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Charlotte Gozlan, Romain Lafon, Nicolas Duguet, Andreas Redl, Marc Lemaire. Catalytic reductive cleavage of methyl α -D-glucoside acetals to ethers using hydrogen as a clean reductant. RSC Advances, 2014, 4 (92), pp.50653-50661. 10.1039/c4ra09350j . hal-03249565

HAL Id: hal-03249565

<https://hal.science/hal-03249565>

Submitted on 4 Jun 2021

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PAPER

Catalytic reductive cleavage of methyl α -D-glucoside acetals to ethers using hydrogen as a clean reductant

Cite this: DOI: 10.1039/x0xx00000x

Charlotte Gozlan,^{a,b} Romain Lafon,^a Nicolas Duguet,^a Andreas Redl^b and Marc Lemaire^a

Received 00th January 2012,

Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

The palladium-catalysed reductive cleavage of methyl glucoside acetals has been studied using hydrogen as a clean reducing agent. The reaction proceeds at 120°C in cyclopentyl methyl ether (CPME) without acid co-catalyst. Under these conditions, the corresponding methyl glucoside monoethers were obtained with poor to good isolated yields (37-81%) and high selectivities (86-99%).

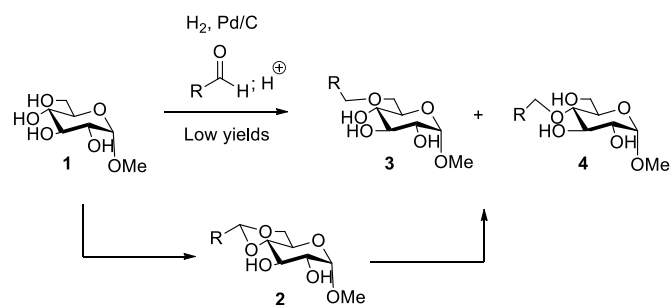
Introduction

Over the last century, environmental issues and ecological impacts awareness have increased the necessity to use nontoxic and biodegradable surfactants.¹ In this context, carbohydrate-derived surfactants have recently been gaining much attention due to their innocuous nature and the fact that they could be obtained from renewable resources in bulk quantities.^{2,3} Sucrose esters,⁴ alkyl glucosides⁵ and polyglucosides (APGs)⁶ and sorbitan esters^{7,8} are representatives of these bio-based surfactants that are commercially produced.⁹ For instance, they are employed in many applications like emulsifiers in food industry and polymerization, detergents, cosmetics and cleaning products. APGs are quite stable under neutral and basic conditions and usually exhibit high hydrophilic-lipophilic balances (HLB's) which make them perfectly adequate for detergent applications. For other applications requiring lower HLB's such as emulsifiers, carbohydrate fatty acid esters are usually preferred. However, these surfactants are vulnerable under acid and basic conditions. As a result, the pH-window of their optimal utilization is relatively narrow. Carbohydrate alkyl ethers have been proposed as alternatives – with similar HLB's – since ethers exhibit higher stability towards hydrolysis and are not affected by esterases. For example, methyl 6-*O*-dodecanyl- α -D-glucopyranoside has an enhanced antimicrobial activity compared to the corresponding ester against *Staphylococcus aureus*^{9,10} and *Listeria spp.*,¹¹ probably due to its greater retention by the bacteria cell. On the downside, even if carbohydrate alkyl ethers present adequate features (a sugar moiety and a linear chain) for biodegradability, they could lead to higher bioaccumulation than their ester derivatives.

The chemical syntheses of sugar ethers are notoriously laborious and most approaches rely on multi-step preparation including protection/deprotection steps due to the polyhydroxylated nature of the carbohydrates. The use of such strategies results in a very high production cost which is not acceptable for widespread industrial applications. Moreover, sugar ethers are usually prepared using polar expensive and/or toxic solvents such as dimethylsulfoxide (DMSO), dimethylformamide (DMF) and dimethylacetamide (DMA). In order to install the ether functionality, traditional methods usually rely on the Williamson synthesis using a strong base and an alkyl halide or pseudo-halide.¹³ For obvious selectivity reasons, this protocol requires multi-step protection/deprotection strategies, resulting in a low atom-economy and the production of large quantities of waste. When carrying out using prior protections, the reaction affords low selectivity and moderate yields. In carbohydrate chemistry, the direct functionalization of individual hydroxyl group by an alkyl chain is very attractive but also challenging due to the great difference of polarity between the sugar and the aliphatic moiety. However, some interesting synthetic routes have been reported in the literature. Queneau et al. have studied the catalytic etherification of sucrose with a fatty terminal epoxide using various tertiary amines or a strongly basic anion-exchange resin as catalysts.¹⁴ The reaction requires an excess of sucrose and the use of DMSO as solvent. These conditions afforded mixtures of sugar monoethers with moderate yields and the formation of diethers could not be avoided. Mortreux et al. have reported a sucrose-butadiene telomerization reaction using a palladium catalyst in water.¹⁵ However, the scope is limited to the access to mono- and dioctadienyl ethers. Moreover, the use of expensive homogeneous catalysts makes difficult the industrialization of this methodology. The main problem of these methods is not the regioselectivity of the substitution (that is not necessarily required for a commercial surfactant) but the possibility to form polysubstituted products. In fact, their presence could dramatically change the physicochemical properties as they could exhibit very different polarities (mono-, di-, and polyethers) and HLB's.

For several years, our group has been interested in developing green methodologies for the catalytic direct reductive *N*- or *O*-alkylation of weak nucleophiles such as anilines,¹⁶ amides,¹⁷ ureas,¹⁸ alcohols¹⁹ and glycerol²⁰ using hydrogen as a clean reducing agent.

This method seemed particularly attractive for the alkylation of carbohydrates since no salts are produced, water is obtained as the by-product and the atom economy is usually very high. To the best of our knowledge, only one patent has described the direct reductive alkylation on sugar derivatives to give the corresponding ethers. Indeed, Tulchinsky *et al.* have reported the alkylation of sorbitol using a range of aldehydes to give sorbitan ethers upon dehydration of sorbitol.²¹ However, we noticed a lack of reproducibility when repeating this protocol on sorbitol but also on other substrates such as methyl glucoside, and the results obtained were not satisfying (< 5 % GC yields). This result corroborates well with our own findings. Indeed, the yield of methyl glucoside ethers were very low when carrying out the direct reductive alkylation of methyl glucoside with a range of aldehydes under our previously optimized conditions [polyol (40 equiv), aldehyde (1 equiv), 5%-Pd/C (0.5 mol% in Pd) and CSA (10 wt%) under hydrogen atmosphere]. Consequently, we turned our attention to the development of a two-step procedure involving the preparation of methyl glucoside acetals and their subsequent reductive cleavage to the corresponding ethers (Scheme 1).



Scheme 1. Synthesis of methyl glucoside monoethers **3** and **4** directly from methyl glucoside **1** (top) and from a two-step procedure *via* an acetal derivative **2** (bottom).

If the acetalisation of sugar or sugar derivatives is relatively well documented, the reductive cleavage of acetals to ethers has been, by far, less studied. It is usually carried out using sodium,²² aluminum,²³ or boron hydrides,²⁴ and hydrosilanes.²⁵ Nevertheless, these hydride sources are very reactive towards air and moisture and require safety precautions. Their hydrolysis should be carefully performed and gives large quantities of salts. In this context, we have recently developed a regioselective cleavage of acetals using hydrosiloxanes such as tetramethyldisiloxane (TMDS) with metal triflates as catalysts.²⁶ This protocol was also extended to the preparation of sugar ethers from the corresponding sugar acetals.²⁷ Even if hydrosiloxanes are safer to use, they are expensive and the work-up could be difficult especially on the large scale. The reductive cleavage of acetals to ethers could also be carried out by catalytic hydrogenolysis.^{20b,28-31} In carbohydrate chemistry, the hydrogenolysis of acetals is mainly used for protection purposes and the resulting ethers should be easily removed at the end of the reaction sequence. That is the reason why, most reported procedures described the hydrogenolysis of benzylidene acetals. However, to the best of our knowledge, such methodologies have never been described on sugar derivatives bearing long alkyl chain acetals that are notoriously more stable and more difficult to reduce.

We now report here an efficient two-step procedure for the preparation of methyl glucoside ethers from methyl glucoside through catalytic hydrogenolysis of the corresponding acetals. By comparison with the direct reductive alkylation, this method provides sugar monoethers with improved yields and higher selectivities.

Results and discussion

Preparation of methyl glucoside acetals

The preparation of methyl glucoside acetals **2a-e** has been carried out by acetalisation of unprotected methyl glucoside **1** using a range of linear alkyl aldehydes. For this purpose, we have adapted our previously reported conditions²⁷ in which DMF and (1*R*)-10-camphorsulfuric acid (CSA) were used as solvent and acid catalyst, respectively. Indeed, DMF has been replaced by a less toxic solvent³² (tetrahydrofuran, THF) and CSA was substituted by an ion-exchange resin (Amberlyst-15). Thus, methyl α -D-glucoside **1** (2 equiv) was treated with one equivalent of aldehyde in dry THF using Amberlyst-15 (20 wt%/aldehyde) as a catalyst in the presence of Na_2SO_4 (1.5 equiv) (Figure 1). Under these conditions, methyl glucoside acetals **2a-e** were obtained with poor to moderate yields (26–44%) after purification by column chromatography. It should be noted that this improved procedure allowed the synthesis of these acetals on a medium laboratory scale (up to 100 mmol).

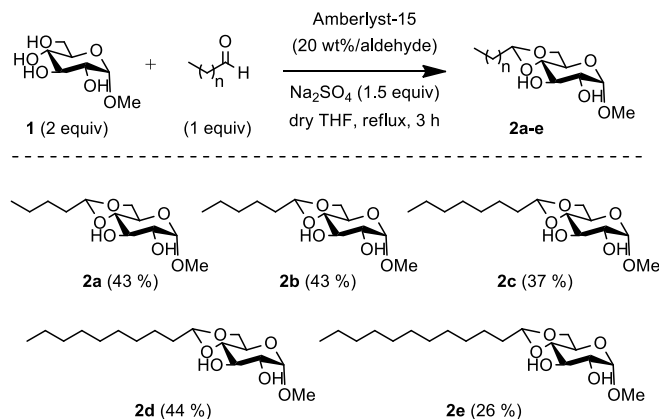


Figure 1. Preparation of methyl 4,6-O-alkylidene α -D-glucoside **2a-e**.

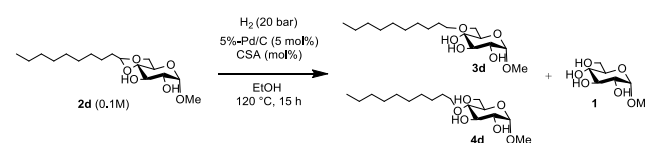
Optimization of the reductive cleavage of acetals

We have recently shown that glycerol acetals were formed as intermediates in the direct reductive alkylation of glycerol with aldehydes and could be converted to their corresponding ethers with low to moderate yields in the presence of an acid co-catalyst.^{20b} Thus, the hydrogenolysis of methyl glucoside acetals was first investigated using these previously optimized conditions and methyl 4,6-*O*-decanylidene α -D-glucopyranoside **2d** was selected as a model substrate for the optimization of reaction parameters.

Acid catalyst loading

Methyl 4,6-*O*-decanylidene α -D-glucopyranoside **2d** (0.1 M in dry EtOH) was first treated under 20 bar of hydrogen in the presence of 5%-Pd/C (5 mol% in Pd) and camphorsulfonic acid (CSA, 5 mol%) as a co-catalyst. The reaction was performed at 120 °C for 15 hours (Table 1). Under these conditions, sugar acetal **2d** was fully converted but no traces of the desired ethers **3d** and/or **4d** were detected by GC after derivatization³³ of the crude reaction mixture (Table 1, Entry 1).

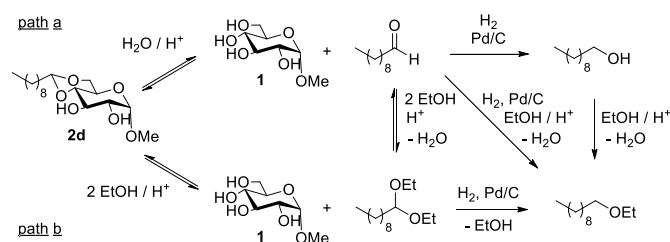
Table 1 Influence of an acid co-catalyst on the hydrogenolysis of methyl 4,6-*O*-decylidene glucoside **2d**^a



Entry	CSA (mol%)	Conv. ^b (2d, %)	Yield ^c (3d+4d, %)	Ratio (3d:4d) ^c
1	5	100	0	-
2	3.5	100	5	80 : 20
3	1.7	99	16	69 : 31
4	0	100	32	63 : 37

^a Experimental conditions: methyl glucoside acetal **2d** (0.33 g), 5%-Pd/C (5 mol% Pd), 20 bar H₂, dry EtOH (10 mL), 120°C, 15 h, stirring speed = 800 rpm. ^b Conversions were determined by ¹H NMR. ^c Yields and ratio of **3d** and **4d** were determined by GC after derivatization of the crude reaction mixture.

However, the only product detected by GC and confirmed by ¹H NMR was found to be ethoxydecane. The formation of this product was probably resulting from the hydrolysis of the starting material **2d** to the corresponding methyl glucoside **1** and decanal, following by its hydrogenation to decanol and subsequent etherification with EtOH under acidic conditions (Scheme 2, path a). Moreover, decanal could also undergo direct catalytic etherification with EtOH in the presence of hydrogen and Pd/C. The presence of methyl glucoside **1** could also be explained by transacetalization of the starting material **2d** with EtOH, leading to the formation of decanal diethylacetal and ethoxydecane after hydrogenolysis (Scheme 2, path b).



Scheme 2. Potential routes to the formation of ethoxydecane by-product.

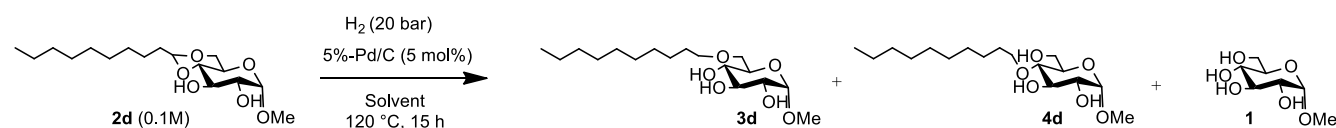
We hypothesized that the acid co-catalyst accelerates the degradation of the acetal in the presence of traces of water. This favours the formation of ethoxydecane, releasing one molecule of

water and thus causing more hydrolysis of the starting material. As a consequence, the reductive cleavage of acetal **2d** was carried out using only 3.5 mol% of CSA and the corresponding methyl glucoside ethers **3d** and **4d** were formed in a 80:20 ratio with 5% overall yield (Table 1, Entry 2). Further decrease of the acid loading to 1.7 mol% led to the formation of the desired ethers with 16% yield in a 69:31 ratio (Table 1, Entry 3). These promising results prompted us to eliminate the acid co-catalyst. Under these conditions, methyl glucoside ethers **3d** and **4d** were obtained with an improved global yield of 32% (Table 1, Entry 4). On the downside, the regioselectivity of the ring-opening was slightly altered and methyl 6-*O*-decylglucoside **3d** was obtained as the major regioisomer in a 63:37 ratio. The influence of the solvent was next probed.

Solvent screening

In order to determine the best solvent for optimum yield and selectivity, a set of experiments was performed for the reduction of acetal **2d** using various polar protic, polar non protic and non polar solvents (Table 2). First, methyl glucoside acetal **2d** (0.1 M) was reduced under hydrogen (20 bar) with 5%-Pd/C (5 mol% in Pd) using dry MeOH as solvent. The reaction was carried out at 120°C for 15 hours and gave a complete conversion of **2d** (Table 2, Entry 1). Similarly to the result obtained in EtOH (Table 2, Entry 2), methyl glucoside ethers **3d** and **4d** were isolated with a low yield (9%) and methoxydecane was obtained as the major product. MeOH or EtOH was replaced by a less nucleophilic alcohol such as ^tBuOH in order to limit the formation of side products. Under these conditions, the desired ethers were formed with an improved yield of 44% but no selectivity in **3d** or **4d** was obtained (Table 2, Entry 3). We next focused our attention on non-protic solvents with medium polarities such as ethereal solvents. The utilization of our home-made glycerol-based 1,2,3-trimethoxypropane³⁴ (TMP) gave a low conversion of **2d** (14%) and a very low yield of the desired ethers (5%) (Table 2, Entry 4). However, when the reaction was performed in methyl *tert*-butylether (MTBE), tetrahydrofuran (THF) or 2-methyltetrahydrofuran (2Me-THF), the conversion was much more satisfying (69-94%) and the best yield (43%) of ethers **3d** and **4d** was obtained using THF as solvent (Table 2, Entries 5-7).

Table 2 Influence of the solvent in the hydrogenolysis of methyl 4,6-*O*-decylidene glucoside **2d**^a



Entry	Solvent	Log P	Conv. ^b (%)	Yields ^c (%)				Selectivity ^c (6-ether 3d / 4-ether 4d)
				Ether 3d	Ether 4d	Ethers 3d+4d	MeGlu 1	
1	MeOH	-0.77	98	9	0	9	2	<i>n.d.</i>
2	EtOH	-0.31	100	20	12	32	-	63 : 37
3	^t BuOH	0.35	89	22	22	44	31	50 : 50
4	TMP	-0.18	14	0	5	5	0	<i>n.d.</i>
5	MTBE	0.94	94	18	16	34	9	53 : 47
6	THF	0.46	69	22	21	43	8	51 : 49
7	2Me-THF	1.20	87	19	23	42	11	45 : 55
8	DBE	1.4	83	37	21	58	20	64 : 36
9	CPME	1.59	83	44	26	70	6	63 : 37
10	Heptane	4.66	60	32	19	51	9	62 : 38
11	Dodecane	6.82	65	27	30	57	5	47 : 53

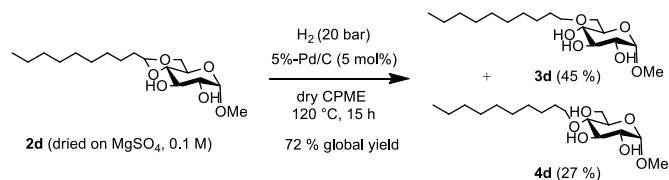
^a Experimental conditions: methyl glucoside acetal **2d** (0.33 g), 5%-Pd/C (5 mol% Pd), 20 bar H₂, dry solvent (10 mL), 120°C, 15 h, stirring speed = 800 rpm.

^b Conversions were determined by ¹H NMR. ^c Yields and ratio of **3d** and **4d** were determined by GC after derivatization of the crude reaction mixture. TMP = 1,2,3-trimethoxypropane, MTBE = methyl *tert*-butylether, DBE = dibutylether, CPME = cyclopentylmethylether.

It should be noted that the formation of methyl glucoside **1** was significantly reduced compared to the result obtained with *tert*-butanol. Increasing the hydrophobic character of the solvent had a positive effect on the reaction outcome. Indeed, the reductive cleavage of acetal **2d** gave the corresponding ethers with 58% yield when the reaction was conducted in di-butylether (DBE) (Table 2, Entry 8). The best result was obtained using cyclopentylmethylether (CPME) as solvent. Under these conditions, the conversion of **2d** reached 83% and methyl decyl glucoside **3d** and **4d** were obtained with 70% combined yield (Table 2, Entry 9). Interestingly, a moderate 63% selectivity was obtained for the 6-ether regioisomer **3d**. The use of non-polar solvents was also investigated. Using heptane or dodecane, the conversion dropped to 60 and 65% and ethers **3d** and **4d** were recovered with 51 and 57% yields, respectively (Table 2, Entries 10–11). These results could be explained by the lower solubility of the sugar acetal **2d** in these non-polar solvent. Finally, CPME was selected as the best solvent for the reductive cleavage of acetal **2d** as it offers a good compromise which preserves high selectivity with a satisfying conversion (Table 2, Entry 9). It should be noted that CPME has been proposed as a safer alternative to other ether solvents due to its narrower explosibility range and greater resistance to peroxide formation.³⁵ Moreover, its high hydrophobicity, limited miscibility in water (1.1g/100g at 23°C) and low vaporization energy allow its use as a potential process solvent that could be recovered and reused. In addition, CPME has a low toxicity and has been considered negative for genotoxicity and mutagenicity.³⁶

Drying agent

As can be seen from this set of results (Table 2), the main limitation of the product yield was due to the production of methyl glucoside **1** from the hydrolysis of the starting material. Considering that traces of water are relatively difficult to avoid, methyl glucoside acetal **2d** was pre-dried using MgSO₄ as a dehydrating agent and submitted to the previously optimized conditions [**2d** (0.1 M in dry CPME), 20 bar H₂, 5%-Pd/C (5 mol%), 120 °C, 15 h]. Under these conditions, the conversion was maintained (82%) and the global yield of **3d** and **4d** was slightly improved to 72% (Scheme 3).



Scheme 3. Hydrogenolysis of **2d** with pre-drying.

Catalyst loading

The influence of the catalyst loading was next probed but the nature of the metal and its support was not investigated in this paper. Indeed, previous studies have already shown that Pd/C was one of the best catalysts to perform the reductive etherification of alcohols with aldehydes or ketones.^{20d,37} Thus, using 1 mol% of Pd (5% on charcoal), the conversion of **2d** reached 18% but no traces of sugar ethers **3d** or **4d** has been detected by GC (Table 3, Entry 1). Increasing the catalyst loading to 5 and 10 mol% had a beneficial effect on the conversion and the desired ethers were formed with 72 % yield in both cases (Table 3, Entries 2-3). Considering the fact that the starting material was not totally converted when using 5 mol% of a 5%-Pd/C catalyst (Table 3, Entry 2), the overall selectivity was better in this case and reached 88%.

Table 3 Influence of the Pd/C loading^a

Entry	Pd catalyst (loading)	Conv. ^b (2d , %)	Yield ^c (3d+4d , %)	Yield ^c (1 , %)
1	5%-Pd/C (1 mol%)	18	0	0
2	5%-Pd/C (5 mol%)	82	72 (63 : 37)	10
3	5%-Pd/C (10 mol%)	> 99	72 (60 : 40)	13
4	10%-Pd/C (5 mol%)	90	55 (64 : 36)	10

^a Experimental conditions: methyl glucoside acetal **2d** (0.33 g, dried on MgSO₄), 5%-Pd/C, 20 bar H₂, dry CPME (10 mL), 120°C, 15 h, stirring speed = 800 rpm. ^b Conversions were determined by ¹H NMR. ^c Yields and ratio of **3d** and **4d** were determined by GC after derivatization of the crude reaction mixture.

It should be noted that the hydrolysis of the acetal **2d** seems to be promoted by Pd/C since more methyl glucoside by-product **1** was produced at high catalyst loading. In order to determine the role of the support, the hydrogenolysis of **2d** was also carried out using 5 mol% of a 10%-Pd/C catalyst (Table 3, Entry 4). Under these conditions, the conversion was improved to 90% but the overall yield was only 55% and the hydrolysis could not be avoided. Finally, the use of 5 mol% of a 5%-Pd/C was found optimum for both the yield and the selectivity.

Influence of the temperature

The influence of the temperature was next studied using **2d** (dry on MgSO₄, 0.1 M in dry CPME) and 5%-Pd/C (5 mol%) under 20 bar of hydrogen for 15 hours (Table 4).

Table 4 Hydrogenolysis of methyl 4,6-*O*-decylidene glucoside **2d** at different temperatures^a

Entry	Temperature (°C)	Conv. ^b (2d , %)	Yield ^c (3d+4d , %)	Selectivity ^c (3d+4d , %)	Yield ^c (1 , %)
1	100	65	33 (60 : 40)	51	0
2	120	82	72 (63 : 37)	88	10
3	135	> 99	77 (65 : 35)	78	13
4	150	83	71 (63 : 37)	86	12

^a Experimental conditions: methyl glucoside acetal **2d** (0.33 g, dried on MgSO₄), 5%-Pd/C (5 mol%), 20 bar H₂, dry CPME (10 mL), 15 h, stirring speed = 800 rpm. ^b Conversions were determined by ¹H NMR. ^c Yield, selectivity and ratio of **3d** and **4d** were determined by GC after derivatization of the crude reaction mixture.

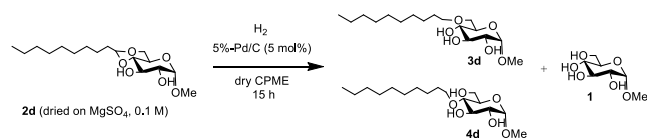
When the temperature was increased from 100 to 135°C, the conversion of methyl glucoside acetal **2d** increased gradually from 65 to > 99% (Table 4, Entries 1-3). A similar trend was observed for the yield of the desired ethers **3d** and **4d** and a maximum yield of 77% was obtained at 135°C (Table 4, Entry 3). At a higher temperature

(150°C), the conversion was surprisingly not complete (83%) and the sugar ethers **3d** and **4d** were recovered with only 71% yield (Table 4, Entry 4). If the yield is only taken into account, the best temperature seems to be 135°C as it gave a 77% yield. However, this result could not be improved since the conversion is complete at this temperature. When the selectivity in **3d** and **4d** is taken into account, the best result (88%) is obtained at 120°C. Moreover, the 72% yield of methyl glucoside ethers could be further improved as the conversion was not complete under these conditions. Finally, a temperature of 120°C was selected for further optimization.

Influence of the pressure

Considering the difficulties encountered to obtain a complete conversion in acetal **2d** while preserving a high selectivity, the influence of the H₂ pressure was next studied. Indeed, the reductive cleavage of an acetal pressure requires the breaking of a C-O bond and the efficiency of this process is directly linked to the hydrogen availability. Thus, the hydrogenolysis of methyl glucoside acetal **2d** (dry on MgSO₄, 0.1 M in dry CPME) was performed using 5%-Pd/C (5 mol%) at 120°C for 15 hours under different hydrogen pressure (Table 5).

Table 5 Hydrogenolysis of methyl 4,6-*O*-decylidene glucoside **2d** at different H₂ pressure^a



Entry	Temp. (°C)	H ₂ (bar)	Conv. ^b (2d , %)	Yield ^c (3d+4d , %)	Yield ^c (1 , %)
1	120	10	61	50 (62:38)	10
2	120	20	82	72 (63:37)	10
3	120	30	94	79 (59:41)	14
4	135	30	> 99	64 (62:38)	13

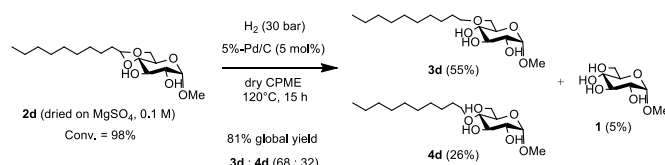
^a Experimental conditions: methyl glucoside **2d** (0.33 g, dried on MgSO₄), 5%-Pd/C (5 mol%), H₂, dry CPME (10 mL), 15 h, stirring speed = 800 rpm. ^b Conversions were determined by ¹H NMR. ^c Yield, selectivity and ratio of **3d** and **4d** were determined by GC after derivatization of the crude reaction mixture.

When the hydrogen pressure was increased from 10 to 30 bar, the conversion of the starting material **2d** increased gradually from 61 to 94% (Table 5, Entries 1-3). A similar trend was observed for the global yield of the desired ethers **3d** and **4d** that reached a maximum (79 %) for a hydrogen pressure of 30 bar (Table 5, Entry 3). It should be noted that the hydrolysis side-reaction was slightly amplified at such pressure. No attempt to further increase the hydrogen pressure was made for technical and safety reasons. Then, the reaction was carried out at 135°C under 30 bar of hydrogen (Table 5, Entry 4). Under these conditions, the conversion of acetal **2d** was complete but more by-products were observed and the desired ethers were only obtained with 64% yield. Finally, a pressure of 30 bar of hydrogen at 120°C was selected for further optimization.

Mechanical stirring

For convenience, the optimization of the reductive cleavage of methyl glucoside acetal **2d** was carried out using a 30-mL stainless steel autoclave using magnetic stirring. Even if this set-up is not perfectly adequate for a tri-phasic system (liquid, solid and gas), it allowed a rapid screening of the reaction parameters and led to the

preparation of methyl glucoside ethers **3d** and **4d** with a satisfying yield of 79%. Conversely, the utilization of a 300-mL stainless steel autoclave fitted with a mechanic stirrer was found more appropriate for preparative purposes. Indeed, the hydrogenolysis of **2d** (1.0 g, 0.1 M in dry CPME) using a perfectly stirred autoclave (800 rpm) under the previously optimized conditions [5%-Pd/C (5 mol%), H₂ (30 bar), 120°C, 15 hours] afforded the desired ethers **3d** and **4d** with an improved 81% GC-yield (Scheme 4).



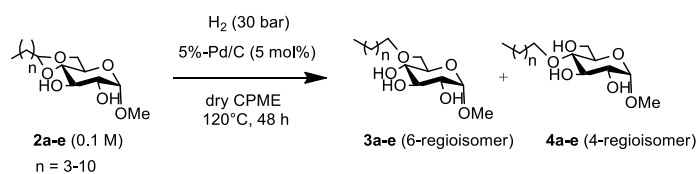
Scheme 4. Hydrogenolysis of **2d** under optimized conditions with mechanic stirring.

Under these conditions, methyl 6-decyl glucoside **3d** was obtained as the major regioisomer with 68% selectivity and the formation of methyl glucoside **1** was strongly minimized (5%).

Scope of methyl glucoside acetals

In order to evaluate the scope and the limitations of the method, the optimized conditions were applied to a range of methyl glucoside 4,6-*O*-acetals **2** bearing different alkyl chain length (Table 6). The reductive cleavage of these acetals was carried out on the large scale without prior drying on MgSO₄ and the reaction time was increased to 48 h in order to obtain better conversion.

Table 6 Scope of methyl glucoside acetals^a



Entry	Substrate 2	Conv. ^b (2 , %)	Product ratio	Yield ^c (3+4 , %)	Selectivity (3+4 , %)
1		42	3a:4a (70 : 30)	38	90
2		37	3b:4b (72 : 28)	37	> 99
3		42	3c:4c (75 : 25)	40	95
4		59	3e:4e (73 : 27)	51	86

^a Experimental conditions: methyl glucoside acetal **2a-e** (20 mmol), 5%-Pd/C (5 mol%), H₂ (30 bar), dry CPME (200 mL), 120°C, 15 h, stirring speed = 800 rpm. ^b Conversions were determined by ¹H NMR. ^c Isolated yields. ^d Ratio of **3a-e** and **4a-e** were determined by GC after derivatization of the crude reaction mixture.

The hydrogenolysis of methyl 4,6-*O*-pentylidene glucoside **2a** afforded the corresponding mixture of methyl 4-pentyl- and 6-pentyl-glucoside ethers **3a** and **4a** in a moderate 38% isolated yield (Table 6, Entry 1). A similar yield (37%) of ethers **3b** and **4b** was obtained

when starting from methyl 4,6-*O*-hexylidene glucoside **2b** (Table 4, Entry 2). Starting from acetals with a longer alkyl chain such as **2c** and **2e**, the yield of the desired ethers increased to 40 and 51%, respectively (Table 6, Entries 3-4). This observation could be explained by the fact that hydrogen is more soluble in a non-polar medium, provided here by the presence of the lipophilic alkyl chain. It should be added that the ratio between 4-alkyl- and 6-alkyl-regioisomers was barely affected with the increase of the alkyl chain length. However, the conversions of the starting materials were not complete even after 48 hours at 120°C. Ethers **3a-e** and **4a-e** have been isolated as the only products of the reaction and no traces of side products, such as methyl glucoside **1**, has been detected under these conditions. This observation is well translated if the selectivities are taken into account. Indeed, the desired ethers were formed with good to excellent selectivities ranging from 86 to > 99% (Table 6, Entries 1-4).

Mechanistic considerations

Contrary to our previous works²⁰ on the reductive alkylation of glycerol with aldehydes, the reductive cleavage of methyl glucoside acetals **2a-e** proceeds in the absence of an acid co-catalyst. Indeed, in the latter case, the presence of CSA was found deleterious for the product yield as it also promotes the hydrolysis of the starting material (see Table 1). Thus, we hypothesized that the acidity of the Pd/C catalytic system is enough to activate the acetal and to promote the hydrogenolysis of the C-O bond. This hypothesis is supported by the works of Kita^{37a} and Marecot^{37b} who have shown that the support acidity has a crucial role in the reductive alkylation of alcohols without acid co-catalyst. Consequently, a mechanistic rationale was proposed to account for the formation of methyl 6-alkyl glucoside ethers **3a-e** as the major regioisomers (Figure 2). The acetal function could be activated by Pd with the assistance of the 3-hydroxyl group of methyl glucoside. In this configuration, hydrogen could be preferentially delivered to the C-O(4) bond that breaks to furnish methyl 6-alkyl glucoside as the major regioisomer.

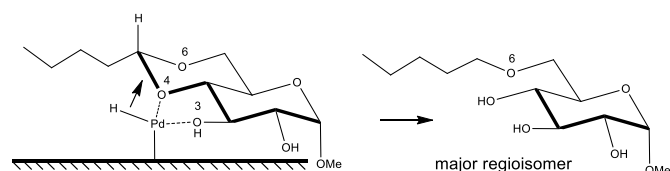


Figure 2. Proposed mechanism for the preferential ring cleavage of acetals.

Conclusions

In conclusion, we have developed a cheap and environmentally-friendly access to methyl glucoside ethers through the catalytic hydrogenolysis of the corresponding acetals. The reductive cleavage of these acetals proceeds in the presence of Pd/C using hydrogen as a clean reducing agent and CPME as solvent. Under these conditions, the desired methyl glucoside ethers were formed with poor to good yields (37-81%) and high selectivities (86-99%). Moreover, we have also shown that the presence of an acid co-catalyst was not necessary and, contrary to our previous reports, could be deleterious for the overall process. It should be added that methyl glucoside ethers have been obtained as a mixture of regioisomers with a preference for the 6-alkyl regioisomer. A mechanism has been proposed to account for this regioselectivity. Current investigations are now focused upon expanding the scope to other sugars or sugar derivatives and increasing the regioselectivity of this method.

Experimental

General information

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Methyl α -D-glucoside **1** (> 98% purity) was purchased from Sigma-Aldrich or Alfa-Aesar and Pd/C (5 or 10 %, Pd on activated carbon, reduced and dry, Escat 1431) from Strem Chemicals. Valeraldehyde, hexanal, octanal, decanal and dodecanal were supplied by Sigma-Aldrich or Alfa-Aesar. Amberlyst 15 dry was bought from Rohm and Haas. All other reagents and solvents were used as received without further purification. NMR spectra were acquired on a Bruker 300 (¹H, 300 MHz; ¹³C, 75 MHz) spectrometer at 293 K. Electrospray ionization (ESI) mass spectra (MS) and High-Resolution Mass Spectra (HRMS) were recorded in the positive mode using spectrometer (MicroTOFQ-II, Bruker Daltonics, Bremen). Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with silica gel Merck 60 F254 (0.25 mm) revealed with a solution of sulfuric acid at 2.5 v/v% in ethanol. Flash column chromatography was performed with silica gel Merck Si 60 (40–63 μ m). Infrared (IR) spectra were recorded in a SMART iTR-Nicolet iS10 spectrometer using Attenuated Total Reflectance (ATR) and the wavenumbers (ν max) are expressed in cm^{-1} . Melting points were measured using a Kofler apparatus and noted in °C.

General procedure for the preparation of methyl α -D-glucoside acetals.

In a 100-mL round bottom flask, under an argon atmosphere, methyl α -D-glucoside **1** (3.22 g, 16.6 mmol, 2 equiv) was dissolved in dry THF (10 mL) with sodium sulfate (1.8 g, 12 mmol, 1.5 equiv) under an argon atmosphere. The aldehyde (8.3 mmol, 1 equiv) was added dropwise over a 1-min period, followed by Amberlyst 15 (20wt%/aldehyde). The mixture was magnetically stirred at reflux (66°C) for 3 hours. After cooling to room temperature, the reaction mixture was filtered, washed with EtOAc (2 \times 25 mL) and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc:cyclohexane) to give methyl 4,6-*O*-alkylidene α -D-glucoside **2a-e** as a single diastereoisomer.

General procedure for the reductive cleavage of methyl α -D-glucoside acetals.

Methyl 4,6-*O*-alkylidene α -D-glucoside **2a-e** (3 mmol) was diluted in dry CPME (30 mL) and 5%-Pd/C (0.45 g, 5 mol% in Pd) was added in a 100-mL stainless steel autoclave. The reactor was tightly closed, purged three times with hydrogen and hydrogen pressure was introduced (30 bar). The system was heated at 120°C and mechanically stirred for 15 hours. After cooling to room temperature, hydrogen pressure was released and the reaction mixture was then dissolved in absolute ethanol (100 mL) and filtered (Millipore Durapore filter 0.01 μ m). The filtrate was evaporated under reduced pressure and the residue was purified by flash chromatography to give methyl glucoside ethers **3a-e** and **4a-e**. GC analysis after silylation revealed a mixture of 4- and 6-ether regioisomers.

Acknowledgments

The authors would like to thank the company TEREOS SYRAL SAS and the Association Nationale de la Recherche et de la Technologie (ANRT) for financial support through a CIFRE grant (2011/1660) for C.G.

Notes and references

^a Laboratoire de CAlyse SYNthèse et ENvironnement (CASYEN), Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), CNRS, UMR-5246, Université Claude Bernard Lyon 1, 43 boulevard du 11 novembre 1918, Bât. Curien/CPE, 69622, Villeurbanne, France. E-mail:

marc.lemaire.chimie@univ-lyon1.fr; Fax: +33-472-43-14-08; Tel: +33-472-43-14-07.

^b TEREOS SYRAL SAS, Z.I et Portuaire B.P.32, 67390 Marckolsheim, France. E-mail: andreas.redl@tereos.com; Tel: +33-388-58-16-15.

Electronic Supplementary Information (ESI) available: [GC method, general procedures and characterization data of products]. See DOI: 10.1039/c000000x/

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