanecarboxylic acid. The only product obtained in this reaction was 2-O-acetyl-1-O-(cyclohexylmethanoyl)-β-D-glucopyranose (32).



22 32

This compound (32) was characterized spectroscopically and then acetylated to give 2,3,4,6-tetra-O-acetyl-1-O-(cyclohexylmethanoyl)-β-D-glucopyranose (15) which was identical with authentic material.

This indicated that the hydroxyl groups of an orthoester need not be protected. Undoubtedly, the carboxylic acid function is more reactive than the alcohol, and thus a glycosyl ester rather than a glycoside is formed preferentially.

This finding offered the possibility that, if desired (see succeeding section) the 1-O-acyl aldose might be more easily obtained in a de-O-acetylated (at positions -2 to -6) form, or that it might subsequently be modified in other ways at positions -3, -4 and -6.

C Mechanism (p. 36).

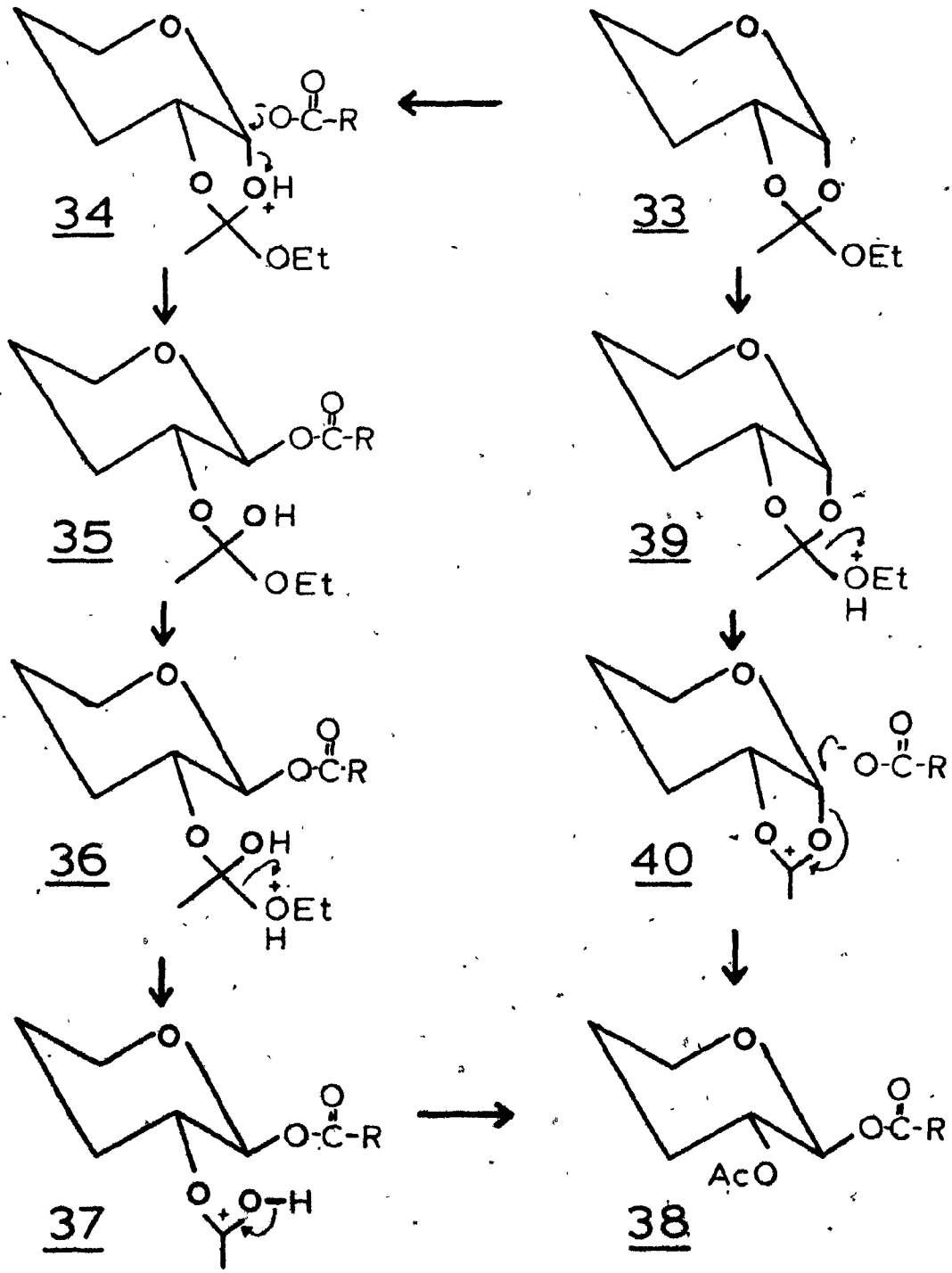
Protonation of an orthoester (33) can lead to 34, and subsequent nucleophilic substitution to the trans 1-O-acyl-2-O-orthoacid (35); protonation of 35 can lead to 36, the latter ion (36) loses alcohol, giving rise to 37 which collapses to product 38. The overall result should be the same if the reaction is initiated by protonation of 33 at the 1' alkoxy oxygen, (39), followed by elimination of alcohol to form the cyclic ion 40; the latter (40) undergoes nucleophilic attack at C-1 and gives rise to the trans 1-O-acyl-2-O-acetyl product 38.

3.4 Selective de-O-acetylation of 1-O-acyl aldoses

In order to obtain 1-O-acyl aldoses unsubstituted at positions -2 to -6, such as a natural bilirubin conjugate rather than its peracetate, it is necessary to effect selective removal of the O-acetyl groups of products synthesized by the orthoester route. This problem has been examined in a preliminary way.

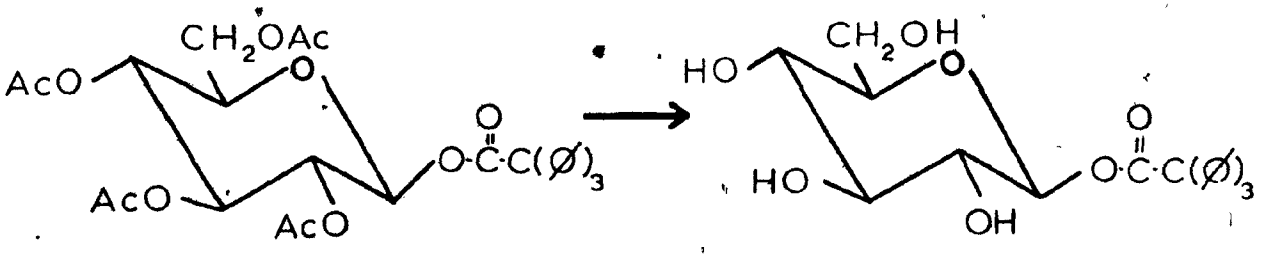
A priori, base catalysed trans-esterification appears to be more promising than an acid catalysed process, to avoid anomerization at C-1 (34)

Mechanisms of the orthoester reaction



(see p. 38). Not surprisingly, therefore, attempts in this direction so far have used base-catalysed conditions. Because of the well-known differences in the rates of alkaline hydrolysis of esters of different structure, there should be a high possibility of selectively removing an O-acetyl group in the presence of certain other O-acyl groups. Thus, for example, ethyl acetate is hydrolyzed 100 times as rapidly as ethyl 2,2-dimethylpropanoate (36).

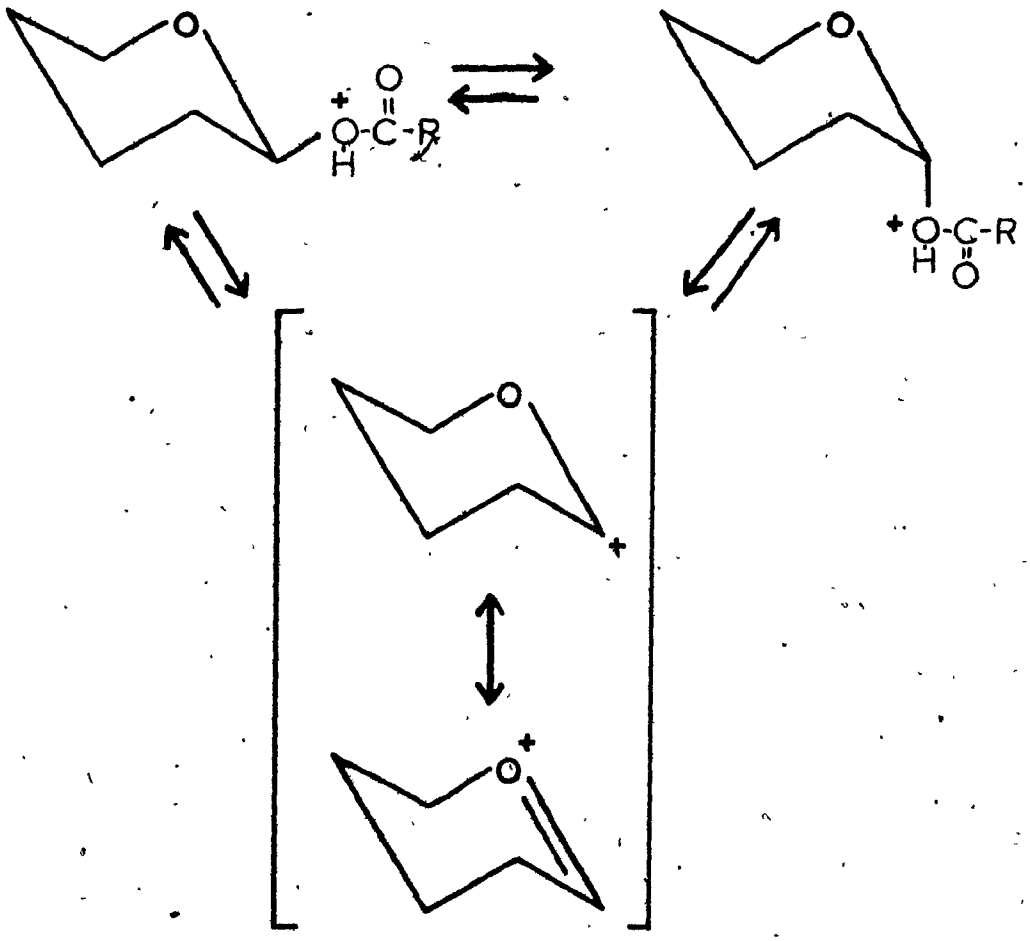
Helferich (11) tried to de-O-acetylate 1-O-acyl-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoses, where the acyl group was 2,4,6-trinitrobenzoyl, 2,2-dimethyl propanoyl, βββ-trimethylpropanoyl, βββ-triphenylpropanoyl, or triphenylacetyl (41). All attempts failed, except with the triphenylacetyl compound 41 which gave triphenylacetyl-β-D-glucopyranose (42):



41 42

Severson, Bohm and Seaforth (12) claim to have prepared 1-O-(cyclohexylmethanoyl)-β-D-glucopyranose* from 2,3,4,6-tetra-O-acetyl-1-O-(cyclohexylmethanoyl)-β-D-glucopyranose (27), by deacetylation with ammonia in methanol. Their product, unfortunately, was not fully characterized and (as they mention themselves) not pure. However, this suggested that by varying

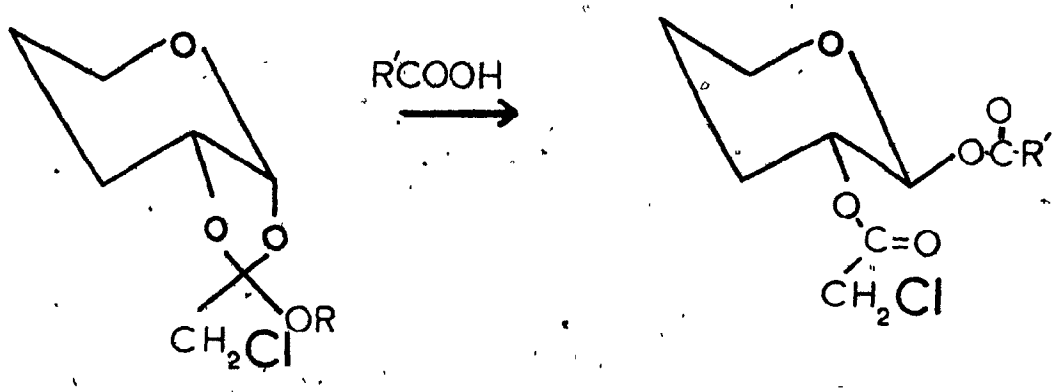
*This compound is of interest because it is formed by Phaseolus vulgaris (common bush bean) as a conjugate when cyclohexanecarboxylic acid is administered to the plant.



Anomerization caused by acid catalyzed deacylation

reaction conditions one might be able to successfully de-O-acetylate the glycosyl esters.

Several experiments were carried out using sodium methoxide in methanol or ammonia in methanol. However, the results were inconclusive, and more extensive studies are required. An alternate approach that has been considered (but not yet tested) is to modify the orthoester structure in an appropriate manner. For example,



Selective de-O-acetylation may become easier since methyl chloroacetate is hydrolyzed 761 times as fast as methyl acetate (36a).

3.5. N.m.r. spectra of the glycosyl esters

A. P.m.r. spectra

The chemical shift and spacing of the H-1 signal of each of the various 1-O-acyl derivatives of 2,3,4,6-tetra-O-acetyl-β-D-glucose are given in Table 4. Values of J_{H1-H2} range from 7.0 to 7.7, which shows that the hydrogens on C-1 and C-2 are anti-periplanar. Thus, all these compounds synthesized from 15 have the β-D-gluco configuration. Product 32 was also shown to have a β-D-gluco configuration, having a $^3J_{H1-H2}$ of 8.0 Hz.

TABLE 4

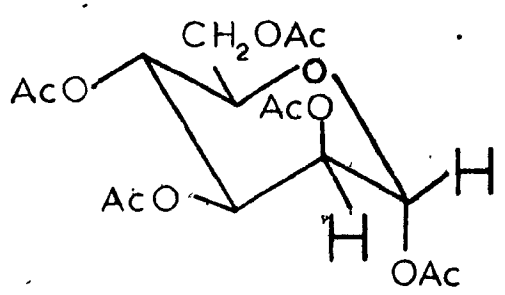
Chemical shift and J_{H1-H2} of derivatives of β-D-glucose

Derivatives of 2,3,4,6-tetra-O-acetyl-1-O-acyl-β-D-glucopyranose O-Acyl		J_{H1-H2}*	δ H-1
Acetyl**	18	7.0	5.7
Acetyl (33)	18	6.9	5.7
Propanoyl	25	7.4	5.8
2,2-Dimethylpropanoyl	26	7.4	5.7
Cyclohexylmethanoyl	27	7.5	5.8
Benzoyl	28	7.6	6.0
Picolyl	29	7.7	6.1
2-O-acetyl-1-O-(cyclohexylmethanoyl) β-D-glucopyranose	32	8.0	5.6

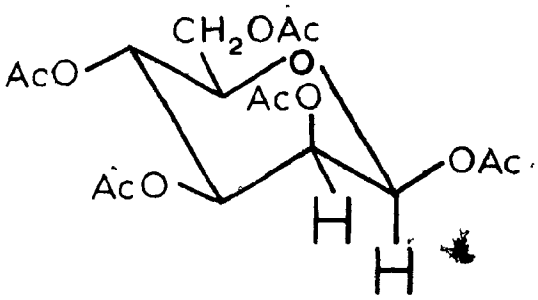
* These are the measured splittings; the coupling constant may be slightly different, especially 28 and 29, which show second order spectra.

** Corresponding values for the α-pentaacetate are: J = 3.4 Hz, 6.36.

The H1-H2 splittings of the mannose derivatives are given in Table 5. It is clear that the difference in J_{H1-H2} between α- and β-mannopyranose derivatives is so small that the correct configuration, on that basis alone cannot be ascertained.



43



44

The reason for the similarity in coupling constant becomes obvious in that in both α- and β-manno configurations H1 and H2 are gauche to each other. The chemical shift of the anomeric proton does not reveal the stereochemistry at C-1, because the difference in chemical shift between the α- and β-manno isomers is too small (cf. Table 5). Other means of ascertaining the configuration of 31 are discussed in section 3.6B, where its c.m.r. and optical rotation are discussed.

B C.m.r. spectra

A comparison of the c.m.r. spectra of 2,3,4,6-tetra-O-acetyl-1-O-acyl-β-D-glucopyranose is in Fig. 8. The pattern for the ring carbons, in comparing one compound with another, is highly constant. Since the assignments for 18 have been made by Dorman and Roberts (38), those for the other compounds are given by comparison with their assignments (Table 6).

TABLE 5

Chemical shifts and $^3J_{H1-H2}$ of 2,3,4,6-tetra-O-acetyl 1-O-acyl-D-mannopyranoses

Acyl		$^3J_{H1-H2}$	δ
α-Cyclohexylmethanoyl	31	1.5	6.1
α-Acetyl	43	1.5	6.0
α-Acetyl (33)	43	3*	6.1
β-Acetyl	44	1.1	5.8
β-Acetyl (33)	44	3*	5.9

*Measured by Lemieux et al. (21) at 40 MHz.

In a subsequent paper Lemieux and Stevens (37) state that the results of paper (21): "were of poor quality by present standards and that many of the signals were poorly resolved".

In all cases, except for compounds 28 and 29, the C3 and C5 signals are superimposed. Carbonyl carbon chemical shifts are listed in Table 7. Aside from the group of signals at lowest field (column 1), which tentatively, are assigned to the C=O of the 1-O-acyl substituent (and hence are expected to vary substantially), a high degree of consistency in chemical shifts is again observed. Chemical shifts for other carbons are listed in Table 8. The outstanding power of c.m.r. to distinguish between non-equivalent carbons is strikingly demonstrated here for the cyclohexane rings of 27 and 31.

Since the pattern for the ring carbons of β-D-glucose pentaacetate (18) is quite different from that of the α-pentaacetate (19) (Fig. 9), the overall consistency of these results indicates that 1-O-acyl-β-D-glucose tetraacetates may be readily distinguished from their anomers by comparing the chemical shifts of their ring carbons. The technique of distinction

FIG. 8 Comparison of the spectra of the 2,3,4,6-tetra-O-acetyl-1-O-acyl-β-D-glucopyranoses. The ring carbons.

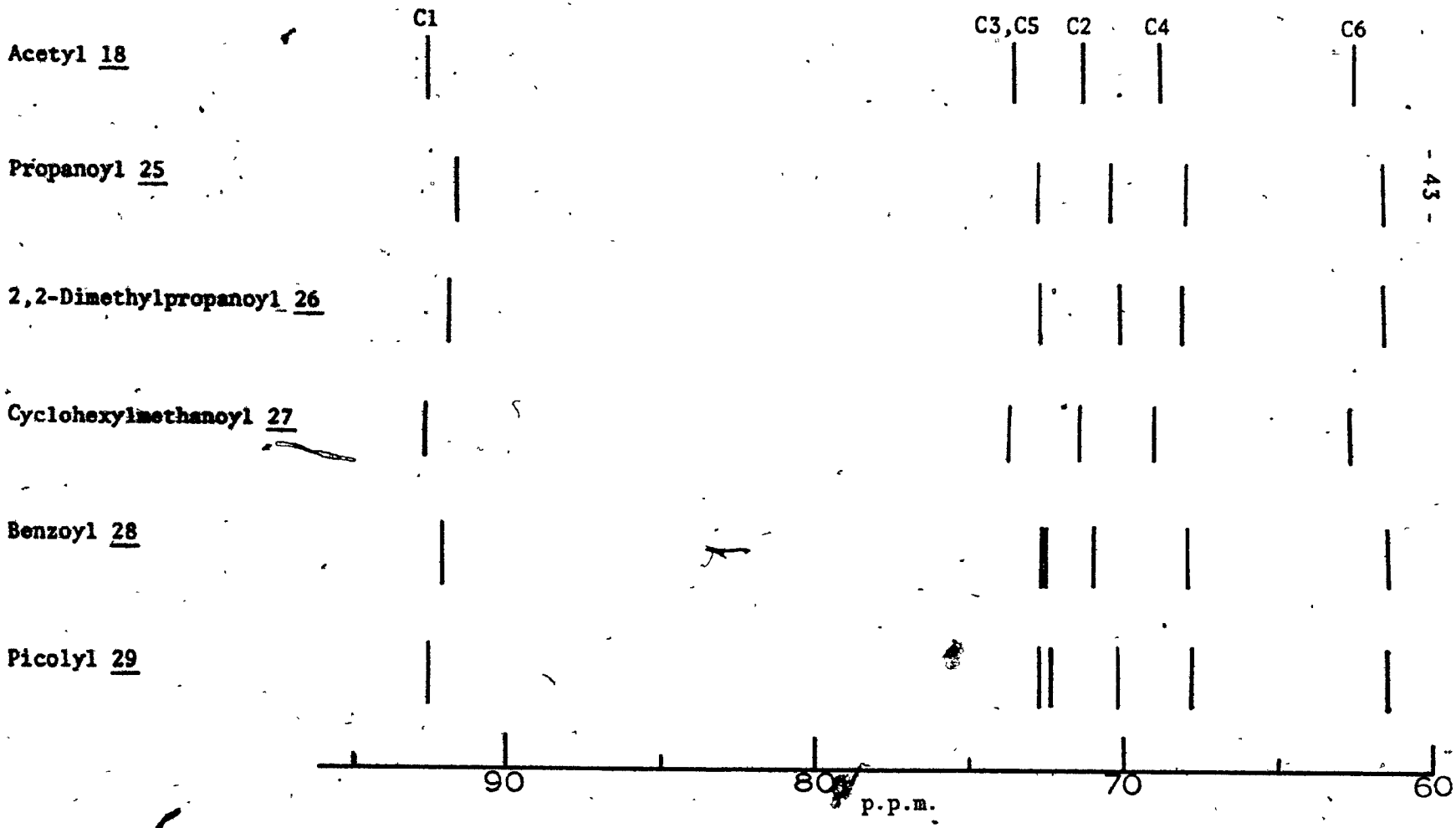


TABLE 6

C.m.r. chemical shifts (p.p.m.)* for 2,3,4,6-tetra-O-acetyl-1-O-acyl-β-D-glucopyranoses. The ring carbons.

1-O-Acyl derivatives		Carbons					
		1	2	3	4	5	6
Acetyl (38)	18	92.5	71.2	73.5	68.8	73.5	62.5
Acetyl	18	92.6	71.4	73.6	68.9	73.6	62.6
Propanoyl	25	91.6	70.3	72.7	67.9	72.7	61.5
2,2-Dimethylpropanoyl	26	91.8	70.2	72.7	68.1	72.7	61.6
Cyclohexylmethanoyl	27	92.5	71.4	73.7	69.0	73.7	62.6
Benzoyl	28	92.1	70.9	72.5**	67.9	72.6**	61.4
Picolyl	29	92.7	70.3	72.6**	67.9	72.9**	61.5

*Relative to upfield TMS.

**C3 and C5 are not identified unambiguously.

TABLE 7

C.m.r. chemical shifts (p.p.m.)* for 2,3,4,6-tetra-O-acetyl-1-O-acyl-β-D-glycopyranoses. The carbonyl carbons.

1-O-Acyl derivative		C=O				
Acetyl (38)	18	171.0	170.5	170.1	169.9	169.6
Acetyl	18	171.0	170.5	170.0	169.8	169.5
Propanoyl	25	172.1	170.3	169.7	169.1	168.9
2,2-Dimethylpropanoyl	26	176.1	170.2	169.8	169.1	168.7
Cyclohexylmethanoyl	27	174.6	171.3	170.7	170.1	169.9
Benzoyl	28	164.1	170.1	169.6	169.0	168.9
Picolyl	29	169.1	169.0	168.8	168.6	168.5

*Relative to upfield TMS.

TABLE 8

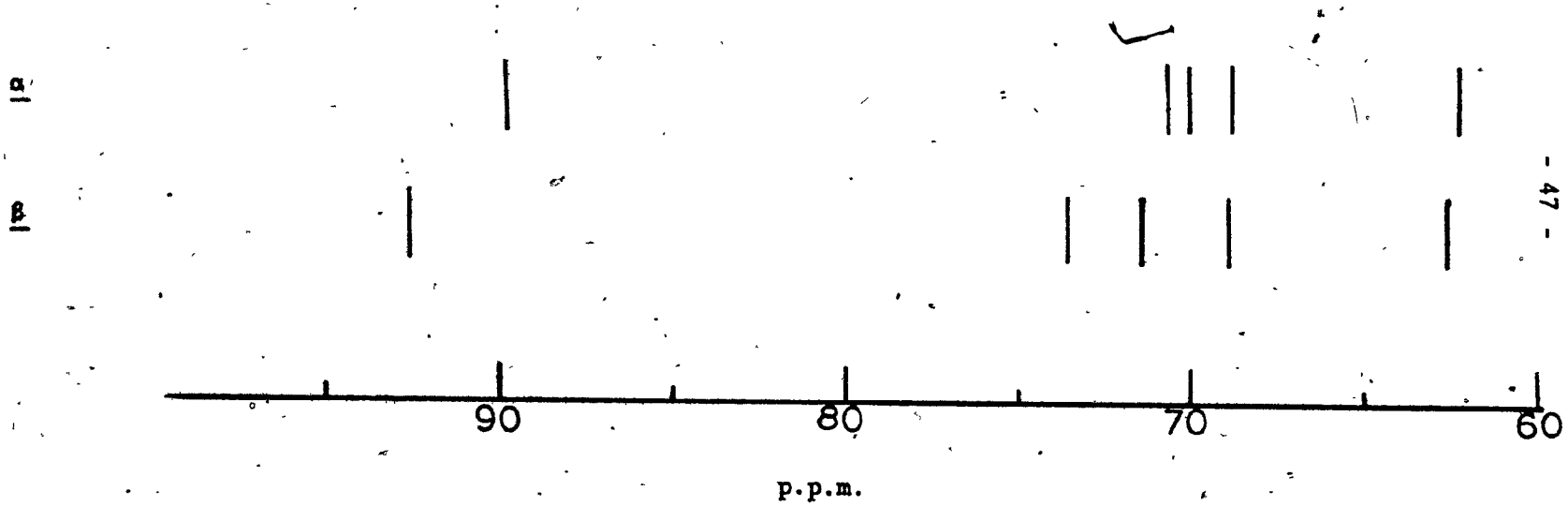
C.m.r. chemical shifts (p.p.m.)* for 2,3,4,6-tetra-O-acetyl-1-O-β-D-glucopyranoses. Other carbons.

1-O-Acyl derivative		
Acetyl	18	$COCH_3$: 21.3 (2x), 21.4 (3x).
Propanoyl	25	$COCH_3$: 20.5 (4x); CH_2 : 27.4; CH_2CH_3 : 8.7.
2,2-Dimethylpropanoyl	26	$COCH_3$: 20.5 (4x); $C(CH)_3$: 26.8; $C(CH)_3$: 38.7
Cyclohexylmethanoyl**	27	$COCH_3$: 21.5 (4x); 3',4',5' : 26.0, 26.4, 26.7; 2',6' : 29.3, 29.8; 1' : 43.6.
Benzoyl	28	$COCH_3$: 20.4 (4x); C' : 133.6, 128.4, 129.9, 129.9.
Picolyl	29	$COCH_3$: 20.5 (4x); C' : 125.6, 127,4, 137.0, 150.2

* Relative to upfield TMS.

** All the carbons in the cyclohexyl ring have a different chemical shift (small, but definite). Magnetic non-equivalence may be due to hindered rotation. Compound 31 exhibited the same phenomenon.

FIG. 9 Comparison of the c.m.r. spectra of α- and β-D-glucose pentaacetate. The ring carbons.



is, perhaps, of limited value for gluco derivatives, because the anomeric configuration is easily deduced from J_{H1-H2}. In the manno series, however where the α- and β-anomers give approximately the same J_{H1-H2} and have a very small difference in the chemical shift of the anomeric proton (see section 3.6A), c.m.r. should be more useful. As shown for α- and β-D-mannose and their methyl glycosides by Perlin, Casu and Koch (39), anomers in this series are clearly distinguishable by differences in chemical shift, particularly of C-3 and C-5. The close similarity in the ^{13}C chemical shift patterns of 31 and α-mannose pentaacetate (43) (Table 9 and Fig. 10), even though all of the individual signals have not yet been unequivocally assigned, strongly indicates that both compounds have the same anomeric configuration.

Confirmatory evidence was provided by rotatory data: i.e., the molecular rotation as compared with those of the α- and β-pentaacetates (as given by Hudson (40)), show that 31 must be an α-anomer.

	$[\alpha]_D$	Molecular rotation/100
31	+59.7	+273
α-D-mannose pentaacetate (43)	+55	+214
β-D-mannose pentaacetate (44)	-25	- 98

C.m.r. spectroscopy should be particularly useful for the determination of configuration in cases when p.m.r. is ambiguous, such as in the manno series, and in those cases when Hudson's isorotation rules break down. It is a well documented fact that highly polarisable aglycones exert distortive effects on optical activity (17,41), and the isorotation rules do not apply. C.m.r. may provide an elegant way of circumventing those difficulties.

TABLE 9

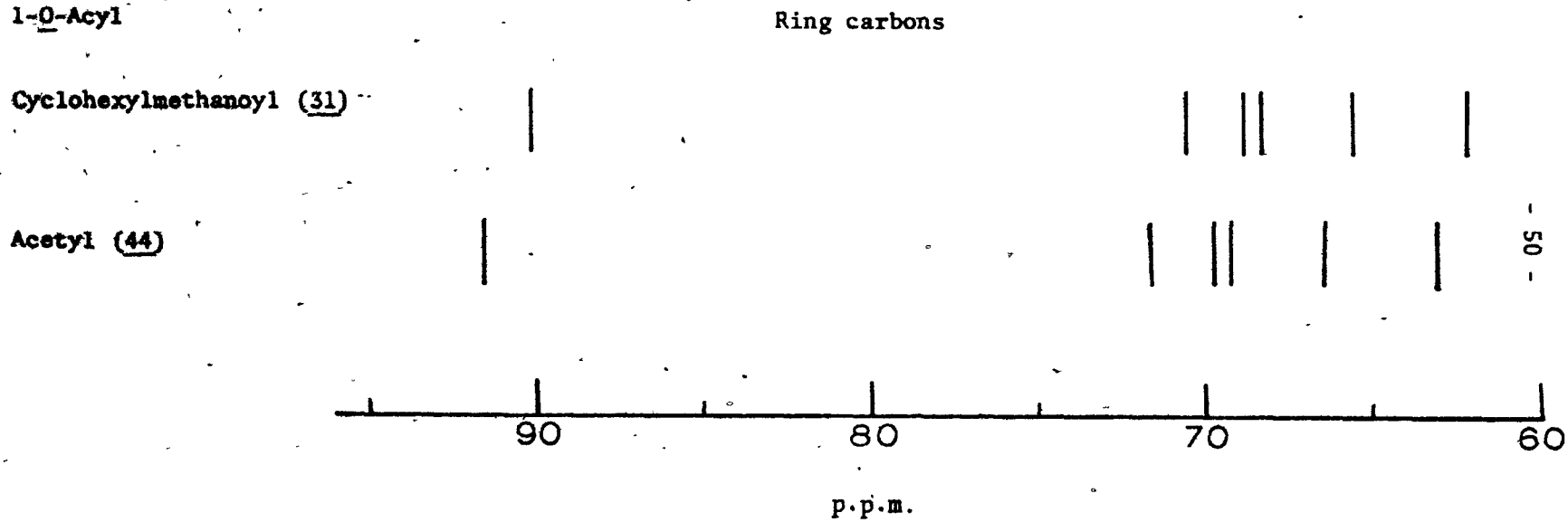
C.m.r. chemical shifts (p.p.m.)* of 2,3,4,6-tetra-O-acetyl-1-O-acyl-α-D-mannopyranoses

	O-acetyl (43)	O-cyclohexylmethanoyl (31)
Methyl	21.5	20.7
3'	-	25.4**
4'	-	25.7
5'	-	28.7
2'	-	28.7
6'	-	29.0
C1'	-	42.9
C6	63.0	62.2
C2	66.4	65.6
C3	69.2	68.4
C4	69.7	68.9
C5	71.5	70.6
C1	91.5	90.2
Carbonyl	168.7	168.9
"	170.2	169.1
"	170.4	169.4
"	170.6	170.0
"	171.2	172.4

*Relative to upfield TMS.

**See footnote in Table 8.

FIG. 10 Comparison of 2,3,4,6-tetra-O-acetyl-1-O-acyl-α-D-mannopyranoses. The ring carbons.



3.6 Resume

Syntheses of 1-O-acyl aldoses, under mild reaction condition, have been carried out by a reaction involving the opening of the 1,2-orthoester ring structure with various carboxylic acids. In the D-gluco series the 1,2-orthoacetate gave the β-glycosyl ester, whereas in the D-manno series the α-glycosyl ester was produced. The scope of these reactions was studied. A p.m.r. and c.m.r. spectral study of the products was made.

CHAPTER 4

EXPERIMENTAL

4.1 General methods

Chromatography

Thin layer chromatography plates were prepared using MN silica gel G as adsorbent. Toluene-ether (9:1, v/v) and chloroform were the solvents commonly used. Visualization was effected by spraying with sulfuric acid (50%, v/v), and heating the sprayed plate at 120° in an oven.

Column chromatographic separations were carried out on columns packed with MN silica gel (grain size 0.08 mm) which had been previously washed with the solvent system being used.

Evaporations

All evaporations were carried out under reduced pressure.

Melting points

Melting points were determined with a Fisher-Johns hot plate apparatus and are uncorrected.

Microanalyses

Organic Microanalyses, Montreal, performed all of the microanalyses.

Optical rotation, $[\alpha]_D$

Optical rotations were measured with a Carl Zeiss polarimeter (model 367732) using the indicated solvent at room temperature.

Spectroscopy

Infra-red spectra were recorded on a Unicam SP-200G grating infrared spectrometer. KBr pellets were used for solids, and syrups were

recorded neat with AgCl plates as support.

Proton magnetic resonance (p.m.r.) spectra were recorded with a Varian HA-100, using tetramethylsilane (TMS) as standard and lock signal.

Carbon-13 magnetic resonance were recorded at 22.63 MHz using a Bruker WH-90 spectrometer. Spectra were obtained with ^{13}C in natural abundance and were proton decoupled.

TMS was used as internal standard unless otherwise mentioned. All chemical shifts (c.m.r. and p.m.r) reported are downfield from TMS. $CDCl_3$ was the solvent used unless otherwise stated.

4.2 The triflate scheme

A. Preparation of 2,3,4,6-tetra-O-benzyl-1-O-triflyl-D-glucopyranose

Methyl 2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside (5).

This procedure was similar to that of Perrine et al. (19). Methyl α-D-glucopyranoside (6, 70 g) was mixed with 376 g of powdered KOH (prepared with a Waring blender) in dioxane (276 ml). To the efficiently stirred mixture benzyl chloride (126 ml) was added, the mixture was heated under reflux, and an extra 250 ml of benzyl chloride was added slowly. Heating was continued for 2 hrs, and upon cooling the liquid layer was collected by decantation. The residue was washed with benzene, and the organic phases were combined and concentrated, giving a yellow oil. The latter was purified by chromatography on a column of silica gel (eluant: chloroform) yielding 5 as a colorless syrup. Compound 5 has been previously synthesized by Tate and Bishop (42).

P.m.r.: 3.36, s(3H); 3.3-3.86, m(5H); 3.96, t(1H); 4.2-5.06, m(9H); 7.26, m(20H).

2,3,4,6-Tetra-O-benzyl-α-D-glucopyranose (6).

Prepared by acid hydrolysis of 5 according to the conditions of Perrine et al. (19), the crystalline product was recrystallized from 9 parts of n-propanol (yield 13%, overall yield from 4 to 6); m.p. 151-152°; $[\alpha]_D$ = 20.9° (c 2.6, chloroform). Lit. (19): m.p. 151-152°; $[\alpha]_D$ = 21.2° (c 2.2, chloroform)).

P.m.r., see section 2.2 and Table 1. Additional p.m.r. data: 3.3-3.8δ, m(5H); 3.8-4.1δ, t(1H); 4.4-5.0δ, m(9H); 7.2δ, m(20H).

2,3,4,6-Tetra-O-benzyl-1-O-triflyl-β-D-glucopyranose (7).

a) Triflic anhydride:trifluoromethanesulfonic acid (3M company) (trade name:fluorochemical acid)) was mixed with an equal amount of P_2O_5, and after 1 hr, the triflic anhydride formed was distilled (boiling point: 80-82°). (Caution: the fumes of triflic acid and anhydride are very corrosive!)

b) Triflic anhydride (8 g) was weighed into an Erlenmeyer flask which was cooled in an ice bath. A solution of 6 (6.0 g) in dry pyridine (20 ml, distilled over BaO and stored over 4A molecular sieves) was added over a period of 5 min. in two equal portions to the triflic anhydride with thorough mixing. After 20 min. the reaction was quenched with cold water (100 ml), and the mixture was extracted with $CHCl_3$ (50 ml, 2x). The organic layer was washed with 1N HCl (2x) and with water (2x), and concentrated. The crude oil resulting was crystallized from pet. ether:ethanol, yielding 7 (4 g; 54% yield). After recrystallization from the same solvents the product (2.5 g of white crystals) had m.p. 151-151.5°, $[\alpha]_D$ = -20.1° (c 4, chloroform). A further 0.5 g was obtained from the mother liquor, m.p. 150-151°.

Analysis:

Calculated for ($C_{35}H_{35}F_3O_8S$): C: 62.5; H: 5.2; S: 4.7; F: 8.5

Found : C: 62.2; H: 5.2; S: 4.6; F: 8.2

P.m.r., see Fig. 3.

C.m.r.: 68.3δ, 73.3δ, 74.5δ, 75.0δ, 75.6δ, 77.0δ, 78.1δ, 80.1δ, 84.9δ, 93.7δ, 126.9δ, 127.6 , 127.8δ, 128.0δ, 128.3δ, 128.6δ, 129.2δ, 136.2δ, 137.5δ, 137.7δ, 141.7δ, 147.5δ.

The c.m.r. spectrum showed $^1J_{C-F}$ = 320 Hz (for triflic acid, $^1J_{C-F}$ = 315 Hz).

B Reactions of the triflate (7)

Attempted synthesis of 1-O-acetyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose

The triflate (7, 0.30 g) was dissolved in DMF (distilled and kept over 4Å molecular sieves), anhydrous sodium acetate (0.60 g) was introduced, and the resulting mixture was heated at 100° for 2.5 hrs. Chloroform was added, and the organic solution was backwashed with water (24), dried over $MgSO_4$, filtered, and concentrated. The p.m.r. spectrum of the residue showed that the material was essentially unreacted 7.

Synthesis of 1-O-benzoyl-2,3,4,6-tetra-O-benzyl-β-D-glucopyranose (10)

Anhydrous sodium benzoate (1 g), compound 7 (0.5 g) and dry DMF (15 ml) were heated together under reflux for 8 hrs, and then stored for 12 hrs at room temperature. Chloroform was added, and the organic layer was washed with water (2x), dried over $MgSO_4$, filtered and concentrated. Brown crystals which were formed were recrystallized twice to yield 0.07 g (14% yield) of light brown crystals. Further recrystallization (5x) afforded colorless crystals, m.p. 84-85°. Other experiments, with different reaction times and solvents (24 hr, Δ; 2 hrs, Δ; 15 min, Δ, HMPA) were all less

successful.

P.m.r., see section 2.3. Additional p.m.r. data:

3.7δ, m(8H); 4.5δ, t(34); 4.8δ, s(2H); 4.9δ, α(1H); 5.9δ, m(H-1); 7.2-7.6δ, m(23H); 8.1δ, q(2H).

Attempted syntheses of methyl 2,3,4,6-tetra-O-acetyl-D-glucopyranose.

Reaction of 7 with methanol. Dry methanol (kept over 3A° molecular sieves) (8 ml) and 7 (0.74 g) were refluxed for 24 hrs. On evaporation of the solvent unreacted 7 was recovered; m.p. 149-150° (pure 7 has m.p. 151-151.5°).

b) Reaction of 7 with sodium methoxide. The triflate 7 (0.27 g) was mixed with a 10 mole excess of sodium methoxide in methanol. The solution was stirred for 24 hrs at room temperature, during which time a dark color developed. Chloroform was introduced, the solution was washed with water and the solvents then evaporated, yielding an orange syrup. The p.m.r. spectrum of the latter was complex, and suggested that little of the methyl glycoside had been formed. Similar results were obtained when 7 and sodium methoxide were heated for 24 hrs under reflux.

C Preparation of model compounds

1-O-Acetyl-2,3,4,6-tetra-O-benzyl-D-glucopyranose

Dry pyridine (distilled over BaO, stored over 4A° molecular sieves) (6.5 g) and acetic anhydride (0.5 g) were cooled in an ice bath. 2,3,4,6-Tetra-O-benzyl-D-glucopyranose (1.0 g) was added, and after 14 hrs at room temperature the reaction mixture was poured dropwise over 20 g of ice. The mixture was extracted with chloroform, the chloroform layer was washed with water, dried, and concentrated, giving a clear oil (0.94 g; 85%). P.m.r. spectroscopy showed the oil to be a mixture of α:β in the ratio of 3:1.

P.m.r. data: 1.8δ, s (CH_3-β); 1.9δ, s(CH_3-α); 3.5-4.0, m; 4.5δ, q; 4.8δ, t; 5.6δ, α(H-1, β-anomer); 6.4δ, α(H-1, α-anomer); 7.2 , (phenyls). J_{H1-H2} = 3 Hz (α-anomer); J_{H1-H2} = 8 Hz (β-anomer).

1-O-Benzoyl-2,3,4,6-tetra-O-benzyl-α-D-glucopyranose

To a solution of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (4.0 g) in cold dry pyridine (distilled from BaO, kept over 4A° molecular sieves) (24 ml), benzoyl chloride (6.0 ml) was added dropwise while the reaction vessel was kept in an ice bath. After 3 hrs at 0°, 12 hrs at -10° and 5 hrs at room temperature, chloroform (25 ml) was added and the mixture was washed with 3N H_2SO_4 (2x), saturated $NaHCO_3$ (2x) and water. The organic layer was dried with $MgSO_4$ and concentrated, yielding a solid residue which was crystallized from hot methanol (30 ml). At this point the p.m.r. spectrum showed the crystals (3.7 g, 78% yield) to consist of a 9:1 mixture of the α- and β-anomers. Three recrystallizations from methanol afforded 2.0 g of pure 1-O-benzoyl-2,3,4,6-tetra-O-acetyl-α-D-glucopyranose, m.p. 79.5-80.5°. $[\alpha]_D$ = 62.5° (c 2.9, chloroform).

Analysis

Calculated for $C_{41}H_{40}O_7$: C: 76.4; H: 6.2

Found : C: 76.1; H: 6.4.

P.m.r. data, see section 2.3. Additional p.m.r. data: 3.5-4.2δ, m(6H); 4.3-5.0δ, m(8H); 6.6δ, α(H-1); 7.0-7.6, m(23H); 8.0δ, m(2H).

4.3 The orthoester reaction

A Preparation of the orthoesters

2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide (21)

The title compound was prepared from D-glucose (100 g) by a

method described by Lemieux (43). After 2 recrystallizations 94.5 g (41% yield) of white crystals were obtained, m.p. 89-89.5, $[\alpha]_D = 206^\circ$ (c 2, chloroform). (Lit. (43), m.p. 88-89°, $[\alpha]_D = 198^\circ$ (c 2, chloroform)). P.m.r. data: 6.6δ, d(H-1, J = 4.0); 5.6δ, t(H-3), J = 9.5); 5.2δ, t(H-4, J = 9.5); 4.8δ, q(H-2, $J_{H1-H2} = 4.0$, $J_{H_2-H3} = 10.0$); 4.2δ, m(H-5, H-6, H-6'), 2.0δ); t(CH_3).

C.m.r. data: 21.5δ (4x, $COCH_3$); 62.1δ (C-6); 68.3δ, 71.3δ, 71.6δ, 73.5δ (C2-5); 88.1δ (C-1); 170.2δ, 170.5 (2x) , 171.2δ (C = O)..

3,4,6-Tri-O-acetyl-α-D-glucopyranose 1,2-(ethyl orthoacetate) (15).

Prepared as described by Lemieux and Morgan (33), 20.5 g of 12 yielded 18 g (96% yield) of syrup which was crystallized and recrystallized to give 11.3 g (60% yield) of 15. Two further recrystallizations gave the pure exo isomer, m.p. 93.5-94.5, $[\alpha]_D = 34.8$ (c 3.56, chloroform). (Lit. (33): m.p. 95-96° (mixture of exo and endo 85:15)) (Lit. (32): $[\alpha]_D = 31^\circ$ (c1, chloroform). P.m.r. spectrum was closely similar to the data given for 15 in ref. 33.

C.m.r.: 14.5δ (CH_2-CH_3); 19.9δ (3x)($COCH_3$); 20.2δ, 58.1 , 62.3δ, 66.3δ, 67.5δ, 69.5δ, 72.5δ, 120.4δ, 96.1δ, 168.1δ, 168.7δ, 169.4δ (C =O).

α-D-Glucopyranose 1,2-(ethyl orthoacetate) (22).

A barium methoxide solution was prepared by adding BaO (1.9 g) to methanol (50 ml). A 0.5 ml portion of this solution (filtered) was added to a stirred solution of 15 (1 g) in methanol (12 ml), kept in a salt-ice mixture for 2 hrs and then at -10° for 2 days. T.l.c. (solvent $CHCl_3$:ethyl acetate (9:1)) then showed the reaction to be complete. Solid CO_2 was added, $BaCO_3$ was removed by filtration, and the solution was evaported to give 0.6 g (90% yield) of a yellowish syrup which was decolorised with Darco G

activated charcoal in ethanol. All attempts to crystallize the product failed.

IR: no carbonyl absorption, but a strong OH absorption (3300-3500 wavenumber).

P.m.r.: 2.7δ, t(CH_2-$\underline{CH}_3$, J = 6 Hz); 2.3δ, s($\underline{CH}_3$-CO_3); 4.0-4.6δ, m(7H); 4.9δ, t(1H); 6.3δ, α, (H-1, J = 5.0).

B Products of the orthoester reaction

1,2,3,4,6-Penta-O-acetyl-β-D-glucopyranose (18)

To a solution of orthoester 15 (0.4 g) in dry dioxane (5 ml) acetic acid (0.7 g) was added, and the mixture was heated on a steam bath for 12 hrs. Chloroform was added, the solution was washed with saturated $NaHCO_3$ and water, dried with $MgSO_4$ and concentrated to yield 114 mg (28% yield) of 18, m.p. 130-131, $[\alpha]_D$ = 5.4° (c 2, chloroform) (Lit. (44): $[\alpha]_D$ = 3.9 (c 6.3, chloroform)) (Lit. (45): m.p. 132°)

P.m.r. and c.m.r., see section 3.6.

2,3,4,6-Tetra-O-acetyl-1-O-propanoyl-β-D-glucopyranose (25)

Orthoester 15 (0.52 g), propanoic acid (1.0 g) and dry dioxane (4 ml) were heated together on a steam bath for 12 hrs. The reaction mixture was worked up as for 18, crystallized from ethanol, yielding 0.27 g (49% of 25; m.p. 98-100°, $[\alpha]_D$ = 3.2 (c 1.7, chloroform). (Lit. (46), m.p. 104-105°, $[\alpha]_D$ = 3.5 (c 1.2, chloroform)).

P.m.r. and c.m.r. see section 3.6. Additional p.m.r. data: 1.1δ, t(J = 8, $CH_2\underline{CH}_3$); 2.1δ, q($COCH_3$); 2.4δ, q($\underline{CH}_2CH_3$); 3.8-4.4δ, m(4H); 5.0-5.4, m(2H).

2,3,4,6-Tetra-O-acetyl-1-O-(2,2-dimethyl-propanoyl)-β-D-glucopyranose (26)

Orthoester 15 (4.0 g), 2,2-dimethylpropanoic acid (2.0 g) and dry

dioxane (15 ml) were heated together on a steam bath for 12 hrs. The reaction mixture was worked up as for 18, crystallized from ethanol, yielding 1.6 g (34% yield). The product was recrystallized (2x); m.p. 136-137.5°, $[\alpha]_D$ = 11.4° (c 2.5, chloroform). (Lit. (11), m.p. 137.5°, $[\alpha]_D$ = 6.3° (c 1, chloroform) P.m.r. and c.m.r. data, see section 3.6. Additional p.m.r. data: 1.3δ, m(t-butyl); 2.1δ ($COCH_3$); 3.8-4.5δ, m(3H); 5.2-5.4δ, m(3H).
Pivalic acid: 1.3δ, s; 12.5δ, s.

2,3,4,6-Tetra-O-acetyl-1-O-(cyclohexylmethanoyl)-β-D-glucopyranose (27)

From 3,4,6-tri-O-acetyl-α-D-glucopyranose 1,2-(ethyl orthoacetate) (15). A solution of 15 (3.7 g), cyclohexanecarboxylic acid (3.9 g) in dioxane (10 ml) was stirred for 2 hrs at room temperature. Evaporation of the solvent left a colorless syrup which was crystallized from ether (2.9 g, 66% yield), m.p. 114-115°. Two recrystallizations from ether-petroleum ether, afforded pure 27, m.p. 114-115.5°, $[\alpha]_D$ = 2.2° (c 2.0, chloroform).

Analysis: Calculated for ($C_{21}H_{30}O_{11}$): C: 55.0; H: 6.5
Found : C: 54.6; H: 6.8

P.m.r. and c.m.r. see section 3.6. Additional p.m.r. data: 1.1-2.5δ, m(11H); 2.0δ, q(12H); 3.8-4.5δ, m(3H); 5.0-5.4δ, m(3H).
Cyclohexanecarboxylic acid: 1.1-2.5δ, m; 12.3δ, s.

2-O-Acetyl-1-O-(cyclohexylmethanoyl)-β-D-glucopyranose (32)

A solution of α-D-glucopyranose 1,2-(ethyl orthoacetate) (22) (0.25 g) in dry dioxane (kept over 4A° molecular sieves) (3 ml) was added dropwise to a solution of cyclohexylmethanoic acid (0.19 g) in dioxane (3 ml). After 24 hrs at room temperature chloroform was added, the solution was washed with 5% bicarbonate, and concentrated to yield 0.3 g

(90% yield) of a yellowish syrup. The syrup was decolorised by Darco G activated charcoal in ethanol.

P.m.r. and c.m.r., see section 3.6. Additional p.m.r. data: 1.1-2.5δ, m(11H); 2.1δ, s($COCH_3$); 3.4-3.9δ, m(5H); 4.9δ, t(1H); (spectrum was D_2O exchanged).

Preparation of 27 from 2-O-acetyl-1-O-(cyclohexylmethanoyl)-β-D-glucopyranose (32)

A solution of 34 (0.27 g) was prepared in acetic anhydride (1 ml) and dry pyridine (redistilled from BaO and kept over 4A° molecular sieves) (1 ml) at 0° and then kept for 20 hrs at -10°, and for 2 hrs at room temperature. Cold water was added, the mixture was extracted with chloroform and ether, and the combined extracts were concentrated. The resulting clear oil was crystallized from methanol, m.p. 112-113° (yield 0.23 g, 62%). I.R. and p.m.r. were identical to those of authentic 27.

2,3,4,6-Tetra-O-acetyl-1-O-benzoyl-β-D-glucopyranose (28)

Orthoester 15 (0.42 g), benzoic acid (.4 g) and dry dioxane (4 ml) were heated together on a steam bath for 12 hrs. The reaction mixture was worked up as for 18, and was crystallized from ethanol, yielding 0.50 g of syrupy crystals. These were recrystallized from ethanol yielding 0.26 g (57%), m.p. 141.5-142.5, $[\alpha]_D$ = -19.5° (c 2.1, chloroform). (Lit. (10), m.p. 143-146°, $[\alpha]_D$ = -28.1° (C = 2, chloroform).

P.m.r. and c.m.r., see section 3.6. Additional p.m.r. data: 2.0δ, m(12H); 3.8-4.5δ, m(3H); 5.1-5.5δ, m(3H); 7.4-7.7δ, m(3H); 8.0-8.1δ, m(2H).

2,3,4,6-Tetra-O-acetyl-1-O-picolyl-β-D-glucopyranose (29).

Orthoester 15 (0.78 g), picolinic acid (1.0 g) and dry dioxane (4 ml) were heated together on the steam bath for 12 hrs. The reaction mixture was worked up as for 18, crystallized from ethanol-water, yielding 0.24 g (25%) of 29; m.p. 131-132.5. Recrystallized (2x) material, m.p. 133-134°, $[\alpha]_D$ = -27.3° (c 1.9, chloroform).

Analysis: calculated for ($C_{20}H_{23}NO_{11}$):

C: 53.0; H: 5.1; N: 3.1

Found: C: 53.1; H: 5.5; N: 3.3

P.m.r. and c.m.r., see section 3.6. Additional p.m.r. data: 2.0δ, t(12H); 4.1-4.5δ, m(H-5, 6, 6'); 3.1-3.5δ, m(H-2, 3, 4); 6.1δ, α(H-1); 7.5δ, m(1H); 7.8-8.2δ, m(3H); 8.8δ, m(1H).

Picolinic acid: 8.0-8.8δ, m(solvent D_2O).

2,3,4,6-Tetra-O-acetyl-1-O-(cyclohexylmethanoyl)-α-D-mannopyranose (31)

A solution of 3,4,6-tri-O-acetyl-β-D-mannopyranose 1,2-(methyl orthoacetate) (30) (0.5 g) and cyclohexanecarboxylic acid (0.6 g) in dry dioxane (6 ml) were heated under reflux for three hours. (There was no reaction in 2 hrs at room temperature). Chloroform was added, the solution was washed with 5% bicarbonate, dried, concentrated, and the resulting colorless syrup was crystallized from ether-petroleum ether. Yield, 0.39 g (63%). After three recrystallizations, m.p. 126.5-127.5, $[\alpha]_D$ = 59.7 (c 2.2, chloroform).

Analysis, calculated for ($C_{21}H_{30}O_{11}$): C: 55.0; H: 6.5

Found : C: 54.9; H: 6.6

P.m.r. and c.m.r., see section 3.6. Additional p.m.r. data: 1.3-2.4δ, m(23H); 4.0-4.2δ, m(3H); 5.4δ, m(3H); 6.1δ, α(1H).

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Claims to original research

2,3,4,6-Tetra-O-benzyl-1-O-trifluoromethanesulfonyl-β-D-glucopyranose was synthesized. Its reaction with nucleophiles was examined. Reaction with sodium benzoate led to the formation of 1-O-benzoyl-2,3,4,6-tetra-O-benzyl-β-D-glucopyranose.

1-O-Benzyl-2,3,4,6-tetra-O-benzyl-α-D-glucopyranose was synthesized for comparison with the β-anomer, mentioned above.

Syntheses of 1-O-acyl-aldoses were effected by reaction of gluco- or manno-1,2-orthoesters with carboxylic acids. Under the conditions used the reaction was shown to be stereospecific and to work with all the carboxylic acids tried. Some of those glycosyl esters were new compounds and others were synthesized for the first time using the ortho ester reaction.

Glycosyl esters obtained from these reactions were examined by p.m.r. and c.m.r.