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PAPER

A heterogeneous Pd–Bi/C catalyst in the synthesis of L-lyxose and L-ribose from naturally occurring D-sugars†

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A critical step in the synthesis of the rare sugars, L-lyxose and L-ribose, from the corresponding D-sugars is the oxidation to the lactone. Instead of conventional oxidizing agents like bromine or pyridinium dichromate, it was found that a heterogeneous catalyst, Pd–Bi/C, could be used for the direct oxidation with molecular oxygen. The composition of the catalyst was optimized and the best results were obtained with 5 : 1 atomic ratio of Pd : Bi. The overall yields of the five-step procedure to L-ribose and L-lyxose were 47% and 50%, respectively. The synthetic procedure is advantageous from the viewpoint of overall yield, reduced number of steps, and mild reaction conditions. Furthermore, the heterogeneous oxidation catalyst can be easily separated from the reaction mixture and reused with no loss of activity.

Introduction

Carbohydrates represent the most abundant renewable source for chemical materials.[1] However, their use in fine chemistry is limited because of the difficulties caused by their high functionalization. In medicinal chemistry, the epimerization of the naturally occurring D-form to the corresponding L-form (not naturally occurring) is extremely important. Nucleoside analogues containing L-ribose have been developed as antiviral and antitumour agents.[2] These L-ribose-containing nucleosides frequently show less toxicity, high metabolic stability and better pharmacological activity than the D-ribose-containing analogues. However, because L-ribose is not found in nature, it must be synthesized by elaborate and laborious chemical or biochemical synthetic methods.[3]

Similarly, L-lyxose which differs from D-ribose only in the absolute configuration of C4 (Fig. 1) has interesting biochemical properties. Reist *et al.*[4] synthesized the L-lyxose derivative, methyl β-L-lyxopyranose, by inversion of the 3-hydroxyl group of an L-arabinose derivative. However, the yield for this method was low (<13%). Kuzuhara *et al.*[5] improved the synthesis method of L-lyxose by starting from a cheaper chemical, D-glucose, but the overall yield was only 30%. Brimacombe *et al.*[6] used 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose as the starting material to produce L-lyxose. However, this synthetic route was carried out on a 0.1–0.3 g scale, which does not fulfil the requirements of industrial production. More recently, access to L-lyxose by biotransformations using microbial and enzymatic reactions has been reported.[7] Although this synthetic route can give a relatively high yield (50%) of L-lyxose from ribitol, the following downstream operation of separating L-lyxose from the mixture of L-ribulose, L-xylulose and L-lyxose was a difficult and time-consuming process. Granström *et al.*[8] used xylitol as the raw material and reduced the number of steps in the biotransformation. However, the final equilibrium distribution between L-xylulose, L-xylose and L-lyxose was 53 : 26 : 21, reducing the overall yield of L-lyxose.

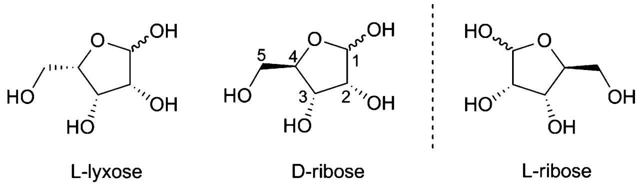

Fig. 1 Structure of D-ribose, L-ribose and L-lyxose.

Although current chemical and biochemical processes[9] can fulfil the task of synthesizing the rare L-sugars, they have disadvantages such as low yields, use of corrosive, toxic, flammable and/or pyrophoric chemicals such as bromine, pyridinium dichromate, concentrated acids, lithium aluminum hydride, difficulties with the separation of the products, control of by-products and disposal of wastewater. In this regard, heterogeneous catalysts have unique advantages, *e.g.*, ease of handling, separation from the reaction mixtures and recovery of the catalysts.[10] Moreover, heterogeneous catalysts often perform well under mild conditions and are seldom corrosive in nature. However, direct epimerization of carbohydrates with heterogeneous catalysts is largely unexplored.

Here, we report an efficient and simple synthetic route to synthesize L-lyxose from the cheap starting material, D-ribose, through the use of a heterogeneous catalyst and readily available reagents (Scheme 1). The proposed synthetic route from D-ribose to L-lyxose consists of five reactions: (i) selective oxidation of D-ribose, (ii) protection of hydroxyl groups (C2 and C3), (iii) epimerization reaction, (iv) reduction of the carbonyl group in

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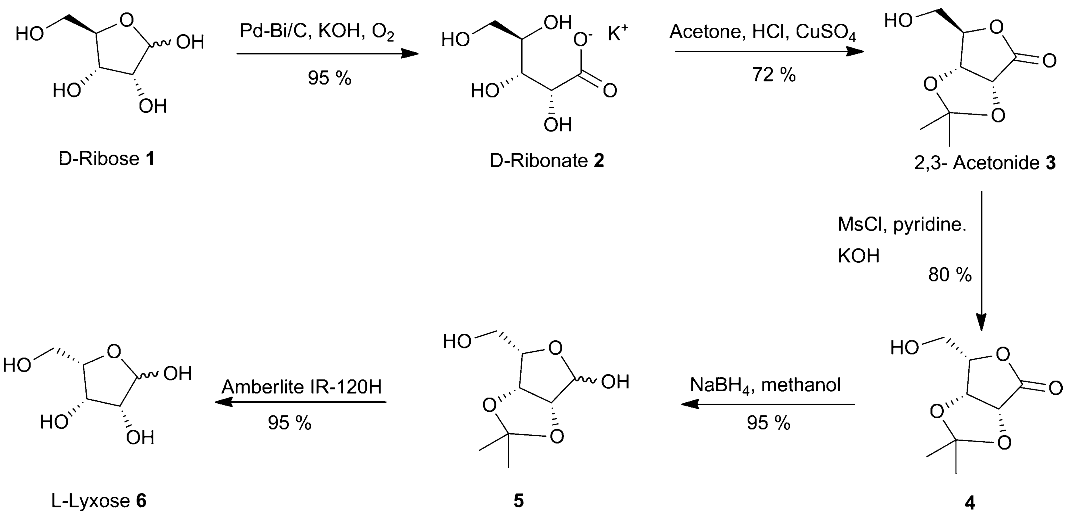


Scheme 1 Synthesis route from D-ribose to L-lyxose.

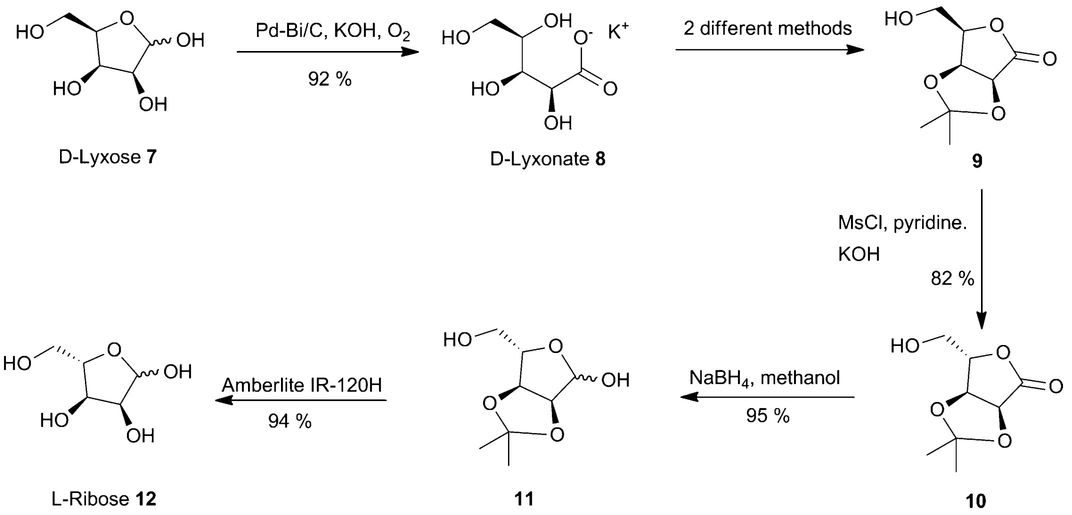
the anomeric carbon to a hydroxyl group, and (v) deprotection of hydroxyl groups (C2 and C3). The key and also the most difficult step in the above reactions is the first step where D-ribose is oxidized to D-ribonolactone. D-Ribonolactone is a very important intermediate in the synthesis of various organic products, such as riboflavin (vitamin B_2) and naturally occurring lactones.[11–13] The present procedure for producing D-ribonolactone is based on the oxidation of ribose with bromine.[11] Although this method can give a relatively high yield (80%) within an acceptable time, bromine is corrosive, volatile and toxic, hence preventing this route from being a safe and efficient way for the production of D-ribonolactone on an industrial scale.

Palladium as well as platinum dispersed on active carbon has been used as a catalyst for the oxidation of D-glucose to D-gluconate.[14] However, the catalyst becomes deactivated in the course of the reaction resulting in lower activity and selectivity for D-gluconate.[15] The addition of bismuth to the catalyst improves the activity and selectivity for the oxidation of glucose.[16,17] The bismuth adatoms prevent oxygen poisoning of the palladium surface by acting as a co-catalyst in the oxidative dehydrogenation mechanism.[18] In view of its good oxidation properties in the oxidation of D-glucose, we decided to investigate its use for the oxidation of D-ribose to D-ribonolactone in the first step of the route to the L-sugar. The applicability of the scheme to the synthesis of L-ribose starting from D-lyxose was also attempted (Scheme 2).

Results and discussion

Catalyst characterization

Samples with different bismuth loadings were prepared from a 10 wt% Pd/C catalyst. The atomic ratio of Pd : Bi was varied from 1 to 8 (ESI†). The nitrogen adsorption-desorption isotherms of the 10 wt% Pd/C and the Pd–Bi/C catalysts are given in Fig. 2a. The steep increase at low P/P° indicates the presence of micropores while the hysteresis above P/P° of 0.5 shows that mesopores are also present. The mesopores are between 3.2 to 4.7 nm, irrespective



Scheme 2 Synthesis route from D-lyxose to L-ribose.

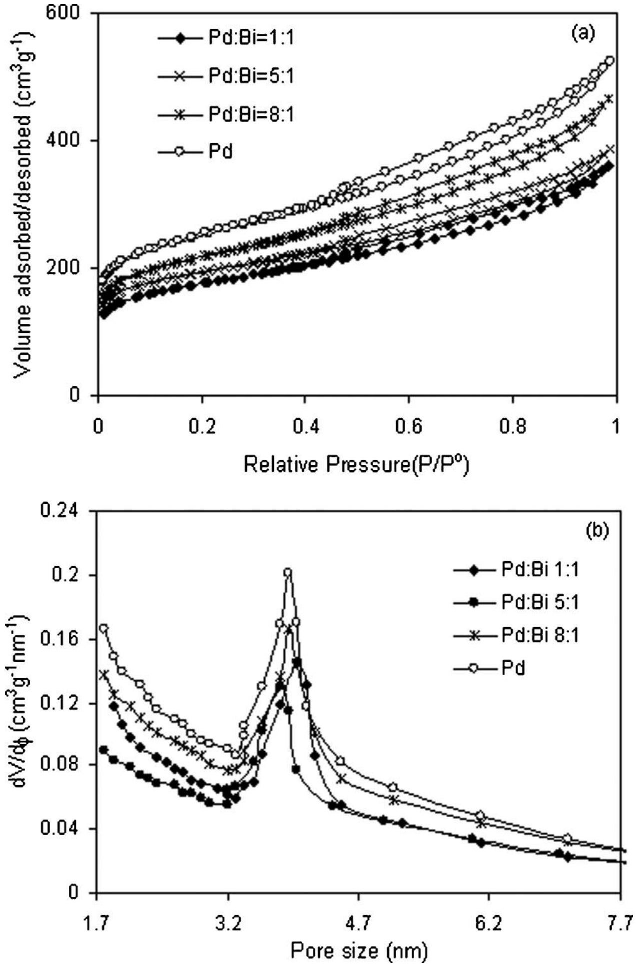


Fig. 2 (a) Adsorption/desorption isotherms and (b) pore size distribution of Pd–Bi/C.

of the bismuth loading (Fig. 2b). The Pd/C sample has a high surface area of 819 m^2 g^{-1} with ~300 m^2 g^{-1} due to micropores. With the incorporation of bismuth, the surface area decreased (Table 1). Concomitant with this was a decrease in both the micropore and mesopore volume, showing that bismuth was deposited into these pores.

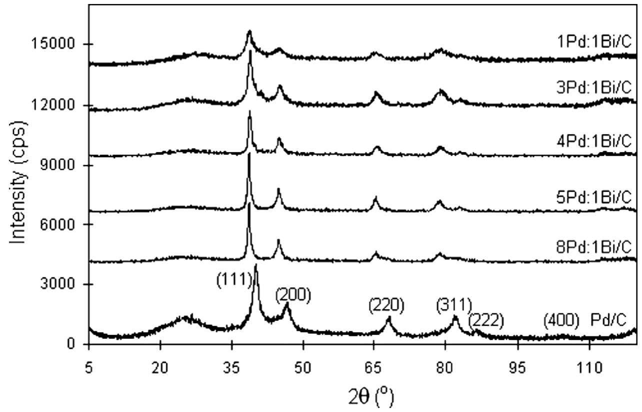


Fig. 3 XRD spectra of Pd–Bi/C catalysts.

Powder X-ray diffraction studies showed that metallic palladium (JCPDS 00-051-0681) was present on Pd/C after hydrogen treatment at 150 °C for 2 h. However, for the reduced Pd-Bi samples, the characteristic peaks of Pd were shifted to smaller angles (Fig. 3). The peak positions are characteristic of palladium hydride, $PdH_{0.706}$ (JCPDS 00-018-0951). To accommodate the hydrogen, an increase in lattice spacing occurred. The width of the peaks in 8Pd-Bi/C and 5Pd-Bi/C are narrower than Pd/C but broadened again with higher bismuth loadings. Furthermore, the peak maximum of the (111) reflex in 8Pd–Bi/C and 5Pd–C/Bi was at 2θ of 38.60° but shifted to higher angles, 38.63–38.87°, as the bismuth loading increased. The shift to higher 2θ indicates that less hydrogen was present in the higher bismuth-containing samples than 8Pd–Bi/C and 5Pd–Bi/C.

Table 1 Surface area and pore volume of Pd–Bi/C catalysts

Catalyst	Surf. area (m^2 g^{-1})	Micropore area (m^2 g^{-1})	Pore vol. (cm^3 g^{-1})	Micropore vol. (cm^3 g^{-1})
Pd	819	300	0.81	0.16
8Pd : Bi	708	260	0.72	0.14
5Pd : Bi	625	268	0.61	0.14
4Pd : Bi	599	234	0.60	0.13
3Pd : Bi	575	231	0.58	0.12
Pd : Bi	570	221	0.56	0.12

X-ray photoelectron spectroscopy (XPS) measurements confirmed that the surface palladium was mostly in the metallic form with a binding energy of Pd $3d_{5/2}$ centred at ~335.2 eV (Fig. 4). Deconvolution of the peaks showed that Pd(II) was also present. The fraction of Pd(II) increased with bismuth loading (Table 2). Bismuth was present as Bi(III) and Bi(0), with Bi(III) being the predominant state for all samples except 5Pd : Bi/C. In this sample, more bismuth was present in oxidation state 0 than +3. With higher bismuth loading, the ratio of Bi(III)/Bi(0) increased. The surface Pd/Bi ratio agrees rather well with the expected ratio except for 8Pd–Bi/C where the relative surface concentration of Pd/Bi is higher than the expected 8 : 1. This may be due to the self-aggregation of bismuth oxide particles rather than spreading out evenly on the surface at the very low loading.

Synthesis of L-lyxose from D-ribose

Oxidation of D-ribose

In the first step as outlined in Scheme 1, the oxidation of D-ribose to D-ribonolactone was investigated using the heterogeneous 5Pd : Bi/C catalyst and oxygen gas as the oxidant. Without any pH control, the reaction started with a high initial rate but then levelled off to reach a conversion of 40% after 180 min (Fig. 5). The pH decreased in the course of the reaction, starting at ~4.4–4.6 and falling to ~2.8–3.1 at the end of the reaction. The decrease in pH can be attributed to the formation of ribonic acid. Despite a longer

Table 2 XPS results of Pd–Bi/C catalysts

Theoretical Pd : Bi	Pd(0)/ Pd(II)	Bi(III)/ Bi(0)	Experimental Pd : Bi
8 : 1	40.4	2.79	13.64
5 : 1	30.0	0.66	5.17
4 : 1	11.9	2.32	4.31
3 : 1	7.01	3.11	2.21
1 : 1	5.93	4.44	1.03

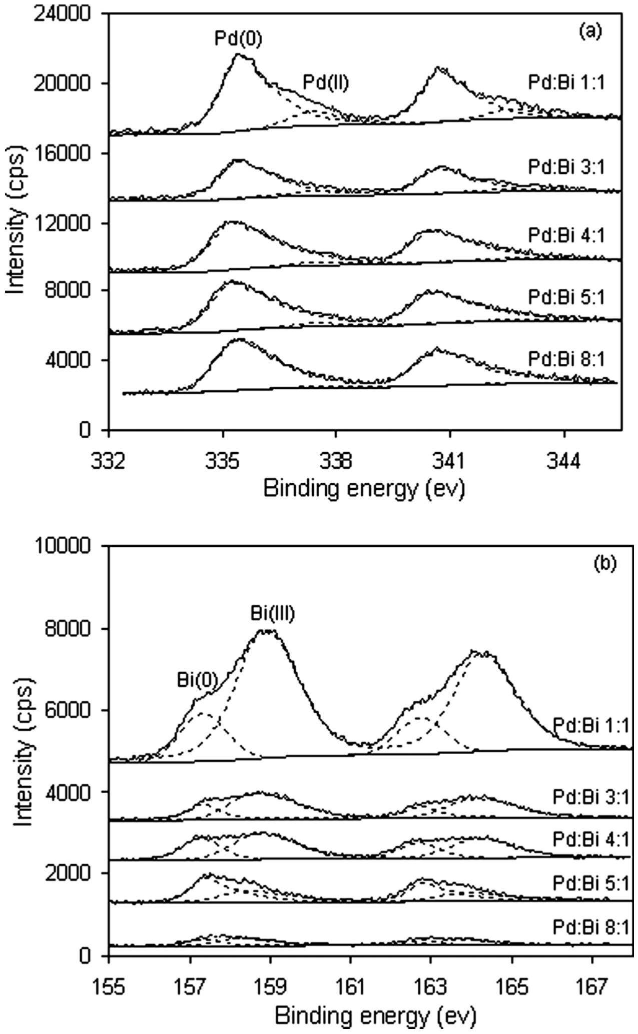


Fig. 4 XPS spectra of Pd–Bi/C catalysts for (a) Pd 3d (b) Bi 4f.

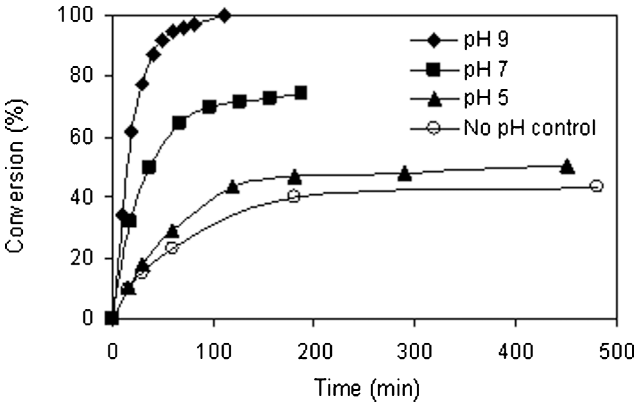


Fig. 5 Oxidation of D-ribose to D-ribonate at different pH. Reaction conditions: D-ribose (0.1 M, 70 cm^3), 5Pd-Bi/C (50 mg), 0.5 L O_2 min^{-1}, 50 °C.

Table 3 Conversion of D-ribose and selectivity to D-ribonate **2** over Pd-Bi/C catalysts

Entry	Catalyst	Time (min)	Conv. (%)	Selectivity (%)
1	Pd	40	95	83
2	8Pd : Bi	80	94	>95
3	5Pd : Bi	110	100	>95
4	4Pd : Bi	130	96	>95
5	3Pd : Bi	130	85	>95
6	Pd : Bi	130	82	>95

Reactions condition: D-ribose (0.1 M, 70 cm^3), catalyst (50 mg), 50 °C, 0.5 L O_2 min^{-1}, pH 9

reaction time, the conversion did not increase, indicating that the catalyst had been poisoned probably by the ribonic acid. Abbadi and van Bekkum[16] showed that for the oxidation of glucose over a palladium catalyst, the poisoning was due to the adsorption of the product, 2-keto-gluconic acid, on the catalyst. Under basic conditions, the gluconate forms instead and could desorb from the catalyst, thus removing the inhibition.

Maintaining the pH at 5 led to a similar reaction profile as that without pH control. A limiting conversion of ~48% was reached after 120 min. However, keeping a constant pH 7 during the reaction led to a higher rate of reaction and 74% conversion was obtained after 180 min. A further increase in the reaction pH to 9 resulted in an even higher rate of reaction and 100% conversion was reached after 110 min. Under the alkaline conditions, the salt, potassium D-ribonate was formed instead of ribonic acid and the absence of inhibition clearly shows that ribonic acid poisoned the catalyst. Hence, there is a very strong influence of pH on the rate of reaction.

Different Pd : Bi/C catalysts were investigated for the oxidation of D-ribose keeping the reaction mixture at pH 9 and 50 °C. The rate of reaction was highest when 10% Pd/C was used as the catalyst. After 40 min, the conversion was 95% (Table 3). However D-ribose was oxidized to D-ribonate with only 83% selectivity. By-products of glutarate and oxalate were formed due to overoxidation and degradation of D-ribose, respectively. In contrast, when Pd–Bi/C samples were used, the reaction was slower but the selectivity to D-ribonate improved to >95%. Of the Pd–Bi catalysts, 5Pd : Bi/C showed the highest activity. Its initial rate was similar to that of Pd/C but decreased with time to reach full conversion after 110 min. The main product was D-ribonate. The promoting effect of bismuth on platinum and palladium catalysts for carbohydrates has been attributed to a number of factors. These include a decrease in the size of the platinum ensembles due to bismuth adatoms, in turn reducing the irreversible adsorption of the substrate and formation of by-products as well as a higher affinity of bismuth for oxygen, thus preventing a high oxygen coverage on the metal.[18] Such over-oxidation on the metal surface can lead to fully oxidized products and oxygen poisoning of the reaction.

Besson *et al.*[18] proposed that glucose oxidation on Pd–Bi/C catalyst proceeds *via* an oxidation dehydrogenation mechanism where bismuth acts as a cocatalyst to prevent overoxidation of the palladium surface. From the XPS results, 5Pd : Bi/C has a high proportion of metallic Pd and Bi at its surface. Chemisorption of oxygen can occur at the surface of Bi(0). The dehydrogenation of D-ribose is facilitated by Pd(0), forming PdH. The ease at which PdH is formed is seen from the XRD spectra of the Pd–Bi/C catalysts as compared to purely Pd/C. The more Pd(0) sites are available at the surface of the catalyst, the faster the dehydrogenation reaction can proceed. Reaction of PdH with chemisorbed oxygen at Bi(0) forms water and regenerates Pd(0), thus completing the catalytic cycle.

A high bismuth loading covers the palladium sites, decreasing the activity of the Pd–Bi catalysts without affecting the selectivity. Conversely, when the bismuth loading is too low, the palladium surface can be subjected to oxygen poisoning. Hence, an optimum balance of available Pd and Bi sites determines the reaction rate.

The temperature also played a significant role in the oxidation reaction (Fig. 6). At 27 °C, the reaction was slow and after 110 min, only 43% conversion was obtained. Increasing the temperature to 44 °C resulted in a higher rate, allowing close to 97% conversion in the same time. The selectivity to D-ribonate (>95%) was unchanged despite the different temperatures. The activation energy was calculated from the Arrhenius equation to be 71.3 kJ mol^{-1}.

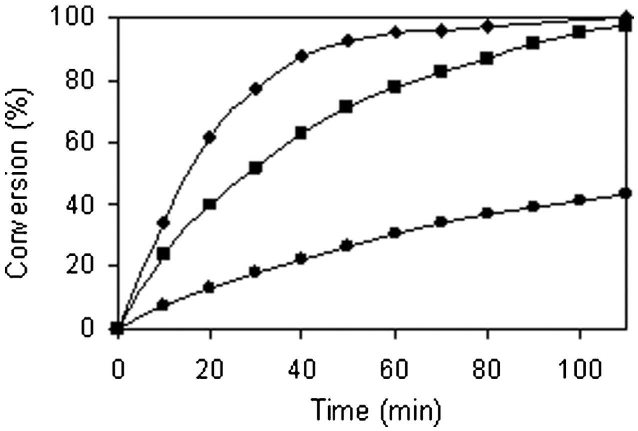


Fig. 6 Oxidation of D-ribose to D-ribonate at (●) 27 (■) 44 and (◆) 50 °C. Reaction conditions: D-ribose (0.1 M, 70 cm^3), 5Pd-Bi/C (50 mg), 0.5 L O_2 min^{-1}, pH 9.

The used catalyst was recovered by filtration of the reaction mixture, regenerated and used in new batch reactions. Washing of the used catalyst followed by drying led to a reduction of activity (Fig. 7). The catalyst became more active after reducing in H_2 at 150 °C for 2 h so that full conversion could be obtained after 400 min. The best activity was obtained after washing the used catalyst with KOH and acetone followed by hydrogen reduction at 150 °C for 2 h. The activity of the regenerated catalyst was very similar to the fresh catalyst, showing that no leaching of Pd or Bi had occurred.

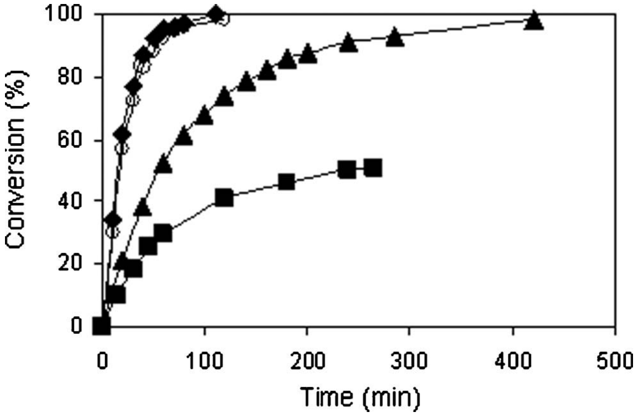


Fig. 7 Activity of (◆) fresh 5Pd : Bi/C and the used catalyst after (■) washing with water and drying, (▲) washing with water and reducing in H_2, and (○) washing with KOH, acetone and H_2 reduction.

The used catalyst was tested in 5 batch reactions without loss of activity and selectivity (Fig. 8). Hence, the results showed that Pd–Bi/C is a reuseable and selective catalyst for D-ribose oxidation.

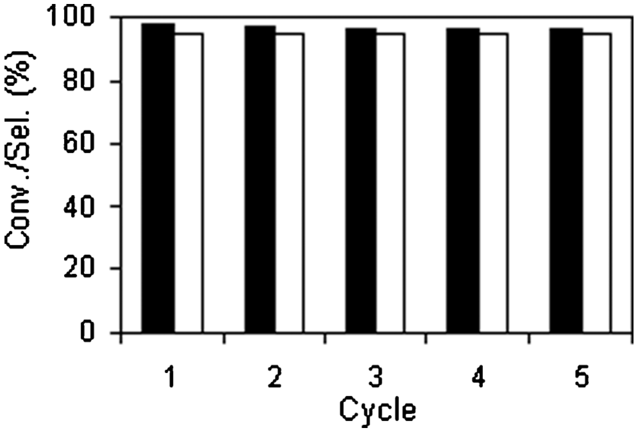
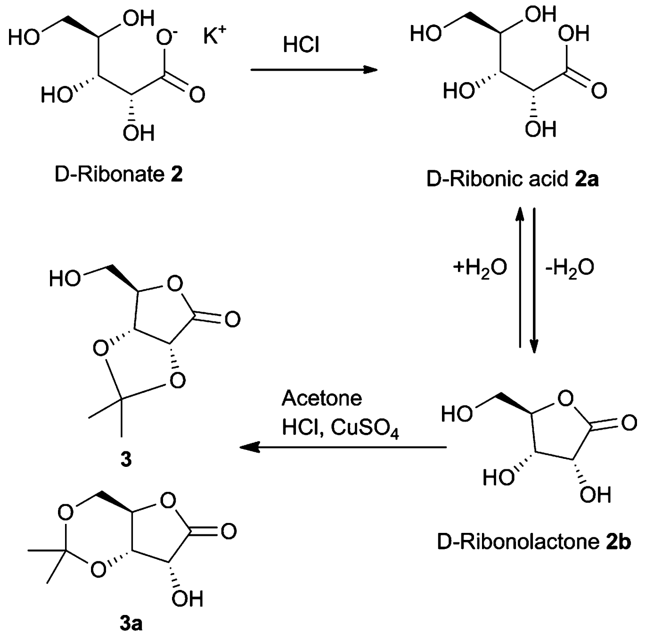


Fig. 8 Conversion and selectivity of D-ribose oxidation with regenerated 5Pd-Bi/C catalyst.

Transformation of D-ribonate to L-lyxose

The synthesis conditions for the conversion of D-ribonate to 2,3-*O*-isopropylidene-D-ribonolactone **3** was investigated (Scheme 3). First, the potassium D-ribonate **2** can be converted to D-ribonic acid **2a** by exchanging the potassium ions with hydrogen ions. Due to the dynamic equilibrium between D-ribonic acid and D-ribonolactone **2b**, reaction of the latter with acetone will result in the desired 2,3-acetonide **3**. Thus, a one-pot transformation from D-ribonate to **3** can be achieved if a suitable acid and reaction conditions can be found.



Scheme 3 One-pot transformation of D-ribonate to 2,3-*O*-isopropylidene-D-ribonolactone.

Concentrated HCl was tested as the acid (Table 4). Based on 2.0 g of crude D-ribonate **2**, 66% yield of 2,3 acetonide **3** was obtained by stirring at 25 °C for 18 h. The addition of anhydrous

Table 4 One-pot transformation from D-ribonate **2** to 2,3-acetonide **3**

Entry	Reagents	Acetone (cm^3)	Condition	Yield **3** (%)
1	*conc.* HCl (20 mmol)	15	Reflux at 60 °C for 4 h, stir at RT for 8 h	48
2	*conc.* HCl (60 mmol)	40	Reflux at 60 °C for 4 h, stir at RT for 8 h	64
3	*conc.* HCl (60 mmol)	40	Stir at RT for 18 h	66
4	*conc.* HCl (24 mmol), $CuSO_4$ (12.5 mol)	40	Reflux at 60 °C for 1.5 h	72
5	*conc.* HCl (24 mmol), $CuSO_4$ (12.5 mol)	40	Reflux at 60 °C for 4 h	84[a]
6	*conc.* H_2SO_4 (30 mmol)	40	Reflux for 4 h and stir at RT for 8 h	8
7	AmberliteIR-120H (5 g)	40	Stir at RT for 18 h	0
8	AmberliteIR-120H (5 g), 2,2 dimethoxypropane (48.8 mmol)	40	Stir at RT for 18 h	30[b]

Based on 2.0 g of crude potassium D-ribonate. Molar ratio of 2,3-acetonide **3** to3,5-acetonide **3a**.[a] 3 : 1. [b] 1 : 2.

$CuSO_4$ reduced the reaction time and increased the yield to 72% when the reaction mixture was refluxed at 60 °C for 1.5 h (entry 4). This was the highest yield of **3** obtained as extending the refluxing time to 4 h led to the formation of the isomeric 3,5-acetonide **3a** (entry 5). The molar ratio of 2,3-acetonide **3** and 3,5-acetonide **3a** was about 3 : 1. The use of *conc.* H_2SO_4 resulted in charring and only 8% yield of **3** was obtained (entry 6). Use of the acidic anion exchange resin Amberlite IR-120H led to the formation of more 3,5-acetonide **3a** than the desired 2,3-acetonide **3** (molar ratio 2 : 1).

In the next step, 2,3-acetonide **3** was reacted in pyridine with methanesulfonyl chloride (MsCl) followed by treatment with potassium hydroxide.[19] 2,3-*O*-Isopropylidene-L-lyxonolactone **4** formed under inversion of the reacting carbon center in 80% yield. The mechanism of the inversion at C4 has been proposed by Batra *et al.*[19] to involve an intermediate C4–C5 epoxide which forms when the D-ribonlactone ring is opened by potassium hydroxide. Subsequent intramolecular nucleophilic substitution by the carboxylate ion in a 5-*endo-tet* process leads to ring opening of the epoxide and inversion of the configuration at C4. The carbonyl group on the anomeric carbon of **4** was reduced with $NaBH_4$ in methanol to give the product **5** as a colorless syrup (95% yield). Finally, compound **5** was hydrolyzed using acidic Amberlite IR-120H resin to afford L-lyxose **6** in 95% yield. Hence, L-lyxose was synthesized from D-ribose in five steps with an overall yield of 50%. This compares very favorably with yields of 13 to 30% for the chemical synthesis of L-lyxose starting from L-arabinose[4] and D-glucose and its derivative.[5,6] The yield is also comparable to that obtained from microbial and enzymatic methods.[7,8]

Synthesis of L-ribose from D-lyxose

The generality of the designed route was tested for the synthesis of L-ribose from D-lyxose (Scheme 2). The aerobic oxidation of D-lyxose **7** to D-lyxonate **8** was carried out successfully with the heterogeneous catalyst, 5Pd : Bi/C, at pH 9. Although the reaction was slightly slower than for D-ribose, the conversion was >99% after 180 min. The selectivity to D-ribonate was >92%.

However, different reaction conditions were required to transform D-lyxonate **8** to 2,3-*O*-isopropylidene-D-lyxonolactone **9** (Table 5). The yield of **9** was <5% even with the use of sufficient *conc.* HCl, acetone and $CuSO_4$ in the reaction mixture (entries 1 & 2). The addition of the organic acid, methanesulfonic acid followed by stirring for 18 h could significantly improve the reaction yield of **9** to 30% (entry 3). Under reflux conditions, the isomer 3,5-acetonide **9a** was formed (entries 4 & 5). Although the yield of each batch reaction after stirring at 25 °C for 18 h was relatively low (30%), the significant difference in solubility of D-lyxonolactone and 2,3-acetonide **9** allows them to be easily separated with liquid–liquid (ethyl acetate/water) extraction. In turn, it was possible to recover the unreacted D-lyxonolactone and carry out further batch reactions to improve the yield. About 70% yield was achieved after four cycles of the reaction.

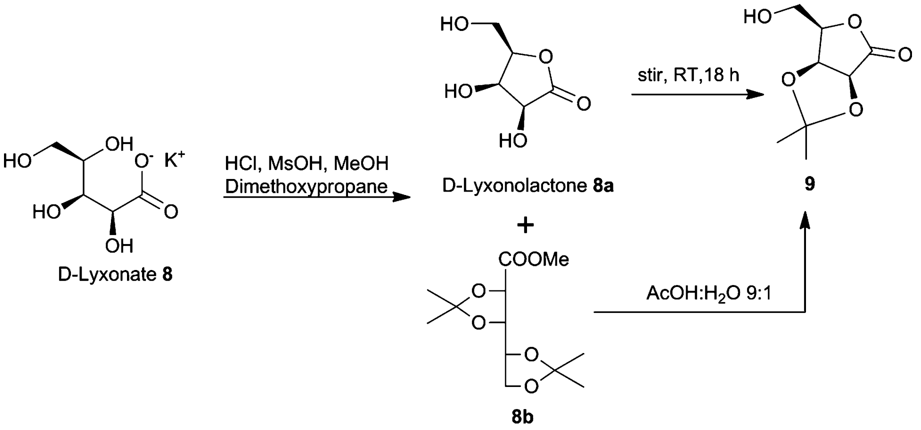
Besides this route, a modified synthesis method was used to produce 2,3-acetonide **9** from D-lyxonate **8** (Scheme 4). Treatment of D-lyxonate **8** with *conc.* HCl, dimethoxypropane and MsOH gave D-lyxonolactone **8a** and the diacetonide compound **8b** which could be easily separated by liquid–liquid extraction (diethyl ether/H_2O). D-Lyxonolactone **8a** was reacted with more dimethoxypropane and MsOH to form 2,3-*O*-isopropylidene-D-lyxonolactone **9**. For the diacetonide **8b**, it was found that acetic acid/H_2O (9 : 1) could selectively deprotect the hydroxyl groups in C4 and C5.[20] Hence, 2,3-*O*-isopropylidene D-lyxonolactone **9** was formed with 70% yield with this strategy.

Compound **9** was next reacted with methanesulfonyl chloride (MsCl) in pyridine solution followed by potassium hydroxide to produce the L-ribonolactone 2,3-acetonide **10** (82% yield) with

Table 5 One-pot transformation of D-lyxonate **8** to 2,3-acetonide **9**

Run	Reagents	Acetone (cm^3)	Condition	Yield **9** (%)
1	*conc*. HCl (60 mmol)	40	Reflux for 4 h, stir at RT for 8 h	0
2	*conc*. HCl (24 mmol), $CuSO_4$ (12.5 mol)	40	Reflux for 4 h	< 5
3	*conc*. HCl (24 mmol), MsOH (15 mmol)	40	Stir at RT for 18 h	30
4	*conc*. HCl (24 mmol), MsOH (15 mmol)	40	Reflux for 4.5 h	30[a]
5	*conc*. HCl (24 mmol), MsOH (15 mmol)	40	Reflux for 12 h	36[b]
6	*conc*. HCl (24 mmol), MsOH (15 mmol), 2,2-dimethoxypropane (48.8 mmol)	40	Stir at RT for 18 h	40[c]

Based on 2.0 g of crude potassium D-lyxonate. Molar ratio of 2,3-acetonide **9** to 3,5-acetonide **9a**.[a] 9 : 1. [b] 3 : 1. [c] 4 : 1.



Scheme 4 D-Lyxonate **8** to 2,3-*O*-isopropylidene-D-lyxonolactone **9**.

inversion of the reacting carbon center. Reduction of the carbonyl group on the anomeric carbon of the 2,3-acetonide **10** by $NaBH_4$ in methanol solution gave product **11** as a colorless syrup (95% yield). Finally, **11** was subjected to hydrolysis using acidic Amberlite IR-120H resin to afford L-ribose **12** in 94% yield. The overall yield of L-ribose was 47% which can be compared with previously reported yields of 18 to 45%.[3,9]

Conclusions

The efficient synthesis of the rare sugars L-lyxose and L-ribose was carried out in a 5-step preparative route starting from naturally occurring D-ribose and D-lyxose respectively. The aerobic oxidation of D-sugar to lactone was carried out over a heterogeneous catalyst, 10 wt% Pd-Bi supported on carbon, with high yields of >95%. The best catalyst contained a Pd : Bi atomic loading of 5 : 1. Under alkaline conditions, the catalyst was not affected by any poisoning and could be reused for subsequent batch reactions, with no significant loss of activity and selectivity. The synthetic route resulted in good yields of L-lyxose and L-ribose of 50% and 47%, respectively.

Acknowledgements

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