Consecutive catalytic hydroformylation-acetalization of glucal derivatives with rhodium–phosphite and pyridinium toluene-*p*-sulfonate as catalysts: the influence of protecting groups.

Elena Fernández,[a] Alfonso Polo,[b] Aurora Ruiz,[a] Carmen Claver[a]* and Sergio Castillón*[a]†

[a] *Departament de Química, Universitat Rovira i Virgili, Pl Imperial Tarraco 1, 43005 Tarragona, Spain*
[b] *Departament de Química, Universitat de Girona, Girona, Spain*

Consecutive catalytic hydroformylation-acetalization of unsaturated carbohydrates (glucals) to give the dimethyl acetal of 2-*C*-formyl-D-alditol derivatives using the catalytic system [Rh(μ-OMe)(cod)]$_2$/P(O-*o*-Bu^{t}C$_6$H$_4$)$_3$/PPTS is strongly dependent on the protecting groups on the carbohydrate.

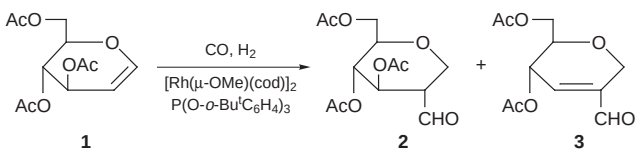
Sequential reactions have emerged as a direct and economic synthesis procedure, because different reactions can be carried out without isolating any intermediates, which means greater economy in solvents and purification.[1] The most popular sequential reactions are the so-called domino[2] (cascade) or tandem[3] reactions, in which several bonds are formed through different intermediates. In the consecutive 'one-flask' reactions, the product of one reaction is the starting material for a second reaction that occurs in the same flask. Although many examples of this methodology have been published, there are few examples of catalytic consecutive reactions which require different catalysts.[1–3]

We have already reported the synthesis of acetals from alkenes by means of a consecutive hydroformylation-acetalization process with rhodium–phosphine and pyridinium toluene-*p*-sulfonate (PPTS) as hydroformylation and acetalization catalysts respectively.[4] Since the catalyst for the hydroformylation process requires the presence of basic phosphine ligands, and the acetalization reaction requires an acid catalyst, the main goal of that process was to find two compatible catalytic systems. The solution was to use phosphonium or pyridinium salts in the presence of phosphine.

Here we show that the consecutive hydroformylation-acetalization of unsaturated carbohydrates (glucals) using rhodium complexes and PPTS as catalysts, respectively, is strongly dependent on the protecting groups in the carbohydrate.

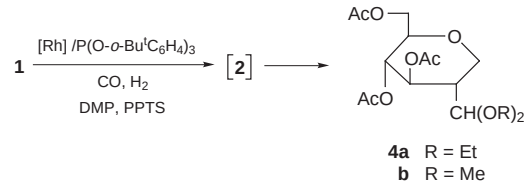
We have previously reported[5,6] the hydroformylation of 3,4,6-tri-*O*-acetyl-D-glucal **1** using the [Rh(μ-OMe)(cod)]$_2$/P(O-*o*-Bu^{t}C$_6$H$_4$)$_3$[7] catalytic system to give a mixture of aldehydes which are the result of introducing the formyl group at position 2 of the sugar ring (Scheme 1). The low selectivity was due to the elimination of AcOH from **2** to give an α,β-unsaturated aldehyde **3**, under the drastic reaction conditions required. In order to prevent this elimination we intend to convert *in situ* the aldehyde function formed in the hydroformylation reaction into the acetal function (Scheme 2). Moreover, this will enable us to deprotect and transform the hydroxy groups and then to take advantage of the reactivity of the acetal or aldehyde function.

Thus, the hydroformylation of **1** was carried out with the catalytic system [Rh(μ-OMe)(cod)]$_2$/P(O-*o*-Bu^{t}C$_6$H$_4$)$_3$, under



1 **2** **3**

Scheme 1



4a R = Et
b R = Me

Scheme 2

standard hydroformylation conditions (50 bar, 100 °C, CH_2Cl_2).[5,6] A mixture of aldehydes **2** and **3** was principally obtained (Table 1, entry 1). When the reaction was performed in $CH(EtO)_3$ under the same reaction conditions, the main compounds obtained were **2** and **3** together with small amounts of several hydroformylation-acetalization products such as the acetal **4a** (entry 2). Adding 60 mg of PPTS per 5 mmol of substrate to the reaction mixture gave a complex mixture, in which the hydroformylation-acetalization product **4a** was predominant, but the aldehydes had not completely disappeared (entry 3). By increasing the amount of PPTS, higher percentages of diethyl acetal **4a** were obtained, although conversion was low (entry 4). When the solvent was $CH(OMe)_3$ conversion decreased, although the selectivity in the dimethoxy derivative **4b**‡ was similar (entry 5). The use of 2,2-dimethoxypropane, another useful reagent for acetal formation, as the solvent did not allow the acetal to form and the elimination product **3** was obtained instead (entry 6). Interestingly, when PPTS was added, acetal **4b** was principally obtained in 66% yield (entry 7). Small quantities of the less reactive α,β-unsaturated aldehyde **3** remained in the mixture.

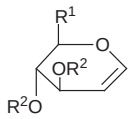
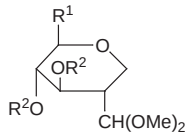
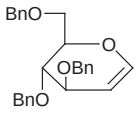
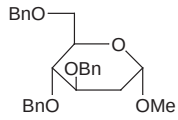
In the presence of PPTS the acetalization reaction is faster than the elimination of AcOH from **2** to give **3**. Moreover, it is interesting to note that there were fewer secondary reaction products, such as isomeric aldehydes (< 10%) and hydrogenation (< 10%) products, under these slightly acid conditions.

Table 1 Hydroformylation-acetalization of 3,4,6-tri-*O*-acetyl-D-glucal **1** with the catalytic system [Rh(μ-OMe)(cod)]$_2$/P-(O-*o*-Bu^{t}C$_6$H$_4$)$_3$/PPTS[a]

Entry	PPTS/mg	Solvent	Conversion (%)[b]	Products (%)[c] **2**	**3**	**4a**	**4b**
1	—	$Cl_2C_2H_4$	90	54	22	—	—
2	—	$HC(OEt)_3$	87	9	24	27	—
3	60	$HC(OEt)_3$	98	28	10	51	—
4	120	$HC(OEt)_3$	74	6	11	55	—
5	60	$HC(OMe)_3$	75	3	2	—	52
6	—	DMP[d]	94	22	43	—	—
7	60	DMP[d]	92	0	9	—	66

[a] Standard conditions: glucal (5 mmol), [Rh(μ-OMe)(cod)]$_2$ (0.05 mmol), P(O-*o*-Bu^{t}C$_6$H$_4$)$_3$ (0.5 mmol), PPTS, solvent (15 ml), 100 °C, 50 bar, CO/H_2 = 1, 48 h. [b] Percentage of transformed product. [c] Detected by GC. Other minor aldehydes and small amounts of the hydrogenation product were also observed. [d] DMP = 2,2-dimethoxypropane.

Table 2 Hydroformylation-acetalyzation of glucal derivatives[a]

Substrate	Product	Yield (%)[b]
		
5 $R^1 = CH_3$, R^2 = Ac	**8** $R^1 = CH_3$, R^2 = Ac	65
6 $R^1 = CH_2OPiv$, R^2 = Piv	**9** $R^1 = CH_2OPiv$, R^2 = Piv	56
7 $R^1 = CH_2OBz$, R^2 = Bz	**10** $R^1 = CH_2OBz$, R^2 = Bz	42
		85
11	**12**	

[a] Standard conditions: glucal (5 mmol), $[Rh(\mu\text{-OMe})(cod)]_2$ (0.05 mmol), $P(O\text{-}o\text{-Bu}^tC_6H_4)_3$ (0.5 mmol), PPTS (0.25mmol), solvent (15 ml), 100 °C, 50 bar, CO/H_2 = 1, 48 h. [b] Isolated yield.

The glucal **5** reacted in similar hydroformylation-acetalization conditions to give the acetal **8** in a 65% yield (Table 2).

When the hydroxy groups in the carbohydrates were protected with other acyl derivatives such as pivaloyl (**6**) or benzoyl (**7**), the hydroformylation-acetalization products **9** and **10** were also obtained as the main products although in lower yields. This was probably because the steric hindrance of these bulkier groups decreases the rate of hydroformylation.

Unexpectedly, benzyl protected glycal **11** gave only the methyl α-glycoside **12** under the hydroformylation-acetalization conditions. As a result, both the rhodium complex and the acidic proton compete to attack the double bond so that when the protecting groups in the hydroxy groups are acyls, the double bond is deactivated. Therefore, the electrophilic attack cannot take place and rhodium coordination is preferred. However, when hydroxy groups are converted to ethers (*e.g.* the benzyl derivative **11**) the double bond is relatively activated and the attack of the acidic proton is faster. The fact that the reactivity of the double bond in the glucal depends on the protecting group can be rationalised as an 'armed-disarmed' effect.[8] This effect has been successfully used in disaccharide synthesis with glycals as glycosyl donors,[9] but to the best of our knowledge this is the first example of this effect being observed in competitive catalytic reactions.

In conclusion, the catalytic system $[Rh(\mu\text{-OMe})(cod)]_2/P(O\text{-}o\text{-Bu}^tC_6H_4)_3$ in the presence of PPTS allows the consecutive hydroformylation-acetalization reaction of glucals, depending on the protecting groups present in the carbohydrate ring. Thus, when hydroxy groups are protected as acyl derivatives the hydroformylation-acetalization leads to the dimethyl acetal of 2-*C*-formylalditol derivatives such as **4a**,**b**, **8**, **9** and **10**. However, when the protecting groups are benzyl, the methyl glycosides resulting from the addition of MeOH to the double bond of glucal are observed, but not the hydroformylation products.

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Notes and References

† E-mail: sergio@argo.urv.es

‡ *Selected data* for **4b**: $\delta_H(CDCl_3)$ 2.01 (s, 3H, $OCOCH_3$), 2.03 (s, 3H, $OCOCH_3$), 2.09 (s, 3H, $OCOCH_3$), 2.33 (tt, *J* 11, 4.8, 1H, H_2), 3.34 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 3.43 (dd, *J* 11.7, 11, 1H, H_{1a}), 3.53 (ddd, *J* 9.1, 4.9, 2.0, 1H, H_5), 4.09 (dd, *J* 12, 2.0, 1H, H_6), 4.12 (dd, *J* 12, 4.9, 1H, $H_{6'}$), 4.22 (dd, *J* 4.8, 1.9, 1H, H_7), 4.24 (dd, *J* 11.7, 4.8, 1H, H_{1e}), 4.95 (t, *J* 9.1, 1H, H_4), 5.19 (dd, *J* 11, 9.1, 1H, H_3): $\delta_C(CDCl_3)$ 20.5, 20.6, 20.6, 43.6, 54.7, 55.6, 62.5, 65.7, 69.4, 72.1, 76.1, 103.6, 169.7, 170.1, 170.6 (Found: C, 51.42; H, 7.00. Calc.: C, 51.72; H, 6.89%).

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