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Note

Synthesis of methylene acetals in the D-glucose, D-galactose, D-mannose, and D-fructose series by an improved transacetalation reaction from dimethoxymethane

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Although methylene acetals of sugars can be synthesized by reaction with formaldehyde in an acidic medium [1] or with dihalomethanes in an alkaline medium [2], they are far less popular than the isopropylidene, benzylidene, or ethylidene acetal derivatives [3]. This may be due to the higher resistance to acid cleavage of the methylene acetal protective group compared with the latter. This higher stability may prove advantageous, for instance if the protected carbohydrate is used as an "off-template" chiral molecule for asymmetric induction in the presence of a Lewis acid [4]. D-Glucose and D-galactose led to the corresponding 1,2:3,4-dimethylene acetal when reacted with formaldehyde in an acidic medium [1b,c,f], and D-ribose led to the 2,3-*O*-isopropylidene-1,5-*O*-methylene-β-D-ribofuranose in the presence of acetone, formaldehyde, and sulfuric acid [5]. When applied to methyl α- or β-D-glycopyranosides, this methodology led to 4,6-*O*-methylene-D-glycopyranosides in very low yields (3.4–13.6%) [1e].

Dimethoxymethane (DMM) has been used as a substitute to chloromethyl methyl ether for the protection of alcohols [6], and to formaldehyde for the synthesis of methylene acetals of diols and alditols [7].

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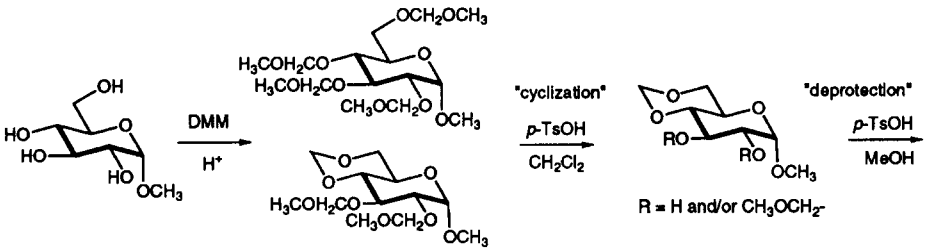


Scheme 1.

In our laboratories, we used the DMM–lithium bromide–*p*-toluenesulfonic acid system for the synthesis of methyl 4,6-*O*-methylene-α- and β-D-glucopyranosides, and methyl α-D-mannopyranoside, although the yields proved not quite satisfactory (~ 33%) [8]. A more convenient method (DMM–sulfuric acid–elimination of methanol) was then applied to D-arabinose, D-ribose, and methyl β-D-arabinopyranoside [9].

We now describe a set of simple experimental conditions to synthesize on a large scale 4,6-*O*-methylene acetals of methyl α-D-gluco- and galacto-pyranoside with high yield and selectivity. In addition, this methodology was extended to the synthesis of dimethylene acetals of D-glucose, D-fructose, and D-galactose.

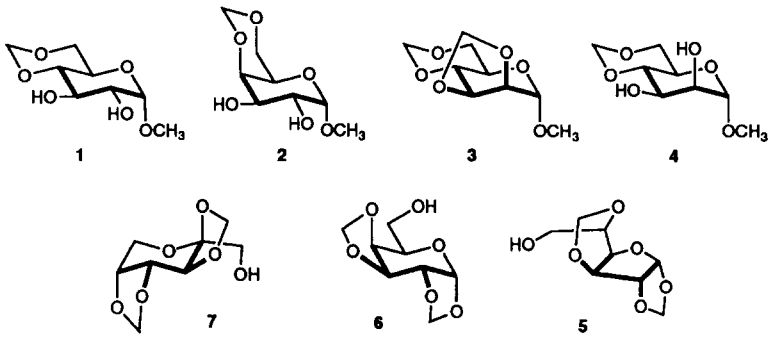
The replacement of *p*-toluenesulfonic acid and lithium bromide in the former conditions by pure sulfuric acid has been shown to result in an efficient synthesis of methyl 4,6-*O*-methylene-α-D-glucopyranoside (**1**) provided that the methanol evolved was trapped. For a large scale synthesis of **1**, the methanol was azeotropically distilled with DMM and trapped on 4 Å molecular sieves contained in a Soxhlet apparatus, while DMM was returned to the reaction flask [6a]. Under these conditions, the medium became homogeneous within 30 min and the reaction was completed within 7 h. Following the two classical cyclization–deprotection steps [8a] (see Scheme 1) and liquid chromatography purification, **1** was obtained in 70% yield.

The use of Amberlyst® 15 ion exchange resin in place of a mineral acid proved to be very efficient for the synthesis of various acetals [10] since it enhanced the yield to 81% in the case of **1** and produced no by-products. Moreover, workup after the first step was limited to filtration, and crystallization in ethyl acetate was sufficient for the final purification of **1**. This reaction could be easily scaled-up to 1 mol of sugar.

The original methylenation conditions (lithium bromide–*p*-toluenesulfonic acid–DMM) transformed methyl α-D-galactopyranoside to the 4,6-*O*-methylene acetal in only 12% yield. The method was significantly improved by adding dimethyl sulfoxide as co-solvent and using a 36% aqueous HCl solution as the acid catalyst. Neutralization, distillation of DMM and liquid–liquid extraction by methylene chloride directly after the first step, furnished pure crystalline methyl 4,6-*O*-methylene-α-D-galactopyranoside (**2**) in 60% yield. Finally, the methodology that we developped for the glucoside (Amberlyst® 15, removal of methanol) led to **2** in 72% yield after liquid chromatography.

Attempts to obtain the monoacetal derivative of methyl α-D-mannopyranoside were unsuccessful under the latter experimental conditions, this procedure leading to methyl 2,3:4,6-di-*O*-methylene-α-D-mannopyranoside (**3**) in quantitative yield. Nevertheless,

methyl 4,6-*O*-methylene-α-D-mannopyranoside (**4**) could be obtained in 75% yield [along with the easily separable diacetal **3** (22%)] by replacing the acidic ion exchange resin by 0.25 mol of sulfuric acid per mol of mannoside.



It was also of interest to react hexoses instead of hexosides under the new conditions. The reaction of anhydrous D-glucose with DMM in the presence of Amberlyst® 15 with continuous removal of methanol, and after the cyclization–deprotection steps, led to two products isolated by column chromatography: the 4,6-acetal **1** and the 1,2:3,5-di-*O*-methylene-α-D-glucofuranose (**5**) (47 and 28% yield, respectively). Under the same conditions, and after a more difficult separation, D-galactose led to the 4,6-acetal **2** and to 1,2:3,4-di-*O*-methylene-α-D-galactopyranose (**6**) (24 and 34% yields, respectively). D-Fructose led to a complex mixture of compounds from which 2,3:4,5-di-*O*-methylene-β-D-fructopyranose (**7**) was obtained after chromatographic purification in 48% yield.

Transacetalation easily converts vicinal *cis*-diols into dioxolanes [6c]. When applied to hexoses, the reaction afforded in all cases a derivative with a dioxolane ring involving the anomeric hydroxyl group and the vicinal secondary alcohol (**5**, **6**, **7**). Thus, transacetalation of hexoses is an alternative method for the synthesis of primary monoalcohols derived from sugars. During the transacetalation of D-glucose or D-galactose, glycosylation by the evolved methanol competed with the dioxolane forming reaction, and **1** or **2** was also obtained along with **5** or **6**.

All methylene acetals were carefully characterized by NMR spectroscopy, **6** and **7** by nuclear Overhauser effect (NOE) difference spectroscopy and $^{1}H-^{13}C$ COSY. It is to be noted that, as expected, the two methylene acetals protons appeared as two singlets in dioxolane-type rings and as two doublets in dioxane-type rings [11].

In conclusion, the set of experimental conditions discussed above affords a general methodology to derivatize various sugars into methylene acetals. The method using Amberlyst® 15, an excess of DMM and continuous removal of methanol proves quite effective to afford protected carbohydrates with one or two free hydroxyl groups, except for the mannoside derivative. The 4,6-methylene acetal of methyl α-D-glucopyranoside and α-D-galactopyranoside (**1** and **2**) are obtained in high yield and with high selectivity. D-Glucose and D-galactose lead to a mixture of the 4,6-methylene acetals **1** and **2** and of

the dimethylene acetals **5** and **6**, respectively. D-Fructose leads to the diacetal **7** with moderate yield and selectivity.

1. Experimental

General methods.—Commercial hexoses and hexosides were dried at 50°C under vacuum (0.5 Pa) prior to use. Dimethoxymethane (DMM, Aldrich) was used as received. Amberlyst™ 15 ion exchange resin (Aldrich) was the anhyd form (1 g $\sim 10^{-3}$ equiv H^+), molecular sieves 4 Å were stored in an oven at 140°C. Dichloromethane (Janssen) is free of MeOH. ^{1}H NMR were recorded in $CDCl_3$ with Me_4Si as internal standard at 200 MHz (or 400 MHz when specified) (Bruker); H-7 refers to the 4,6-methylene acetal protons for compounds **1–4**. Optical rotations were measured at 25°C with a Perkin–Elmer 241 polarimeter. For the transacetalization reaction, the flask was fitted either with a Soxhlet or a liquid–liquid extractor for solvents heavier than water filled with 4 Å molecular sieves.

Methyl 4,6-O-methylene-α-D-glucopyranoside (**1**).—(*a*) Method with H_2SO_4: methyl α-D-glucopyranoside (9.71 g, 50 mmol) was suspended with magnetic stirring in DMM (100 mL) containing concentrated H_2SO_4 (2.5 g). The mixture was heated for 7 h at such a temperature that refluxing DMM returned in the reaction flask after percolation on a molecular sieves bed (200 g). After neutralization by solid K_2CO_3 and filtration, the DMM was evaporated under reduced pressure. The syrupy residue was dissolved in CH_2Cl_2 (100 mL) and refluxed for 12 h with *p*-TsOH (0.7 g). MeOH (50 mL) was then added and CH_2Cl_2 slowly evaporated. After further addition of MeOH (100 mL), water (2 mL) and *p*-TsOH (0.7 g), the solution was refluxed for 12 h (deprotection step, see Scheme 1). After neutralization with solid Na_2CO_3, filtration and concentration under reduced pressure, purification of the residue on silica gel (80:20 ether–acetone) led to pure **1** (7.22 g, 70%). (*b*) Method with Amberlyst: the experimental conditions including quantities were the same as above; Amberlyst (5.1 g), reaction time 4 h, filtration of the resin instead of neutralization; for purification, the residue resulting from the deprotection step was dissolved in hot $CHCl_3$ (100 mL) and on standing (12 h) small amounts of recovered methyl α-D-glucopyranoside crystallized. After filtration and concentration, the syrup was dissolved in hot EtOAc; on cooling ($\sim$ 15°C), pure **1** crystallized (8.35 g, 81%); mp 124°C, lit. [1e] 127–128°C; $[\alpha]_D$ +117° (*c* 0.29, CH_2Cl_2), lit. [1e] +120.5° (*c* 1, H_2O); ^{1}H NMR: δ 5.07 (d, 1 H, $J_{7a,7e}$ 6.2 Hz, H-7), 4.75 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 4.62 (d, 1 H, H-7), 4.14 (dd, 1 H, $J_{6a,6e}$ 10.0, $J_{6e,5}$ 4.6 Hz, H-6*e*), 3.88 (t, 1 H, $J_{3,4} = J_{3,2} = 9.5$ Hz, H-3), 3.68 (td, 1 H, $J_{5,6a} \sim J_{5,4} = 9.5$ Hz, H-5), 3.57 (dd, 1 H, H-2), 3.46 (apparent dd, H-6*a*), 3.43 (s, 3 H, OCH_3), 3.43 (s-broad, 2 H, OH), 3.22 (t, 1 H, H-4); ^{13}C NMR: δ 100.03 (CH), 93.72 (CH_2), 80.80 (CH), 72.78 (CH), 71.06 (CH), 68.70 (CH_2), 62.59 (CH), 55.44 (CH_3). Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.62; H, 6.84.

Methyl 4,6-O-methylene-α-D-galactopyranoside (**2**).—(*a*) Method with Amberlyst: the experimental conditions, including quantities, were the same as for methyl α-D-glucopyranoside. Purification on silica gel (60:20:20 ether–acetone–MeOH) yielded **2** (1.49 g, 72%). (*b*) Method with LiBr and HCl: a vigourously stirred mixture of methyl α-D-galactopyranoside (1.94 g, 10 mmol), DMM (1.8 mL, 20 mmol), Me_2SO (1 mL),

LiBr (1.22 g, 10 mmol) and 36% HCl (1.22 g, 10 mmol) was refluxed for 48 h. After neutralization with solid $NaHCO_3$ and filtration, the DMM was evaporated and the residue transferred with the aid of water and CH_2Cl_2 in a liquid–liquid extractor. After 48 h of extraction with CH_2Cl_2, white crystals of **2** deposited in the extraction flask, half of CH_2Cl_2 was evaporated at room temperature and the crystals were filtered off (suction); a second crop of **2** was obtained by evaporation of a mother liquor and recrystallized from a minimum of CH_2Cl_2 (1.24 g, yield 60%); mp 214°C, lit. [1e] 222–223°C; $[\alpha]_D$ +166° (*c* 0.6, MeOH), lit. [1e] +180° (*c* 1, H_2O); ^1H NMR: δ 5.17 (d, 1 H, $J_{7a,7e}$ 6.4 Hz, H-7), 4.89 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1), 4.75 (d, 1 H, H-7), 4.12 (d, 1 H $J_{6a,6e}$ 12.5 Hz, H-6), 4.01 (d, 1 H, $J_{4,3}$ 3.9 Hz, H-4), 3.90 (m, 3H), 3.65 (s, 1 H, H-5), 3.44 (s, 3 H, OCH_3), 3.01 (s, 2 H, OH); ^{13}C NMR (Me_2SO-d_6): δ 100.66 (CH), 92.46 (CH_2), 75.97 (CH), 68.16 (CH_2), 68.04 (CH), 67.85 (CH), 63.11 (CH), 54.79 (CH_3). Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.57; H, 6.83.

*Methyl 2,3:4,6-di-*O*-methylene-α-*D*-mannopyranoside* (**3**).—Methyl α-D-mannopyranoside (1.94 g, 10 mmol), DMM (20 mL), Amberlyst (1 g), or concentrated H_2SO_4 (0.94 g), were refluxed (with the Soxhlet) during 6 h. After filtration (resin), or neutralization by solid K_2CO_3, filtration (H_2SO_4), and evaporation of the DMM, the syrupy residue was refluxed with EtOH (20 mL). On cooling, **3** crystallized as needles (2.1 g, 96%); mp 139°C, lit. [1e] 144–145°C; $[\alpha]_D$ +15.3° (*c* 2.0, $CHCl_3$), lit. [1e] +19.4° (*c* 0.33, $CHCl_3$); ^1H NMR: δ 5.25 (s, 1 H, H-8), 5.04 (d, 1 H, $J_{7a,7e}$ 6.3 Hz, H-7), 5.03 (s, 1 H, H-8), 4.98 (s, 1 H, H-1), 4.66 (d, 1 H, H-7), 4.30 (dd, 1 H, $J_{3,4}$ 8.0, $J_{3,2}$ 5.5 Hz, H-3), 4.18 (dd, 1 H, $J_{6a,6e}$ 10.0, $J_{6e,5}$ 4.8 Hz, H-6*e*), 3.96 (d, 1 H, H-2), 3.68 (td, 1 H, $J_{5,4}$ 10, $J_{5,6a}$ 10 Hz, H-5), 3.48 (t, 1 H, H-6*a*), 3.40 (dd-partially hidden, 1 H, H-4), 3.39 (s, 3 H, OCH_3); ^{13}C NMR: δ 98.52 (CH), 94.88 (CH_2), 93.96 (CH_2), 77.79 (CH), 76.75 (CH), 73.54 (CH), 68.58 (CH_2), 60.45 (CH), 55.13 (CH_3). Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.50; H, 6.46.

*Methyl 4,6-*O*-methylene-α-*D*-mannopyranoside* (**4**).—Methyl α-D-mannopyranoside (1.94 g, 10 mmol), DMM (20 mL), dioxane (10 mL) and concd H_2SO_4 (0.25 g) were refluxed for 7 h (with Soxhlet). After neutralization with solid K_2CO_3, filtration and evaporation of the DMM, the residue was refluxed 14 h with *p*-TsOH (0.19 g, 1 mmol) in CH_2Cl_2 (30 mL). After addition of MeOH (30 mL), the CH_2Cl_2 was slowly evaporated at room temperature. After further addition of MeOH (30 mL) and water (1 mL), the solution was refluxed 20 h, neutralized with solid K_2CO_3, filtered and evaporated. Purification of the residue on silica gel (70:30 ether–acetone) led successively to 0.48 g of **3** (22%) and 1.54 g of **4** (75%); mp 129°C, lit. [1e] 122–123°C; $[\alpha]_D$ +84.4° (*c* 2.1, $CHCl_3$), lit. [1e] +58° (*c* 1, H_2O); ^1H NMR: δ 5.07 (d, 1 H, $J_{7a,7e}$ 6.2 Hz, H-7) 4.70 (s, 1 H, H-1), 4.67 (d, 1 H, H-7), 4.12 (dd, 1 H, $J_{6a,6e}$ 9.7, $J_{6e,5}$ 3.4 Hz, H-6*e*), 4.0 (m, 2 H), 3.70 (m, 2 H), 3.55 (t, 1 H, $J_{6a,6e} \sim J_{6a,5} = 9.7$ Hz, H-6*a*), 3.40 (s, 3 H, OCH_3), 2.6 (s-broad, 2 H, OH); ^{13}C NMR: δ 101.79 (CH), 94.13 (CH_2), 78.87 (CH), 71.07 (CH), 68.59 (CH_2), 68.38 (CH), 63.56 (CH), 55.03 (CH_3). Anal. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.61; H, 6.91.

*1,2:3,5-Di-*O*-methylene-α-*D*-glucofuranose* (**5**).—The experimental conditions were the same as for methyl α-D-glucopyranoside: D-glucose (9.01 g, 50 mmol), DMM (100 mL) and Amberlyst (10.4 g) under reflux for 12 h. Purification on silica gel with ether as eluant yielded **5** (2.86 g, 28%, syrup), then elution with 70:30 ether–acetone led to a

mixture of **1** and its β anomer, 4.85 g (47%). **5**: $[\alpha]_D$ +35° (*c* 1.3, MeOH), lit. [1a] +32° (*c* 2.5, EtOH); ^{1}H NMR, (H-7 refers to the 3,5- and H-8 to the 1,2-methylene acetal protons): δ 6.04 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.08 (s, 1 H, H-8), 5.04 (s, 1 H, H-8), 5.00 (d, 1 H, $J_{7a,7e}$ 5.9 Hz, H-7), 4.84 (d, 1 H, H-7), 4.51 (d, 1 H, H-2), 4.31 (d, 1 H, $J_{3,4}$ 2.4 Hz, H-3), 4.13 (t, 1 H, $J_{5,6B} \sim J_{5,6A} = 5.2$ Hz, H-5), 4.01 (dd, 1 H, $J_{4,5} \sim 1$ Hz, H-4), 3.88 (ABX, 2 H, $J_{6A,6B}$ 11.6 Hz, H-6A, H-6B); ^{13}C NMR: δ 104.29 (CH), 96.45 (CH_2), 87.02 (CH_2), 83.57 (CH), 76.30 (CH), 75.44 (CH), 73.19 (CH), 61.22 (CH_2). Anal. Calcd for $C_8H_{12}O_6$: C, 47.06; H, 5.92. Found: C, 47.10; H, 5.91.

1,2:3,4-Di-O-methylene-α-D-galactopyranose (**6**).—The experimental conditions, including quantities, were the same as for D-glucose. Purification on silica gel (60:20:20 ether–acetone–MeOH) yielded **6** (3.47 g, 34%) contaminated by unidentified (NMR) and inseparable (HPLC) impurities, and then **2** (2.47 g, 24%). **6**: ^{1}H NMR (400 MHz), (H-7 and H-8 refer to the methylene acetal protons): δ 5.50 (d, 1 H, $J_{1,2}$ 5.1 Hz, H-1), 5.23, 5.06, 4.76, 4.73 (4 s, 4 × 1 H, 2 H-7, 2 H-8), 4.48 (dd, 1 H, $J_{3,4}$ 8.0, $J_{3,2}$ 2.5 Hz, H-3), 4.16 (dd, 1 H, $J_{4,5}$ 1.9 Hz, H-4), 4.09 (dd, 1 H, H-2), 3.86 (ddd, 1 H, $J_{5,6A}$ 7.2, $J_{5,6B}$ 4.5 Hz, H-5), 3.73 (ABX, 2 H, $J_{6A,6B}$ 11.5 Hz, H-6A, H-6B); ^{13}C NMR (100 MHz): δ 95.43 (C-1), 95.35 (C-8), 94.50 (C-7), 71.31 (C-2), 71.16 (C-4), 70.52 (C-3), 68.66 (C-5), 61.56 (C-6). NOE experiments: irradiation of [H-1], [H-2], [H-3], [H-4]; enhancements (respectively) [H-2, 8%], [H-1, 9.9%; H-3, 5.5%; H-7, 2.4%], [H-2, 7%; H-4, 9%; H-8, 2%], [H-3, 8%; H-5, 4%]. Anal. Calcd for $C_8H_{12}O_6$: C, 47.06; H, 5.92. Found: C, 46.99; H, 5.95.

2,3:4,5-Di-O-methylene-β-D-fructopyranose (**7**).—The experimental conditions, including quantities, were the same as for D-glucose. Purification on silica gel (95:5 CH_2Cl_2–MeOH) yielded a first fraction which contained 4.95 g of syrupy **7** (48%), and then, more polar fractions which contained unidentified products (NMR 400 MHz); $[\alpha]_D$ −30° (*c* 1.5, MeOH), lit. [1f] −34.9° (*c* 2, H_2O); ^{1}H NMR (400 MHz), (H-7 and H-8 refer to the methylene acetal protons): δ 5.24, 5.12, 4.80, 4.78 (4s, 4 × 1 H, 2 H-7, 2 H-8), 4.48 (dd, 1 H, $J_{4,5}$ 7.9, $J_{4,3}$ 2.6 Hz, H-4); 4.20 (d, 1 H, H-3), 4.16 (dd, 1 H, $J_{5,6A}$ 2.0 Hz, H-5), 3.83 (ABX, 2 H, $J_{6A,6B}$ 13.2 Hz, H-6A, H-6B), 3.68 (AB, 2 H, $J_{1A,1B}$ 11.8 Hz, H-1A, H-1B); ^{13}C NMR (100 MHz): δ 102.41 (C-2), 95.16 (C-8), 94.85 (C-7), 71.03 (C-3), 70.86 (C-5), 70.28 (C-4), 64.81 (C-1), 61.21 (C-6). NOE experiments: irradiation of [H-3], [H-4], [H-5]; enhancements (respectively) [H-4, 4%; H-7, 2%], [H-3, 4%; H-5, 4%; H-8, 2%], [H-4, 7.8%; H-6A, 4.5%; H-6B, 3%]. Anal. Calcd for $C_8H_{12}O_6$: C, 47.06; H, 5.92. Found: C, 47.21; H, 5.98.

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