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A NEW AND DIRECT ACCESS TO GLYCONO-1,4-LACTONES FROM GLYCOPYRANOSES BY REGIOSELECTIVE OXIDATION AND SUBSEQUENT RING RESTRICTION.

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Abstract : Treatment of partially protected or unprotected carbohydrates with the $RhH(PPh_3)_4$-benzalacetone system leads exclusively to glycono-1,4-lactones by regioselective oxidation and subsequent ring restriction.

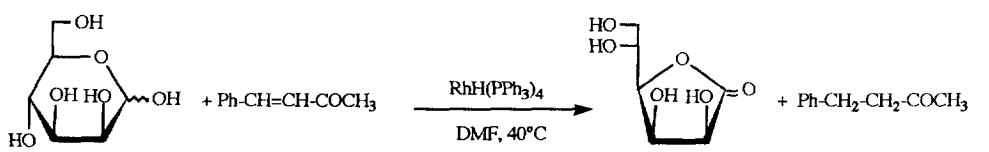
A large number of natural products have the 1,4-lactone moiety in their structural constitution. Therefore, glyconolactones seem to be interesting synthons for the preparation of such substances or their analogs.[1]

The oxidation of unprotected carbohydrates leading to glyconolactones was first achieved with aqueous bromine. When D-glucose is treated with this reagent in the presence of $BaCO_3$, it gives the glucono-1,5-lactone,[2] while, under the same conditions, L-rhamnose gives a mixture of 1,4 and 1,5-lactones.[3]

In the case of partially protected sugars, with a free anomeric hydroxyl group, several oxidizing systems are used to prepare glyconolactones.[4] Catalytic hydrogen transfer, by which the alcohol donor is oxidized, has also been applied to sugars.[5] So, in the presence of benzalacetophenone and $RuH_2(PPh_3)_4$, 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose was oxidized into the corresponding lactone. Simultaneously, a disproportionation reaction occurred, leading to 2,3:5,6-di-*O*-isopropylidene-D-mannitol in a 5 % yield with a two-fold excess of hydrogen acceptor.[6,7] With $RuCl_2(PPh_3)_4$ as a catalyst, the oxidation of D-glucose led to the 1,5-lactone accompanied by sorbitol as a side product.[8] In a previous work,[9] we have studied the regioselective reduction of enones by catalytic hydrogen transfer. The hydrogen donors were mono and disaccharides and the chosen catalyst was $RhH(PPh_3)_4$.

We report here the use of the $RhH(PPh_3)_4$-benzalacetone system, which may be a general method for the preparation of glycono-1,4-lactones from glycopyranoses.

As a matter of fact, we observed that treatment of D-mannose with $RhH(PPh_3)_4$ (0.05 eq.) and benzalacetone (2 eq.) in DMF for 4 hours at 40°C led to D-mannono-1,4-lactone **1** with a 90 % isolated yield :

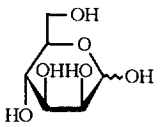
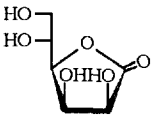
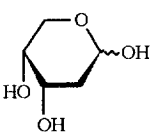
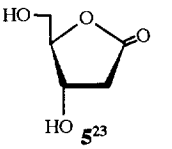
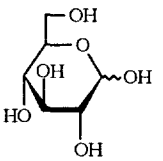
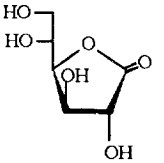
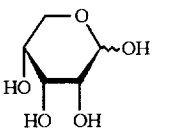
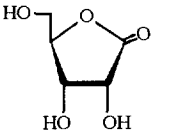
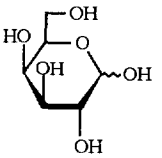
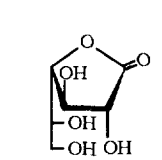
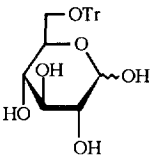
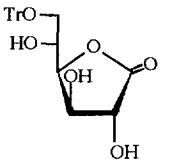
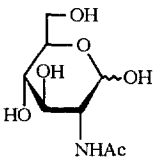
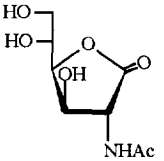
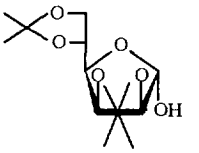
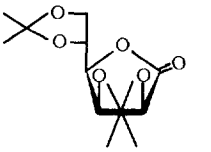


1

D-mannitol could not be detected in the reaction mixture.

This method, applied to free or partially protected lactols, efficiently yielded the corresponding 1,4-lactones, as shown in Table 1. In all cases, under our conditions, the oxidation is limited to the anomeric hydroxyl group.

Table 1 : Oxidation of lactols by catalytic hydrogen transfer [(a)] :

Substrates	Products	Isolated yields (%)	Substrates	Products	Isolated yields (%)
	 **1**[22]	90		 **5**[23]	93
	 **2**[22]	90		 **6**[24]	>99 [(b)]
	 **3**[22]	90		 **7**[25]	73
	 **4**[12]	62		 **8**[26]	93

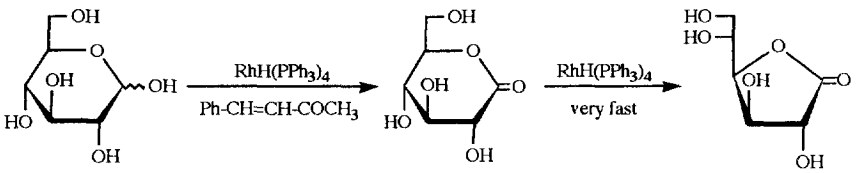
[(a)] [Lactols] = 0.5 M, Ph-CH=CH-CO-CH_3 (2eq.), $RhH(PPh_3)_4$ (0.05 eq.), DMF, 40°C, 4 hours - [(b)] 1.5 hours

Concerning the oxidation of D-glucopyranose, literature data reported the formation of D-glucono-1,5-lactone.[2,8] With our procedure, we obtained exclusively the corresponding 1,4-lactone **2** in 90% yield. Such a result was still obtained for the oxidation of D-galactopyranose which led to the lactone **3**. So, the oxidation yield did not depend on the configuration at C-2 and C-4. Partially protected sugar as the 6-*O*-trityl-D-glucopyranose, led also to the corresponding 1,4-lactone **7**, via a cycle restriction.

The chemical oxidation of N-acetyl-D-glucosamine which has been widely studied,[10-12] was generally accompanied by side products, the only way that could provide directly this lactone in good yield being the enzymatic one.[13] By the catalytic hydrogen transfer, the 2-acetamido-2-deoxy-D-glucopyranose afforded the

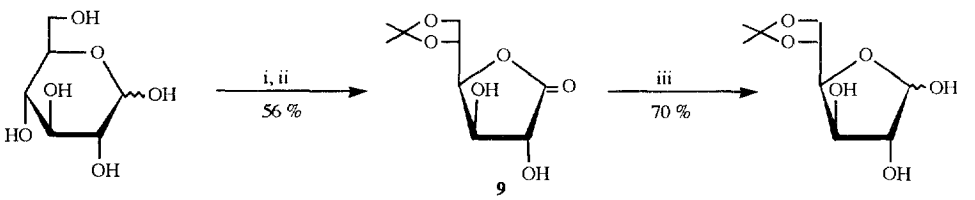
lactone **4** in 62 % yield while 30 % of the starting material was recovered. The lactonization of 2-deoxy-D-ribopyranose and D-ribopyranose afforded **5** and **6** respectively. Under our conditions, hexo and pentopyranoses led to the glycono-1,4-derivatives,without any disproportionation reaction.

To determine whether the oxidation preceeds the isomerization, we have followed the evolution of a solution of D-glucose dissolved in deuterated DMF, by ^{13}C NMR spectroscopy. At 40°C, this solution containing $RhH(PPh_3)_4$ (0.05 eq.) did not allow us to observe any formation of D-glucofuranose. On the contrary, under the same catalytic conditions, the glucono-1,5-lactone in DMF was isomerized into the corresponding glucono-1,4-lactone.[14] This isomerization was quantitative and too fast for its monitoring by NMR spectroscopy. According to these observations, we can make the assumption that the oxidation step takes place before the isomerization one :



The mechanism of the ring restriction is not readily apparent. It is possible that the catalyst coordinates to both the carbonyl group and the endocyclic oxygen atom and makes easier the opening of the cycle and the subsequent cyclisation into the more thermodynamically stable furanic form.[15]

One interesting application of this new route to glycono-1,4-lactones is the easy synthesis of 5,6-*O* protected glycofuranoses which are generally difficult to obtain. 5,6-*O*-isopropylidene-D-glucofuranose was prepared either by direct acetonation of D-glucopyranose[16], in a poor yield, or by acetonation of D-glucosylamine.[17] By our procedure, the oxidation of D-glucose followed by the acetonation of D-glucono-1,4-lactone yielded 56 % of 5,6-*O*-isopropylidene-D-glucono-1,4-lactone **9**[18], in a one-pot reaction. Then, the intermediate **9** was reduced[19] into 5,6-*O*-isopropylidene-D-glucofuranose.



9

i) Ph-CH=CH-$COCH_3$; $RhH(PPh_3)_4$; DMF at 40°C ; 4 hours.

ii) BF_3-Et_2O 10^{-4} eq. ; acetone ; 45 min.

iii) Diisoamylborane ; THF.

The same one-pot procedure carried out with D-mannose afforded 5,6-*O*-isopropylidene-D-mannono-1,4-lactone[20] in 50 % yield.

In conclusion, we have shown that the oxidation of glycopyranoses by catalytic hydrogen transfer using $RhH(PPh_3)_4$ as the catalyst and benzalacetone in excess, affords efficient preparations of glycono-1,4-lactones under mild and neutral conditions. This method can be applied to unprotected or partially protected carbohydrates in which OH-4 must be free.

General procedure :

The $RhH(PPh_3)_4$ catalyst was prepared using the Levinson and Robinson's[21] method.

To a solution of carbohydrate (5 mmol) and $RhH(PPh_3)_4$ (0.25 mmol) in anhydrous DMF (6 ml), at 40°C, under argon atmosphere, was added a solution of benzalacetone (10 mmol) in DMF(4 ml). The oxidation of the monosaccharide was controled by TLC. After total consumption of the sugar and concentration under vacuum, the crude product was purified through a silica gel column. All products were identified according to their literature data or their ^1H, ^{13}C NMR spectra and their elemental analyses data.

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25 **7** : $[\alpha]^{24}_D$+30°C (c1.5, $CHCl_3$), ^{13}C NMR (75.47 MHz ; $CDCl_3$) δ_c 63.46, 69.62, 72.45, 73.32, 77.67, 86.21, 126.24-127.65, 142.57, 174.55.
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