Green synthesis of 1,5-dideoxy-1,5-imino-ribitol and 1,5-dideoxy-1,5-imino-DL-arabinitol from natural D-sugars over Au/Al₂O₃ and SO₄²⁻/Al₂O₃ catalysts

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A green synthetic route for the synthesis of some potential enzyme active hydroxypiperidine iminosugars including 1,5-dideoxy-1,5-imino-ribitol and 1,5-dideoxy-1,5-imino-DL-arabinitol, starting from commercially available D-ribose and D-lyxose was tested out. Heterogeneous catalysts including Au/Al₂O₃, SO₄²⁻/Al₂O₃ as well as environmentally friendly reagents were employed into several critical reaction of the route. The synthetic route resulted in good overall yields of 1,5-dideoxy-1,5-imino-ribitol of 54%, 1,5-dideoxy-1,5-imino-D-arabinitol of 48% and 1,5-dideoxy-1,5-imino-L-arabinitol of 46%. The Au/Al₂O₃ catalyst can be easily recovered from the reaction mixture and reused with no loss of activity.

Iminosugars are analogues of carbohydrates, chemically named as polyhydroxylated secondary and tertiary amines and found to be widespread in plants and microorganisms. Thanks to their structural similarity to sugar molecules and excellent metabolic stability, iminosugars are endowed with a high pharmacological potential for a wide range of diseases such as viral infections, tumor metastasis, AIDS, diabetes and lysosomal storage disorders²¹⁻¹².

Iminosugars are generally classified into five structural classes: pyrrolidines, piperidines, indolizidines, pyrrolizidines and nortropanes¹². Hydroxypiperidines are structurally six-membered iminosugars. Some of the hydroxypiperidines such as 1,5-dideoxy-1,5-iminohexitol derivatives have now been commercialized as drugs to treat type II diabetes mellitus, type I Gaucher disease, Niemann-Pick disease type C (NP-C) and Fabry disease¹³⁻¹⁵. Other Hydroxypiperidines like 1,5-Dideoxy-1,5-imino-ribitol and 1,5-Dideoxy-1,5-imino-arabinitol derivatives have also attracted considerable attention as enzyme inhibitors that mimic glycoside and nucleoside substrates. For example, 1,5-dideoxy-1,5-imino-ribitol derivatives was found to be a potent inhibitor of bovine β-galactosidases and almond β-glucosidase¹⁹, while 1,5-Dideoxy-1,5-imino-arabinitol N-carboxypentyl derivatives permitted the isolation of pure α-L-fucosidase from bovine kidney homogenate²⁰.

There are a diversity of synthetic methodologies have been developed to access iminosugars in hydroxypyrrolidines series²¹⁻²⁵, while the reports for hydroxypiperidine iminosugars synthesis, especial for hydroxypiperidine of pentitols, are limited²⁶. Therefore, there is a need to develop a simple method for the preparation of 1,5-Dideoxy-1,5-imino-ribitol and 1,5-Dideoxy-1,5-imino-arabinitol (Fig. 1). In this report, we like to present an efficient and environmentally friendly route for 1,5-dideoxy-1,5-imino-ribitol and 1,5-dideoxy-1,5-imino-1-arabinitol synthesis (Scheme 1) from D-ribose. The synthetic strategy employs many principles of Green Chemistry such as avoiding toxic or noxious chemical, and recycling and reusing the reagents²⁷.

The oxidation of D-ribose to D-ribonolactone is the critical and also the most difficult reaction in our proposed route. Pd–Bi/C heterogeneous catalyst²⁸ with molecular oxygen has been successfully applied to directly convert D-ribose to D-ribonolactone. However, Bi–gluconate complexes formed due to the interaction between the leached Bi (from Pd–Bi/C catalyst) and glucose substrate would contaminate the gluconic acid products. As a
result, further purification of products are needed, introducing large amounts of metal pollution. Additionally, to prevent the catalyst poisoning due to the adsorption of the product during reaction, the reaction medium has to be maintained at pH 9.0 by continual addition of alkaline solution. Thus, the alkaline systems induce plenty of wastes (e.g., inorganic salts). Hence, the alkaline-free direct oxidation of d-ribose over heterogeneous catalysts is an ideal green process to pursue. Recently, Song Guo et al. reported a simple incipient wetness protocol to prepare ultra-small gold clusters on TiO₂ through using anthranilic acid as a stabilizing agent. The resultant Au/TiO₂ catalyst exhibits excellent catalytic activity in the alkaline-free oxidation of glucose. Because of the excellent material physical properties of γ-Al₂O₃, such as high thermal stability, large surface area, and superior mechanistic strength, highly mesoporous γ-Al₂O₃ has been widely used in the chemical industry as catalyst support. Moreover, there are abundant of cation vacancies on γ-Al₂O₃ surface. This unique surface structure of γ-Al₂O₃ helps to stabilize Au clusters and prevent clusters agglomeration on its surface. Thus, we decided to explore ultra-small gold clusters on γ-Al₂O₃ (Au/Al₂O₃) as catalyst for alkaline-free oxidation of d-ribose. To achieve small gold particles (2–3 nm) deposited on Al₂O₃ support, a simple solid grinding method was used in catalyst preparation. The applicability of the Scheme 1 to the synthesis of 1,5-dideoxy-1,5-imino-d-arabinitol starting from d-lyxose was also attempted (Scheme 2).

Figure 1. Structures of some hydroxypyrrolidine and hydroxypiperidine iminosugars.

Scheme 1. Synthesis route from d-ribose to 1,5-dideoxy-1,5-imino-d-ribitol 4 and 1,5-dideoxy-1,5-imino-L-arabinitol 6.
Results and discussion

Catalyst characterization. The Au/Al₂O₃ catalysts were prepared through the solid grinding method. The Al₂O₃-supported gold clusters were calcined in static air at 300 °C, and the sample is denoted Au/Al₂O₃-Air. Prior to use, the catalysts were reduced under H₂ flow for 2 h at 150 °C and denoted Au/Al₂O₃-H₂. The nitrogen adsorption–desorption isotherms (Fig. 2) of catalyst samples with type IV shape designated the presence of mesopores with uniform pore size distribution. Table 1 presents the composition, BET surface area, pore volume, average pore diameter of γ-Al₂O₃ support and Au/Al₂O₃ catalysts. The BET surface area, pore volume and

| Catalyst                  | Surf. area (m²·g⁻¹) | Pore vol. (m³·g⁻¹) | Ave. pore. diameter (nm) | Au content (wt. %)² |
|----------------------------|----------------------|--------------------|--------------------------|---------------------|
| γ-Al₂O₃                    | 176                  | 0.62               | 6.14                     | –                   |
| 1 wt.% Au/Al₂O₃-Air        | 161                  | 0.59               | 5.53                     | 0.93                |
| 1 wt.% Au/Al₂O₃-H₂         | 156                  | 0.58               | 5.49                     | 0.91                |

Table 1. Textural properties of γ-Al₂O₃ and γ-Al₂O₃ supported nano Au catalysts. Based on ICP-OES analysis.

Scheme 2. Synthesis route from d-ribose to 1,5-dideoxy-1,5-imino-D-arabinitol 10.
average pore diameter were found to decrease slightly with the loading of Au content, showing that Au was deposited into the pores of γ-Al₂O₃ support.

XRD and TEM were then used to analyse these catalysts to determine the differences in the size and distribution of gold particles on γ-Al₂O₃ support. As shown in Fig. 3, no reflections associated with Au nanoparticles were found on XRD patterns of the Au/Al₂O₃. Actually, the diffraction pattern Au/Al₂O₃ is well in accordance with γ-Al₂O₃ supports (JCPDS 29-63). The XRD results indicate that the gold particles are uniformly dispersed on the oxide surface.

As shown in Fig. 4, the gold nanoparticles are uniformly distributed on Al₂O₃-H₂ support. The average particle size of an Au/Al₂O₃-H₂ catalyst is 2–3 nm, which was similar to particle size reported in the literature. The small clusters and uniform dispersion results are in agreement with XRD analysis.

To understand the surface state of Au particles on γ-Al₂O₃ surface, the XPS Au 4f spectra were carefully examined for the catalysts before and after H₂ reduction. Based on some XPS spectra obtained from various Au catalysts previously, Au 4f₅/₂ 87.7 eV and Au 4f₇/₂ 84.0 eV could be referred as neutral Au species. As shown in Fig. 5, compared with Au/Al₂O₃ without H₂ reduction, H₂ reduction reduce positive gold species and lead Au 4f peaks shift upward in binding energies (BEs) by 0.3–0.4 eV to neutral Au species. The XPS results reveal that the H₂ reduction could help to reduce positive gold species and produce neutral Au species on the γ-Al₂O₃ surface.

Synthesis of 1,5-dideoxy-1,5-imino-D-ribitol 4 and 1,5-dideoxy-1,5-imino-L-arabinitol 6 from D-ribose. Oxidation of D-ribose. In the first step as outlined in Scheme 1, the aerobic D-ribose oxidation was carried out in pure water using O₂ gas (1 MPa) as an oxidant agent. We first examined the catalytic performance of conventional gold nanoparticles (Au/C of 3–5 nm Au particle size) and commercial Pd/C catalyst as well as the synthesized Pd–Bi/C catalyst. It is found that the Au/C catalyst gave a 72% D-ribose conversion with a relatively
By-products of glutarate and oxalate were formed due to overoxidation and degradation of d-ribose, respectively. The Pd/C and Pd–Bi/C catalysts showed much lower catalytic performance (45% and 36% for d-ribose conversion (Table 2, entries 3 and 4) due to catalyst poison28.

Intriguingly, their selectivities to ribonolactone was low (≤ 20%) due to the over-oxidized targeted products. For Au/Al2O3-Air catalyst, 24% low yield with > 95% selectivity for ribonolactone was obtained. Interestingly, simply pretreated the Au/Al2O3-Air under H2 flow for 2 h at 150 °C could significantly improve its catalytic activity, and 93% conversion with > 95% selectivity to ribonolactone (Table 2, entry 6) was achieved. Of note, Au/Al2O3 catalyst showed low activity under relatively low reaction temperature conditions (Table 2, entries 7).

Song Guo et al.30 proposed that the glucose and dioxygen molecules are adsorbed and activated on the Au0 sites and support, respectively. The occupancy of Auδ+ species at the particles surface by water solvents and oxygen species would block the nearby active Au0 sites for glucose and O2 absorption, which would result in a low catalytic performance. From the XPS results (Fig. 5), pretreating the Au/Al2O3-Air catalyst under H2 flow for 2 h at 150 °C could significantly improve its catalytic activity, and 93% conversion with > 95% selectivity to ribonolactone (Table 2, entry 6) was achieved. Of note, Au/Al2O3 catalyst showed low activity under relatively low reaction temperature conditions (Table 2, entries 7).

The recyclability of Au/Al2O3 was evaluated under the same reaction conditions using recycled catalysts. Five cycles were carried out for d-ribose oxidation at 100 °C for 2 h under 1 MPa O2 using a recycled Au/Al2O3 catalyst and fresh reactants. After each reaction, the catalyst was simply recovered by filtration and washed alternately with water and ethanol followed by drying before being used again. The used catalyst was tested in 5 batch reactions without loss of activity and selectivity (Fig. 6). Hence, the results showed that Au/Al2O3 is a reusable and selective catalyst for d-ribose oxidation.

Acetalization of d-ribonolactone to 2,3-O-isopropylidene-d-ribonolactone. It was found that anhydrous CuSO4 served as critical Lewis catalyst28 for the conversion of ribonolactone to 2,3-O-isopropylidene-d-ribonolactone. Although relatively high yield (72%) was achieved, the CuSO4 is hard to be fully recovered due to its excellent solubility in water. Marek Marczewski22 reported a SO42-/Al2O3 system, where the acid strength of SO42-/Al2O3 catalyst could be tuned based on the concentration of H2SO4 solution through incipient wetness method. There-

Figure 5. XPS spectra of γ-Al2O3 and Au/Al2O3 catalysts for Au 4f.

Table 2. d-Ribose oxidation under different conditions. Reaction conditions: 0.15 g of d-ribose in 10 mL of H2O, 36 mg of catalyst, 2 h, 1 MPa O2. The Au loading of the prepared catalysts is 1 wt.%, and ribose/Au (molar ratio) = 550/1. The conversions (conv.) of ribose and selectivity (Sel.) for ribonolactone were determined by the HPLC analysis.

| Entry | Catalyst       | Temp. (°C) | Conv. (%) | Sel. (%) |
|-------|----------------|------------|-----------|----------|
| 1     | –              | 100        | –         | –        |
| 2     | 1 wt.% Au/C    | 100        | 72        | 82       |
| 3     | 10 wt.% Pd/C   | 100        | 45        | 15       |
| 4     | 10 wt.% Pd–Bi/C| 100        | 36        | 20       |
| 5     | 1 wt.% Au/Al2O3-Air | 100 | 24       | > 95     |
| 6     | 1 wt.% Au/Al2O3-H2 | 100 | 94       | > 95     |
| 7     | 1 wt.% Au/Al2O3-H2 | 70      | 67       | > 95     |
fore, we next optimized the condition of SO$_4^{2-}$/Al$_2$O$_3$ catalysts for the acetalization of ribonolactone with acetone to produce 2,3-O-isopropylidene-d-ribonolactone.

As shown in Table 3, no 2,3-acetonide 3a was formed when there was no catalyst in the reaction system. The addition of anhydrous CuSO$_4$ improved the yield to 68% when the reaction mixture was refluxed at 60 °C for 2 h (Table 3, entry 2). Interestingly, the surface sulfates of γ-Al$_2$O$_3$ created through H$_2$SO$_4$ solution treatment could increase 2,3-acetonide 3a yield significantly: The yield for commercial γ-Al$_2$O$_3$ is only 37%, while the reactions using 1 wt.% SO$_4^{2-}$/Al$_2$O$_3$ and 3 wt.% SO$_4^{2-}$/Al$_2$O$_3$ produced 71% and 85% 2,3-acetonide 3a, respectively. However, the use of 9 wt.% SO$_4^{2-}$/Al$_2$O$_3$ resulted in charring and only 11% yield of 3a was obtained (Table 3, entry 7). In addition, extending the refluxing time to 4 h with 3 wt.% SO$_4^{2-}$/Al$_2$O$_3$ catalyst led to the formation of some unknown products (Table 3, entry 6).

Table 3. Acetalization of ribonolactone with acetone.

| Entry | Catalyst | Super acid sites (mmol/g)$^a$ | Acetone (cm$^3$) | Condition | Yield 3 (%) |
|-------|----------|-------------------------------|-----------------|------------|-------------|
| 1     | –        | –                             | 40              | Reflux at 60 °C for 6 h | 0           |
| 2     | CuSO$_4$ | –                             | 40              | Reflux at 60 °C for 2 h | 68          |
| 3     | γ-Al$_2$O$_3$ | 0.082                  | 40              | Reflux at 60 °C for 2 h | 37          |
| 4     | 1 wt.% SO$_4^{2-}$/Al$_2$O$_3$ | 0.276               | 40              | Reflux at 60 °C for 2 h | 71          |
| 5     | 3 wt.% SO$_4^{2-}$/Al$_2$O$_3$ | 0.623               | 40              | Reflux at 60 °C for 2 h | 86          |
| 6     | 3 wt.% SO$_4^{2-}$/Al$_2$O$_3$ | 1.114              | 40              | Reflux at 60 °C for 2 h | 95$^b$  |
| 7     | 9 wt. % SO$_4^{2-}$/Al$_2$O$_3$ | 0.448              | 40              | Reflux at 60 °C for 2 h | 11          |
| 8     | Recycled$^c$ 3 wt.% SO$_4^{2-}$/Al$_2$O$_3$ | 0.647              | 40              | Reflux at 60 °C for 2 h | 73          |
| 9     | Re-generated$^d$ 3 wt.% SO$_4^{2-}$/Al$_2$O$_3$ | 0.647              | 40              | Reflux at 60 °C for 2 h | 85          |

Reaction conditions: 1.5 g of crude d-ribonolactone (10 mmol) in 40 mL of acetone, 3 mmol of catalyst. $^a$Were determined by NH$_3$-TPD analysis. $^b$Unknown products probably be 3,4-acetonide. $^c$See Recyle procedure in SI. $^d$See Re-generation procedure in SI.

To further understand the catalytic performance of the Al$_2$O$_3$ samples, catalysts were examined with NH$_3$-TPD and Pyridine-IR. As shown in Fig. 7, all the catalysts show two NH$_3$ desorption peaks at around 104 and 524 °C,
which are attributed to the weak and strong acid sites, respectively. In addition, the third peak at around 800 °C was observed on SO$_4^{2-}$/Al$_2$O$_3$ samples. The NH$_3$ desorption peak at 800 °C could be ascribed to the super strong acid sites, demonstrating the presence of super-acidic centers on SO$_4^{2-}$/Al$_2$O$_3$ catalysts. The peak at 800 °C was increased with the introduction of more SO$_4^{2-}$ species. Figure 8 shows the Pyridine-IR of the catalysts. Note that both Brønsted and Lewis acid are present on SO$_4^{2-}$/Al$_2$O$_3$ catalyst, whereas the γ-Al$_2$O$_3$ has a very little peak at 1540 cm$^{-1}$, indicating that there is only a small amount of Bronsted acid sites on γ-Al$_2$O$_3$ surface. Thus, the good catalytic activity of the 3 wt.% SO$_4^{2-}$/Al$_2$O$_3$ should be from the synergetic effect of Brønsted and Lewis acid sites as well as its appropriate amount of surface super-acid sites.

It was found that the catalytic activities of recycled SO$_4^{2-}$/Al$_2$O$_3$ catalysts dropped significantly (Table 3, entry 9) even after re-calcination at 500 °C for 24 h under dry air. The total super acid sites of recycled 3 wt.% SO$_4^{2-}$/Al$_2$O$_3$ sample was reduced to 0.448 mmol/g comparing to 0.623 mmol/g of fresh 3 wt.% SO$_4^{2-}$/Al$_2$O$_3$, indicating the release of substantial sulfate species from Al$_2$O$_3$ surface in reaction (Figure S1). To recover the performance of SO$_4^{2-}$/Al$_2$O$_3$ catalyst, re-deposition of SO$_4^{2-}$ on spent catalyst (upto 3 wt.%) by incipient wetness method is required (Table 3, entry 10).

Treated 2,3-acetonide 3a with methanesulfonyl chloride (MsCl) in pyridine to afford mesylate 3 as yellow crystals (91% yield). Mesylate 3 then was treated with aq ammonia and worked up, the 2,3-O-isopropylidene ribonolactam could be isolated crystalline in 84% yield. The carbonyl group on the anomeric carbon of the resulting lactam was reduced with NaBH$_4$ in methanol to give colorless syrup (95% yield). Finally, the resulting syrup was hydrolyzed using acidic Amberlite IR-120H resin to afford 1,5-dideoxy-1,5-imino-d-ribitol 4 in 96% yield. On the other pathway, treated mesylate 3 with potassium hydroxide to inverse the reacting carbon center and then followed by reacting with MsCl in pyridine to afford mesylate 5 in 80% yield. Following the same experiment procedures (treated with aq ammonia, reduction with NaBH$_4$ and hydrolysis using acidic Amberlite
The generality of this new synthetic protocol was tested for the synthesis of 1,5-dideoxy-1,5-imino-d-arabinitol \(10\) from d-lyxose (Scheme 2). d-lyxonolactone could be obtained by oxygenation of the far cheaper d-galactose by the Humphlett oxygenation\(^{45}\). However, the yield is low (68%) and potassium d-lyxonate instead of d-lyxonolactone was obtained, which requires extra work to convert potassium d-lyxonate to d-lyxonolactone. Different from Humphlett oxygenation, the aerobic oxidation of d-lyxose with 1 wt.% Au/Al\(_2\)O\(_3\) gave higher yield of desirable lactone product and > 99% conversion was achieved after 3 h. The selectivity to d-lyxonolactone was > 95%.

Table 4 shows the transformation of d-lyxonolactone \(8\) to 2,3-O-isopropylidene-d-lyxonolactone \(9a\) under different reaction conditions. The yield for \(9a\) was < 5% with the use of CuSO\(_4\) or \(\gamma\)-Al\(_2\)O\(_3\) in reaction (Table 4, entries 1 and 2). When the reaction mixture were refluxed over 1 and 3 wt.% SO\(_4^{2-}/\)Al\(_2\)O\(_3\), the isomer 3,5-acetonide \(9b\) was formed. Refluxing the reaction mixture over 9 wt.% SO\(_4^{2-}/\)Al\(_2\)O\(_3\), charred the reactant and products. To achieve single isomer product acetonide \(9a\), the reaction mixture was stirred for 18 h at room temperature, a 43% yield of \(9a\) could be obtained over 3 wt.% SO\(_4^{2-}/\)Al\(_2\)O\(_3\), which is significantly improved comparing with 27% yield through using methane sulfonic acid as catalyst. Fortunately, the significant difference in solubility of d-lyxonolactone \(8\) and 2,3-acetonide \(9a\) allows them to be easily separated with liquid–liquid (ethyl acetate/water) extraction. In turn, it was possible to recover the unreacted lyxonolactone and carry out further batch reactions to improve the yield. About 80% yield was achieved after three cycles of the reaction. Compound \(9a\) was next reacted with MsCl in pyridine solution followed by reducing the carbonyl group on the anomeric carbon of the resulting lactam with NaBH\(_4\) in methanol, then hydrolyzing over acidic Amberlite IR-120H resin to produce 1,5-dideoxy-1,5-imino-d-arabinitol \(10\). The overall yield of 1,5-dideoxy-1,5-imino-d-arabinitol \(10\) was 48%. The yield to d-arabinitol \(10\) can be compared with previously reported yields of 40% from d-arabinose\(^{20}\).

**Conclusion**

The novel strategy for synthesis of the iminosugars 1,5-dideoxy-1,5-imino-ribitol and 1,5-dideoxy-1,5-imino-dl-arabinitol synthesis was tested out in an environment friendly route starting from naturally occurring d-ribose and d-lyxose. Using ultra small gold clusters on Al\(_2\)O\(_3\) (Au/Al\(_2\)O\(_3\)) could effectively oxidize d-ribose and d-lyxose to corresponding lactones under alkaline-free condition. SO\(_4^{2-}/\)Al\(_2\)O\(_3\) showed good catalytic activities to replace homogenous Concentrated HCl and MsOH catalysts for acetalization of d-ribonolactone and d-lyxonolactone. The synthetic route resulted in good overall yields of 1,5-dideoxy-1,5-imino-d-ribitol of 54%, 1,5-dideoxy-1,5-imino-d-arabinitol of 48% and 1,5-dideoxy-1,5-imino-l-arabinitol of 46%. In addition, the heterogeneous catalysts and reagents applied in this synthetic strategy show environmental benefit and utilize the principles of green chemistry.

**Experimental section**

See experiment detail in supplemental information.
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**Author contributions**

H.G. contributed to perform the experiment and write the manuscript. A.F. contributed the conception of the study and manuscript preparation.

**Competing interests**

The authors declare no competing interests.

**Additional information**

**Supplementary Information**

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