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Converting Unprotected Monosaccharides into Functionalised Lactols in Aqueous Media: Metal-Mediated Allylation Combined with Tandem Hydroformylation–Cyclisation

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The utilisation of biomass and especially carbohydrates for the production of fine chemicals is in accordance with the general principles of sustainable development as agreed in the Rio Declaration.[1] Besides their use in traditional carbohydrate chemistry involving synthetic modification of monosaccharides and synthesis of well defined oligosaccharides, carbohydrates have been utilised as starting material for the production of synthetically valuable intermediates.[2] Literature examples showing the conversion of unprotected carbohydrates into fine chemicals or precursors thereof with potential biological relevance are, however, scarce.

The natural carbonyl functionality of reducing carbohydrates is utilised to extend the carbon chain of unprotected aldoses. One-carbon elongation is classically performed by adding hydrogen cyanide to the carbonyl group of an aldose.[3] More recently, other synthetic approaches extending the carbon chain of monosaccharides with two- or three-carbon atoms have been developed utilising the Wittig reaction[4] and metal-mediated allylation.[5] The products of these reactions have been transformed into higher sugars by dihydroxylation or ozonolysis, whereas the additional synthetic potential of these structures is completely unutilised.

Hydroformylation of olefins into aldehydes and products derived thereof is one of the most important industrial applications of homogeneous catalysis.[6] The combination of high atom efficiency with highly active and selective catalysts makes this transformation a very attractive tool in organic synthesis with complex natural product targets. Hydroformylation of higher alkenes with negligible solubility in water is generally performed in a monophasic system in organic solvents where the catalyst is situated in the same phase with the substrate. Hydroformylation of such alkenes in an aqueous biphasic system enables recycling of the catalyst but generally requires special arrangements, such as a phase transfer agent to reduce the mass transfer limitations.[7] Hydroformylation of polar substrates with minimal solubility in organic solvents, on the other hand, requires non-traditional solvent systems.[8]

In the present work, we have combined the metal-mediated allylation of unprotected monosaccharides with a subsequent highly regioselective hydroformylation reaction. The functional groups of the multifunctionalised polyol structures were targeted selectively in the absence of any kind of protective groups, giving ultimately rise to the formation of functionalised lactols. Moreover, the reactions were performed in aqueous media thus significantly reducing the need for organic solvents.

Sn-mediated allylation of D-mannose and L-rhamnose: D-Mannose (**1**) and L-rhamnose (**2**; that is, 6-deoxy-L-mannose) were allylated in aqueous ethanol using tin as the mediating metal. The reactions were successfully scaled up to 5 g scale (Scheme 1). The monosaccharides were allylated with full conversion giving the corresponding products in a diastereomeric ratio of 3:1 (*threo*/*erythro*). The main diastereomer **3t** derived from D-mannose was further isolated by recrystallisation from ethanol.

Rh-catalysed hydroformylation of polyhydroxylated alkenes: Aldehydes bearing an additional hydroxyl group are expected to undergo an intramolecular acetal formation especially in cases where stable five- or six-membered rings can be formed.[9] We therefore considered that compounds **3** and **4** might prove to be optimal substrates for hydroformylation leading to spontaneous formation of lactols by subsequent intramolecular cyclisation. For this purpose, the commercially available bidentate xantphos ligand (xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) as well as

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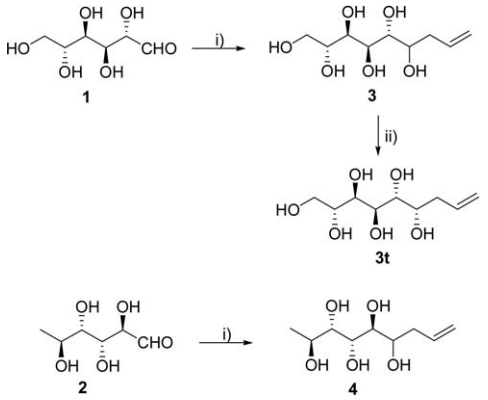


Scheme 1. i) Allyl bromide (3 equiv), Sn (2 equiv), EtOH/H_2O 10:1, 60 °C, 24 h. ii) Recrystallisation from EtOH.

the water soluble counterpart, sulfoxantphos (Figure 1), were applied. In hydroformylation reactions, the corresponding Rh catalysts are known to promote the formation of the linear aldehydes with high selectivity. Moreover, the highly polar sulfoxantphos system provides the possibility to perform the hydroformylation reaction of substrates **3** and **4** in water.

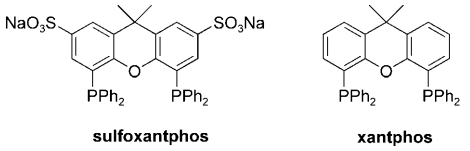


Figure 1. Sulfoxantphos and xantphos ligands.

The reaction conditions were optimised in small-scale experiments in an automated reactor system (AMTEC SPR16). The course of the hydroformylation was followed by online detection of the gas uptake of CO/H_2 and the reaction was stopped when full conversion was achieved (Figure 2). The catalyst was removed by filtration through neutral alumina and the products were analysed by NMR and HRMS measurements. Interestingly, we found that the crude product clearly consisted of one major product only. As anticipated from the considerations above, the ring-closed lactol product containing a six-membered ring had indeed been formed selectively from the linear hydroformylation product. This tandem reaction sequence is depicted in Scheme 2.

The hydroformylation was also performed in synthetically preparative scale in 75 or 100 mL autoclaves with either magnetic or mechanical stirring. The scale up with Rh/substrate ratio 1:150–200 was successful and the results comparable with the small scale experiments (Table 1, entries 1 and 2).

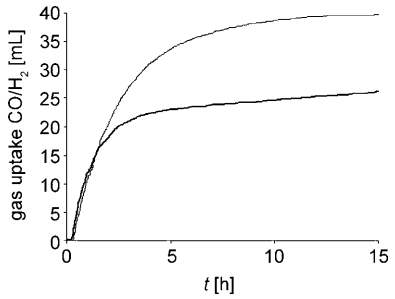
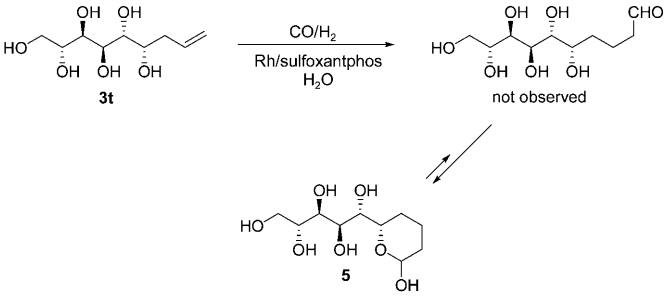


Figure 2. Gas uptake of CO/H_2 in the small scale Rh/sulfoxantphos-catalysed hydroformylations in water. Hydroformylation of **3t** (——): $n_{substrate} = 0.60$ mmol, substrate/Rh = 50, $p(CO/H_2) = 20$ bar, $T = 100$ °C. Hydroformylation of **4** (——): $n_{substrate} = 0.90$ mmol, substrate/Rh = 75, $p(CO/H_2) = 20$ bar, $T = 100$ °C.



Scheme 2. Hydroformylation of the polyol **3t**.

Rh-catalysed hydroformylation of the polyhydroxylated substrate in an aqueous biphasic system: Encouraged by our results, we became interested in finding out whether the polyhydroxylated substrate might also be suitable for further functionalisation in inverted biphasic solvent systems. Thus, the hydroformylation was performed in a biphasic system water/toluene using the hydrophobic Rh/xantphos catalyst. The utilisation of this type of biphasic systems would enable a simple product separation and recycling of the catalyst as the products of the hydroformylation reaction are water soluble and the hydrophobic catalyst remains in the organic phase.[8a]

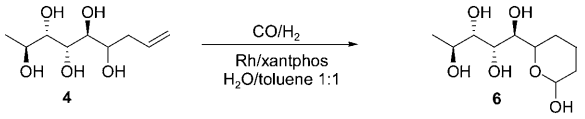
Hydroformylation of the L-rhamnose derived substrate **4** was performed in a 100 mL autoclave with mechanical stirring under the standard reaction conditions (Scheme 3).

The conversion was monitored by the gas uptake of CO/H_2 and the reaction was stopped after 60 h (Figure 3 and Table 1, entry 3).

Table 1. Hydroformylation of the polyhydroxylated substrates **3t** and **4** in synthetically preparative scale.

Entry	Substrate	Ligand	Solvent	Substrate/Rh	Conversion/Yield [%][a]
1	**3t**	sulfoxantphos	H_2O	200	>99:>95
2	**4**	sulfoxantphos	H_2O	150	>99:>95
3[b]	**4**	xantphos	H_2O/toluene 1:1	150	>99:>95

[a] Conversion and yield determined by ^1H NMR. [b] [Rh] in the aqueous layer (determined with ICP) below the detection limit 0.05 mg L^{-1}.



Scheme 3. Hydroformylation of the polyol **4** in inverted biphasic solvent system.

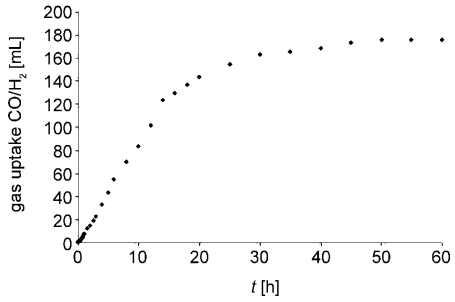


Figure 3. Gas uptake of CO/H_2 in the Rh/xantphos-catalysed hydroformylation of **4** in an inverted aqueous biphasic system.

Gratifyingly, the results were comparable with the hydroformylation in water using the Rh/sulfoxantphos catalyst. These results nicely demonstrate that this concept is indeed suitable for efficient catalyst recycling, which is often difficult to achieve in homogeneous catalysis.

It should be mentioned here that the polyhydroxylated lactol is a structural mimic for a number of naturally occurring and biologically active δ-lactones.[10] The reaction protocol presented herein thus provides an access to valuable intermediates for the synthesis of complex natural product targets or analogues with biological relevance. Currently, we are investigating selective oxidation methods that would allow the conversion of the lactols formed into the corresponding lactones without the use of protective groups. The relative stereochemistry of the lactol ring formed is not locked and the *cis*/*trans* equilibrium is defined by the minimum energy of the ring structure, not by the catalytic reaction itself. Thus, by converting the obtained lactol product into the corresponding lactone, the single stereocentre that is formed in the hydroformylation–cyclisation sequence becomes insignificant, whereas the biological relevance of the product increases.

In conclusion, we have shown that readily available starting material (naturally occurring monosaccharides) can efficiently be converted into highly functionalised polyhydroxylated lactols by the combination of two simple transformations: allylation and tandem hydroformylation–cyclisation. Moreover, the reaction sequence can be carried out in aqueous medium avoiding the use of organic solvents and resource consuming protection/deprotection strategies. By applying the inverted biphasic system, the product can easily be separated by phase separation and the catalyst recycled. Finally, the lactol products obtained may be utilised as intermediates in the synthesis of natural products by mimicking the original synthetic strategy of nature with seamless combination of elegant and selective transformations without the need for protective groups.

Experimental Section

Hydroformylation in automated reactor system (AMTEC SPR16): Catalysis experiments on a small scale were performed in the parallel autoclave system AMTEC SPR16, equipped with pressure sensors and a mass-flow controller and suitable for monitoring and recording gas uptakes throughout the reactions. The stainless steel autoclaves (12 mL) of the AMTEC SPR16 were flushed automatically with argon 6 times to remove oxygen traces. The reactors were charged with a solution of the precatalyst under argon. The atmosphere was further exchanged with a 1:1 mixture of CO/H_2 (gas exchange cycle 1) and the reactors were heated to $T = 80\,°C$ and pressurised with CO/H_2 to 20 bar. The preformation of the catalyst under the applied conditions was performed for 2 h. Subsequently, the substrate dissolved in water (**3** mL) was injected and the desired temperature as well as the final pressure was adjusted and kept constant throughout the experiment. The gas uptake of CO/H_2 was monitored and recorded automatically. At the end of the catalysis experiments, the reactors were cooled to room temperature and the autoclave contents were analysed by means of NMR.

General procedure for the hydroformylation in water: In a typical experiment, the autoclave was charged with a solution of $[Rh(CO)_2(acac)]$ (acac = acetylacetonate) (7.6 mg, 0.030 mmol) and sulfoxantphos (46.4 mg, 0.060 mmol) in degassed H_2O (10 mL). The catalyst was preformed at 20 bar (CO/H_2) and 80 °C for 2 h at 2000 rpm. Subsequently, the substrate **4** (0.92 g, 4.5 mmol) dissolved in 15 mL of degassed H_2O was added from a dropping funnel and the temperature was raised to 100 °C. Hydroformylation at 20 bar (CO/H_2) and 100 °C for 2 h at 2000 rpm was continued until full conversion was achieved (based on gas uptake). The reaction was stopped by cooling the reactor to room temperature and venting. Catalyst was removed by filtration through neutral alumina, the solvent was evaporated and the product characterised by NMR and HRMS.

General procedure for the hydroformylation in inverted aqueous biphasic system: In a typical experiment, the autoclave was charged with a solution of $[Rh(CO)_2(acac)]$ and (7.6 mg, 0.030 mmol) and xantphos (34.7 mg, 0.060 mmol) in 15 mL of toluene. The catalyst was preformed at 20 bar (CO/H_2) and 80 °C for 2 h at 2000 rpm. Subsequently, the substrate **4** (0.92 g, 4.5 mmol) dissolved in 15 mL of degassed H_2O was added from a dropping funnel and the temperature was raised to 100 °C. Hydroformylation at 20 bar (CO/H_2) and 100 °C for 2 h at 2000 rpm was continued until full conversion was achieved (based on gas uptake). The reaction was stopped by cooling the reactor to room temperature and venting. Phase separation was immediate and the aqueous layer was concentrated and the product analysed as above.

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