A General Procedure for One-Pot Benzylidenation and Methyl (or Benzyl) Glycosidation of Aldoses

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Cyclic acetals of aldoses and aldosides are frequently employed in synthesis. Their value is generally attributed to their

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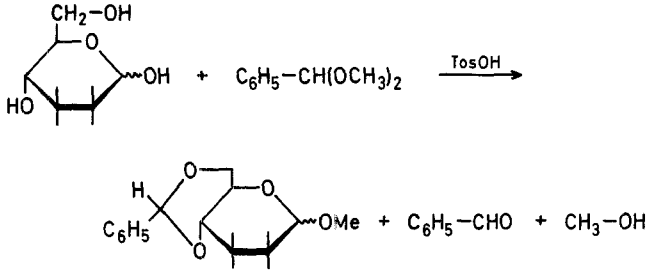
easy preparation in good yield, their stability to a wide variety of reagents, and also to the fact that the subsequent acid hydrolysis of the acetal protecting groups or hydrogenolysis (for benzylidene acetals) can be effected under mild conditions. Furthermore, benzylidene acetals can play the role of synthetic intermediates since their reactivity has been largely developed recently by use of *N*-bromosuccinimide[1] or by use of the lithium aluminium hydride/aluminium chloride cleavage reaction[2].

Usually, the preparation of methyl *O*-benzylidenehexopyranosides or -furanosides requires at least two steps, methyl glycosidation of the free sugar in a more or less stereoselective way, followed by the ring acetal construction.

Some reports have appeared recently concerning a one-step preparation of isopropylidene acetals and furanoid or pyranoid glycosides starting from aldoses, either by means of acetone in presence of methanol in acidic medium[3] or using a mixture of hydrochloric acid, 2,2-dimethoxypropane, acetone, and methanol[4,5]. It was shown that aldohexoses in dry dimethylformamide react with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid as catalyst to give *O*-isopropylidene derivatives in which the oxygen atom *O*-1 is unsubstituted[6,7,8]. However some highly contrasting results were obtained when the same reagent mixture was employed at 80 °C[7,8,9]. Under the more drastic conditions, furanose structures are more frequently encountered and methoxy transfer, to give methyl glycosides, generally occurs[9].

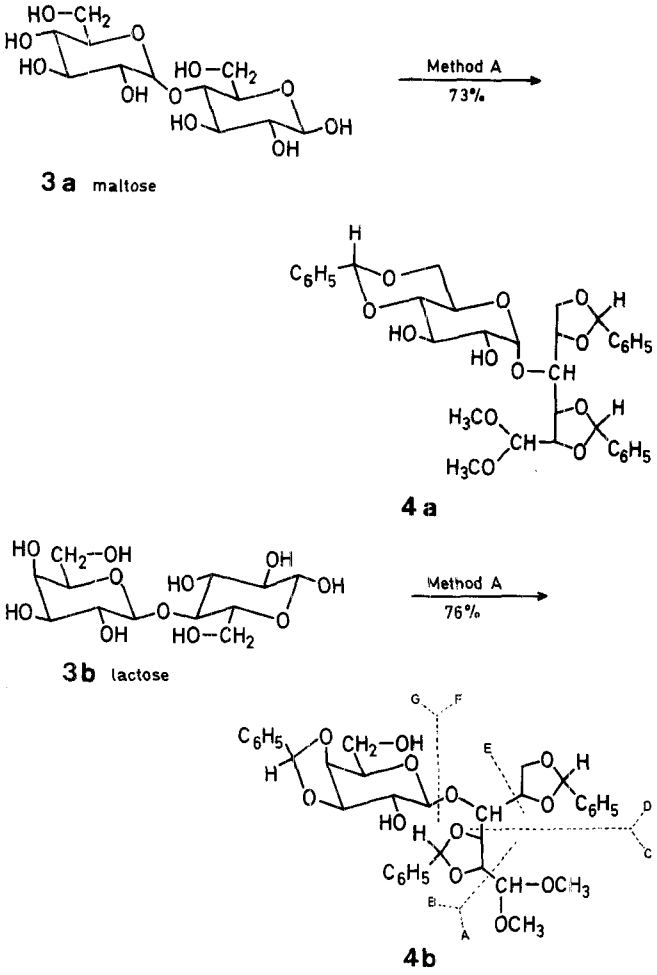
To our knowledge, benzylidene acetals of methyl glycosides have not been obtained starting from the free sugars in a one-pot reaction. Thus, we have developed a simple, versatile access to these compounds based on the general reaction shown in Scheme A.



Scheme A

As shown in the Table, this method allowed us to prepare[10] in a stereospecific way the previously unknown methyl 2,3-*O*-benzylidene-6-deoxy-α-L-mannofuranoside, **(2a)** and methyl 2,3 : 4,6-di-*O*-benzylidene-α-D-mannofuranoside **(2b)**[11]. Then, this method was also applied to D-ribose **(1c)** and *N*-acetylglucosamine **(1d)** and the products **2c** and **2d**, compared to the literature data[12,13], were isolated in better yield and with higher stereospecificity. It should be also noticed that treatment of D-glucal **(1e)** under these conditions is particularly interesting since obtention of the enose **2e** required, according to one of the most practical routes[14], methyl α-D-glucopyranoside as starting material and three steps to give an overall yield of 25%[15]. In the case of 2-deoxy sugars such as 2,6-dideoxy-D-glucose **(1f)** or digitoxose **(1g)**, α- and β-anomers were obtained in a ratio of 1 : 1 but with exclusive formation of the pyranose derivative (see Table).

The great interest in selective protection in disaccharide chemistry as well as recent reports[21,22] prompted us to investigate the reaction on maltose **(3a)** and lactose **(3b)**. The derivatives **4a** and **4b** were respectively obtained (Scheme B) and the structures of the compounds established by means of electron impact mass spectra[21], ^{1}H-N.M.R. spectrometry, and microanalytical data.



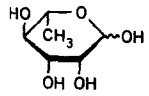
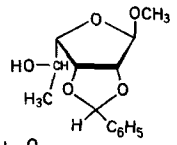
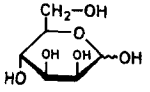
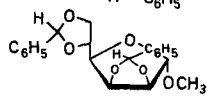
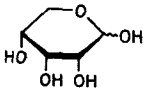
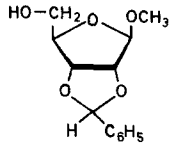
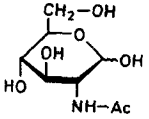
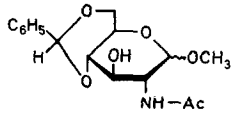
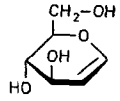
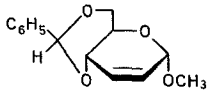
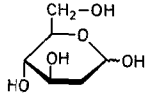
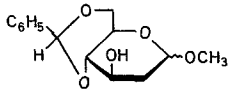
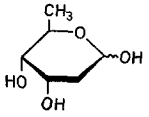
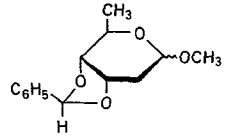
Scheme B

This method can be extended to the preparation of benzyl *O*-benzylidenehexosides simply by using benzyl alcohol (large excess) and benzaldehyde instead of methanol and benzaldehyde dimethyl acetal. In this manner, in a one-step reaction, the benzyl glycoside of 3-acetamido-4,6-*O*-benzylidene-α-D-glucopyranose was prepared in 40% yield from *N*-acetylglucosamine. This derivative is of interest in the synthesis of *N*-acetylmuramic acid. Although one of the previous syntheses[23] gave a better yield (65%), our method remains worthwhile as it involves only one step and achieves a higher stereoselectivity in the glycosidation step.

Methyl *O*-Benzylidenehexosides 2; Typical Procedures:

Method A: To a solution of D-mannose (**1b**; 1 g, 55 mmol) in anhydrous methanol (8 ml) are added benzaldehyde dimethylacetal (6 ml, 36 mmol) and *p*-toluenesulfonic acid (200 mg, 1.2 mmol). After stirring of the mixture at room temperature for 15 min, hexane (5 ml) is added and the solution heated under reflux until all the methanol is removed (10–15 ml) by azeotropic distillation (Dean-Stark apparatus). After cooling, excess saturated aqueous sodium hydrogen carbonate solution (5 ml) is added and evaporation of the mixture under reduced pressure gives a residue which is evaporated with water (5 × 10 ml) until excess reagent is removed. Extraction with dichloromethane (3 × 30 ml) is then carried out in usual manner. The combined extracts are washed with water (2 × 15 ml), dried with sodium sulfate, and the solvent evapo-

Table. Benzylidene Acetals of Methyl Glycosides **2** from Monosaccharides **1**

Monosaccharide	Product	Method	Yield [%][a]	Anomers and ratio	Diastereo-isomers (*endo, exo*)	m.p. [°C] found	m.p. [°C] reported	$[\alpha]_D$ (20 °C, *c*, $CHCl_3$) found	$[\alpha]_D$ (20 °C, *c*, $CHCl_3$) reported	Molecular formula[b]
1a 	**2a** 	A	90	α	2	syrup	syrup[10]	—[d]	—[d]	$C_{14}H_{18}O_5$ (266.3)
1b 	**2b** 	A	80	α	4	syrup	syrup[10,11]	—[d]	—[d]	$C_{21}H_{22}O_6$ (370.4)
1c 	**2c** 	A	85–90	β	2	40–41°	44°[12]	−41° (*c* 1.2)	−59°[12]	$C_{14}H_{16}O_5$ (264.3)
1d 	**2d** 	B	40–50[c]	$\alpha+\beta$, 9 : 1	(α) 1 (β) 1	(α) 245–250°	260°[13]	+31° (*c* 1.1)	+40°[13]	$C_{16}H_{21}NO_6$ (323.3)
1e 	**2e** 	B	90	α	1	117°	117–119[14,15]	+120° (*c* 1.1)	+126[14,15]	$C_{14}H_{16}O_6$ (248.3)
1f 	**2f** 	C	50–60	$\alpha+\beta$, 1 : 1	(α) 1 (β) 1	(α) 147° (β) 155°	151°[16,17] 155°[18,19]	+93° (*c* 1.2) −70° (*c* 1.4)	+90°[16,17] −67°[18,19]	$C_{14}H_{18}O_5$ (266.3)
1g 	**2g** 	C	50–60	$\alpha+\beta$, 1 : 1	(α) 2 (β) 2	(α) syrup (β) syrup	syrup[20]	+105° (*c* 1.0) +14° (*c* 2.7)	+105°[20] —	$C_{14}H_{16}O_4$ (250.3)

[a] Yield of pure product obtained after column chromatography on silica gel.
[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.30; microanalyses performed by Service Central de microanalyses du CNRS.
[c] β-Anomer not isolated; pure α-anomer obtained after repeated crystallizations from methanol.
[d] Not determined as diastereomeric mixtures.

rated in vacuo to afford virtually pure **2b** as determined by ^{1}H-N.M.R. spectroscopic, T.L.C., and microanalytical data; yield: 1.6 g (80%); syrup.

$C_{21}H_{22}O_6$	calc.	C 68.09	H 5.99
(370.4)	found	67.80	5.80

Method A′: see reference[10].

Method B: To a solution of glucal (**1e**; 300 mg, ~2 mmol) in benzaldehyde dimethylacetal (5 ml, 30 mmol) is added *p*-toluenesulfonic acid (30 mg, 0.18 mmol). The reaction mixture is worked up as indicated in Method A to afford pure **2e**; yield: 450 mg (90%); m.p. 117 °C

$C_{14}H_{16}O_4$	calc.	C 67.73	H 6.50
(248.3)	found	67.97	6.39

Method C: Benzaldehyde dimethyl acetal (5 ml, 30 mmol) and *p*-toluenesulfonic acid (100 mg, 0.6 mmol) are added to a solution of digitoxose (**1g**; 1.0 g, 6.75 mmol) in dichloromethane (25 ml). The solution was heated under reflux until T.L.C. (silica gel plates, hexane/ethyl acetate, 4:1) shows complete disappearance of **1g**. Extraction as described in Method A affords the crude product **2g** as a mixture of α- and β-anomers; yield: 1 g (50–60%). The anomers are separated by column chromatography on silica gel eluting with 10:1 hexane/ethyl acetate, the *β(exo)*-anomer being eluted first. Further elution gives a mixture of *β(endo)*- and *α(endo)*-anomers (0.65 g, 32%) and then the *α(exo)*-anomers.

*Methyl 3,4-O-Benzylidene-2,6-dideoxy-α-*D*-ribohexopyranoside* (**α-2g**): yield: 0.2 g (10%); syrup; $[\alpha]_D^{20}$: +105°.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.31 (d, 3H); 3.33 (s, 3H); 4.66 (dd, 1H, J = 5 Hz, 5 Hz); 5.73 (s, 1H); 7.26 ppm (m, 5H).

*Methyl 3,4-O-Benzylidene-2,6-dideoxy-β-*D*-ribohexopyranoside* (**β-2g**): yield: 0.15 g (7%); syrup; $[\alpha]_D^{20}$: +14° (*c* 2.8, chloroform).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.31 (d, 3H); 3.43 (s, 3H); 4.63 (dd, 1H, *J* = 8 Hz, 3 Hz); 5.20 (s, 1H); 7.3 ppm (m, 5H).

4-*O*-(4,6-*O*-Benzylidene-*α*-D-glucopyranosyl)-2,3:5,6-di-*O*-benzylidene-aldehydo-D-glucose Dimethyl Acetal (4a):

Prepared from maltose (**3a**; 2 g, 5.8 mmol) according to Method A as a mixture of diastereoisomers; yield: 2.8 g (73%); syrup.

$C_{35}H_{40}O_{12}$	calc.	C 64.41	H 6.13	O 29.45
(652.7)	found	64.67	6.14	28.70

^{1}H-N.M.R. ($CDCl_3$/TMS, 250 MHz); δ = 3.4–3.5 (m, 6H); 5.1–6.0 (m, 5H); 7.2–7.7 ppm (m, 15H).

M.S. (for fragmentation: compare with **4b**, Scheme **B**): *m/e* = 652 (M^+, trace); 577 (B, 0.5%); 429 (D, 1%); 401 (F, 1%); 251 (G, 13%); 223 (C, 1%); 149 (E, 33%); 121 (98%); 105 (98%); 75 (A, 100%).

4-*O*-(4,6-*O*-Benzylidene-*α*-D-galactopyranosyl)-2,3:5,6-di-*O*-benzylidene-aldehydo-D-glucose Dimethyl Acetal (4b):

Prepared from lactose (**3b**; 2 g, 5.8 mmol) according to Method A as a mixture of diastereoisomers; yield: 2.94 g (76%); syrup.

$C_{35}H_{40}O_{12}$	calc.	C 64.41	H 6.13	O 29.45
(652.7)	found	64.06	6.07	29.20

^{1}H-N.M.R. ($CDCl_3$/TMS, 250 MHz): δ = 3.4–3.5 (m, 6H); 4.8–6.3 (m, 5H); 7.1–7.7 ppm (m, 15).

M.S. (see Scheme **B**): *m/e* = 652 (M^+, trace); 577 (B, 0.4%); 429 (D, 0.4%); 401 (F, 1%); 251 (G, 35%); 223 (C, 0.4%); 149 (E, 29%); 121 (94%); 105 (95%); 75 (A, 100%).

Benzyl 3-Acetamido-4,6-O-benzylidene-*α*-D-glucopyranoside:

N-Acetylglucosamine (**1d**; 2 g, 9 mmol) is added to a mixture of benzaldehyde (10 ml), benzyl alcohol (10 ml), *p*-toluenesulfonic acid (400 mg), and benzene (3 ml). The mixture is heated under reflux for 4 h in an adaptation of a Dean-Stark apparatus. After cooling, it is poured into a solution of hexane/ether (1:1, 50 ml). The precipitate is collected; dissolved in dichloromethane (50 ml), and washed as described Method A to give the crude product (2 g). The pure α-anomer is obtained by crystallization from dioxan/isopropanol; yield: 1.5 g (42%); m.p. 260–261 °C (Lit.[23], m.p. 263–264 °C, Lit.[24], m.p. 262 °C); $[\alpha]_D^{20}$: +105° (*c* 1, pyridine) [Lit.[23], $[\alpha]_D^{26}$: +120°, Lit.[24] $[\alpha]_D^{23}$: +114° (*c* 1, pyridine)].

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