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Combined catalytic conversion involving an enzyme, a homogeneous and a heterogeneous catalyst: one-pot preparation of 4-deoxy-D-glucose derivatives from D-galactose

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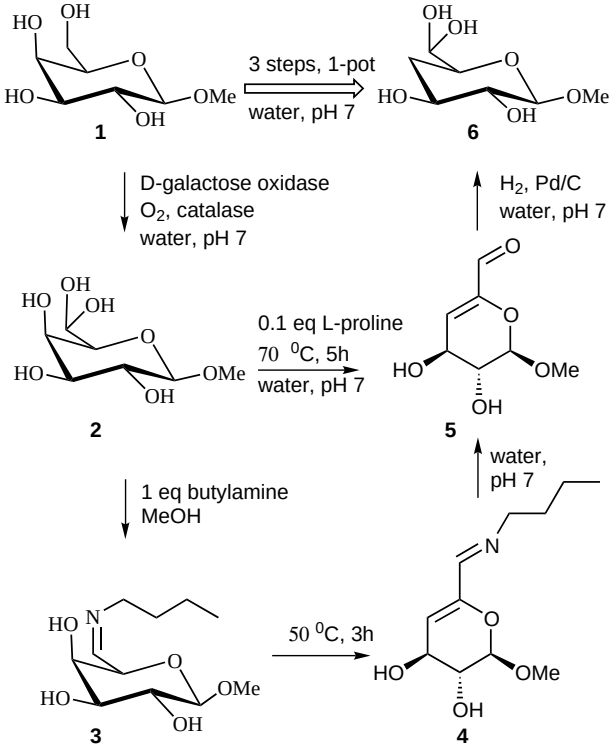
Abstract—Consecutive catalytic oxidation (oxygen, D-galactose oxidase), dehydration (L-proline) and reduction (hydrogen, palladium) of methyl β-D-galactoside in water at neutral pH yielded methyl 4-deoxy-6-aldehydo-β-D-glucoside without intermediate recovery steps demonstrating the potential power of a multi-catalytic approach, using both bio- and chemo-catalysts, for carbohydrate conversions without the use of protective groups or stoichiometric amounts of reagents.

Complex carbohydrates play an important role in various types of biochemical processes like growth, development, immune response, infection, cell adhesion, metastasis and numerous signal transduction events. They are synthetically accessible by application of chemo–enzymatic methods.[1] Combined catalytic, multi-step, one-pot conversions, based on the principle of metabolic pathways in vitro,[2,3] offer potential advantages for the preparation of these materials (and even fine chemicals), i.e. reducing the amount of reagents (waste) and recovery steps (energy).[4] Recently, we have investigated this approach for the enzymatic oxidation of D-galactose[5] to its dialdehyde,[6] followed by amination and rearrangement reactions with amines, in a study of its potential use as a cross-linking agent for proteins.[7] In particular, C-13 labeling together with in situ C-13 NMR analysis[8] of the reaction mixtures allowed monitoring and full assignment of the intermediates and products of such a multi-step, one-pot, conversion without any work-up.

The present study gives an example (Scheme 1) of the modification of methyl β-D-galactoside **1** into a 4-deoxy-D-glucose derivative by the combined use of three different types of catalysts in a row, in one pot, without any intermediate work-up procedure, i.e. the enzyme D-galactose oxidase,[9] the homogeneous catalyst L-proline and a heterogeneous palladium metal catalyst.[10] The consecutive oxygenation, dehydration and hydrogenation reactions in water resulted in the quantitative formation of methyl 4-deoxy-6-aldehydo-β-D-glucoside **6** using only oxygen and hydrogen as reagents



Scheme 1. An aqueous *one-pot* route to 4-deoxy-D-glucose derivatives.

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and water as solvent, without use of protective groups. This is a profound improvement on existing synthetic methods[11,12] for 4-deoxy-D-glucose derivatives. Additionally an aldehyde functionality is introduced at C-6 which cannot be accomplished enzymatically starting with D-glucose.

Oxygenation of **1** with the enzyme D-galactose oxidase, in the presence of catalase to degrade hydrogen peroxide, quantitatively forms its 6-aldehyde **2** as the hydrated form. Essential for the subsequent dehydration step is the abstraction of the α-hydrogen atom at the C-5 position. However, this proton is not very acidic since the aldehyde group is hydrated. After formation of an imine, the C-5 hydrogen will become much more acidic, making the deprotonation and dehydration more progressive. Addition of 1 equiv. butylamine to an aqueous or alcoholic solution of **2** at room temperature gives the corresponding imine **3**. In methanol **3** is formed quantitatively within a few minutes, as can be seen by the clearing of the solution and NMR. Heating of compound **3** in dry methanol—to avoid Maillard reactions—gives complete dehydration into the α,β-unsaturated ene-imine **4**. Subsequent aqueous treatment (pH 7) hydrolyzed the ene-imine **4** into the α,β-unsaturated aldehyde **5**.[13,14] The aldehyde is not hydrated, presumably because it is conjugated with the double bond. With less than 1 equiv. butylamine conversion also takes place: with 0.1 equiv. a conversion of 30% is reached after one day (at 50°C). This demonstrates that the dehydration reaction is catalytic.

The ease and selectivity of the conversion of **2** into **5** led us to look for a more efficient catalytic transformation. In that respect, the recent powerful action of L-proline as a catalyst for aldol condensations[15] interested us, as the first step for aldol reactions is also an a-deprotonation of the aldehyde, a prerequisite for our dehydration of **2**. Although L-proline catalysis for aldol condensation is only apparent in non-aqueous media, we expected possible catalytic dehydration activity through the reversible formation of low amounts of iminium ion products, between L-proline and the hydrated aldehyde **2**. Indeed, heating **2** with a catalytic amount of L-proline (0.1 equiv., 70°C, 5 h) gave a quantitative dehydration into **5**. This step now gives the advantage that, besides the fact that water is the favorable sugar solvent, the dehydration now takes place in water and becomes compatible with the other two aqueous reactions in the sequence. After cooling of the aqueous solution of **5** to room temperature, a palladium-on-carbon catalyst was added. Subsequent stirring under 1 atmosphere of hydrogen gave the methyl 4-deoxy-6-aldehydo-β-D-glucoside **6**. This compound has a hydrated aldehyde function that is easily converted by the addition of butylamine into its imine. Further investigations are in progress using other multi-catalytic, one-pot preparations of carbohydrate-based synthons. The results show the power of the use of different types of catalysts for multi-step conversions without intermediate recovery steps, use of protective groups or reagents other than oxygen and hydrogen. In this case it was possible to combine the broadest possible array of catalysts: an enzyme, a homogeneous and a heterogeneous chemo catalyst. Water based reactions are beneficial for this approach: they assure easy compatibility of bio- and chemo-catalysts during the different steps in the reaction sequence.

References

1. Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465–4493.
2. Fessner, W.-D.; Walter, C. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 614–616.
3. Koeller, K. M.; Wong, C.-H. *Glycobiology* **2000**, *10*, 1157–1169.
4. Schoevaart, R.; Kieboom, T. *Chem. Innov.* **2001**, *31*, 33–39.
5. Hamilton, G. A.; de Jersey, J.; Adolf, P. K. In *Oxidases and Related Redox Systems*; King, T. E., Ed. Galactose oxidase: the complexities of a simple enzyme; Pergamon: Oxford, 1973; Vol. 1, pp. 103–124.
6. Schoevaart, R.; Kieboom, T. *Carbohydr. Res.* **2001**, *334*, 1–6.
7. Schoevaart, R.; Kieboom, T. *Carbohydr. Res.* **2002**, accepted.
8. Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem. Biochem.* **1983**, *41*, 27–66.
9. Cooper, J. A. D.; Smith, W.; Bacila, M.; Medine, H. *J. Biol. Chem.* **1959**, *234*, 445.
10. A 10 ml solution (pH 7.3) of 0.1 M methyl β-D-galactoside (192 mg, 1 mmol) containing 185 units D-galactose oxidase and 2000 units catalase in a 100 ml bottle ($T=$ 10°C), under an oxygen atmosphere was left for 2 days and then concentrated (freeze drying) to 1 ml. Then 12 mg (10 mol%) of L-proline was added and incubated for 5 h at 70°C. At room temperature 10 mg 10% Pd/C was added and maintained under a hydrogen atmosphere for 2 h, giving methyl 4-deoxy-6-aldehydo-β-D-*xylo*-hexopyranose (yield >95%) as the single product. Crystallization from 2-propanol/40–60 petroleum ether yielded **6** as a pale yellow powder. ^{13}C NMR (75 MHz, H_2O+5% D_2O, pH 7.3) δ: 33.21; 57.12; 70.27; 73.93; 74.85; 90.28; 103.56.
11. Helliwell, M.; Phillips, I. M.; Pritchard, R. G.; Stoodley, R. J. *Tetrahedron Lett.* **1999**, *40*, 8651–8655.
12. Berkin, A.; Szarek, M. A.; Plenkiewicz, J.; Szarek, W. A.; Kisilevsky, R. *Carbohydr. Res.* **2000**, *325*, 30–45.
13. Maradufu, A.; Cree, G. M.; Perlin, A. S. *Can. J. Chem.* **1971**, *49*, 3429–3437.
14. Beving, H. F. G.; Theander, O. *Acta Chem. Scand.* **1975**, *B29*, 641–646.
15. List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.