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A new method of orthoesterification, under kinetic control, at non-anomeric positions. Application to the D-glucose and D-mannose series and selective hydrolysis of the corresponding orthoesters ☆

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Abstract

The reaction of ketene acetals with D-glucose, D-mannose, and their methyl glycosides is described as a new route to unusual cyclic orthoesters (at non anomeric positions). The reaction proceeds by preferential attack of the reagent on the primary hydroxyl group. The synthesis of strained rings (2,3-diequatorial orthoester) is possible. The resulting methoxyethylidene derivatives are very sensitive to hydrolysis, and mild conditions lead to hydroxyacetates that are potentially useful intermediates for carbohydrates synthesis.

Keywords: Orthoester; Orthoesterification; Ketene acetal; D-Hexose; Methyl D-hexopyranoside

Introduction

The success realized in the reactions using vinyl ethers as acetonation reagents for sugars under kinetic control [1,2] suggested that the use of ketene acetals would lead to orthoesters under kinetically controlled conditions, thus favouring an attack at primary hydroxyl groups and at the non-anomeric position.

☆ This work has been partly presented in the Thesis of M.B. (Clermont–Ferrand No. 7, 1985).

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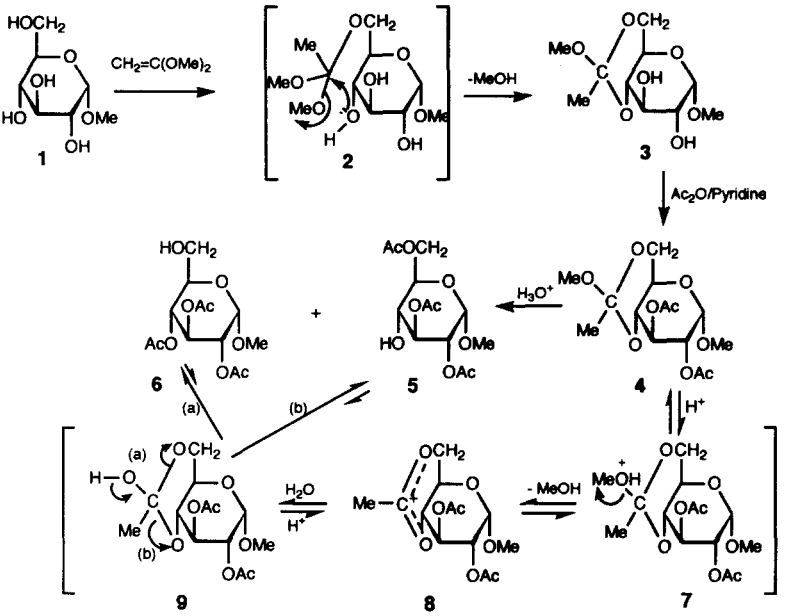
This paper is concerned with the use of 1,1-dimethoxyethene [3] as an orthoesterification reagent for sugars and the selective hydrolysis of the corresponding orthoesters.

2. Results and discussion

Treatment of methyl α-D-glucopyranoside (**1**) in *N*,*N*-dimethylformamide with twice the stoichiometric amount of 1,1-dimethoxyethene and a trace of *p*-toluenesulfonic acid gave in excellent yield (more than 80%, after purification by column chromatography) pure methyl 4,6-*O*-methoxyethylidene-α-D-glucopyranoside (**3**), identified by NMR spectroscopy. The ^{1}H NMR spectrum in Me_2SO-d_6 showed signals for the C-methyl and O-methyl groups of the orthoester group and exchangeable doublets for two hydroxyl groups. Lack of a triplet signal for one of the hydroxyl groups established that the primary hydroxyl group was involved in the orthoester substitution. For different fractions of compound **3**, isolated by column chromatography, it was possible to observe in the ^{1}H and ^{13}C NMR spectra signals that indicated the presence of the two diastereoisomers at the orthoester carbon (ratio 70:30 to 99:1).

Acid-catalysed opening of five-membered ring orthoesters of pyranosides is rather well explored. It is used in synthetic pathways [4,5] and leads almost exclusively to the compound with an axial acyl group, while alternatives for a regioselective monoesterification of α-diols gives mixtures of esters [6,7]. Opening of six-membered ring orthoesters is far less well investigated. Thus, the orthoester **4** was treated with a mixture of water and chloroform in the presence of *p*-toluenesulfonic acid and gave a mixture of two compounds (TLC) in high yield. Chromatographic separation of the mixture on a silica gel column gave successively the pure 2,3,6-tri-*O*-acetyl derivative **5** (60% yield) and its 2,3,4-tri-*O*-acetyl isomer **6** (30%), both of which were identified by NMR spectroscopy and compared with values reported in the literature [8,9]. The partial hydrolysis of the diacetate **4** was assumed to proceed through the protonation of the methoxyl group (**7**), leading to the dioxocarbenium ion **8** and the orthoacid **9**, according to a mechanism generally proposed [10] (Scheme 1).

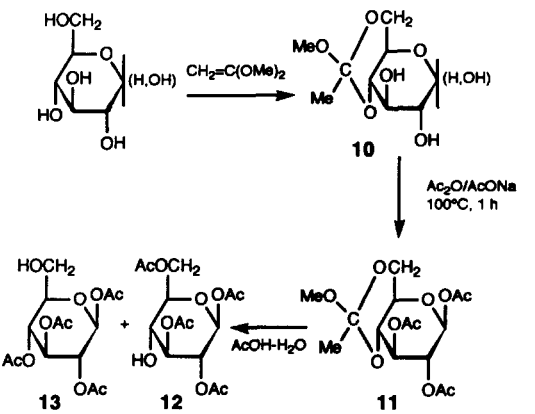
We then tested the capacity of ketene acetals for the orthoesterification of unprotected free sugars under kinetic control to obtain products having a mode of substitution different from that of the compounds obtained by orthoesterification controlled under classical thermodynamic conditions [11–14]. Thus, under conditions similar to those used for kinetic orthoesterification of **1**, the reaction of D-glucose with 1,1-dimethoxyethene (Scheme 2) gave quantitatively the 4,6-*O*-methoxyethylidene-D-glucopyranose (**10**), which was isolated after acetylation in 77% yield (after purification) as a syrup identified as the β anomer of triacetate **11** (NMR spectroscopy). In chloroform, the H-1 signal appeared as a wide doublet at low field (5.68 ppm; $J_{1,2}$ 8.5 Hz), and H-2 and H-3 appeared as wide doublets that resonated substantially downfield from the remaining protons, as anticipated for ring protons at positions substituted by acetoxyl groups (5.50 ppm; $J_{2,3} = J_{3,4} = 9$ Hz). Two singlets (1.43 and 3.26 ppm) corresponded respectively to the C-methyl and O-methyl groups of the orthoester function. The structures of orthoesters **10** and **11** were also consistent with their mass spectra. Selective hydrolysis of **11** was satisfactorily accomplished by use if 1:3 acetic acid–



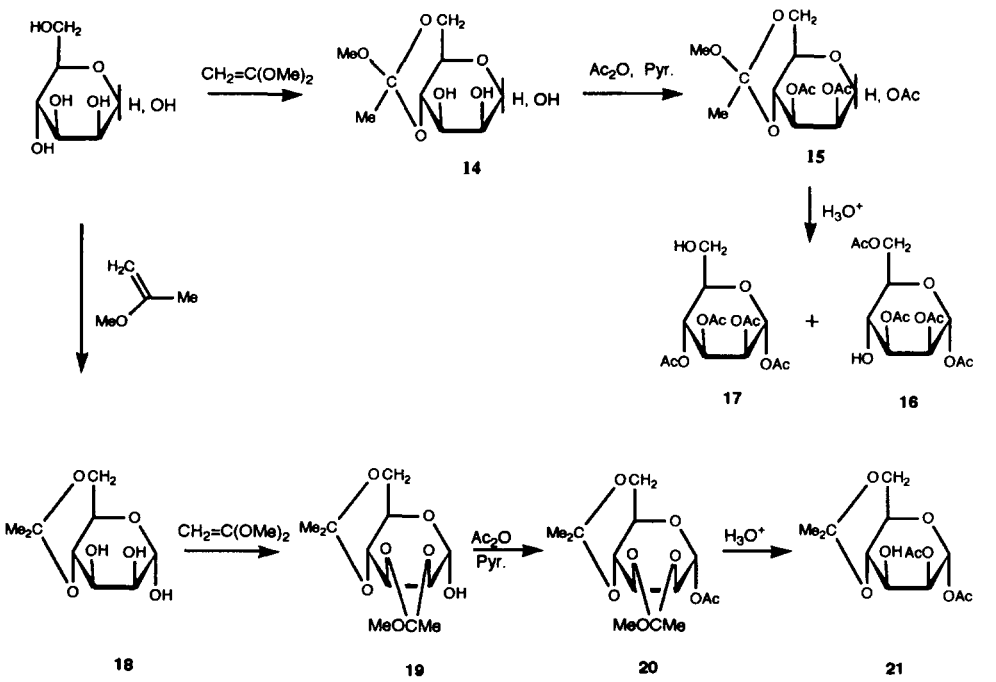
Scheme 1.

water. The 4,6-*O*-methoxyethylidene group was quantitatively removed, and a mixture of regioisomers was obtained and separated by column chromatography to afford two crystalline compounds that were identified as 1,2,3,6-tetra-*O*-acetyl-β-D-glucopyranose (**12**) (55% yield) and 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (**13**) (30% yield) by NMR spectroscopy and by comparison with the values reported in the literature [15,16].

The absence of competition between the anomeric hydroxyl group and the OH-6 in the addition of ketene acetal was confirmed by the orthoesterification of D-mannose



Scheme 2.



Scheme 3.

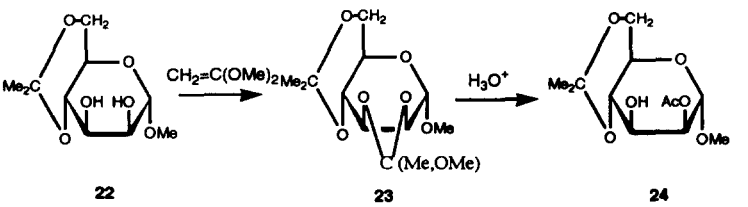
under kinetic control. Thus, treatment of D-mannose with 1,1-dimethoxyethene by the procedure used for **1** led (Scheme 3) to 4,6-*O*-methoxyethylidene-D-mannopyranose (**14**) (isolated in 60% yield after purification). The ^{1}H NMR spectrum of **14** in Me_2SO-d_6 showed low-field resonances for the OH-1 protons of the two anomeric forms, and after hydroxyl–proton exchange by deuterium oxide, only two signals remained at low field for H-1α (down field) and H-1β. Acetylation of compound **14**, followed by chromatographic separation, gave 1,2,3-tri-*O*-acetyl-4,6-*O*-methoxyethylidene-α-D-mannopyranose (**15**α) and its β anomer (**15**β), which were identified by ^{1}H NMR spectroscopy. Partial hydrolysis of **15**α under similar conditions to those used for **10** gave the known [17] mixture of 1,2,3,6-tetra-*O*-acetyl-α-D-mannopyranose (**16**α) and 1,2,3,4-*O*-acetyl-α-D-mannopyranose (**17**α). The ^{1}H NMR spectrum of the mixture in Me_2SO-d_6 showed, in particular, a doublet of doublets at 5.60 ppm ($J_{HOCH_2\text{-}6}$ 5.2 Hz) and a doublet at 4.70 ppm ($J_{HOCH\text{-}4}$ 5.6 Hz). These two signals disappeared after addition of deuterium oxide.

It may be noted that the selective hydrolysis of the 4,6-*O*-methoxyethylidene group of orthoesters could provide good access to derivatives with the hydroxyl group at the C-4 position. To increase the yield of OH-4 derivatives and make the partial hydrolysis synthetically useful, a basic medium can transform the compounds with an OH-6 into regioisomers with an OH-4 by acetyl migration [18,19].

Having demonstrated the preferential formation of the 4,6-*O*-orthoesters, we examined the possibility whether ketene acetals could lead to 2,3-*O*-orthoesters if positions 4

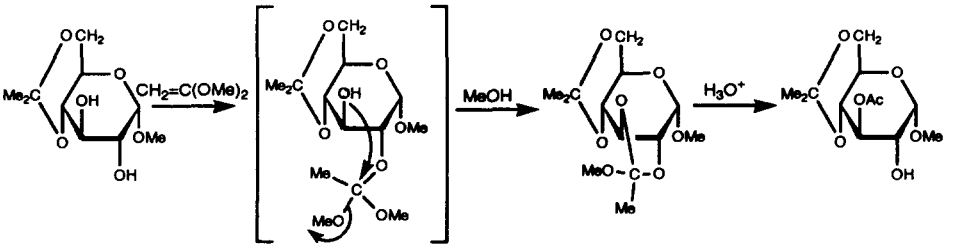
and 6 were not available. Thus, the 4,6-*O*-isopropylidene-D-mannopyranose (**18**) [20] was treated with 1,1-dimethoxyethene under the standard conditions used for D-mannose (Scheme 3). A diastereoisomeric mixture of endo and exo isomers of 4,6-*O*-isopropylidene-2,3-*O*-methoxyethylidene-α-D-mannopyranose (**19**), identified by NMR spectroscopy, was obtained without any participation of the anomeric hydroxyl group. Acetylation led to the acetate **20**, which was identified by NMR spectroscopy. Selective hydrolysis of **20** was found to be regiospecific, as only one diacetate derivative was isolated and identified as the 1,2-di-*O*-acetyl-4,6-isopropylidene-α-D-mannopyranose (**21**) by NMR spectroscopy. The ^{1}H NMR spectrum in Me_2SO-d_6 showed essentially the anticipated downfield shift of H-1 (5.90 ppm, $J_{1,2}$ 1.6 Hz), a low-field doublet of doublets at 5.03 ppm attributed to H-2, whose couplings ($J_{1,2} = J_{2,3} = 3.6$ Hz) were only consistent with an equatorial proton [and not with an axial proton (H-3) geminal to an acetoxyl group]. Also observed was a doublet at 5.38 ppm that disappeared after addition of deuterium oxide and is attributed to OH-3. This regiospecifity was in accordance with other examples described in cyclohexane [21] and carbohydrate [4,22,23] series and for which an interpretation has been given [5].

An analogous diastereoisomeric mixture (exo–endo) of methyl 4,6-*O*-isopropylidene-2,3-*O*-methoxyethylidene-α-D-mannopyranoside (**23**) was obtained from the orthoesterification of methyl 4,6-*O*-isopropylidene-α-D-mannopyranoside (**22**) [18] (Scheme 4). Its partial hydrolysis was also regiospecific, leading to 2-*O*-acetyl-4,6-*O*-isopropylidene-α-D-mannopyranoside (**24**). The orthoester and the corresponding acetate were identified by NMR spectroscopy.



22 23 24

D-*manno series* (cis diol).



25 26 27 28

D-*gluco series* (trans diol).

Scheme 4.

Based on the foregoing results, we have been interested in applying the method to the case to vicinal trans diols, which are well known to be quite reluctant to give five-membered cyclic derivatives [26]. Methyl 4,6-*O*-isopropylidene-2,3-*O*-methoxyethylidene-α-D-glucopyranoside (**27**) was in fact prepared in 80% yield by treatment of methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside (**25**) [25,26] (Scheme 4) with 1,1-dimethoxyethene under the conditions previously described. TLC and NMR spectroscopic analysis showed that **27** was also a mixture of two diastereoisomers (exo–endo). Selective hydrolysis of this orthoester gave a unique compound that was identified as methyl 3-*O*-acetyl-4,6-*O*-isopropylidene-α-D-glucopyranoside (**28**) by NMR spectroscopy. The NMR spectrum of **28** revealed a signal at 5.56 ppm as a wide triplet characteristic of an axial proton coupled with two vicinal axial protons and corresponding to H-3. Had the acetoxyl-group been at C-2, the signal of the lowest-field ring proton (H-2) would have been a doublet of narrow doublets. The origin of what appears to be an interesting regiospecificity remains to be explained.

3. Experimental

General methods.—Melting points were determined on a Büchi apparatus. Evaporations were performed under reduced pressure. Optical rotations were measured on a Perkin–Elmer 141 polarimeter in 1-dm tubes (*c* 1, 20°C). Column chromatography was performed with Silica Gel 60 (E. Merck 70–230 mesh), and TLC was carried out on precoated plates (E. Merck 5724), with detection by charring with H_2SO_4. Chromatographic solvents were distilled with the use of a 130-cm static column. Pyridine and *N*,*N*-dimethylformamide were dried and distilled under diminished pressure. ^{1}H NMR spectra were recorded on a Varian T60 spectrometer, and ^{13}C NMR spectra were recorded on a Jeol FX 60 spectrometer. Chemical shifts data are given in δ units (ppm) measured downfield from internal Me_4Si. Spin–spin coupling data are in Hz.

*Methyl 4,6-*O*-methoxyethylidene-α-*D*-glucopyranoside (3).*—To a stirred solution (maintained below 5°C) of methyl α-D-glucopyranoside (**1**) (3.1 g) in dry *N*,*N*-dimethylformamide (60 mL) containing a small crystal of *p*-toluenesulfonic acid, was added 1,1-dimethoxyethene (1.8 g, 12 mmol) (prepared according to [3]). The mixture was stirred magnetically at 0–5°C until monitoring by TLC (EtOAc) indicated that all starting material had disappeared (4 h). Then sodium carbonate was added, and the mixture was stirred vigorously for 1 h. The mixture was filtered, concentrated, and the residue was chromatographed (EtOAc) to give **3** as a amorphous solid (2.3 g, 92%); mp 97–98°C; $[\alpha]_D$ +112.2° (acetone); ^{1}H NMR (Me_2SO-d_6): δ 4.60 (d, 1 H, $J_{1,2}$ 1.2 Hz, H-1), 4.96 (m, 1 H, OH), 3.66 (d, 1 H, H-2), 3.43 (m 5 H, H-3,4,5,6,6′), 3.33 (s, 3 H, MeCO*Me*), 3.26 (s, 3 H, OMe), 1.40 (s, 3 H, *Me*COMe). Anal. Calcd for $C_{10}H_{18}O_7$: C, 48.00; H, 7.20; O, 44.80. Found: C, 48.05; H, 7.24; O, 44.76.

*Methyl 2,3-di-*O*-acetyl-4,6-*O*-methoxyethylidene-α-*D*-glucopyranoside* (**4**).—Compound **3** (4 g, 10 mmol) in dry pyridine (60 mL) was treated with acetic anhydride (4.08 g, 40 mmol). The mixture was shaken until complete dissolution was achieved, then it was stirred for 24 h at room temperature, poured onto ice containing sodium carbonate,

and stirred vigorously. The product was extracted with CH_2Cl_2, and the solution was washed with satd aq sodium hydrogencarbonate and water. After drying over anhyd sodium sulfate, the extracts were evaporated and coevaporated with toluene to give **4** as an amorphous solid (2.5 g, 75%); mp 57–58°C; $[\alpha]_D + 85°$ ($CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.40 (t, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 4.90 (dd, 1 H, $J_{2,3}$ 9.5 Hz, H-2), 4.73 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 3.90 (m, 4 H, H-4,5,6,6'), 3.40 (s, 3 H, MeCO*Me*), 3.30 (s, 3 H, OMe), 2.5 and 2.00 (2s, 6 H, OAc), 1.43 (s, 3 H, *Me*COMe); ^{13}C NMR ($CDCl_3$): δ 170.23 and 169.84 (CO), 112.60 (Me*C*OMe), 97.65 (C-1), 71.73 (C-2), 70.89 (C-3), 68.94 (C-4), 61.59 (C-5), 62.18 (C-6), 55.29 (O*Me*-1), 50.61 (MeCO*Me*), 21.51 (*Me*COMe), 20.65 and 20.75 (*Me*CO). Anal. Calcd for $C_{14}H_{22}O_9$: C, 50.30; H, 6.59; O, 43.11. Found: C, 50.38; H, 6.62; O, 43.02.

*Preparation of Methyl 2,3,6-tri-*O*-acetyl-α-*D*-glucopyranoside* (**5**) *and methyl 2,3,4-tri-*O*-acetyl-α-*D*-glucopyranoside* (**6**).—To a solution of **4** (1.7 g, 5 mmol) in $CHCl_3$ (10 mL) was added three drops of water and *p*-toluenesulfonic acid (20 mg). The mixture was stirred for 3 h at room temperature. After disappearance of all starting material (TLC, 1:1 EtOAc–hexane), the mixture was neutralized with anhyd sodium carbonate, filtered, and concentrated to give a solid residue which was chromatographed (1:1 EtOAc–hexane) to afford, successively **5** (0.87 g, 60%) and **6** (0.43 g, 30%). Compound **5**: mp 53°C, lit. [8] mp 53–54°C; $[\alpha]_D + 92°$ ($CHCl_3$), lit. [8] $[\alpha]_D + 91°$; ^1H NMR (Me_2SO-d_6): δ 5.66 (s, 1H, $J_{OH,4}$ 6 Hz, OH-4), 5.23 (t, 1 H, $J_{3,4}$ 8.8 Hz, H-3), 4.83 (dd, 1 H, $J_{2,3}$ 8.8 Hz, H-2), 4.60 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.26 (m, 3 H, H-5,6,6'), 3.60 (m, 1 H, H-4), 3.36 (s, 3 H, OMe), 2.03 (s, 9 H, OAc). Compound **6**: mp 109.5–110°C, lit. [9] mp 110°C; $[\alpha]_D + 137°$ ($CHCl_3$), lit. [9] $[\alpha]_D + 145.5°$; ^1H NMR (Me_2SO-d_6): δ 5.33 (t, 1 H, $J_{3,4}$ 9.2 Hz, H-3), 5.00 (t, 1 H, H-4), 4.90 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1), 4.73 (dd, 1 H, $J_{2,3}$ 9.2 Hz, H-2), 3.76 (s, 1 H, $J_{OH,6}$ 5.2 Hz, OH-6), 3.50 (m, 3 H, H-5,6,6'), 3.36 (s, 3 H, OMe), 2.00 (s, 9 H, OAc).

*1,2,3-Tri-*O*-acetyl-4,6-*O*-methoxyethylidene-β-*D*-glucopyranose* (**11**).—Treatment of D-glucose (7 g, 38 mmol) with 1,1-dimethoxyethene as for **3**, afforded **10** as a syrup in high yield (8.2 g, 92%). ^1H NMR (Me_2SO-d_6): δ 5.06 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1α), 4.50 (d, 1 H, $J_{1,2}$ 7.2 Hz, H-1β), 3.4–4.2 (m, 6 H, H-2,3,4,5,6,6'), 3.40 (s, 3 H, OMe), 6.52 (d, 1 H, J_{HOCH} 4.4 Hz, OH-1α), 6.83 (d, 1 H, J_{HCOH} 6.8 Hz, OH-1β); the mass spectrum showed a peak at m/z 205 ($M^+ - OCH_3$) and comparable fragmentation to that of 4,6-O-isopropylidene-α-D-glucopyranose [25]. A mixture of **10** (8.2 g, 34 mmol), anhyd sodium acetate (3 g), and acetic anhydride (18.4 mL), 195 mmol) was heated at 100°C with stirring for 1 h, until TLC indicated the disappearance of **10** and formation of a single component **11**. The cooled mixture was poured onto a mixture of ice and sodium carbonate, filtered, and extracted with CH_2Cl_2. The dried extract was evaporated to give **11** as a syrup (9.6 g, 77%); $[\alpha]_D -37°$ ($CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.68 (d, 1 H $J_{1,2}$ 8.5 Hz, H-1_{ax}); 5.50 (dd, 1 H $J_{2,3}$ 9 Hz, H-2), 5.10 (dd, 1 H, $J_{3,4}$ 9 Hz, H-3), 3.26 (s, MeCO*Me*), 1.43 (s, 3 H, *Me*COMe); the mass spectrum showed a peak at m/z 331 ($M^+ - OCH_3$) and a comparable fragmentation to that of 4,6-*O*-isopropylidene-α-D-glucopyranose [25]. Anal. Calcd for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.07; O, 44.20 Found: C, 49.67; H, 6.02; O, 44.26.

*Preparation of 1,2,3,6-Tetra-*O*-acetyl-β-*D*-glucopyranose (12) and 1,2,3,4-tetra-*O*-acetyl-β-*D*-glucopyranose* (**13**).—A solution of **11** (14.3 g, 3 mmol) in 1:3 HOAc–water

was stirred for 1 h at room temperature. The reaction monitored by TLC (1:1 EtOAc–hexane) was freeze-dried to afford a solid residue. TLC indicated two components. Separation by column chromatography 1:1 (EtOAc–hexane) gave **12** (0.57 g, 55%); mp 130–132°C lit. [15] mp 131°C, $[\alpha]_D$ −31° ($CHCl_3$), lit. [15] $[\alpha]_D$ −33° ($CHCl_3$) and **13** (0.31 g, 30%); mp 128–129°C (lit [16] mp 129–130°C), $[\alpha]_D$ + 11° ($CHCl_3$), lit. [16] $[\alpha]_D$ + 12° ($CHCl_3$).

4,6-O-Methoxyethylidene-α-D-mannopyranose (**14**).—D-Mannose (7.2 g 40 mmol) in solution with *N,N*-dimethylformamide (60 mL) was treated with dimethoxyethene (5.3 g, 80 mmol) by the foregoing general procedure. TLC showed two components, the major of which was separated by column chromatography (EtOAc) to give **14α** (5.6 g, 60%); mp 67–68°C; $[\alpha]_D$ + 170° ($CHCl_3$); ^{1}H NMR (Me_2SO-d_6): δ 6.46 (d, 1 H, OH-1), 4.91 (m, 1 H, H-1), 4.90–3.65 (m, 6 H, H-2,3,4,5,6,6′), 4.80 (m, 2 H, OH-2,3), 3.23 (s, 3 H, MeCO*Me*), 1.40 (s, 3 H, *Me*COMe). *Anal.* Calcd for $C_9H_{16}O_7$: C, 45.76; H, 6.78; O, 47.45. Found: 45.80; H, 6.50; O, 47.32.

1,2,3-Tri-O-acetyl-4,6-O-methoxyethylidene-α,β-D-mannopyranose (**15α**) *and* (**15β**).—Acetylation of **14** (5.5 g, 23 mmol) following the procedure used for **4** afforded an amorphous solid (5.2 g, 67%) for which TLC (1:1 EtOAc–hexane) revealed two products. Elution (1:1 EtOAc–hexane) from column chromatography gave first **15α** (2.7 g, 52%); mp 42–43°C; $[\alpha]_D$ + 48° ($CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 6.00 (d, 1 H, H-1), 5.30 (dd, 1 H, H-2), 5.26 (dd, 1 H, H-3), 4.30 (m, 1 H, H-4), 4.01–3.66 (m, 3 H, H-5,6,6′), 3.33 (s, 3 H, MeCO*Me*), 2.16, 2.00 (1s, 2s, 9 H, OAc), 1.50 (s, 3 H, *Me*COMe); (C_6D_6): δ 6.28 (d, 1 H, $J_{1,2}$ 1.4 Hz, H-1), 5.66 (m, 2 H, H-2,3), 4.73 (d, 1 H, $J_{4,5}$ 8.8 Hz, H-4), 4.21 (m, 1 H, H-5), 3.88 (m, 2 H, H-6,6′), 3.08 (s, 3 H, MeCO*Me*), 1.50, 1.68, 1.75 (3 s, 9 H, OAc), 1.45 (s, 3 H, *Me*COMe); ^{13}C NMR ($CDCl_3$): δ 170.16, 169.71, and 168.41 (CO), 112.98 (Me*C*OMe), 91.54 (C-1), 68.87 (C-2), 68.02 (C-3), 67.50 (C-4), 65.82 (C-5), 61.14 (C-6), 50.81 (MeCO*Me*), 21.63 (*Me*COMe), 20.79 (*Me*CO). *Anal.* Calcd for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.07; O, 44.20. Found: C, 49.61; H, 6.10; O, 44.34.

Eluted second was **15β** (1.4 g, 19%); mp 49–51°C; $[\alpha]_D$ −17°5 ($CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.93 (dd, 1 H, $J_{1,2}$ 1.2 Hz, H-1), 5.60 (dd, 1 H, $J_{2,3}$ 4.4 Hz, H-2), 5.16 (dd, 1 H, $J_{3,4}$ 10.2 Hz, H-3), 4.46–3.30 (m, 4 H, H-4,5,6,6′), 3.36 (s, 3 H, MeCO*Me*), 2.06, 2.10, 2.23 (3s, 9 H, OAc), 1.46 (s, 3 H, *Me*COMe); (C_6D_6): δ 5.70 (m, 2 H, H-2,3), 5.23 (dd, 1 H, $J_{3,4}$ 10.2 Hz, H-3), 4.60 (dd, 1 H, $J_{4,5}$ 10.4 Hz, H-4), 3.90–3.30 (m, 3 H, H-5,5,6′), 3.00 (s, 3 H, MeCO*Me*), 1.56, 1.70, 1.73 (3s, 9 H, OAc), 1.40 (s, 3 H, MeCO*Me*); ^{13}C NMR ($CDCl_3$): δ 170.42, 170.29, and 168.54 (CO), 113.65 (Me*C*OMe), 91.03 (C-1), 70.11 (C-2), 69.53 (C-3), 68.10 (C-4), 67.45 (C-5), 61.15 (C-6), 51.01 (MeCO*Me*), 21.77 (*Me*COMe), 20.93 (*Me*CO).

Preparation of 1,2,3,4-O-acetyl-α-D-mannopyranose (**16α**) *and 1,2,3,6-tetra-O-acetyl-α-D-mannopyranose* (**17α**).—A solution of **15** (1.5 g, 4 mmol) treated as **11** gave after lyophilization a residue which was chromatographed (1:3 EtOAc–hexane) to afford a mixture of the two isomers **16α** and **17α** (0.9 g, 65%); $[\alpha]_D$ + 21.5° ($CHCl_3$); lit. [17] $[\alpha]_D$ + 23° ($CHCl_3$); ^{1}H NMR (Me_2SO-d_6): δ 5.96 (d, 1 H, $J_{1,2}$ 1.4 Hz, H-1), 5.60 (dd, 1 H, $J_{OH,6}$ 6.0 Hz and $J_{OH,6'}$ 3.2 Hz, OH-6,6′), 5.13 (m, 2 H, H-2,3), 4.10–3.16 (m, 4 H, H-4,5,6,6′), 4.06 (d, 1 H, $J_{OH,4}$ 5,6 Hz, OH-4), 1.96, 2.00, 2.03, 2.13 (4 s, 12 H, OAc).

4,6-O-Isopropylidene-2,3-O-methoxyethylidene-α-D-mannopyranose (**19**).—Treatment of 4,6-*O*-isopropylidene-α-D-mannopyranose (**18**) [20] (4 g, 18 mmol) with 1,1-dimethoxyethene (2.3 g, 36 mmol), afforded a solid residue **19**, which was purified by column chromatography (EtOAc) (3.9 g, 80%); mp 115–116°C; $[\alpha]_D$ −14° ($CHCl_3$); ^{1}H NMR (Me_2SO-d_6): δ 1.58 (s, 3 H, *Me*COMe), 3.23 (s, 3 H, *Me*COMe), 5.25 (d, 1 H, $J_{1,OH}$ 5.0 Hz, H-1), 6.86 (d, 1 H, $J_{OH,1}$ 5.0 Hz, OH). Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.17; H, 7.30; O, 40.57. Found: C, 52.22; H, 7.35; O, 39.90.

1-O-Acetyl-4,6-O-isopropylidene-2,3-O-methoxyethylidene-α-D-mannopyranose (**20**).—Treatment of **19** (5.9 g, 21 mmol) with acetic anhydride (2 g, 42 mmol) by the foregoing procedure led to a solid residue which was chromatographed (1:2 EtOAc–hexane) to give **20** as a solid compound (3.9 g, 60%); mp 108–109°C; $[\alpha]_D$ + 26° ($CHCl_3$); ^{1}H NMR (Me_2CO-d_6): δ 6.25 (s, 1 H, H-1), 4.26 (m, 3 H, H-2,3,4), 3.73 (m, 3 H, H-5,6,6′), 3.36 (s, 3 H, MeCO*Me*), 2.11 (s, 3 H, OAc), 1.50 and 1.36 (C*Me*$_2$), 1.5 (s, 3 H, *Me*COMe); (C_6D_6): δ 6.55 (d, 1 H, H-1), 4.28 (m, 2 H, H-2,3), 3.95–3.71 (m, 4 H, H-4,5,6,6′), 3.28 (s, 3 H, MeCO*Me*), 1.61 (s, 3 H, OAc), 1.45 and 1.28 (2s, 6 H, CMe_2) 1.45 (s, 3 H, *Me*COMe); ^{13}C NMR ($CDCl_3$): δ 168.73 (CO), 122.99 and 121.63 (MeCOMe), 99.86 (CMe_2), 91.54 (C-1), 76.34 (C-2), 74.72 (C-3), 71.14 (C-4), 63.67 (C-5), 62.05 (C-6), 50.68 and 50.81 (MeCO*Me*), 29.04, 22.22, 20.98, and 18.90 (*Me*$_2$C, *Me*COME, and *Me*CO). *Anal.* Calcd for $C_{14}H_{22}O_8$: C, 52.83; H, 6.92; O, 40.25. Found: C, 52.85; H, 7.05; O, 39.92.

1,2-Di-O-acetyl-4,6-O-isopropylidene-α-D-mannopyranose (**21**).—Treatment of **20** (1 g, 3 mmol) with 1:3 HOAc–water (10 mL) at 0°C according to the procedure described for **16**α, gave after purification (1:2 EtOAc–hexane) **21** (0.57 g, 60%); mp 125–126°C; $[\alpha]_D$ +43.5° ($CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.81 (d, 1 H, H-1), 5.0 (m, 1 H, H-2), 4.13–3.63 (m, 5 H, H-3,4,5,6,6′), 2.73 (s, 1 H, OH-3), 2.0 and 1.96 (2s, 6 H OAc), 1.36 and 1.25 (2s, 6 H, CMe_2); ^{13}C NMR ($CDCl_3$): δ 170.29 and 169.06 (CO), 100.25 (*C*Me$_2$), 93.62 (C-1), 70.75 (C-2), 68.74 (C-3), 68.09 (C-4); 67.18 (C-5), 62.05 (C-6), 29.05, 21.05, and 19.23 (C*Me*$_2$, *Me*CO); Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.58; O, 42.10. Found; C, 51.28; H, 6.40; O, 42.30.

Methyl 4,6-O-isopropylidene-2,3-O-methoxyethylidene-α-D-mannopyranoside (**23**).—Treatment of 4,6-*O*-isopropylidene-α-D-mannopyranoside **22** [24] (2.5 g, 12 mmol) according to the procedure described for **2** gave after separation by column chromatography (1:1 EtOAc-hexane) a diastereoisomeric mixture of the two orthoesters (endo and exo) **23** (1.6 g, 46%); $[\alpha]_D$ + 20°; ^{1}H NMR ($CDCl_3$): δ 4.95 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 4.30 (m, 2 H, $J_{2,3}$ 3.0 Hz, H-2,3), 3.76 (m, 4 H, H-4,5,6,6′), 3.40 and 3.36 (2s, 3 H, MeCO*Me*, exo and endo), 3.31 (s, 3 H, OMe-1), 1.65 and 1.53 (2S, 3H, *Me*COMe, exo and endo), 1.43 and 1.53 (2s, 6 H, *Me*$_2$C); ^{13}C NMR ($CDCl_3$): δ 121.23 and 122.53 (Me*C*OMe), 99.66 (Me$_2$*C*), 98.79 (C-1), 77.00 (C-2), 76.15 (C-3), 72.58 (C-4), 71.47 (C-5), 61.99 (C-6), 54.90 (*Me*O), 50.49 and 50.36 (MeCO*Me*), 28.98 and 22.55 (*Me*$_2$C), 18.84 and 18.71 (*Me*CO*Me*). Anal. Calcd for $C_{13}H_{22}O_7$: C, 53.79; H, 7.58; O, 38.62. Found: C, 53.88; H, 7.60; O, 38.35.

2-O-Acetyl-4,6-O-isopropylidene-α-D-mannopyranoside (**24**).—Compound **23** (1 g, 3 mmol) was dissolved in $CHCl_3$ (10 mL) containing a small crystal of *p*-toluenesulfonic acid. Six drops of water were added, and the mixture was stirred for 20 min at room temperature until monitoring by TLC (1:1 EtOAc–hexane) indicated that all original

material had disappeared; then the mixture was neutralized with anhyd sodium carbonate, filtered, and evaporated to afford **24** as a solid (0.7 g, 84%); mp 97–98°C; $[\alpha]_D$ + 32.6° ($CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.2 (dd, 1 H, $J_{2,3}$ 3.0 Hz, H-2), 4.63 (d, 1 H, $j_{1,2}$ 1.5 Hz, H-1), 3.90 (m, 4 H, H-4,5,6,6′), 3.38 (s, 3 H, OMe-1), 2.71 (s, 1 H, OH-4), 1.43 and 1.56 (2s, 6 H, Me_2C); (Me_2SO-d_6): δ 5.30 (d, 1 H, $J_{OH,4}$ 5.6 Hz, OH-4), 5.10 (dd, 1 H, $J_{2,3}$ 3.0 Hz, H-2), 4.73 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-1), 3.86 (m, 4 H, H-4,5,6,6′), 1.46 and 1.63 (2s, 6 H, Me_2C); ^{13}C NMR ($CDCl_3$): δ 170.47 (CO), 101.12 (C-1), 99.47 (Me_2C), 72.32 (C-2), 71.54 (C-3), 67.25 (C-4), 63.13 (C-5), 62.05 (C-6), 29.11 and 20.99 (Me_2C), 19.23 (*Me*CO). Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.17; H, 7.30; O, 40.57. Found: C, 52.33; H, 7.18; O, 39.88.

*Methyl 4,6-*O*-isopropylidene-2,3-*O*-methoxyethylidene-α-*D*-glucopyranoside* (**27**).—Treatment of 4,6-*O*-isopropylidene-α-D-glucopyranoside (**25**) [25,26] (2.34 g, 10 mmol) with 1,1-dimethoxyethene (1.76 g, 20 mmol) according to the procedure described for **1** gave a diastereoisomeric mixture of orthoesters **27** (2.32 g, 80%); $[\alpha]_D$ +77.7° ($CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.10 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1); 4.0 (t, 1 H, $J_{2,3}$ 9 Hz H-2), 4.36–3.60 (m, 5 H, H-3,4,5,6,6′), 3.50 (s, 3 H, OMe-1), 3.40 and 3.36 (2s, MeCO*Me*), 1.58 and 1.56 (2s, *Me*COMe), 1.50 and 1.46 (2s, CMe_2); ^{13}C NMR ($CDCl_3$): δ 123.51 (Me*C*OMe), 99.67 (Me_2C), 98.82 (C-1), 78.86 (C-2), 73.35 (C-3); 72.83 (C-4), 63.74 (C-5), 62.22 (C-6), 55.55 (OMe-1), 50.80 and 49.70 (MeCO*Me*), 26.83 and 26.38 (Me_2C), 21.57 and 19.10 (*Me*COMe). Anal. Calcd for $C_{13}H_{22}O_7$: C, 53.79; H, 7.58; O, 38.62. Found: C, 52.54; H, 7.50; O, 38.95.

*Methyl 3-*O*-acetyl-4,6-*O*-isopropylidene-α-*D*-glucopyranoside* (**28**).—A mixture of **27** (1.1 g, 4 mmol) in $CHCl_3$ (10 mL) and water (13 mL) was poured overnight on a silica gel column, then eluted (1:1 EtOAc–hexane) to give **28** (0.6 g, 54%); mp 83–84°C; $[\alpha]_D$ + 56° ($CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.16 (t, 1 H, H-3), 4.78 (d, 1 H, H-1), 3.73 (m, 5 H, H-2,4,5,6,6′), 3.46 (s, 3 H, OMe-1), 2.61 (m, 1 H, OH-2), 2.11 (s, 3 H, OAc), 1.46 and 1.18 (2s, CMe_2); (Me_2SO-d_6): δ 5.15 (d, 1 H, $J_{OH,2}$ 7.2 Hz, OH-2), 5.01 (t, 1 H, H-3), 4.68 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 3.73 (m, 4 H, H-4,5,6,6′), 3.61 (m, 1 H, H-2), 3.35 (s, 3 H, OMe-1), 2.01(s, 3 H, OAc), 1.58 and 1.28 (2s, CMe_2); ^{13}C NMR $CDCl_3$): δ 171.95 (CO), 111.39 (CO), 98.07 (C-1), 76.45 (C-2), 75.86 (C-3), 71.74 (C-4), 70.01 (C-5), 62.80 (C-6), 55.78 (OMe-1), 29.14, 26.94, and 26.54 (*Me*COMe and C*Me*$_2$). Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.17; H, 7.30; O, 40.58. Found; C, 52.02; H, 7.47; O, 40.80.

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