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Reaction of mono- and oligo-saccharides with keto or ethylenic enol ethers as a route to functionalized acetals and monomers for polymerization

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ABSTRACT

Synthesis of new sugar functionalized acetals has been studied using keto or ethylenic enol ethers. Complete chemoselectivity was observed for the reaction of the keto enol ether.

INTRODUCTION

The synthesis of cyclic acetals is a well-explored area of the chemistry of mono- and oligo-saccharides[1,2]. The acetal function is traditionally a good protecting group, and different methods for its preparation have been explored: reaction of sugars with carbonyl compounds[2], reaction by transacetalation[3,4], and reaction with enol ethers[4,5]. More recently this protecting group has also been recognized as a functional group in its own right with its own reactivity[4]. Studies of this reactivity have been essentially devoted to that of hydrolysis[6]. While oxidation, photolysis, halogenation, hydrogenolysis, and the action of strong bases and other reagents have been largely explored[4], the modification of the acetal group itself and its polymerization without any alteration in the sugar moiety have been far less studied. Our laboratory has been recently involved in a program concerning the polymerization of sucrose ethylenic acetals obtained from transacetalation of ethylenic acetals with sucrose that leads to materials with the polymer backbone supporting lateral sucrosyl residues[7]. This paper deals with the synthesis of new acetals characterized by the presence of an ethylenic or a carbonylated chain introduced by the reaction of the sugar with a functionalized enol ether. We

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expected that the very mild procedure of acetalation with enol ethers[4,5], which can be applied to sucrose[8], might be convenient for this purpose.

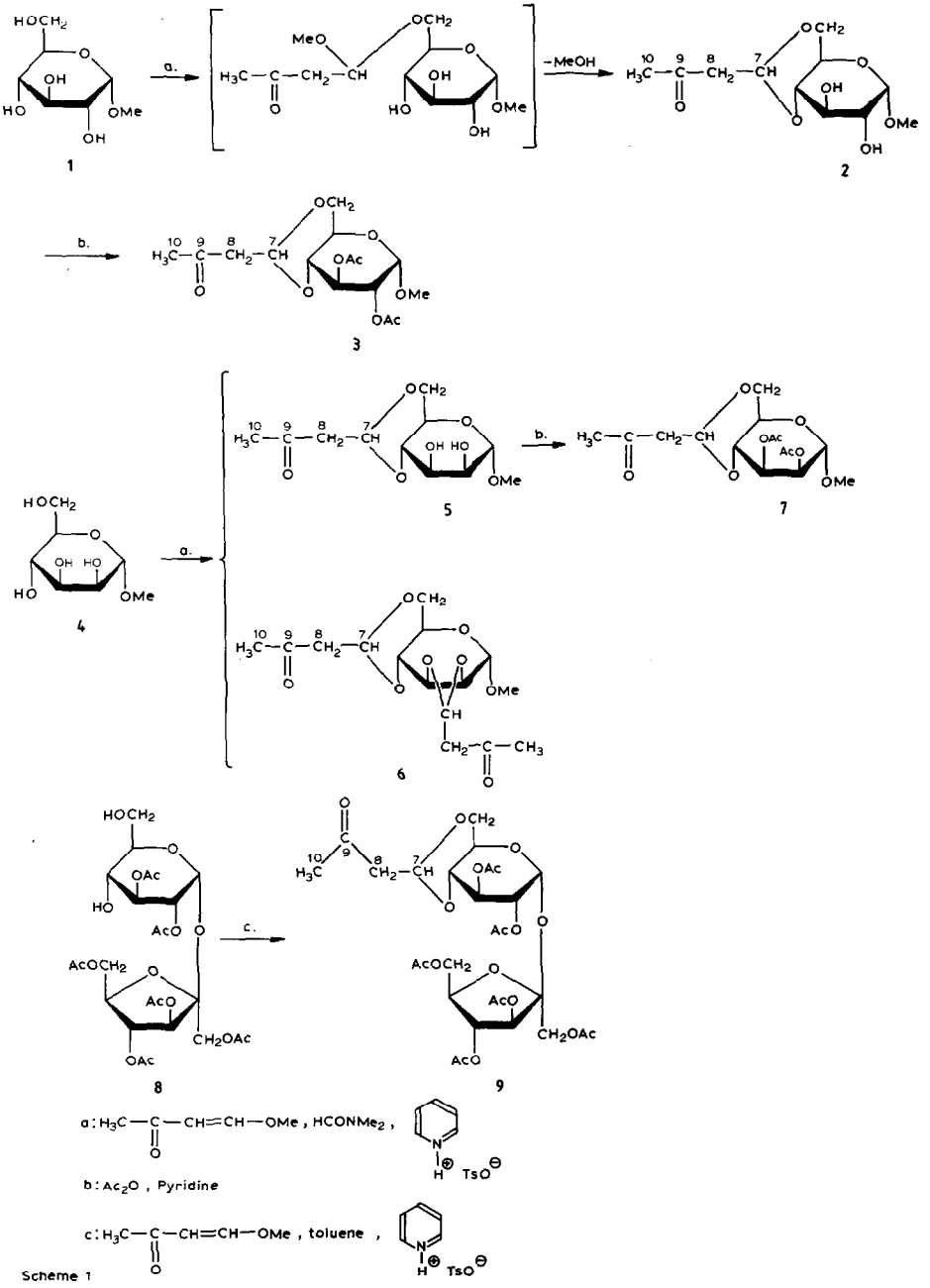
RESULTS AND DISCUSSION

In order to introduce, respectively, an ethylenic double bond or a ketone functional group, we chose either 1-methoxy-1,3-butadiene or 4-methoxy-3-butene-2-one as reagents for the acetalations. In the latter case, the problem of the chemoselectivity of the acetalation (reaction of either the keto group or the enol ether function of the same reagent) was in question.

When methyl α-D-glucopyranoside (**1**) was treated with a three-fold molar excess of 4-methoxy-3-butene-2-one in *N*,*N*-dimethylformamide in the presence of pyridinium *p*-toluenesulfonate, the formation of only one compound was observed. It was isolated in an unoptimized yield of 50% (after purification by column chromatography) and was identified as the 4,6-*O*-(2-oxobutylidene) derivative **2** (Scheme 1) by its ^{1}H NMR spectrum, which showed *inter alia* the presence of a unique acetalic proton (H-7, triplet, at 5.00 ppm) coupled with a methylene group (H_2C-8, doublet, at 2.76 ppm) and a methyl group with a vicinal ketone (singlet at 2.16 ppm). This structure was confirmed by the conversion of compound **2** to its diacetate **3**. The ^{13}C NMR spectrum of the latter showed, in particular, a signal at 99.15 ppm, which served to characterize the acetal carbon atom of a 1,3-dioxane with an hydrogen atom as has been demonstrated[9] in an extension of the criteria established by Buchanan and co-workers[10a] for isopropylidene derivatives and according to NMR spectroscopic data described by Grindley and Wickramage[10b] for ethylidene acetals. The reaction was thus highly chemoselective, as only the reaction of the enol ether with the 4,6-diol was observed, and none of the compound derived from reaction with the keto group could be detected. We also confirmed[4,5] that the reaction of the enol ether proceeded essentially under kinetic control, with preferential initial attack of the most reactive primary hydroxyl group at the 6-position. Finally, we also observed that only one acetal, most likely corresponding to the one with the alkyl side chain exclusively equatorial on the 1,3-dioxane ring, was obtained.

Even if a concurrent 2,3-acetal could have been obtained[11], the trans-diequatorial acetalation of the corresponding hydroxyl groups was a most disfavored process. On the other hand, starting with methyl α-D-mannopyranoside (**4**) afforded an easier competition between both reactions. When compound **4** was treated with 4-methoxy-3-butene-2-one under the same conditions described for the D-*gluco* series, the formation of two derivatives was observed. These compounds were separated (column chromatography) and isolated, respectively, in yields of 40 and 13%. The major compound was identified (^{1}H and ^{13}C NMR spectra) as the 4,6-monoacetal **5** (Scheme 1), and the minor compound was the 2,3 : 4,6-di-acetal **6**. Diol **5** was also converted to its diacetate **7**. It should be noted that if compound **5** were a unique diastereoisomer, diacetal **6** would be a mixture

of the two *endo* and *exo* diastereoisomers due to the chirality of the 2,3-acetal. This was demonstrated by the presence of two triplets for the acetal proton and two additional doublets for the methylene group attached to the acetalic carbon



Scheme 1

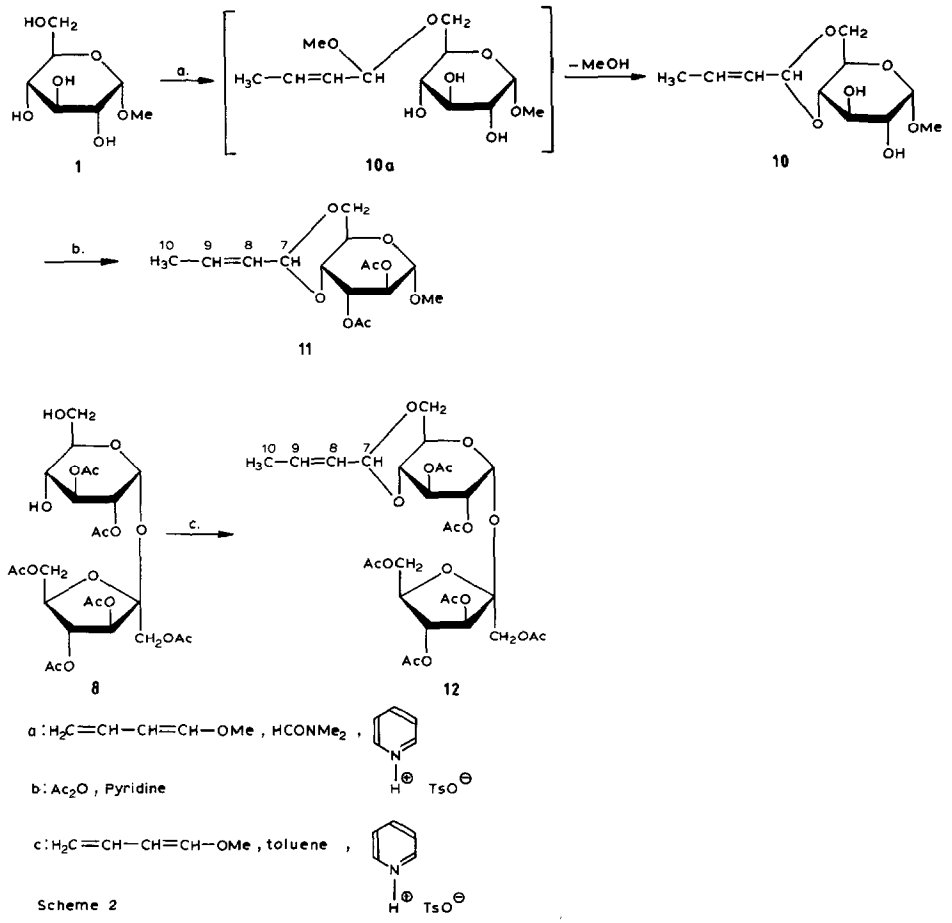
atom observed in the ^1H NMR spectrum, as were two signals at 100.7 and 101.4 ppm in the ^{13}C NMR spectrum for the acetal carbon atom. The presence of both a six-membered acetal (signal at 99.2 ppm) and a five-membered acetal (signals at 101–102 ppm) was clearly indicated for structure **6**, in accordance with spectral data (^1H and ^{13}C NMR) already published for five- and six-membered ethylidene acetals[10b] and for *endo* and *exo* diastereoisomers of dioxolane-type benzylidene and ethylidene derivatives[10c,d]. In addition, two signals were assigned for C-1, showing the influence of the cyclic 2,3-acetal on the anomeric carbon atom. Selective acid hydrolysis of **6** led to the monoacetal **5**, as the dioxolane-type acetal was preferably removed. The 4,6-acetal was more stable, as in the case of ethylidene-type acetals and contrary to that generally observed for di-*O*-isopropylidene derivatives[2b,2d,6,12].

It was possible to improve the yield of the diacetalation by operating with 5 molar equivalents of 4-methoxy-3-butene-2-one in refluxing toluene, which gave only the diacetal **6** in 40% yield after column chromatography.

Lastly, the diol **8** derived from sucrose[8] can be functionalized in the same way (refluxing toluene in the presence of pyridinium *p*-toluenesulfonate), when treated with 4-methoxy-3-butene-2-one, to give the 4,6-acetal **9** in 55% yield. The structure of **9** was deduced from the NMR spectral data (notably three signals in the ^{13}C NMR spectrum corresponding to the three acetalic carbon atoms, one of these signals being at 99.2 ppm, which corresponds to the new six-membered ring acetal as it has also been described for compound **3**).

When methyl α-D-glucopyranoside (**1**) was treated with 1-methoxy-1,3-butadiene in *N*,*N*-dimethylformamide at room temperature in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate, a new acetal **10** was obtained in 50% yield (Scheme 2) and identified on the basis of its ^1H NMR spectrum. The structure of **10** was confirmed by its conversion to the diacetate **11**. The ^{13}C NMR spectrum of **11** showed a signal at 101.1 ppm corresponding to the acetal carbon atom of the six-membered ring. This signal is displaced in respect to the corresponding signal observed for the 1,3-dioxane ring of compound **3**, because of the presence of the double bond; however, this influence is weaker than that of a phenyl substituent[10c,d]. In the case of the sucrose derivative **8**, the same reaction (carried out in toluene in the presence of pyridinium *p*-toluenesulfonate) led to 1′,2,3,3′,4′,6′-hexa-*O*-acetyl-4,6-*O*-2-butenylidene sucrose (**12**) identified on the basis of its NMR spectra. The characteristic signal at 101.1 ppm for the new acetal carbon atom of the molecule was present in the ^{13}C NMR spectrum.

Thus these two reactions of 1-methoxy-1,3-butadiene proceeded with the observation that a complete isomerization of the double bond from the terminal position to the 2-position has occurred. A partial isomerization had already been observed during acetalation using ethylenic aldehyde dimethylacetals[7]. In the case of the reaction with enol ethers, it could be explained by the initial protonation of the reagent at C-4 to give a carbocation stabilized by resonance with the methoxy and the vinyl groups. Then, the addition of the sugar occurred at the electron-poor site



Scheme 2

on C-1 to give **10** (addition at C-3 would lead to thermodynamically and kinetically disfavored rings). The presence of *E* and *Z* isomers for acetals **10** and **12** was suggested by the presence of double signals for the carbon atoms of the double bond in the ^{13}C NMR spectrum. As the *E* isomer was far more preponderant than the *Z* isomer, only the coupling constant typical of the *E* isomer was clearly observed in the ^{1}H NMR spectrum.

In conclusion, we have demonstrated that the reaction of functionalized enol ethers with monosaccharides and sucrose is a convenient route to sugar acetals bearing a keto group or an ethylenic double bond, which could be engaged in further chemical transformations.

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. Column chromatography was carried out 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. ^1H NMR spectra (60 or 300 MHz) were recorded on a Varian T-60 spectrometer or on a Bruker MLS 300 spectrometer. Chemical shift data are given in δ-units (ppm) measured downfield from internal Me_4Si, and spin–spin coupling data are in Hz. ^{13}C NMR spectra were recorded on a JEOL FX 60 spectrometer. Elemental analyses for C and H were carried out by the Service Central d'Analyses du CNRS in Lyon, France.

Methyl 4,6-O-(2-*oxobutylidene*)-α-D-*glucopyranoside* (**2**).—To a solution of methyl α-D-glucopyranoside (**1**) (8 g, 41 mmol) in anhyd *N*,*N*-dimethylformamide, were added 4-methoxy-3-butene-2-one (3 mol equiv) and a catalytic amount of pyridinium *p*-toluenesulfonate. This solution was stirred at 50°C, and the reaction was monitored by TLC (EtOAc). After 20 h the solution was neutralized with Na_2CO_3, then filtered, and the solvent was evaporated under diminished pressure. Column chromatography (EtOAc) of the syrupy residue gave **2** in 50% yield. ^1H NMR (Me_2SO-d_6): δ 5.00 (t, 1 H, H-7), 4.60 (d, 1 H, H-1), 2.80 (d, 2 H, $J_{7,8}$ 6.0 Hz, H-8,8′), 2.10 (s, 3 H, H-10,10′,10″). Anal. Calcd for $C_{11}H_{18}O_{17}$: C, 50.38; H, 6.87; Found: C, 50.02; H, 7.02.

Methyl 2,3-*di*-O-*acetyl*-O-(2-*oxobutylidene*)-α-D-*glucopyranoside* (**3**).—Compound **2** (2.62 g, 0.01 mol) was dissolved in anhyd pyridine (30 mL), acetic anhydride (4.08 g, 40 mmol) was added to the solution, and the mixture was stirred at 0°C. After 24 h the solution was poured onto ice–water mixed with Na_2CO_3, and the mixture was extracted with CH_2Cl_2. The extracts were washed with satd aq $NaHCO_3$ and dried over sodium sulfate. The solvent was coevaporated with toluene to give 3.3 g (95%) of **3** which could be further purified by column chromatography (1 : 1 EtOAc–hexane): mp 141–143°C; $[\alpha]_D^{20}$ + 127° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 3.40 (s, 3 H, OMe), 2.78 (d, 2 H, $J_{7,8}$ 6.0 Hz, H-8,8′), 2.10 (m, 9 H, OAc and H-10,10′,10″); ^{13}C NMR ($CDCl_3$): δ 204.4 (C-9), 169, 170 (MeCO), 97.6 (C-7), 99.2 (C-1), 55.3 (OMe), 47.9 (C-8), 31.1 (C-10), 20.6–20.1 (OAc). Anal. Calcd for $C_{15}H_{22}O_9$: C, 52.02; H, 6.36. Found: C, 51.89; H, 6.36.

Methyl 4,6-O-(2-*oxobutylidene*)-α-D-*mannopyranoside* (**5**) *and methyl* 2,3 : 4,6-*di*-O-(2-*oxobutylidene*)-α-D-*mannopyranoside* (**6**).—To a solution of methyl α-D-mannopyranoside (**4**) (8 g, 41 mmol) in anhyd *N*,*N*-dimethylformamide, were added 4-methoxy-3-butene-2-one (2 mol equiv) and a catalytic amount of pyridinium *p*-toluenesulfonate. The solution was stirred 18 h at 70°C, and the reaction was monitored by TLC (EtOAc), which showed the formation of two compounds. The solution was neutralized with Na_2CO_3, then filtered, and the solvent was evaporated under reduced pressure. Column chromatography of the amorphous residue gave **6** in 13% yield and **5** in 41% yield.

Compound **5** had: mp 149–151°C; $[\alpha]_D^{20}$ + 68° (*c* 1.0 $CHCl_3$); ^1H NMR (Me_2SO-d_6): δ 5.00 (m, 3 H, H-7, HO-2, HO-3), 4.60 (s, 1 H, H-1), 4.00 (m, 1 H, H-4), 3.60 (m, 5 H, H-2,3,5,6,6′), 3.25 (s, 3 H, OMe), 2.75 (d, 2 H, $J_{7,8}$ 5.5 Hz, H-8,8′), 2.15 (s,

3 H, H-10,10′,10″); after addition of D_2O, H-7 became δ 5.00 (t, 1 H, $J_{7,8}$ 5.5 Hz, H-7). Anal. Calcd for $C_{11}H_{18}O_7$: C, 50.38; H, 6.87. Found: C, 50.41; H, 6.89.

Compound **6** had: mp 93–97°C; $[\alpha]_D^{20}$ + 5° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.60, 5.40 (2 t, 1 H, H-11), 4.90 (m, 1 H, H-1), 3.37 (s, 3 H, OMe), 2.83 (m, 4 H, H-8,8′ and H-12,12′), 2.20 (s, 6 H, H-10,10′,10″ and H-14,14′,14″); ^{13}C NMR ($CDCl_3$): δ 204.6, 204.3, 204.2 (C-9), 101.4, 100.7 (C-11), 99.2 (C-7), 98.5, 98.2 (C-1), 55.1 (OMe), 48.9, 48.2 (C-12, C-8), 31.0 (C-10). Anal. Calcd for $C_{15}H_{22}O_8$: C, 54.54; H, 6.80. Found: C, 54.68; H, 6.67.

Methyl 2,3-*di*-O-*acetyl*-4,6-O-(2-*oxobutylidene*)-α-D-*mannopyranoside* (**7**).—Starting from **5**, classical acetylation was carried out as for compound **3** to give **7**: mp 101–105°C; $[\alpha]_D^{20}$ + 58° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.30 (m, 2 H, H-2,3), 5.00 (t, 1 H, $J_{7,8}$ 6.0 Hz, H-7), 4.60 (m, 1 H, H-1), 3.90 (m, 4 H, H-4,5,6,6′), 3.40 (s, 3 H, OMe), 2.77 (d, 2 H, $J_{7,8}$ 6.0 Hz, H-8,8′), 2.15 (s, 6 H, OAc), 2.00 (s, 3 H, H-10,10′,10″); ^{13}C NMR ($CDCl_3$): δ 204.4 (C-9), 169.8 (MeCO), 99.7 (C-7), 99.3 (C-1), 55.1 (OMe), 48.1 (C-8), 31.1 (C-10), 20.7 (OAc). Anal. Calcd for $C_{15}H_{22}O_9$: C, 52.02; H, 6.36. Found: C, 51.93; H, 6.37.

Methyl 2,3;4,6-*di*-O-(2-*oxobutylidene*)-α-D-*mannopyranoside* (**6**).—A solution of methyl α-D-mannopyranoside (**4**) in anhyd toluene, containing 4-methoxy-3-butene-2-one (5 mol equiv) and a catalytic amount of pyridinium *p*-toluenesulfonate was refluxed for 4 h, and the reaction was monitored by TLC (1:1 EtOAc–hexane), which showed the formation of a single compound. The solution was cooled to room temperature, neutralized with Na_2CO_3, then filtered, and the solvent was evaporated. The crude product was purified by column chromatography (1:1 EtOAc–hexane) to give the pure diacetal **6** in 40% yield. The compound was identical with **6** prepared from **4** in *N*,*N*-dimethylformamide.

1′,2,3,3′,4′,6′-*hexa*-O-*acetyl*-4,6-O-(2-*oxobutylidene*) *sucrose* (**9**) *and* 1′,2,3,3′,4′,6′-*hexa*-O-*acetyl*-4,6-O-(2-*butenylidene*) *sucrose* (**12**).—To a solution of the diol **8** (ref. 8) in anhyd toluene were added 4-methoxy-3-butene-2-one or 1-methoxy-1,3-butadiene (2 mol equiv) and a catalytic amount of pyridinium *p*-toluenesulfonate. The solution was refluxed, and the reaction was monitored by TLC. After 20 h, the solution was neutralized with Na_2CO_3, filtered, and the solvent was evaporated. Column chromatography of the residue gave **9** or **10** in 55% yield.

Compound **9** had: mp 41–44°C; $[\alpha]_D^{20}$ + 50° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.65 (d, 1 H, H-1), 5.45 (m, 3 H, H-3,3′,4), 4.80 (m, 2 H, H-2,7), 3.90 (m, 9 H, CH_2-1′,6,6′, H-4,5,5′), 2.75 (d, 2 H, $J_{7,8}$ 5.0 Hz, H-8,8′), 2.10 (4 s, 21 H, OAc, H-10,10′,10″); ^{13}C NMR ($CDCl_3$): δ 204.2 (C-9), 170.4, 169.6 (MeCO), 104.0 (C-2′), 99.1 (C-7), 90.4 (C-1), 47.7 (C-8), 31.0 (C-10), 20.5 (OAc). Anal. Calcd for $C_{23}H_{38}O_{18}$: C, 50.75; H, 5.74. Found: C, 50.31, H, 5.84.

Compound **12** had: mp 60–62°C; $[\alpha]_D^{20}$ + 64° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.80 (m, 2 H, H-8,9), 5.60 (d, 1 H, H-1), 5.30 (m, 4 H, H-3,3′,4′,7), 4.80 (d, 1 H, H-2), 3.90 (m, 9 H, H-4,5,5′, CH_2-1′,6,6′), 2.10 (2 s, 18 H, OAc), 1.70 (d, 3 H, H-10,10′,10″); ^{13}C NMR ($CDCl_3$): δ 170.5, 170.3, 170.1 (OAc), 131.1, 130.8, 126.9,

126.7 (C-8,C-9), 104.1 (C-2'), 101.3 (C-7), 90.6 (C-1), 20.6 (OAc), 17.5 (C-10). Anal. Calcd for $C_{28}H_{28}O_{17}$: C, 52.20; H, 5.89. Found: C, 51.76; H, 5.89.

Methyl 4,6-O-(*2-butenylidene*)-α-D-*glucopyranoside* (**10**).—Compound **10** was prepared under the same conditions as compound **2**, using 1-methoxy-1,3-butadiene, in 50% yield; mp 80–82°C; $[\alpha]_D^{20}$ + 130° (*c* 1.0, $CHCl_3$); ^1H NMR (Me_2SO-d_6): δ 5.00 (d, 1 H, $J_{7,8}$ 5.6 Hz, H-7), 4.60 (d, 1 H, H-1), 5.70 (m, 2 H, $J_{7,8}$ 5.6 Hz, H-8,9), 1.70 (d, 3 H, $J_{9,10}$ 6.0 Hz, CH_3-10).

Methyl 2,3-*di*-O-*acetyl*-4,6-O-(*2-butenylidene*)-α-D-*glucopyranoside* (**11**).—Classical acetylation was carried out as for compound **2**, starting from **10**: syrup; $[\alpha]_D^{20}$ + 119° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 5.70 (m, 3 H, H-1,8,9), 4.90 (m, 3 H, H-2,3,7), 3.90 (m, 7 H, H-4,5,6,6', OMe), 2.10 (s, 6 H, OAc), 1.75 (d, 3 H, CH_3-10); ^{13}C NMR ($CDCl_3$): δ 169.7, 169.6 (Me*C*O), 131.0, 130.7, 126.9, 126.6 (C-8,9), 101.1 (C-7), 97.6 (C-1), 55.2 (OMe), 20.6 (*Me*CO), 17.5 (C-10). Anal. Calcd for $C_{13}H_{19}O_8$: C, 51.48; H, 6.27. Found: C, 51.28; H, 6.46.

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