Carbohydrate Research
Elsevier Publishing Company, Amsterdam
Printed in Belgium

MODIFICATIONS OF THE ORTHOESTER METHOD OF GLYCOSYLATION

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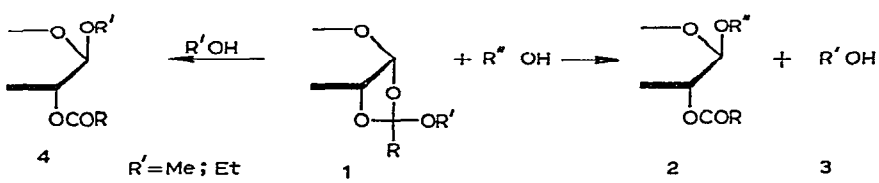
(Received February 2nd, 1970; in revised form, March 26th, 1970)

ABSTRACT

A new catalyst–solvent system (1,2-dichloroethane or chlorobenzene and pyridinium or 2,6-dimethylpyridinium perchlorate) is described for glycosylation with sugar orthoesters. Two-stage glycosylation, involving re-esterification of the starting orthoester with the starting alcohol and glycosylation with the resulting orthoester, allows an approximately two-fold increase in yield. *tert*-Butyl orthoacetates of sugars are more advantageous glycosylating agents than are the methyl or ethyl homologues. Several D-glucose disaccharides (including laminaribiose) have been synthesised by the modified orthoester method. The mechanism of the reaction is discussed.

INTRODUCTION

The orthoester method of synthesis of 1,2-*trans*-glycosides previously developed in this laboratory[1,2] and extensively used [1–13] involves the condensation of sugar orthoesters (**1**) with alcohols. Nitromethane was originally used as solvent and mercuric bromide as catalyst. As a rule, the reaction led stereospecifically to 1,2-*trans*-glycosides (**2**). However, with aglycons of low reactivity, the yield was poor (10–21%) due to competing glycosylation of the lower alcohol (**3**) split off from the initial orthoester (**1**) to produce a glycoside (**4**) isomeric with **1**.



Attempts to improve the yield by varying the solvent and/or catalyst only diverted the reaction to the unfavoured route. In solvents of low polarity or in nitromethane, but with other catalysts, attempted condensation resulted in re-esterification to yield an orthoester (**5**) isomeric with the expected glycoside[2,3]. Many problems of glycoside synthesis are concerned with the glycosylation of hydroxyl groups of relatively low reactivity. One of the most interesting applications

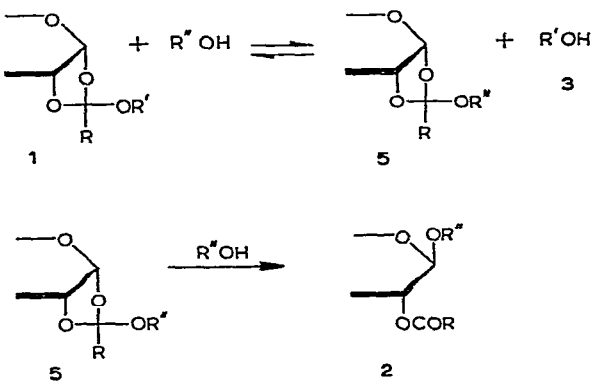
of the orthoester method involves the synthesis of polysaccharides[14–19], the success of which (yield and molecular weight of the products) decisively depends on the yield at each stage of glycosylation. The availability of only one type of glycosylation condition ($MeNO_2$–$HgBr_2$) was a serious limitation of the reaction, giving no possibility for its application to aglycons that are insoluble in nitromethane. Hence, the development of different reaction conditions is important.

We now reports on some new modifications of the method, which overcome, to some extent, the difficulty mentioned above.

RESULTS AND DISCUSSION

Two-stage glycosylation

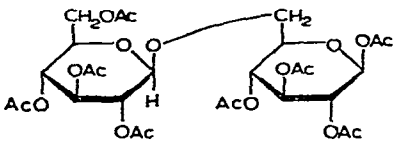
A two-stage scheme of glycosylation has been devised. The first stage involves the condensation of the orthoester with an alcohol under re-esterification conditions to yield a new orthoester (**5**) isomeric with the glycoside to be synthesized. The second stage involves the conversion of the resulting orthoester into the glycoside (**2**) under the glycosylation conditions.



In the first stage, which is reversible, the lower alcohol **3** released can be almost completely removed by azeotropic distillation, with an equilibrium shift to the right. This allows the glycosylation (**5**→**2**) to proceed without the competing formation of **4**.

The synthesis of gentiobiose octa-acetate (**6**) from 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (**7**) and 3,4,6-tri-*O*-acetyl-α-D-glucopyranose 1,2-(ethyl orthoacetate) (**8**) has been used as a model reaction. The re-esterification conditions found previously for the orthoester **8** and cholesterol[2,3] proved to be suitable in this case as well. The condensation of **7** and **8** in dichloroethane in the presence of 20 mmoles of toluene-*p*-sulphonic acid per mole of orthoester gave rise to orthoester **11** in 75% yield. The structure of **11** was supported by analytical data, by hydrolysis of the orthoester group[2,5], and by the n.m.r. spectrum which exhibited a singlet at 8.30 p.p.m. characteristic[20,21] of *endo* C–CH_3 orthoacetate protons.

New glycosylating catalysts which promote reaction in solvents of low polarity have been found during a study of the second stage of the conversion of orthoester **11**



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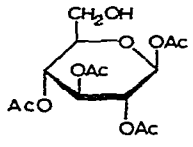

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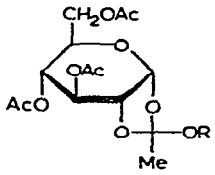
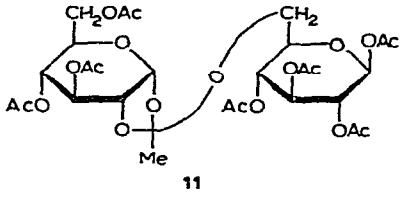


8 R = Et
9 R = i-Pr
10 R = *tert*-Bu



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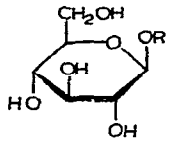


12 R = Et
13 R = i-Pr
14 R = *tert*-Bu

into gentiobiose octa-acetate (**6**). Thus, complete conversion occurs in boiling dichlorethane in the presence of 20 mmoles of pyridinium perchlorate and 20 mmoles of toluene-*p*-sulphonic acid per mole of orthoester. The yield of **6** under these conditions was 59%. It is essential that 0.1–0.2 mole of tetra-acetate **7** per mole of orthoester should be added to the reaction mixture, otherwise the reaction proceeds slowly. Under the same conditions, but in the absence of toluene-*p*-sulphonic acid, practically no conversion **11**→**6** occurs[22].

From the preparative standpoint, it is convenient to carry out the two-stage glycosylation without isolation of the intermediate orthoester (see Experimental). The yield of octa-acetate **6** under these conditions was 60.5%. The direct (one stage) condensation of **7** and **8**, under comparable conditions, gave **6** in lower (38%) yield.

The use of other alkyl orthoacetates of D-*glucose*

In order to suppress the side-formation of lower glycosides (type **4**), it was important to find orthoesters the glycosylation by which is accompanied by release of an alcohol (**3**) which exhibits low reactivity with orthoesters. The condensation of tetra-acetate **7** with acetylated ethyl (**8**), isopropyl (**9**), and *tert*-butyl (**10**) orthoacetates of D-glucose was therefore studied. The reaction of orthoesters **8**–**10** with tetra-acetate **7** proceeded under the standard conditions described above for the conversion **11**→**16**, by two pathways (t.l.c. monitoring): (*i*) the direct glycosylation, because octa-acetate **6** was found in the reaction mixture at the very beginning; and (*ii*) the two-stage glycosylation, because it was observed that the content of the intermediate orthoester **11** increased, and then declined to zero, whereas that of octa-acetate **6** progressively increased. The final yields of gentiobiose, glucosides **12**–**14**, and D-glucose are shown in Table I (*cf.* Ref. 24). The D-glucose probably originated from the unreacted tetra-acetate **7** and from decomposition products of the starting orthoester.

As seen from Table I, the yield of gentiobiose increases along the series of

orthoesters **8–10**, where R = Et, i—Pr, and *tert*-Bu, whereas that of the lower glucosides **12–14** decreases. Hence, the formation of the desired product and the glucoside isomeric with the starting orthoester appears to involve competing reactions. The reactivity of the orthoesters also increases along the above series as shown by the decreasing reaction time. Also, the amount of orthoester decomposing during the reaction increases. It is clear that the *tert*-butyl orthoacetate is the best glycosylating reagent among those studied. During glycosylation with this reagent, care should be taken to remove continuously the released *tert*-butyl alcohol, and to prevent the ingress of moisture, by azeotropic distillation with the solvent. By these means, the octa-acetate **6** was obtained in 55% yield.

TABLE I

CONDENSATION OF 3,4,6-TRI-*O*-ACETYL-α-D-GLUCOPYRANOSE 1,2-(ALKYL ORTHOACETATES) (**8–10**) (1.00 MMOLE) WITH 1,2,3,4-TETRA-*O*-ACETYL-β-D-GLUCOPYRANOSE (**7**) (1.00 MMOLE) (see Experimental)

Starting orthoester	*Reaction time (h)*	*Yields of reaction products*				*Amount of orthoester decomposed during reaction (%)*[c]
		Content in reaction mixture after saponification (mmoles)[a]			*Octa-acetate* **6**, (%)[b]	
		Gentiobiose	*Glucosides* **12–14**	*D-Glucose*		
8, R = Et	5	0.31	0.55	0.84	18	14
9, R = i-Pr	4	0.33	0.46	0.80	19	21
10, R = *tert*-Bu	2	0.50	0 20	0.80	39	30

[a]Determined quantitatively[23] after paper chromatography. [b]Determined by weight after crystallization. [c]Calculated from the other data in the Table.

The *tert*-butyl orthoacetate **10** also appears to be the most advantageous glycosylating agent in the two-stage reaction. The yield of gentiobiose octa-acetate (**6**) (75%) is twice as high as that obtained by the direct glycosylation of **7** with orthoester **8** in nitromethane[2,6]. The yields of gentiobiose octa-acetate are as follows:

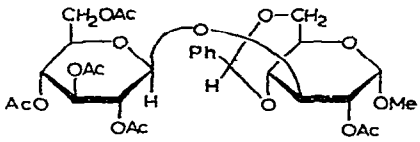
Orthoester	**8**	**8**	**10**	**8**	**10**
Condensation conditions[a]	Direct glycosylation			Two-stage glycosylation	
Octa-acetate yield (%)	35[b]	38	55	60.5	75

[a]Solvent: 1,2-dichloroethane; catalysts: pyridinium perchlorate and toluene-*p*-sulphonic acid. [b]Nitromethane, in the presence[2,6] of $HgBr_2$.

Glycosylation of aglycones with secondary hydroxyl groups

In extending the orthoesters method to secondary alcohols, the reaction of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**15**) with the *tert*-butyl

orthoester **10** was investigated. The product, methyl α-laminaribioside hepta-acetate



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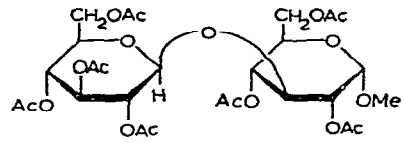

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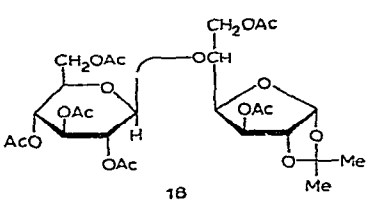
(**17**), has been synthesized previously by the direct glycosylation[2,8] of **15** with orthoester **8**; the yield of derivative **16** was 28%. The two-stage synthesis with dichloroethane and pyridinium perchlorate–toluene-*p*-sulphonic acid presented some difficulty, since the second stage proceeded very slowly and was accompanied by considerable decomposition of the intermediate orthoester, possibly because of the high acidity of the catalysts. As might be expected from the reaction mechanism presented later, 2,6-dimethylpyridinium perchlorate catalysed the glycosylation without the addition of extra acid. Moreover, the second stage proceeded without decomposition, but again very slowly (*cf.* Ref. 25). The use of chlorobenzene as solvent permitted a higher reaction temperature, and the condensation of **10** and **15** in the presence of 10 mmoles of 2,6-dimethylpyridinium perchlorate proceeded readily. After removal of the benzylidene group from the product **16** and acetylation, the hepta-acetate **17** was obtained in 50% overall yield.

The efficiency of these modified reaction conditions was verified by the synthesis of the 5-*O*-β-D-glucopyranosyl-α-D-glucofuranose derivative **18**, previously obtained (10%) from 3,6-di-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**19**) and orthoester **8** by direct glycosylation[2,6]. The condensation of **19** with orthoester **10** in chlorobenzene gave **18** in improved yield (27%).

The amount of the catalyst may be decreased tenfold in the glycosylation in chlorobenzene of alcohols of high reactivity. For instance, the reaction of orthoester **10** with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose in the presence of 1 mmole of 2,6-dimethylpyridinium perchlorate gave disaccharide **20** in 60% yield.



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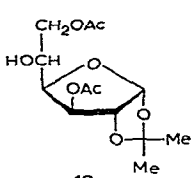

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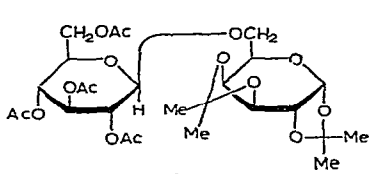

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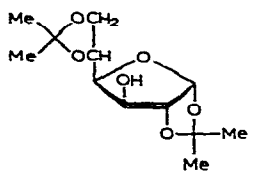
An attempt to produce gentiobiose by the condensation of orthoester **10** and tetra-acetate **7** in chlorobenzene gave, after removal of the protective groups, a mixture of cellobiose and an insignificant amount of gentiobiose. Clearly, acetyl migration had occurred in the starting tetra-acetate **7**. On the other hand, condensation of orthoester **10** with ethyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside under the same conditions (10 mmoles of the catalyst), followed by removal of the protective groups, gave gentiobiose uncontaminated cellobiose. Hence, one may conclude that

the migration observed is probably characteristic of acetates but not of benzoates.

The modified glycosylation procedure with the *tert*-butyl orthoacetate allowed a convenient synthesis of laminaribiose from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**21**). Numerous attempts to glycosylate this compound by the Koenigs–Knorr reaction[26–28] and by the orthoester method (either in nitromethane or according to the two-stage scheme in dichloroethane in the presence of pyridinium perchlorate–toluene-*p*-sulphonic acid) always resulted in acetal migration and glycosylation mainly at O-6. The synthesis from benzyl 4,6-*O*-benzylidene-β-D-glucopyranoside[29,30] involves a tedious isolation procedure, and thus no convenient synthesis of laminaribiose was previously available. The condensation of **21** with orthoester **10** in chlorobenzene in the presence of 2,5-dimethylpyridinium perchlorate proceeded smoothly, with insignificant formation of the gentiobiose derivative **22**. The major product (36%) was the laminaribiose derivative **23** which was readily isolated from the reaction mixture by crystallization. When standard procedures (hot, dilute acid) were used to remove the isopropylidene groups from the saponification product of **23**, considerable cleavage of the glycosidic linkages occurred. However, hydrolysis with 0.5M sulphuric acid at 20° removed the acetal groups, without cleaving the glycosidic linkage, to give laminaribiose in 23% overall yield.



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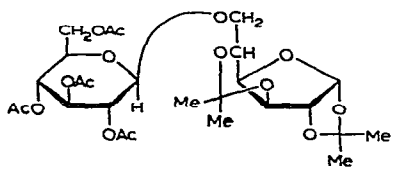

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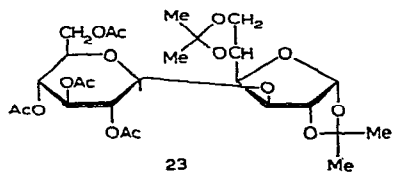

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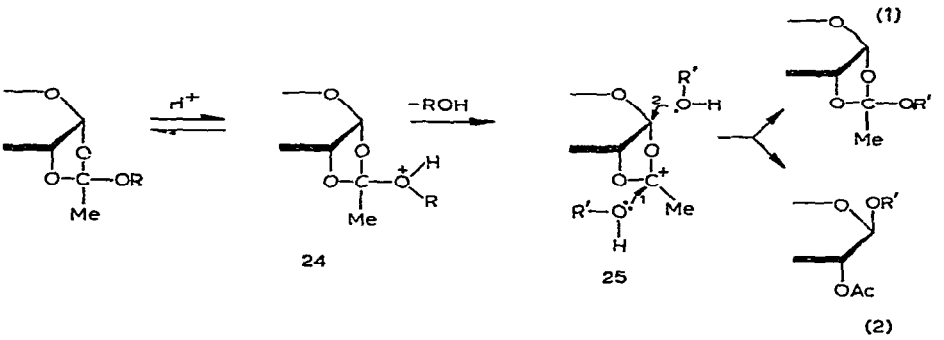
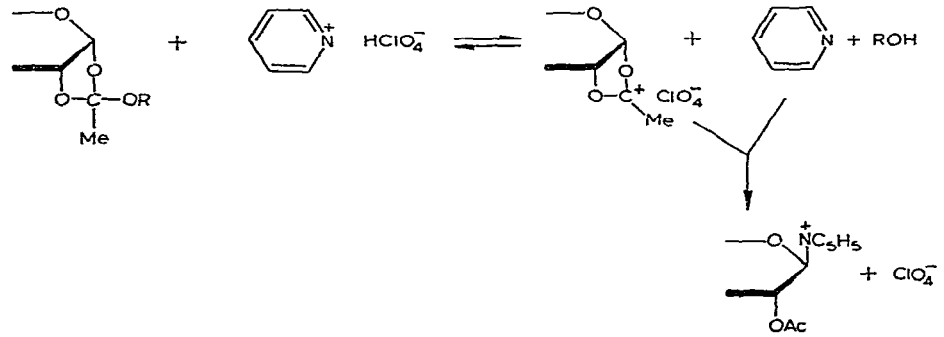
The two-stage glycosylation has also been employed with advantage in the synthesis of aryl glycosides[31], *O*-(β-D-glucopyranosyl)-L-threonine[32], and in the chemical synthesis of a laminarin-like polysaccharide[19].

Although no special investigation of the reaction mechanism (see Ref. 33) was undertaken, the available experimental data enable certain comments to be made. By analogy with the mechanism of glycosylation in the nitromethane–mercuric bromide system[2,3], protonation of the starting orthoester is postulated to yield the oxonium ion **24** which decomposes to give the ambident acyloxonium cation **25**. That ion **24** originates in the first stage of the reaction is supported by the dependence of orthoester reactivity on the structure of the alkoxy group; an increase in the electron-donating ability of the alkyl groups in the orthoester series **8–9–10** increases the basicity of the alkoxy oxygen atom and hence the stability of the intermediate oxonium ion **24**. The reaction of the acyloxonium ion **25** by alcohol-reesterification (route 1) and glycosylation (route 2) depends on the association of **25** with the catalyst anion. If this occurs, the electrophilic centre of the cation is shielded, and pathway 2 predominates. If an ion-pair is not formed, reaction by pathway 1 can occur, which gives rise to re-esterification. The fact that pyridinium perchlorate catalyzes only re-esterification can be explained as follows. The reaction between the orthoester



and perchlorate anion yields the acyloxonium ion, alcohol, and pyridine. The free base undergoes *N*-glycosylation by cation **25** to give the *N*-glycosylpyridinium perchlorate which exists as an ion-pair in media of low polarity:



This side-reaction results in the binding of most of the perchlorate anion, which makes shielding of cation **25** unlikely, and re-esterification is therefore favoured. The addition of extra acid removes the free pyridine, and re-esterification is thus blocked. When 2,6-dimethylpyridinium perchlorate is used as catalyst, *N*-glycosylation is sterically hindered (*cf.* Ref. 34), and glycosylation occurs without the addition of acid.

The role played by tetra-acetate **7** in converting orthoester **11** into glycoside **6** also becomes clear. Indeed, the formation of the acyloxonium ion **25** as a result of protonation of orthoester **11** is accompanied by the formation of an equi molar amount of tetra-acetate **7**. Since the concentrations of **25** and **7** are low and do not exceed that of the catalyst, the formation of glycoside by their interaction proceeds slowly. Addition of alcohol **7** initiates the reaction, and the initial concentration remains constant throughout. The dependence of the reaction rate on the initial alcohol concentration provides evidence that the isomerization of orthoesters into glycosides is a stepwise process involving release of an alcohol molecule from the orthoester and its subsequent glycosylation with a cation **25**, rather than an intramolecular rearrangement. A similar process has been reported for the polymerization of 3-*O*-acetyl-β-L-arabinofuranose 1,2,5-orthobenzoate, which also required alcohol as an initiator[17,18]. Some instances of isomerization of orthoesters into glycosides without

alcohol as an initiator have been described[35–37], but these required large quantities of acidic catalysts and, hence, were characterized by relatively high concentration of acyloxonium ions and the corresponding alcohols.

EXPERIMENTAL

1,2-Dichloroethane was washed with 20% aqueous sodium hydroxide and water, dried ($CaCl_2$), and distilled through a column. Chlorobenzene was washed with conc. sulphuric acid and water, dried ($CaCl_2$), and distilled through a column. Anhydrous chloroform was prepared by two-fold distillation from phosphorus pentaoxide. *tert*-Butyl alcohol was purified by repeated recrystallization and then distilled through a column. Evaporations were carried out under diminished pressure at 40–50°. Melting points were determined on a Kofler hot-stage. Thin-layer chromatography (t.l.c.) was performed on alumina (neutral, Brockmann III) with chloroform–butanone (98.5:1.5) or chloroform–pentan-2-one (80:20). Chromatography on "Goznak" or "Leningradskaya S" paper was performed with butyl alcohol–pyridine–water (6:4:3).

All the compounds described were chromatographically homogeneous. The identity of known compounds was established by co-chromatography and by mixed melting-point determinations with authentic compounds. All orthoesters were completely cleaved under the conditions of the orthoester hydrolysis test[2,5].

The course of reaction in the syntheses of oligosaccharides was monitored by t.l.c.; the reaction was stopped when complete disappearance of orthoester was achieved.

3,4,6-Tri-O-acetyl-α-D-glucopyranose 1,2-(1,2,3,4-tetra-O-acetyl-β-D-glucopyranose-6-yl orthoacetate). — A solution of orthoester **8** (0.5 g, 1.5 mmoles) and **7** (0.35 g, 1.0 mmole) in 1,2-dichloroethane (5 ml) was evaporated at atmospheric pressure, with the addition of fresh solvent to keep the volume constant. After a few ml of solvent had been distilled off, toluene-*p*-sulphonic acid (3.5 mg, 0.02 mmole) was added, and the mixture was distilled under the same conditions for 1 h. Pyridine (2–3 drops) was added, the mixture was evaporated, and the residue was crystallised from ether to yield **11** (0.52 g, 76%), m.p. 137–138°, $[\alpha]_D$ +39° (*c* 1.0, chloroform) (Found: C, 50.14; H, 5.97. $C_{28}H_{38}O_{19}$ calc.: C, 49.55; H, 5.64%).

3,4,6-Tri-O-acetyl-α-D-glucopyranose 1,2-(tert-*butyl orthoacetate)* (**10**). — To a solution of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (19.5 g, 50 mmoles) in dry chloroform (170 ml), anhydrous aluminium chloride (6.65 g, 50 mmoles) was added with stirring and cooling (0–5°), and stirring was continued for 2 h under anhydrous conditions; the optimal reaction time depends on the activity of the aluminium chloride. 2,6-Dimethylpyridine (30 ml) and *tert*-butyl alcohol (150 ml) were added, and the mixture was stored for 2 days at room temperature. The solution was poured into ice–water (500 ml) and extracted with ether, and the extract was washed with ice–water (twice), 2M silver nitrate (100 ml), and water (4 times), and dried (Na_2SO_4). Evaporation of the ether solution and crystallization of the residue from ether–heptane gave **10** (12.0 g, 60%), m.p. 152–154°, $[\alpha]_D$ +34.5° (*c* 1.5; chloroform);

lit.[21] m.p. 152.5–154.5°, $[\alpha]_D$ −34.5° (chloroform).

1,2,3,4-Tetra-O-acetyl-6-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-β-D-glucopyranose (**6**). — In all syntheses described below, the octa-acetate **6** had a m.p. in the range 194–197° and $[\alpha]_D$ −5° (*c* 2.8, chloroform); lit.[38] m.p. 196°, $[\alpha]_D$ −5.35° (chloroform).

Condensation of orthoesters **8–10** *with tetra-acetate* **7**. — The orthoester (1.0 mmole) and tetra-acetate **7** (1.0 mmole) were dissolved in 1,2-dichloroethane (10 ml), and 5 ml of the solvent were distilled off at atmospheric pressure. Pyridinium perchlorate[39] (3.5 mg, 0.02 mmole) and toluene-*p*-sulphonic acid (3.5 mg, 0.02 mmole) were then added, and the mixture was refluxed until reaction was complete (t.l.c). The volume of the mixture was brought to 10 ml with dichloroethane, and aliquots (0.1 ml) were used for quantitative analysis (see below). The remaining solution was treated with pyridine (1 drop) and evaporated, and the residue was crystallized from ethanol (7 ml). The product was filtered off, washed with cold ethanol (3 ml), and dried. The yields are given in Table I. The 0.1-ml aliquots were evaporated, the residue was deacetylated with 0.1M sodium methoxide and analysed by paper chromatography, followed by quantitative determination[23] of glucose, gentiobiose, and alkyl glucoside. The results are listed in Table I.

Direct glycosylation of the tetra-acetate **7** *with orthoesters* **8** *or* **10**. — Under the conditions described for preparation of **11**, the orthoesters **8** or **10** (1.0 mmole) and tetra-acetate **7** (1.0 mmole) were condensed in 1,2-dichloroethane (5 ml) in the presence of pyridinium perchlorate (3.5 mg, 0.02 mmole) and toluene-*p*-sulphonic acid (3.5 mg, 0.02 mmole). The octa-acetate **6** was isolated as described above. The yields obtained are reported in the Discussion.

Two-stage glycosylation of tetra-acetate **7** *with orthoesters* **8** *and* **10**. — The orthoester (1.0 mmole) and tetra-acetate **7** were condensed under the conditions described for **11**. When the formation of orthoester was nearly complete (*ca.* 1 h), pyridinium perchlorate (3.6 mg, 0.02 mmole) was added, and the mixture was refluxed for *ca.* 1 h. The octa-acetate **6** was isolated as described above. The yields are given in the Discussion.

2,6-Dimethylpyridinium perchlorate. — A mixture of 2,6-dimethylpyridine (1 ml), 37% aqueous perchloric acid (1 ml), and 1,2-dichloroethane (15 ml) was evaporated at atmospheric pressure. The resulting syrup was dried *in vacuo* over calcium chloride and crystallized from 1,2-dichloroethane (1.5 ml) and dry ether (40 ml). Very hygroscopic crystals were obtained, m.p. ~100°. It is convenient to use the reagent as a dry solution in dry 1,2-dichloroethane or chlorobenzene. The solution should be evaporated a few times before use to remove moisture consumed, and the residue dissolved in the definite volume of solvent.

Methyl 2,4,6-tri-O-acetyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**17**). — A solution of orthoester **10** (0.405 g, 1.0 mmole) and methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside[40] **15** (0.37 g, 1.0 mmole) in chlorobenzene (10 ml) was distilled at atmospheric pressure with the addition of fresh solvent to maintain constant volume. After distillation of a few ml of solvent, 2,6-

dimethylpyridinium perchlorate (0.01 mmole) was added, and the mixture was boiled under the same conditions with accelerated distillation for 30 min. The mixture was evaporated, the residue was dissolved in 60% aqueous acetic acid (10 ml), and the solution was heated for 15 min at 80° and evaporated to dryness. After acetylation of the residue with acetic anhydride–pyridine in the usual manner and crystallisation of the product from ether–light petroleum, **17** (0.34 g, 50%), m.p. 189–191°, $[\alpha]_D$ +39° (*c* 2.0, chloroform), was obtained; lit.[2,8] m.p. 189–192°, $[\alpha]_D$ +39° (chloroform).

3,6-Di-O-acetyl-1,2-O-isopropylidene-5-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-D-glucofuranose. (**18**). — Orthoester **10** (0.405 g, 1.0 mmole) and 3,6-di-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucopyranose[26] **19** (0.30 g, 1.0 mmole) were condensed under the conditions of the previous experiment. Evaporation of the reaction mixture, followed by crystallisation of the residue from methanol (5 ml, 0°), gave **18** (0.17 g, 27%), m.p. 173°, $[\alpha]_D$ −28° (*c* 2.2, chloroform); lit.[26] m.p. 173°, $[\alpha]_D$ −28° (chloroform).

1,2:3,4-Di-O-isopropylidene-6-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-D-galactopyranose (**20**). — Orthoester **10** (0.405 g, 1.0 mmole) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.26 g, 1.0 mmole) were condensed, as described above, with 1 μmole of 2,6-dimethylpyridinium perchlorate. The reaction product was crystallised from ether–heptane to give **20** (0.36 g, 60%), m.p. 140–141°, $[\alpha]_D$ −52° (*c* 2.5, chloroform); lit.[41] m.p. 141°, $[\alpha]_D$ −52.6° (chloroform).

1,2:5,6-Di-O-isopropylidene-3-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-α-D-glucofuranose (**23**). — Orthoester **10** (4.05 g, 10 mmoles) and 1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranose (6.50 g, 25 mmoles, m.p. ≥108°) were condensed in 100 ml of chlorobenzene in the presence of 0.10 mmole of 2,6-dimethylpyridinium perchlorate as described above. The mixture was evaporated, the residue was crystallised from ether (50 ml) and heptane (20 ml) to give **23** (2.15 g, 36%), m.p. 132–134°, $[\alpha]_D$ −21° (*c* 2.5, chloroform) (Found: C, 52.46; H, 6.54%; $C_{26}H_{38}O_{15}$ calc: C, 52.79; H, 6.43%).

Laminaribiose. — Compound **23** (0.40 g) was deacetylated with 0.1M methanolic sodium methoxide. Sodium ions were removed with a cation-exchange resin, the solution was evaporated, and the residue was dissolved in 0.5M sulphuric acid (3 ml). The solution was allowed to stand at room temperature overnight, neutralised with Amberlite IRA-400 (HCO_3^-) resin, and evaporated. Crystallisation of the residue from the minimal volume of aqueous methanol gave laminaribiose (0.14 g, 65%), m.p. 196–198°, $[\alpha]_D$ +15 (10 min) → +18.5° (24 h) (*c* 3.0, water); lit.[27] m.p. 198–201°, $[\alpha]_D$ +25 (20 min) → +18.6° (9 h) (water).

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