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Enolic Ortho Esters. VI*
A New 'Pyranose → Cyclohexane' Transformation via 1,6-Dideoxy-1,1-ethylenedioxy-2,3,4-tri-*O*-methyl-D-*xylo*-hex-5-enopyranose†

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Hydrolysis of methyl 6-chloro-6-deoxy-2,3,4-tri-*O*-methyl-α-D-glucopyranoside (19b) and Swern oxidation of the resulting anomeric hemiacetals (20) gave 6-chloro-6-deoxy-2,3,4-tri-*O*-methyl-D-glucono-1,5-lactone (21), treatment of which with 1,2-bis(trimethylsilyloxy)ethane in the presence of trimethylsilyl trifluoromethanesulfonate gave 6-chloro-1,6-dideoxy-1,1-ethylenedioxy-2,3,4-tri-*O*-methyl-D-glucopyranose (23a). Conversion of (23a) into the corresponding 6-iodo compound (23b) and treatment of this with 1,8-diazabicyclo[5.4.0]undec-7-ene afforded the enolic ortho ester 1,6-dideoxy-1,1-ethylenedioxy-2,3,4-tri-*O*-methyl-D-*xylo*-hex-5-enopyranose (26). Reaction of (26) with methylmagnesium iodide, or with titanium tetrachloride, gave (1*R*,6*S*,7*R*,8*R*,9*S*)-7,8,9-trimethoxy-6-methyl-2,5-dioxabicyclo[4.3.1]decan-1-ol (34), or (2*S*,3*R*,4*R*)-5,5-ethylenedioxy-2,3,4-trimethoxycyclohexanone (28), respectively.

Introduction

The concept of tandem nucleophilic/electrophilic addition to an enolic ortho ester was first demonstrated with the coumarin-derived enolic ortho ester (1a).[1] Reaction of (1a) with methylmagnesium iodide in benzene, Lewis acid-catalysed by magnesium iodide, effected methylation at the ortho ester carbon atom with generation of the iodomagnesium enolate (2); this was methylated *in situ* by addition of methyl iodide and dimethyl sulfoxide to give the dimethyl keto acetal (3).[2] Reduction of (1a) with lithium aluminium hydride (aluminium hydride-catalysed) and isomerization over alumina gave the keto acetal (4);[3] reaction of the related enolic ortho ester (1b) with ketene silyl acetals (5) in the presence of titanium tetrachloride gave the keto ester acetals (6).[4] These reactions (see Sheme 1), which proceed via aluminium or titanium enolates, respectively, have potential for tandem consummation with various electrophiles.

Enolic ortho esters of the general types (7) or (8) are potential sources of a range of polyoxygenated synthons. For example, hexose-derived enolic ortho esters (9a,b), having suitable ether protecting groups at C 2, C 3 and C 4, could undergo Lewis acid-catalysed reaction with a nucleophile (Nu^-), and reaction *in situ* of the resulting enolate with an electrophile (E^+) to give compounds (10a,b). Our eventual aim is to exploit the keto acetal system in compounds (10a) or (10b) in sequential regiospecific modifications of the virtual 1,5-dicarbonyl system, including cyclization reactions.

In this paper we describe an efficient synthesis of the glucose-derived enolic ortho ester (26), which reacted very readily with methylmagnesium iodide, but attempts to isolate the expected keto acetal (29) failed owing to the extraordinary ease with which the intermediate magnesium enolate (30) undergoes intramolecular attack on the 1-acetal group to give the cyclohexane derivative (34). Circumvention of this problem has yet to be achieved, but experiments led to our discovery that reaction of the enolic ortho ester (26) with Lewis acids under very mild conditions gives the cyclohexane keto acetal (28) in high yield. This new pyranose → cyclohexane conversion has synthetic potential.

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† It is an honour to dedicate this paper to Stephen Angyal in recognition of his contributions to chemical science.

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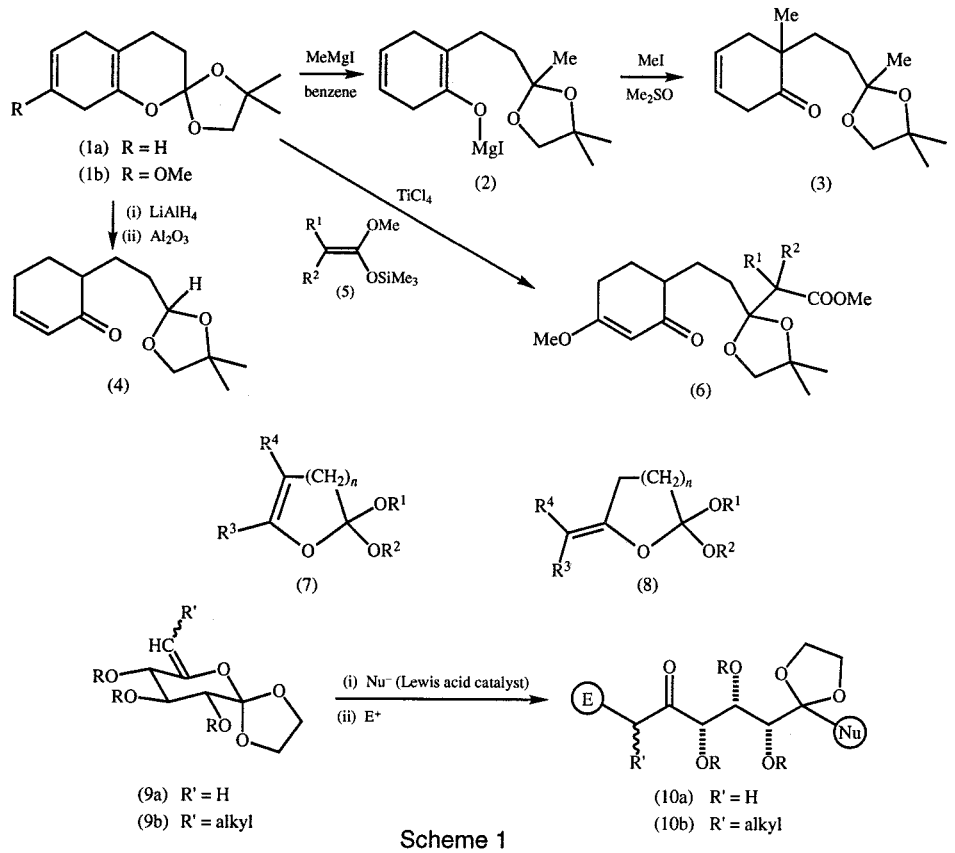
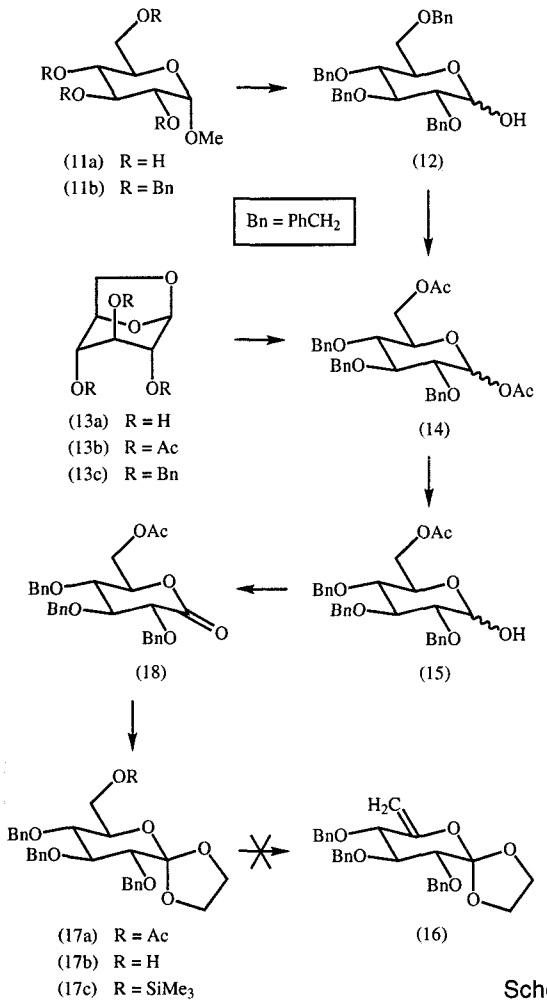


Scheme 1

Results and Discussion

The key requirements for the conversion of β-D-glucose into an enolic ortho ester of the type (9) are (i) relatively stable ether protecting groups at positions 2, 3 and 4, and (ii) a good leaving group at C6. The first goal was compound (16) (Scheme 2) because the benzyl ether groups would enable mild deprotection in subsequent transformation products. With acetoxy as a potential, though not ideal, leaving group at C6, compound (17a) was chosen as a possible progenitor of the enolic ortho ester (16). We initially prepared the intermediate 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose (14) from 1,6-anhydro-β-D-glucopyranose (13a).[5–9] In the procedure described by Zottola *et al.*[7] for the preparation of the anhydro sugar (13a) from glucose 6-tosylate, a pH of 9 was not high enough for effective deprotonation of the 1-hydroxy group and concomitant intramolecular displacement of the 6-tosylate group; at a pH of about 10 (Kloosterman *et al.*[8]), this reaction is more efficient. Acetolysis of the tribenzyl ether (13c) by means of acetic anhydride containing sulfuric acid to give compound (14)[5] was improved by the addition of sodium acetate to increase the concentration of acetate ion for nucleophilic attack on C1; the yield of (14) from (13c) was thereby increased to 93%. In spite of this, and a recent claim for improvement in the preparation of the anhydro sugar (13a) on a relatively large scale,[7] this route to compound (14) is time-consuming, and the overall yield from β-D-glucose was only about 16%. The 1,6-diacetate (14) was more efficiently prepared as follows. Benzylation of methyl α-D-glucopyranoside (11a) with benzyl chloride and potassium hydroxide in dioxan[9] gave the corresponding 2,3,4,6-tetrabenzyl ether (11b). Hydrolysis of (11b) to the anomeric hemiacetals (12) was carried out with 2 M trifluoromethanesulfonic acid in acetic acid, as described by Jansson *et al.*;[10] 2 M methanesulfonic acid was equally effective. Treatment of the 2,3,4,6-tetrabenzyl ether (12) with acetic anhydride containing a small amount of concentrated sulfuric acid as described by Eby *et al.*[11] gave the 1,6-diacetate (14) in 90% yield. The overall yield of (14) from (11a) was about 42%. Selective solvolysis of the 1,6-diacetate (14) by means of benzylamine (Horito *et al.*[12]) gave 89% of the anomeric 6-monoacetates (15), oxidation of which with pyridinium chlorochromate afforded 90% of the lactone (18). Reaction of the lactone (18) with 1,2-bis(trimethylsilyloxy)ethane in dichloromethane in the presence of trimethylsilyl trifluoromethanesulfonate (cf. Horito *et al.*[12]) gave, after flash chromatography, 55% of the ortho ester (17a). The ^{13}C n.m.r. spectrum of (17a) showed the ortho ester carbon atom at 119·5 ppm, the ethylenedioxy carbon atoms at 64·8 and 65·3 ppm, and the 6-acetoxy methyl group at 20·8 ppm. Two significant by-products which accompanied the



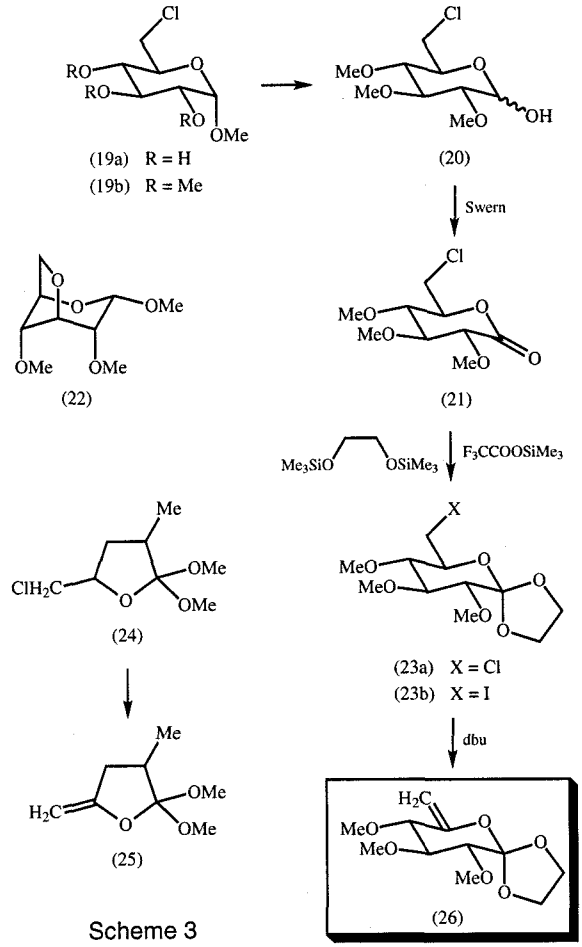
Scheme 2

formation of (17a) were the corresponding 6-hydroxy ortho ester (17b), and a less polar compound which was formulated as the 6-trimethylsilyloxy ortho ester (17c).

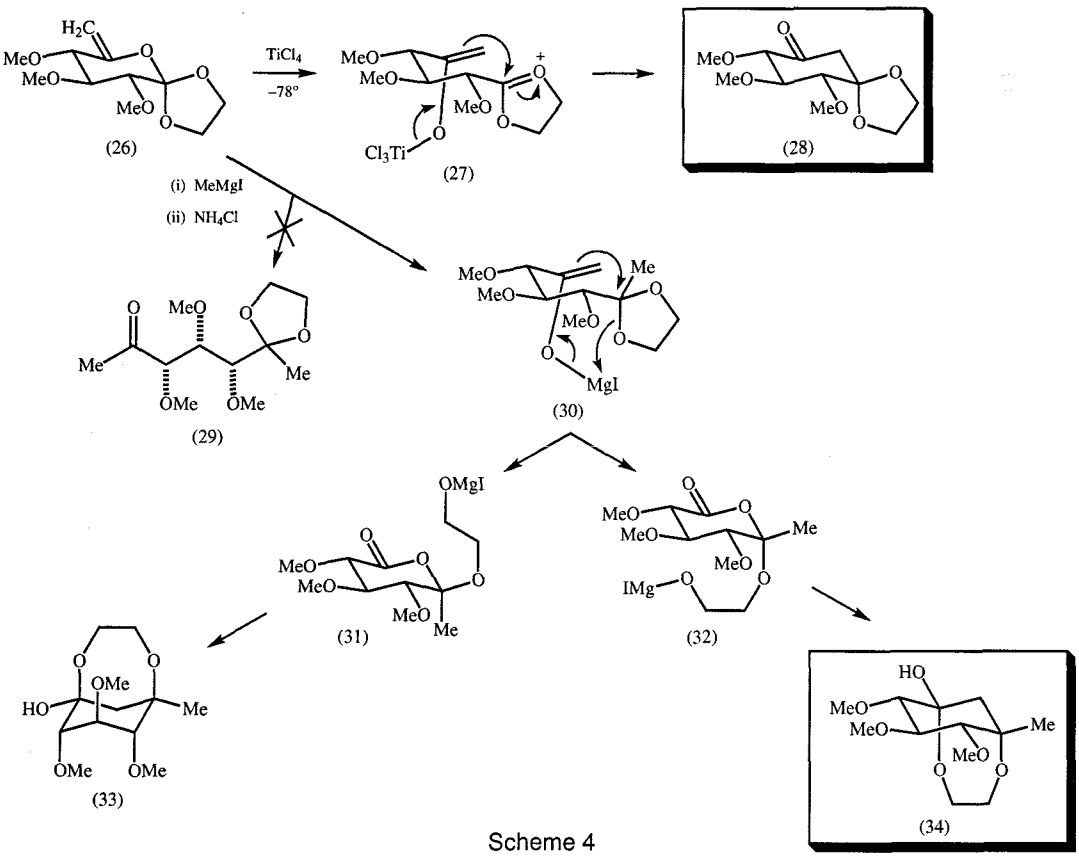
Flash vacuum pyrolysis of the acetoxy ortho ester (17a) at 400°/0·02 mm gave a complex mixture of products; the ^{1}H n.m.r. spectrum of this showed three acetate methyl signals at 2·05, 2·07 and 2·20 ppm, olefinic signals at about 5·5 and 6·4 ppm, weak signals between 7·2 and 8·1 ppm, and loss of benzyl ether group(s), but no signals corresponding to compound (16). No attempt was made to separate and identify the pyrolysis products. Pyrolysis of the 2,3,4-tri-*O*-methyl analogue of (17a) might have been more productive, but this approach was abandoned. Attempts to effect 1,2-elimination of acetic acid from the 6-acetoxy ortho ester (17a) by treatment with potassium t-butoxide gave only the 6-hydroxy compound (17b), formed during workup. If competitive deprotonation of the acetate methyl group was the main problem here, a non-enolate forming formate or benzoate group at C 6 might have facilitated the desired elimination reaction, but the observed susceptibility of the acetyl group at C 6 to displacement during conversion of the lactone (18) into the ortho ester (17a) made it desirable to have a different type of leaving group at C 6. Attention was therefore turned to synthesis of the 6-chloro ortho ester (23a), methyl ether groups being chosen for positions 2, 3 and 4, at least in the first instance, because of their high stability to reagents required in the synthetic sequence (Scheme 3).

Reaction of methyl α-D-glucopyranoside (11a) with triphenylphosphine/carbon tetrachloride in pyridine (Whistler *et al.*[13]), with modified workup for removal of the triphenylphosphine, gave 90% yield of the pure chloro compound (19a). This was converted into its 2,3,4-trimethyl ether (19b) in about 90% yield with sodium hydride/methyl iodide according to a modification of the procedure of Engdahl *et al.*[14] It was necessary to keep the reaction mixture at 20–30°; when the temperature was allowed to rise to 35–40°, a significant by-product was the 3,6-anhydro sugar (22), previously obtained by another route.[15]

Acid-catalysed hydrolysis of the 6-chloro-D-glucoside (19b) was appreciably slower than for the 6-*O*-methyl analogue of (19b);[14] reaction of (19b) with 2 M hydrochloric acid at reflux for 24 h gave 80% of a 70:30 α/β anomeric mixture of the hemiacetal (20). Repeated recrystallization from light petroleum gave the pure α-anomer of (20), the ^{1}H n.m.r. spectrum of which showed the anomeric proton at 5·34 ppm with a coupling constant of 3·6 Hz. Swern oxidation[16] of the epimeric mixture of hemiacetals (20) afforded the lactone (21) in 90% yield. The infrared spectrum of (21)



Scheme 3



Scheme 4

showed carbonyl absorption at 1763 cm^{-1}, and the ^{13}C n.m.r. spectrum showed C1 at 168 ppm. Treatment of the lactone (21) with 1,2-bis(trimethylsilyloxy)ethane and trimethylsilyl trifluoromethanesulfonate gave the ortho ester (23a) in 90% yield after crystallization. The ^{13}C n.m.r. spectrum of (23a) showed the ortho ester carbon atom (C1) at 119·4 ppm, and the ^{1}H n.m.r. spectrum showed a four-proton signal at 3·66–4·24 ppm for the ethylenedioxy group. Attempted elimination of hydrogen chloride from (23a) with potassium t-butoxide in ether for 3 h at room temperature, a procedure which was successful for the conversion of (24) into (25),[17] gave none of the enolic ortho ester (26). Treatment of (23a) with the same base in dimethyl sulfoxide at 70° for 3 h gave mainly starting material, together with 5% of (26); similar reactions in refluxing toluene or xylene containing 18-crown-6 for extended times were also unsuccessful. Attention was then turned to the corresponding iodo compound (23b). Treatment of (23a) with sodium iodide in acetone at reflux gave only 10% of the iodo compound (23b) after 72 h; a comparable reaction in refluxing butan-2-one afforded 30% of (23b). It required 7 days in refluxing pentan-3-one to achieve *c.* 95% conversion of (23a) into (23b).* Treatment of the pure iodo ortho ester (23b) with 1,8-diazabicyclo[5.4.0]undec-7-ene (dbu) in acetonitrile at 80–90° for 3 h gave 76% of the enolic ortho ester (26). The ^{1}H n.m.r. spectrum of (26) showed two doublets (*J* 1·5 Hz) at 4·82 and 4·92 ppm for the exocyclic methylene group. The ^{13}C n.m.r. spectrum showed signals for the exocyclic double bond at 155·0 (C5) and 96·0 ppm (C6), and a resonance at 120·5 ppm for the quaternary ortho ester carbon atom (C1).

The enolic ortho ester (26) reacted readily with methylmagnesium iodide in ether or in benzene, but the expected acyclic keto acetal (29) was not obtained; the product contained a *C*-methyl group, but lacked a keto group, and the ^{1}H and ^{13}C n.m.r. data were fully in accord with the bicyclic hemiacetal structure (34) (Scheme 4). Intramolecular attack of the iodomagnesium enolate group on the acetal function in (30) may generate the diastereomeric compounds (31) and/or (32); the latter can cyclize in the conformation shown (either before or after aqueous workup) to give the hemiacetal (34). The diastereomer (31) could only cyclize in the alternative chair conformation to give compound (33) in which all three of the methoxy groups are axial. Proof that the bicyclic hemiacetal has structure (34) follows from the fact that the coupling constants of 9·5, 9·6 and 9·8 Hz for the (vicinal) interactions between H7, H8 and H9 show that all three protons are axial. Examination of molecular models indicates that cyclization can only readily occur

* During exploratory studies, iodine was introduced at C6 at an earlier stage of the sequence but this led to troublesome side reactions during pyridinium chlorochromate oxidation of the hemiacetal to the lactone. This problem may not arise with the Swern oxidation which was subsequently found to be preferable for this step.

in that conformation of (30) in which the methyl group attached to the acetal carbon atom is oriented away from the enolate methylene, leading to diastereomer (32). Intramolecular attack of the iodomagnesium enolate on the acetal group in (30) was not expected under such mild conditions. It is probably mainly due to the fact that the enolate is a *primary* one. Another factor may be that transfer of *MgI* from the enolate to one of the acetal oxygen atoms may occur intramolecularly via the six-membered ring transition state implied in (30): but an intermolecular process, perhaps involving magnesium iodide, cannot be excluded. In addition to the high reactivity of the primary magnesium enolate, another facilitating factor in the intramolecular process (30) → (32) → (34) is probably the fact that all of the substituents at C 2, C 3 and C 4 in the progenitor (26) and the corresponding substituents in the final product (34) are equatorial. In this respect, it will be of interest to examine the reactivity of mannose- or galactose-derived diastereomers of the enolic ortho ester (26) with Grignard reagents; the axial oxygen functions at C 2 or C 4, respectively, should increase the energy of the transition state in the cyclization reactions analogous to (30) → (32).

Attempts to avoid intramolecular attack of the iodomagnesium enolate on the acetal group were unsuccessful—the mildest conditions for initial nucleophilic attack (MgI_2-assisted) on C 1 of (26) also resulted in the formation of the hemiacetal (34); none of the open-chain keto acetal (29) was detected in any of the crude products. Attempts to trap the iodomagnesium enolate as the trimethylsilyl enol ether gave a complex mixture. Lithium dimethylcuprate, and diethylcadmium failed to react with the enolic ortho ester (26). Treatment of (26) with methylcerium dichloride[18] in benzene at reflux gave starting material; dimethylcerium chloride and dimethyltitanium dichloride also failed to react with (26), but treatment of it with methyltitanium trichloride in ether at −78° for 3 h gave a mixture of starting material and the keto acetal (28). Not surprisingly, compound (26) was recovered unchanged after treatment with methyllithium in ether at room temperature for 4 h, but the same reagent in the presence of trimethysilyl triflate in toluene at −78 to −40° for 3 h also gave only starting material; a similar reaction mixture kept at room temperature for 2 h afforded the hemiacetal (34).

Treatment of the enolic ortho ester (26) with titanium tetrachloride in dichloromethane at −78° gave an almost quantitative yield of the keto acetal (28) which showed carbonyl absorption at 1732 cm^{-1}. The ^{13}C n.m.r. spectrum of (28) showed a signal for a keto group at 201·1 ppm, an acetal carbon atom at 106·8 ppm, methylene resonances at 66·2 and 68·8 ppm for the ethylenedioxy group, and the ring methylene group at 47·5 ppm. The ^1H n.m.r. spectrum was also consistent with structure (28). The conversion of (26) → (28) is a potentially useful transformation. The conversion of carbohydrates into cyclohexane and cyclopentane derivatives has been reviewed recently by Ferrier and Middleton.[19] The facile conversion of (26) into (28) is somewhat similar to the very useful Ferrier transformation (see ref. 19), but in our reaction C 1 of the sugar is at a higher oxidation level, opening up a different range of possible uses. The previously unknown keto acetal (28) preserves the asymmetry in what is potentially a *meso* β-diketone and it, or its analogues potentially derivable from other sugars, could be exploited by nucleophilic addition to the free keto group, and subsequent unmasking and manipulation of the other carbonyl group.

For convenience in this exploratory study, methyl ether protecting groups were used during development of the synthetic route to the enolic ortho ester (26). Under the conditions now used, we believe that the sequence could also be carried out with benzyl ether protecting groups to give compound (16) which would have more synthetic utility.

While a stratagem may yet be found for conversion of the enolic ortho ester (26) into the open-chain keto acetal (29), or compounds of the general structure (10) resulting from tandem nucleophilic/electrophilic addition reactions, current studies are focused on (i) the generation of 6-alkylated analogues of (26) [or (16)], the *secondary* magnesium enolates derivable from which should be less prone to intramolecular acetal cleavage, and (ii) the synthesis of galactose or mannose analogues of (16) in which the bulky axial benzyl ether group at C 4 or C 2, respectively, may favour formation of open-chain keto acetals analogous to (29).

Experimental

Melting points were determined with a Reichert microscope melting point apparatus and are uncorrected. Microanalyses were carried out by Chemical and Micro Analytical Services Pty Ltd. ^1H n.m.r. spectra were measured at 200 MHz on a Bruker AC-200 spectrometer or at 300 MHz on a Bruker AM-300 spectrometer. ^{13}C n.m.r. spectra were measured at 50·3 MHz with a Bruker AC-200 spectrometer. Chemical shifts (δ) for ^1H n.m.r. spectra were measured in ppm downfield from $SiMe_4$; for ^{13}C n.m.r. spectra, chemical shifts were measured with the specified solvent as reference. ^{13}C n.m.r. signals were determined to be due to methyl, methylene, methine or quaternary carbon atoms by using JMODXH and assignments were made accordingly. Mass spectra were obtained with a VG Micromass 7070 F spectrometer or a Hewlett–Packard VG TRIO-1 instrument, operating at 70 eV, with a source temperature of 200°. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. Analytical thin-layer chromatography (t.l.c.) was carried out on precoated plastic sheets, Polygram SIL G/UV_{254}. Silica gel 60 (230–400 mesh, Merck 9385) was used for flash chromatography. Light petroleum refers to the fraction of b.p. 67–70°.

(a) 2,3,4-Tri-O-acetyl-1,6-anhydro-β-D-glucopyranose (13b)

A solution of *p*-toluenesulfonyl chloride (159·0 g, 0·83 mol) in pyridine (300 ml) was added dropwise during 30 min to a stirred solution of β-D-glucopyranose (100 g, 0·55 mol) in pyridine (500 ml). The mixture was stirred for 90 min, then it was

made alkaline (pH 10) by the addition of 3 M sodium hydroxide (400 ml), and stirred for a further 90 min. Hydrochloric acid (3 M; 15–20 ml) was added to bring the pH to 7, then the solvent was removed under reduced pressure to give a pale brown gum. Residual pyridine was removed by azeotropic distillation with toluene (3×200 ml). The gum was dissolved in absolute ethanol (1 litre), and the solution was filtered through a Florisil pad (60–100 mesh) which was washed with absolute ethanol (*c.* 2 litres). The combined filtrate was evaporated under reduced pressure to give crude 1,6-anhydroglucopyranose (13a) as a brown gum. To a stirred solution of this in pyridine (700 ml), acetic anhydride (450 ml) was added dropwise during 1 h. Stirring was continued for an additional 3 h, then the solvent was removed under reduced pressure, and the dark viscous residue was dissolved in dichloromethane (1·5 litres), then washed with water (1·0 litre) and saturated sodium bicarbonate solution (1·0 litre). Evaporation of the dried (Na_2SO_4) extract, and trituration of the red/brown gum with absolute ethanol gave a solid, recrystallization of which from propan-2-ol gave 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (13b) (44·8 g, 28%), m.p. 108° (lit.[7] 108–110°). ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 2·12, 2·15 and 2·18, all s, 3×COMe; 3·82, dd, *J* 5·4, 7·7 Hz, H**6**,6; 4·17, d, *J* 8·1 Hz, H6,**6**; 4·61–4·65, overlapping d, H 2–4; 4·85–4·88, m, H 5; 5·47, s, H 1. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) 20·89, 20·99, 3×CO**M**e; 65·39, C 6; 69·19, 69·69, 70·37 and 73·80, 4×CH; 99·27, C 1; 169·07, 169·64 and 170·02, 3×**C**OMe.

*(b) 1,6-Anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (13c)*

A mixture of the triacetate (13b) (14·0 g, 48·61 mmol) and powdered potassium hydroxide (25·0 g, 0·45 mol) was added portionwise with stirring during 2 h to benzyl chloride (100 ml). The mixture was heated at 95° with vigorous stirring for 4 h, then cooled to room temperature and poured into water (150 ml). The mixture was extracted with dichloromethane (3×100 ml); the combined organic extract was washed with water (100 ml), and most of the benzyl chloride was removed by distillation under reduced pressure. The orange oil was steam-distilled to remove the remaining benzyl chloride, then the residue was cooled in ice to give an orange solid. Recrystallization from absolute ethanol gave 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (13c) (12·92 g, 62%) as pale brown microcrystals, m.p. 89–90° (lit.[5] 86–87°). ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 3·35, s, 2H; 3·59, s, 1H; 3·68, m, H**6**,6; 3·91, d, *J* 7·1 Hz, H6,**6**; 4·42, d, *J* 1·7 Hz, OC**H$_2$**Ph; 4·5–4·7, overlapping doublets for 2×OC**H$_2$**Ph and CH; 5·46, s, H 1; 7·22–7·34, m, aromatic H. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) 65·29, C 6; 71·06, 71·65 and 71·88, 3×O**C**H$_2$Ph; 74·27, 75·90, 76·00 and 76·65, 4×CH; 100·50, C 1; 127·64–128·37, overlapping signals for aromatic CH; 137·76 and 137·84, 3×quaternary aromatic C.

*(c) α- and β-Anomers of 1,6-Di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose (14)*[5]

Sodium acetate (0·40 g, 4·80 mmol) was added to a stirred suspension of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (13c) (2·00 g, 4·62 mmol) in acetic anhydride (10 ml) at 35°. Concentrated sulfuric acid (0·2 ml) was added and the reaction mixture was stirred for 3 min, then poured into water (500 ml), and stirred for 15 h. The product was extracted with diethyl ether (3×50 ml), and the combined extract was washed with saturated sodium bicarbonate, then with water, dried ($MgSO_4$) and evaporated to give a 3:1 α/β mixture of 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose (14) (2·30 g, 93%) as a pale yellow oil. ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 1·96, overlapping s, COMe (α- and β-anomers); 2·05, s, COMe (β-anomer); 2·11, s, COMe (α-anomer); 3·49–3·80, overlapping m; 3·90–4·05, overlapping m; 4·15–4·35, m; 4·54–5·08, overlapping m; 5·63, d, *J* 8·1 Hz, H 1 (β-anomer); 6·32, d, *J* 3·5 Hz, H 1 (α-anomer); 7·23–7·36, overlapping m. ^{13}C n.m.r., α-anomer, δ (50 MHz, $CDCl_3$) 20·63 and 20·87, 2×CO**M**e; 65·68, C 6; 70·93, CH; 73·03, 75·09 and 75·57, 3×O**C**H$_2$Ph; 76·39, 78·71, 81·47 and 89·48, 4×CH; 126·72–128·38, 15 overlapping aromatic CH; 137·35, 137·42 and 138·29, 3×quaternary aromatic C; 169·11 and 170·45, 2×**C**OMe. ^{13}C n.m.r., β-anomer, δ (50 MHz, $CDCl_3$) 20·63 and 20·87, 2×CO**M**e; 66·11, C 6; 73·57, CH; 74·85, 74·90 and 75·09, 3×O**C**H$_2$Ph; 80·89, 84·61 and 93·68, 3×CH; 126·72–128·37, overlapping aromatic CH; 137·47, 137·84 and 138·03, 3×quaternary aromatic C; 168·92 and 170·10, 2×**C**OMe.

*(d) Preparation of an Anomeric Mixture of 1,6-Di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose (14) from Methyl α-D-Glucopyranoside*

Methyl α-D-glucopyranoside (5·0 g, 26·0 mmol) was added to a stirred suspension of powdered potassium hydroxide (25·0 g) in 1,4-dioxan (20 ml), and benzyl chloride (10 ml) was added dropwise while the mixture was slowly heated to reflux with vigorous stirring. Additional benzyl chloride (20 ml) was added dropwise, then refluxing was continued for 2 h. Most of the solvent was distilled off during 3 h, and the concentrated mixture was poured into water (100 ml), and extracted with chloroform (3×100 ml). Evaporation of the washed, dried ($MgSO_4$) extract and removal of the residual benzyl chloride and benzyl alcohol in vacuum (0·5 mm) with vigorous stirring gave an anomeric mixture of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside as a brown oil. ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 3·34, s, OMe; 3·43–3·76, m, 5H; 3·96–4·05, m, 2H; 4·39–4·53, m, 2H; 4·56–4·68, m, 3H; 4·70–4·88, m, 2H; 4·92–5·06, m, 1H; 7·10–7·49, m, 20H, Ar. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) 55·1, OMe; 68·4, CH_2; 70·0, CH; 71·9, 73·2, 73·4 and 74·9, 3×O**C**H$_2$Ph; 77·8, 79·8, 82·0 and 98·1, 4×CH; 127·5–128·7, 20 aromatic C; 137·8, 138·2, 138·4 and 138·7, 4×quaternary aromatic C.

This oil was dissolved in glacial acetic acid (130 ml), and stirred vigorously while 2 M aqueous trifluoromethanesulfonic acid (26 ml) was added. The mixture was heated at 80° for 5 h then cooled to room temperature and extracted with dichloromethane (200 ml, total). The extract was washed with saturated sodium hydrogen carbonate solution (3×150 ml), dried (Na_2SO_4) and evaporated to give a pale brown solid. Recrystallization from propan-2-ol gave 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (12) (5·45 g, 80% as an approximately 6:4 mixture of the α/β anomers, respectively). ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 3·56–4·01, overlapping m; 4·44–4·98, overlapping m; 5·22, d, *J* 3·5 Hz, H 1 (α-anomer); 7·11–7·36, overlapping m. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) only the signals for the α-anomer were readily distinguishable: 68·6, C 6; 70·6, CH; 73·0, 73·4, 74·9 and 75·7, 4×O**C**H$_2$Ph; 77·7, 79·9 and 81·7, 3×CH; 91·1, C 1; 127·5–128·9, 20 aromatic C; 137·9, 138·2, 138·5 and 138·6, 4×quaternary aromatic C. In an analogous reaction in which methanesulfonic acid was used the yield of (12) was similar (75%).

To a solution of the anomeric mixture of the tetrabenzyl ether (12) (0·80 g, 1·48 mmol) in acetic anhydride (10 ml) was added a 2% solution of concentrated sulfuric acid in acetic anhydride (10 drops from a Pasteur pipette). The mixture was stirred at room temperature for 5 h then poured into water (100 ml), and stirred overnight. The product was extracted with dichloromethane (3×50 ml); the combined extract was washed with saturated sodium hydrogen carbonate solution (3×100 ml), water (3×100 ml), and dried (Na_2SO_4). Evaporation, and flash chromatography of the residue (SiO_2, initially light petroleum/ethyl acetate 9:1 followed by light petroleum/diethyl ether 2:3) gave an approximately 6·5:3·5 mixture of the α/β anomers of 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose (14) (0·73 g, 90%) as a colourless oil. The ^{1}H and ^{13}C n.m.r. spectra were similar to those given above in (*c*).

(e) α- and β-Anomers of 6-O-Acetyl-2,3,4-tri-O-benzyl-D-glucopyranose (15)[12]

A solution of the epimeric mixture of diacetates (14) (0·40 g, 0·76 mmol) in benzylamine (2·6 ml) was vigorously stirred at room temperature for 3 h. The mixture was poured into chloroform (20 ml), and washed with 3 M hydrochloric acid (3×20 ml). The extract was washed with water (50 ml), dried ($MgSO_4$) and evaporated. Flash chromatography (SiO_2, diethyl ether/light petroleum 3:2) gave a 60:40 α/β mixture of 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose (15) (0·34 g, 89%) as a colourless oil. ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 2·01, s, COMe (α-anomer); 2·04, s, COMe (β-anomer); 3·42–3·75, overlapping m; 3·85–5·00, overlapping m; 5·20, d, *J* 3·5 Hz, H1 (α-anomer); the signal for H1 of the β-anomer was not resolved (<5·0 ppm); 7·25–7·34, overlapping m. ^{13}C n.m.r., α-anomer, δ (50 MHz, $CDCl_3$) 21·26, COMe; 63·61, C6; 68·88, CH; 73·33, O**C**H_2Ph; 75·34, 2×O**C**H_2Ph; 79·42, 80·48 and 82·11, 3×CH; 91·33, C1; 127·34–130·18, 15 overlapping aromatic CH; 138·64, 138·88 and 138·99, 3×quaternary aromatic C; 171·38, **C**OMe. ^{13}C n.m.r., β-anomer, δ (50 MHz, $CDCl_3$) 21·41, COMe; 66·74, C6; 73·18, CH; 75·10, 2×O**C**H_2Ph; 77·67, O**C**H_2Ph; 83·54, CH; 85·02, 2×CH; 97·89, CH; 127·35–130·18, 15 overlapping aromatic CH; 138·17, 138·34 and 138·84, 3×quaternary aromatic C; 171·03, **C**OMe.

(f) 6-O-Acetyl-2,3,4-tri-O-benzyl-D-glucono-1,5-lactone (18)

Powdered pyridinium chlorochromate (0·39 g, 1·8 mmol) was added to a stirred solution of an anomeric mixture of 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose (15) (0·30 g, 0·60 mmol) in anhydrous dichloromethane (10 ml). The mixture was stirred at room temperature for 2 days by which time analytical t.l.c. (SiO_2, diethyl ether/light petroleum 3:2) indicated conversion of about half of the starting material. Additional pyridinium chlorochromate (0·39 g 1·8 mmol) was added and stirring was continued for another 2 days. Dry diethyl ether (50 ml) was added and the mixture was stirred, then decanted. The residue was washed with additional diethyl ether (3×20 ml), and the combined ether extract was filtered through a silica pad which was washed with additional ether (150 ml). Evaporation of the solvent and flash chromatography (SiO_2, diethyl ether/light petroleum 3:2) of the residue gave 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucono-1,5-lactone (18)[12] (0·27 g, 90%) as a colourless oil. ν_{max} (Nujol): 1745 cm^{-1}. ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 2·00, s, COMe; 3·78, dd, *J* 9·4, 5·4 Hz, 1H; 3·95, t, *J* 5·6 Hz, 1H; 4·13, d, *J* 4·9 Hz, 1H; 4·24–4·32, m, 2H; 4·46, d, *J* 6·7 Hz, 1H; 4·53, d, *J* 6·7 Hz, 1H; 4·60–4·70, m, 2×OC**H**$_2$Ph; 4·93, d, *J* 11·5 Hz, 1H; 7·20–7·39, m, 15 overlapping aromatic H. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) 20·74, COMe; 62·31, C6; 73·10, O**C**H_2Ph; 73·34, 2×O**C**H_2Ph; 75·50, 75·60, 76·71 and 80·85, 4×CH; 128·17–129·78, 15 aromatic CH; 136·52, 136·92 and 137·04, 3×quaternary aromatic C; 168·34, **C**OMe; 170·50, C1.

(g) 6-O-Acetyl-2,3,4-tri-O-benzyl-1-deoxy-1,1-ethylenedioxy-D-glucopyranose (17a)

A solution of trimethylsilyl trifluoromethanesulfonate (triflate) (0·1 ml) in dichloromethane (5 ml) was added to a stirred solution of the lactone (18) (0·10 g, 0·20 mmol) and 1,2-bis(trimethylsiloxy)ethane (0·08 ml, 0·31 mmol) in dichloromethane (10 ml) kept at 0°. The ice bath was removed and the mixture was stirred at room temperature for 2 h. Pyridine (0·1 ml) was added and the mixture was poured into saturated sodium bicarbonate solution (10 ml), and extracted with diethyl ether (3×20 ml). The extract was washed with water (3×20 ml), dried (K_2CO_3) and evaporated. The residue (0·12 g) was chromatographed over alumina (light petroleum/diethyl ether 1:1). The least polar component which was isolated was *2,3,4-tri-O-benzyl-1-deoxy-1,1-ethylenedioxy-6-O-trimethylsilyl-D-glucopyranose* (17c) (Found: M$^{+\bullet}$, 564·254±0·006. $C_{32}H_{40}O_7Si$ requires M$^{+\bullet}$, 564·254). ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 0·10–0·14, m, Me_3Si; 3·56–3·78, m, 6H; 4·00–4·22, m, 4H; 4·60–4·96, m, 6H; 7·23–7·37, m, 15 aromatic H. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) −0·40, CH_3Si; −0·20, CH_3Si; 0·03, CH_3Si; 61·71, C6; 64·69 and 65·01, OCH_2CH_2O; 74·05, CH; 74·84, 75·22 and 75·84, 3×O**C**H_2Ph; 77·39, 80·06 and 83·83, 3×CH; 119·58, C1; 127·59–128·38, 15 aromatic CH; 138·33, 138·46 and 138·70, 3×quaternary aromatic C.

The second component was *6-O-acetyl-2,3,4-tri-O-benzyl-1-deoxy-1,1-ethylenedioxy-D-glucopyranose* (17a) (0·06 g, 55%), obtained as a colourless oil, $[\alpha]_D$ +42·5° (*c*, 1·25 in chloroform) (Found: C, 69·4; H, 7·0%; M$^{+\bullet}$, 534·225±10·003. $C_{31}H_{34}O_8$ requires C, 69·7; H, 6·4%; M$^{+\bullet}$ 534·225). ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 2·01, s, OMe; 3·59–3·64, m, 1H; 3·72–3·91, m, 3H; 4·05–4·24, m, 7H; 4·56, d, *J* 10·9 Hz, 1H; 4·74–5·00, m, 2×OC**H**$_2$Ph; 7·21–7·36, m, 15 aromatic H. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) 20·89, COMe; 62·92, C6; 64·86 and 65·30, OCH_2CH_2O; 71·14, CH; 74·94, 75·24 and 75·83, 3×O**C**H_2Ph; 77·02, 79·80 and 83·72, 3×CH; 119·54, C1; 127·68–128·48, 15 aromatic CH; 137·78, 138·05 and 138·45, 3×quaternary aromatic C; 170·77, **C**OMe. Mass spectrum: *m/z* 534 (5%), 443 (25), 338 (10), 337 (40), 265 (13), 240 (12), 181 (10), 101 (18), 91 (100), 65 (10).

The third, and most polar, component was found to be *2,3,4-tri-O-benzyl-1-deoxy-1,1-ethylenedioxy-D-glucopyranose* (17b) which was obtained as an oil (Found: M$^{+\bullet}$, 492·215±0·003. $C_{29}H_{32}O_7$ requires M$^{+\bullet}$, 492·214). ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 3·66–3·95, m, 7H; 3·95–4·19, m, 4H; 4·62–4·93, m, 6H; 7·26–7·35, m, 15 aromatic H. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) 61·75, C6; 64·86 and 65·32, OCH_2CH_2O; 73·55, CH; 75·03, 75·27 and 75·77, 3×O**C**H_2Ph; 77·31, 79·93 and 83·59, 3×CH; 119·75, C1; 127·59–128·45, 15 aromatic CH; 138·04, 138·06 and 138·54, 3×quaternary aromatic C. Mass spectrum: *m/z* 492 (M, 0·1%), 401 (2), 295 (4), 240 (12), 101 (11), 91 (100), 65 (10).

(h) Attempted 1,2-Elimination of Acetic Acid from 6-O-Acetyl-2,3,4-tri-O-benzyl-1-deoxy-1,1-ethylenedioxy-D-glucopyranose (17a)

Compound (17a) (50·0 mg, 0·09 mmol) was added to a stirred solution of potassium t-butoxide (21·0 mg, 0·18 mmol) in t-butyl alcohol (5 ml) under dry nitrogen. The mixture was heated under reflux for 4 h, then poured into saturated aqueous sodium bicarbonate (20 ml), and extracted with diethyl ether (3×20 ml). The washed, dried (K_2CO_3) extract was evaporated under reduced pressure to give a pale yellow oil, the ^{1}H and ^{13}C n.m.r. spectra of which showed it to be 2,3,4-tri-*O*-benzyl-1-deoxy-1,1-ethylenedioxy-D-glucopyranose (17b), identical with the material described above in (*g*).

(i) Methyl 6-Chloro-6-deoxy-α-D-glucopyranoside (19a)

Methyl α-D-glucopyranoside (11a) (1·0 g, 5·2 mmol) was added to a solution of triphenylphosphine (3·0 g, 11·4 mmol) in pyridine (50 ml) at 0°. To this was added carbon tetrachloride (0·5 ml), and the mixture was heated at 65° for 1 h. Removal of the pyridine under reduced pressure gave a thick brown oil which was dissolved in chloroform (100 ml), and extracted with water (3×100 ml). Evaporation of the aqueous extract under reduced pressure gave a pale brown oil, which upon flash chromatography (SiO_2, ethyl acetate) afforded methyl 6-chloro-6-deoxy-α-D-glucopyranoside (19a) (0·98 g, 90%) as a white powder, m.p. 111° (lit.[20] 112–113°). ^{1}H n.m.r. δ [200 MHz, $(CD_3)_2SO$] 3·11, t, *J* 9·1 Hz, 1H; 3·24, dd, *J* 9·6, 3·6 Hz, 1H; 3·28, s, OMe; 3·43, t, *J* 8·9 Hz, 1H; 3·48–3·57, m, 1H; 3·68, dd, *J* 11·5, 6·3 Hz, 1H; 3·88, dd, *J* 11·5, 2·1 Hz, 1H; 4·56, d, *J* 3·5 Hz, H1. ^{13}C n.m.r. δ (50 MHz, $(CD_3)_2SO$] 45·84, C6; 54·99, OMe; 71·66, 2×CH; 72·27 and 73·71, 2×CH; 100·17, C1.

*(j) Methyl 6-Chloro-6-deoxy-2,3,4-tri-*O*-methyl-α-*D*-glucopyranoside (19b)*

Methyl 6-chloro-6-deoxy-α-D-glucopyranoside (19a) (1·0 g, 4·7 mmol) was added to a cooled (15–20°) solution of sodium hydride (0·98 g, 33·0 mmol; 80% dispersion in mineral oil, washed with light petroleum) in dimethyl sulfoxide (30 ml) under dry nitrogen. This mixture was stirred at 20–30° for 30 min, then methyl iodide (4·67 g, 32·9 mmol) was added dropwise with cooling to maintain the temperature at 20–30°. The mixture was stirred overnight at room temperature, then it was cooled to 10° and glacial acetic acid was added carefully with stirring to quench the excess of sodium hydride. The mixture was poured into water, and extracted with dichloromethane (3×100 ml). The combined extract was washed with water (3×250 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a brown oil. Flash chromatography of this (SiO_2, diethyl ether/light petroleum 1:3 followed by diethyl ether/light petroleum 4:1) gave methyl 6-chloro-6-deoxy-2,3,4-tri-*O*-methyl-α-D-glucopyranoside (19b) (1·1 g, 90%) as colourless crystals, m.p. 60–61° (lit.[14] 62–64°). ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 3·20, m, H4; 3·24, d, *J* 3·5 Hz, H2; 3·43, s, OMe; 3·51, m, H3; 3·52, 3·58 and 3·62, all s, 3×OMe; 3·68–3·72, m, H5; 3·76–3·79, m, H6,6; 4·84, d, *J* 3·5 Hz, H1. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) 44·31, C6; 54·96, 58·69, 60·35 and 60·53, 4×OMe; 69·50, C5; 79·84, C4; 81·41, C2; 83·10, C3; 97·21, C1.

In other runs in which the temperature was allowed to rise above 35–40°, flash chromatography (SiO_2, diethyl ether/light petroleum 1:3 followed by diethyl ether/light petroleum 4:1) gave a by-product identified as methyl 3,6-anhydro-1,2,4-tri-*O*-methyl-D-glucopyranoside (22), m.p. 62° (lit.[21] 66°). ν_{max} (Nujol) 1228w, 1212m, 1193m, 1167m, 1150m, 1120s, 1096w, 1063s, 1040s, 1020s, 990m, 958w, 914m, 904s, 814m, 721w cm^{-1}. ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 3·44–3·48, m, H2; 3·48, 3·52 and 3·57, all s, 3×OMe; 3·68, dd, *J* 5·1, 2·5 Hz, H4; 3·95, dd, *J* 10·5, 3·0 Hz, H**6**,6; 4·19, d, *J* 10·5 Hz, H6,**6**; 4·38–4·45, m, H3,5; 4·98, d, *J* 3·1 Hz, H1. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) 57·4, 58·5 and 61·2, 3×OMe; 68·7, C6; 71·5, C3; 72·3, C5; 78·7, C2; 79·3, C4; 98·8, C1. Mass spectrum: *m/z* 113 (11%), 101 (65), 88 (13), 75 (34), 71 (100), 53 (6).

*(k) 6-Chloro-6-deoxy-2,3,4-tri-*O*-methyl-α-*D*-glucopyranose (20)*

Methyl 6-chloro-6-deoxy-2,3,4-tri-*O*-methyl-α-D-glucopyranoside (19b) (0·4 g, 1·5 mmol) was heated in refluxing 2 M hydrochloric acid (15 ml) for 6–7 h with constant stirring. The mixture was cooled to room temperature, poured into saturated sodium bicarbonate solution (50 ml), and then extracted with dichloromethane (3×50 ml). The extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a colourless oil. Flash chromatography (SiO_2, diethyl ether/light petroleum/methanol 1:1:0·1) gave an anomeric mixture of (20) (0·30 g, 80%) which was used directly in the next step. Six successive recrystallizations of a sample from light petroleum gave the pure α-anomer, *6-chloro-6-deoxy-2,3,4-tri-*O*-methyl-α-*D*-glucopyranose*, m.p. 103–104°, $[\alpha]_D$ +119·3° (*c*, 1·1 in chloroform) (Found: C, 44·9; H, 7·3. $C_9H_{17}ClO_5$ requires C, 44·9; H, 7·1%). ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 2·98, br s, OH (exch.); 3·18–3·27, m, 2H; 3·53 and 3·59, both s, 2×OMe; 3·63, overlapping CH and OMe; 3·81, dd, *J* 3·2, 1·6 Hz, 2H; 3·96–4·03, m, 1H; 5·34, d, *J* 3·6 Hz, H1. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) 44·61, C6; 58·75, 60·56 and 60·77, 3×OMe; 69·45, C5; 79·78, C4; 81·66, C2; 82·83, C3; 90·42, C1. Subtraction of these values from the spectrum of a mixture gave for the β-anomer: ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) 43·99, C6; 60·42, 60·52 and 60·67, 3×OMe; 73·96, 79·78, 84·48 and 86·04, 4×CH; 96·85, C1.

*(l) 6-Chloro-6-deoxy-2,3,4-tri-*O*-methyl-*D*-glucono-1,5-lactone (21)*

Dimethyl sulfoxide (1·42 ml, 19·7 mmol) in dichloromethane (24 ml) was added dropwise during 5 min to a stirred solution of oxalyl chloride (1·2 ml, 13·0 mmol) in dichloromethane (60 ml) kept at −60°. The reaction mixture was stirred for 15–20 min at −60°, then a solution of the hemiacetal (20) (2·48 g, 103 mmol) in dichloromethane (60 ml) was added dropwise during 15 min. Stirring was continued for 40 min, then triethylamine (4·3 ml) was added dropwise during 5 min. The mixture was stirred for 15 min, then the cooling bath was removed and it was allowed to warm up to room temperature. Water (50 ml) was added and the mixture was stirred vigorously for 10 min. The aqueous layer was extracted with dichloromethane (2×100 ml), and the combined dichloromethane extract was washed with water (100 ml), dried ($MgSO_4$) and evaporated in vacuum. Recrystallization of the residue from absolute ethanol gave *6-chloro-6-deoxy-2,3,4-tri-*O*-methyl-*D*-glucono-1,5-lactone* (21) (2·21 g, 90%) as long colourless needles, m.p. 70–71°, $[\alpha]_D$ +110·8° (*c*, 1·0 in chloroform) (Found: C, 45·2; H, 6·2. $C_9H_{15}ClO_5$ requires C, 45·4; H, 6·3%). ν_{max} (Nujol) 3130s, 2995s, 2834m, 1763s, 1460m, 1399s, 1192s, 1094s, 995m, 841m, 744m, 679w, 615w, 499w, 428w cm^{-1}. ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 3·51 and 3·53, both s, 2×OMe; 3·54, m, 1H; 3·55, s, OMe; 3·56–3·59, m, 1H; 3·79–3·83, m, 3H; 4·51–4·56, m, 1H. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) 43·60, C6; 58·71, OMe; 59·38, 2×OMe; 76·37, 78·11, 79·50 and 82·55, 4×CH; 168·07, C1. Mass spectrum: *m/z* 288 (1%), 149 (95), 101 (34), 89 (8), 88 (100), 75 (75), 73 (37), 72 (44), 71 (50), 59 (7), 53 (8).

*(m) 6-Chloro-1,6-dideoxy-1,1-ethylenedioxy-2,3,4-tri-*O*-methyl-*D*-glucopyranose (23a)*

Trimethylsilyl triflate (0·1 ml) was added to a stirred solution of 1,2-bis(trimethylsilyloxy)ethane (1·5 ml, 0·62 mmol) and the lactone (21) (1·5 g, 6·3 mmol) in dichloromethane (30 ml) at 0° under dry nitrogen. The mixture was allowed to warm up to room temperature, then stirred for 4 h. After the addition of pyridine (2·8 ml) the mixture was poured into saturated sodium bicarbonate solution (100 ml), and extracted with diethyl ether (3×50 ml). The extract was washed with water, dried (K_2CO_3), and evaporated to give a pale yellow oil which solidified. Recrystallization from absolute ethanol gave *6-chloro-1,6-dideoxy-1,1-ethylenedioxy-2,3,4-tri-*O*-methyl-*D*-glucopyranose* (23a) (1·65 g, 92%) as colourless crystals, m.p. 83–84°, $[\alpha]_D$ +68·3° (*c*, 1·0 in chloroform) (Found: C, 46·8; H, 6·8. $C_8H_{19}ClO_6$ requires C, 46·7; H, 6·8%). ν_{max} (Nujol) 3129s, 2995m, 2838m, 1638m, 1618m, 1472w, 1399s, 1307w, 1271w, 1226w, 1127m, 1130m, 1092s, 1052m, 1025s, 990w, 952w, 930w, 822m, 755m, 670m, 620m, 478m cm^{-1}. ^{1}H n.m.r. δ [200 MHz, (D_6)benzene] 3·20–3·45, m, 3H; 3·58, 3·60 and 3·64, all s, 3×OMe; 3·66–3·79, m, 3H; 4·01–4·24, m, 4H. ^{13}C n.m.r. δ [50 MHz, (D_6)benzene] 45·20, C6; 60·49, 60·61 and 60·73, 3×OMe; 65·17 and 65·36, OCH_2CH_2O; 72·96, 80·58, 82·24 and 85·92, 4×CH; 119·94, C1. Mass spectrum: *m/z* 116 (17%), 101 (21), 89 (6), 88 (100), 75 (7), 73 (14), 71 (13).

*(n) 1,6-Dideoxy-1,1-ethylenedioxy-6-iodo-2,3,4-tri-*O*-methyl-*D*-glucopyranose (23b)*

A stirred solution of the 6-chloro ortho ester (23a) (0·1 g, 0·35 mmol) in pentan-3-one (10 ml) containing sodium iodide (0·26 g, 1·77 mmol) was heated under reflux for 7 days. Ether (50 ml) was added and the solution was washed with water (50 ml). The aqueous layer was reextracted with diethyl ether (3×30 ml), and the combined reextract was dried (K_2CO_3) and evaporated to give a pale yellow solid. The ^{13}C n.m.r. spectrum of this showed that only about 5% of starting material was present. Purification by flash chromatography (alumina, diethyl ether/light petroleum 2:1) followed by recrystallization

from ethanol gave *1,6-dideoxy-1,1-ethylenedioxy-6-iodo-2,3,4-tri-O-methyl-D-glucopyranose* (23b) (0·11 g, 83%) as colourless crystals, m.p. 68·5–70°, $[\alpha]_D$ +56·9° (*c*, 1·05 in chloroform) (Found: C, 35·6; H, 5·2. $C_{11}H_{19}IO_6$ requires C, 35·3; H, 5·1%). ^{1}H n.m.r. δ [200 MHz, (D_6)benzene] 3·03, dd, *J* 9·4, 8·7 Hz, 1H; 3·15, dd, *J* 10·5, 6·9 Hz, 1H; 3·35, dd, *J* 10·5, 2·5 Hz, 1H; 3·41, 3·49 and 3·52, all s, 3×OMe; 3·40–3·90, overlapping m for 6H, including OCH_2CH_2O. ^{13}C n.m.r. δ [50 MHz, (D_6)benzene] 7·35, C6; 60·42, 60·63 and 60·70, 3×OMe; 64·57 and 64·75, OCH_2CH_2O; 72·65, 82·23, 83·70 and 85·64, 4×CH; 119·78, C1. Mass spectrum: *m/z* (no parent molecular ion) 336 (20%), 255 (40), 215 (10), 197 (13), 185 (30), 184 (15), 171 (21), 159 (20), 127 (20), 116 (70), 101 (75), 88 (100), 86 (10), 75 (12), 73 (20), 71 (95), 55 (10).

(o) 1,6-Dideoxy-1,1-ethylenedioxy-2,3,4-tri-O-methyl-D-xylo-hex-5-enopyranose (26)

1,8-Diazabicyclo[5.4.0]undec-7-ene (0·1 ml, 0·66 mmol) was added to a stirred solution of the iodo ortho ester (23b) (60 mg, 0·16 mmol) in acetonitrile (5 ml). The mixture was stirred at 80–90° for 3 h under nitrogen, and then poured into saturated sodium bicarbonate solution (30 ml), and extracted with diethyl ether (3×40 ml). The extract was washed with water (3×100 ml), dried (K_2CO_3) and evaporated under reduced pressure to give a pale brown oil. Bulb-to-bulb distillation (oven temperature 100–105°/0·5 mm) gave pure *1,6-dideoxy-1,1-ethylenedioxy-2,3,4-tri-O-methyl-D-xylo-hex-5-enopyranose* (26) (30 mg, 76%) as a colourless oil, $[\alpha]_D$ +14·2° (*c*, 1·0 in chloroform) (Found: C, 53·7; H, 7·9. $C_{11}H_{18}O_6$ requires C, 53·7; H, 7·4%). ν_{max} (film) 3372w, 2936s, 2906s, 2837s, 1695m, 1666s, 1467m, 1446m, 1373m, 1316m, 1290m, 1271m, 1183s, 1094s, 1028s, 994s, 964s, 865m, 831w, 757s, 682w, 666w cm^{-1}. ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 3·33, s, OMe; 3·47, m, 1H; 3·51 and 3·52, both s, 2×OMe; 3·53–3·76, m, 7H; 4·82, d, *J* 1·5 Hz, H**6**,6; 4·92, d, *J* 1·5 Hz, H6,**6**. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) 59·68, 60·70 and 60·76, 3×OMe; 64·86 and 65·17, OCH_2CH_2O; 82·07, 82·15 and 84·34, 3×CH; 95·97, C6; 120·46, C1; 154·09, C5. Mass spectrum: *m/z* 246 (7%), 199 (10), 159 (100), 158 (11), 151 (12), 143 (11), 123 (15), 116 (75), 103 (35), 101 (92), 97 (12), 88 (38), 85 (25), 73 (15), 71 (19), 69 (21), 57 (23), 55 (28).

(p) Reaction of the Enolic Ortho Ester (26) with Methylmagnesium Iodide

An ether solution of methylmagnesium iodide prepared from magnesium (0·022 g, 0·90 mmol) was evaporated under nitrogen, and benzene (5 ml) was added. To this stirred mixture, at room temperature, was added dropwise during 5 min a solution of the enolic ortho ester (26) (0·11 g, 0·45 mmol) in benzene (5 ml). The mixture was stirred for 2 h under reflux, then cooled to 0° and quenched by dropwise addition of saturated aqueous ammonium chloride (10 ml). The mixture was poured into saturated aqueous sodium bicarbonate, and extracted with dichloromethane (3×50 ml). The extract was washed with water, dried (K_2CO_3) and evaporated to give an oil. Bulb-to-bulb distillation (oven temperature 115°/0·5 mm) gave pure *(1R,6S,7R,8R,9S)-7,8,9-trimethoxy-6-methyl-2,5-dioxabicyclo[4.3.1]decan-1-ol* (34) as a colourless oil, $[\alpha]_D$ +3·4° (*c*, 1·7 in chloroform) (Found: C, 55·0; H, 8·5. $C_{12}H_{22}O_6$ requires C, 55·0; H, 8·5%). ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 1·25, s, Me; 1·73, AB system, *J* 14·7 Hz, H10,10; 2·82, d, *J* 9·5 Hz, CH; 3·14, d, *J* 9·8 Hz, CH; 3·42, t, *J* 9·6 Hz, H8; 3·61, 3·64 and 3·65, all s, 3×OMe, overlapped by OH (exch.); 3·93–4·10, m, 3H, and 4·10–4·25, m, 1H, OCH_2CH_2O. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) 26·14, Me; 42·69, C10; 61·13, 61·64 and 61·99, 3×OMe; 65·22 and 66·56, OCH_2CH_2O; 71·36, C6; 84·42, 86·53 and 87·86, C7–9; 109·19, C1. Mass spectrum: *m/z* 214 (20%), 177 (20), 170 (11), 155 (50), 149 (35), 143 (57), 141 (20), 129 (100), 101 (20), 87 (23); the parent molecular ion was not observed.

*(q) (2S,3R,4R)-5,5-Ethylenedioxy-2,3,4-trimethoxycyclohexanone (28)**

Titanium tetrachloride (0·15 ml, 1·3 mmol) was added dropwise to a stirred solution of the enolic ortho ester (26) (110 mg, 0·45 mmol) in benzene (2 ml) and dry ether (8 ml) at −78°. The solution was stirred at −78° for 1 h, then it was quenched by pouring it into a saturated sodium hydrogen carbonate solution (10 ml). The mixture was filtered through a pad of Celite which was washed with several portions of dichloromethane (100 ml, total). The aqueous phase of the filtrate was again extracted with dichloromethane, and the combined extract was washed with water, dried (K_2CO_3) and evaporated to give an oil (100 mg). Bulb-to-bulb distillation (oven temperature 105°/0·5 mm) gave *(2S,3R,4R)-5,5-ethylenedioxy-2,3,4-trimethoxycyclohexanone* (28) as a colourless oil (85 mg, 77%), $[\alpha]_D$ +0·47° (*c*, 1·7 in chloroform) (Found: C, 53·2; H, 7·7. $C_{11}H_{18}O_6$ requires C, 53·6; H 7·4%). ν_{max} (film) 2935s, 2836s, 1732s, 1660s, 1446s, 1366m, 1287s, 1124s, 952s, 814m, 754m, 694w, 649m cm^{-1}. ^{1}H n.m.r. δ (200 MHz, $CDCl_3$) 2·44, d, and 2·65, d (A–B system), *J* 14·1 Hz, H6,6; 3·28–3·45, m, 2H; 3·46, 3·55 and 3·58, all s, 3×OMe; 3·73, d, *J* 4·3 Hz, 1H; 3·90–4·18, overlapping m, 4H. ^{13}C n.m.r. δ (50 MHz, $CDCl_3$) 47·5, C6; 59·5, 60·9 and 61·4, 3×OMe; 66·2, 68·8, OCH_2CH_2O; 82·9, 85·7 and 87·8, 3×CH; 106·8, C5; 201·1, C1. Mass spectrum: *m/z* 246 (M, 2%), 215 (15), 214 (70), 212 (15), 199 (45), 187 (20), 173 (50), 171 (48), 158 (65), 143 (50), 115 (18), 113 (22), 101 (100), 88 (11), 86 (23), 85 (25). The crude product (100 mg, 91%) was shown by n.m.r. spectroscopy to be essentially pure keto acetal (28).

(r) Treatment of the Enolic Ortho Ester (26) with Methyltitanium Trichloride

An ether solution of methyllithium (1·2 M, 0·62 ml, 0·7 mmol) was added to a solution of titanium tetrachloride (0·07 ml, 0·67 mmol) in dry ether (10 ml) at −78°. The mixture was stirred for 30 min, then a solution of the enolic ortho ester (26) (0·11 g, 0·45 mmol) in dry ether (10 ml) was added. The mixture was stirred at −78° for 3 h, then allowed to warm up to room temperature and quenched by the addition of saturated aqueous sodium hydrogen carbonate (15 ml). The product was extracted with dichloromethane (3×50 ml), and the extract was washed with water, dried (K_2CO_3) and evaporated to give a pale yellow oil (94 mg). The ^{1}H and ^{13}C n.m.r. spectra of this showed it to be a mixture of starting material and the keto acetal (28) in the approximate ratio of 3:2.

A similar experiment with dimethyltitanium dichloride gave only starting material.

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