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Note

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C-3 Epimerization of glucose, via regioselective oxidation and reduction

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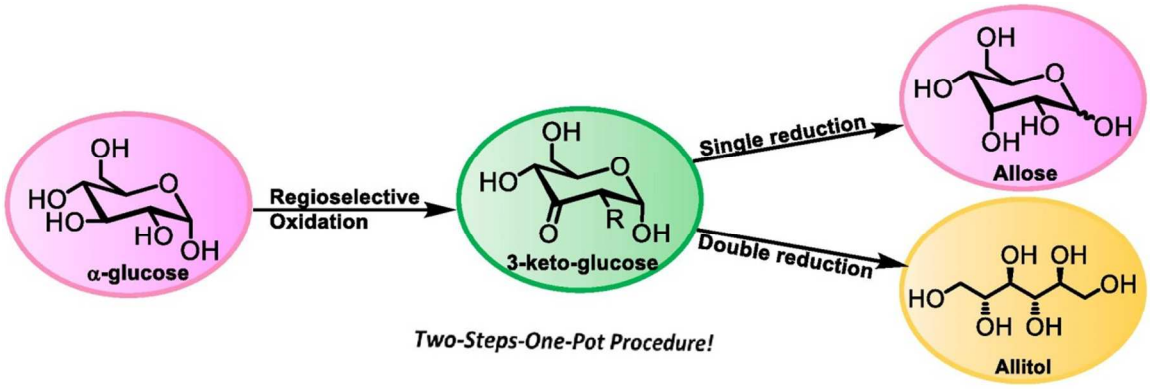


Palladium catalysed oxidation is able to single out the secondary hydroxyl group at C3 in glucose, circumventing the more readily accessible hydroxyl at C6 and the more reactive anomeric hydroxyl. Oxidation followed by reduction results in either allose or allitol, rare sugars that are important in biotechnology. Also N-acetyl glucosamine is selectively oxidized at C3. These results demonstrate that glucose and N-acetyl glucosamine, the most readily available chiral building blocks, can be versatile substrates in homogeneous catalysis.

Glucose, an aldohexose, is arguably the most important monosaccharide because it is used in respiration to provide energy for cells. Of the sixteen stereoisomeric aldohexoses, only D-glucose, D-mannose, and D-galactose (Figure 1), are readily available. The others, and in particular most L-sugars, are rare or do not occur as such in nature.[1] As a consequence, the properties of most of these rare aldohexoses have not been studied extensively, although these could be of importance in chemical biology and pharmacy, as mimics of the commonly occurring aldohexoses.

Some rare sugars have been obtained by selectively epimerizing asymmetric centers in other monosaccharides. This field, in which readily available hexoses are interconverted into the desired rare hexose, is largely the realm of enzyme catalysis, applying a highly versatile but limited set of transformations.[2] Important biotechnological processes are for instance the conversion of glucose into fructose, and the conversion of fructose into psicose (Figure 1).[3] The possible enzymatic interconversions of the hexoses have been beautifully represented in the so-called Izumoring (see SI), a scheme that relates all aldohexoses, 2-ketohexoses and hexitols.[4] From this scenario it becomes apparent that many of these hexoses are not readily accessible using the currently known enzymatic transformations.

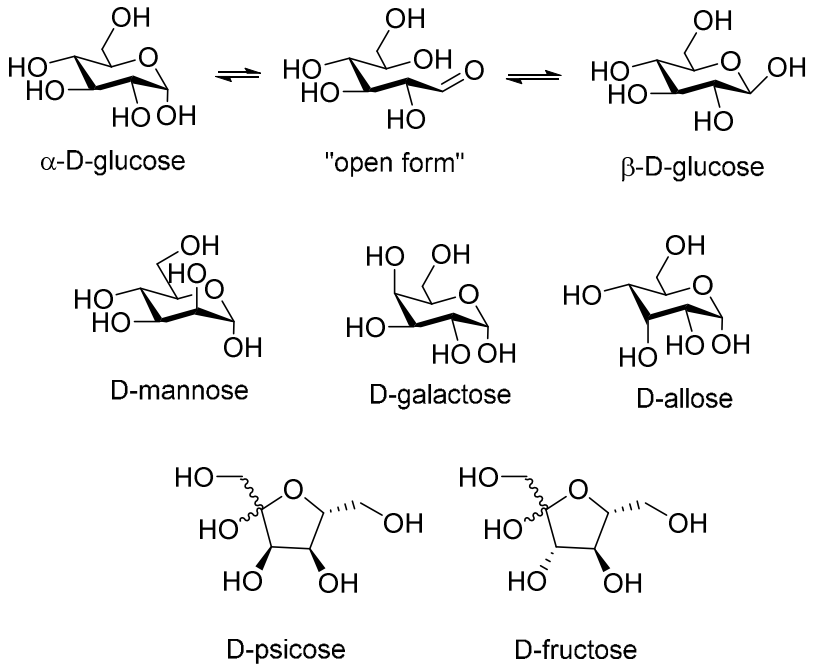


Figure 1. Mutarotation in glucose, and the most readily available monosaccharides

Chemical interconversion of hexoses provides a viable alternative to these enzymatic transformations. On lab scale, this has been worked out for several hexoses using (multi-step) synthetic procedures involving protection-deprotection strategies.[5] Depending on the target sugar, this approach can be elegant and efficient, as shown by recent work of Fleet, Jenkinson and Kanai.[6–8] Surprisingly, however, homogeneous catalysis has refrained from this field entirely. This is rather surprising as several of the reactions used by enzymes to interconvert hexoses, in particular oxidation and reduction, are studied intensively in transition metal catalysis and organocatalysis.[9–12]

Focusing on oxidation, the main challenge clearly is to single out a particular hydroxyl group, as the number of hydroxyl groups in carbohydrates closely equals the number of C-H bonds. The selective oxidation of the primary hydroxyl function in pyranoses and furanoses can often be achieved with reasonable selectivity exploiting the limited steric hindrance compared to the secondary hydroxyl groups.[13–15] The anomeric hydroxyl group on the other hand is readily oxidized selectively in the presence of both primary and secondary hydroxyl groups due to its lower pKa value, like in the classic oxidation with bromine.[16] This leaves in the case of glucopyranosides, the very similar secondary hydroxyl groups.

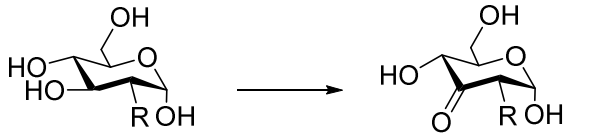
The group of Waymouth has shown that certain palladium catalysts can effectively discriminate between primary and secondary hydroxyl groups, preferentially oxidizing the secondary hydroxyl group.[17,18] Based on this, we demonstrated the highly regioselective oxidation of glucopyranosides, thereby expanding the selectivity to the differentiation among secondary hydroxyl groups.[19] Oxidation takes place at the C3-position to provide the corresponding 3-keto sugars. The method was shown to be effective as well for the disaccharides maltose and cellobiose, and recently even for oligomaltoses up to the 7-mer.[20] Waymouth and coworkers recently revealed that 6-deoxyglycosides, like L-rhamnopyranosides and L-fucopyranosides, and pentoses like D-xylopyranosides and D-arabinopyranosides are selectively oxidized by these catalysts as well.[21] Invariably, glycosides have been used as substrates with the anomeric center as part of an acetal to avoid oxidation of the anomeric alcohol and to lock the equilibrium in one anomeric form. Glucose itself, being a so-called reducing sugar, consists of

a mixture of the α and β-anomer in aqueous solution, together with small amounts of furanoses and the inferred open form. In attempts to selectively oxidize glucose at a secondary hydroxyl position, one therefore has to cope not only with the reactive anomeric hydroxyl group (C1-OH) and the more accessible primary hydroxyl group (C6-OH), but also with a potentially complex equilibrium. However, we realized that the palladium-catalyzed selective oxidation of glucose would be worthwhile to pursue as it would silence the common opinion that unprotected, reducing sugars are unsuitable substrates for homogeneous catalysis.

Recent studies in our group have revealed that the palladium catalyst chelates preferentially with vicinal bis-equatorial hydroxyl groups, preceding oxidation. This was concluded based on the observation that methyl glucoside oxidizes faster than methyl mannoside (C2-OH axial) and considerably faster than methyl galactoside (C4-OH axial).[22] Glucose preferentially crystallizes as the α-anomer (C1-OH axial), and we reasoned that this readily available isomer would not have an inherent preference for oxidation at the anomeric position because it lacks a vicinal bis-equatorial diol at C1-C2. Equilibration (mutarotation) of α-glucose results in the formation of β-glucose, which does possess a vicinal bis-equatorial diol at the anomeric center and hence is likely to be oxidized to the corresponding gluconolactone (vide infra). To successfully oxidize glucose, it is therefore essential to suppress mutarotation during the oxidation reaction. This process is rapid in protic solvents, including water, and catalyzed by both acid and base.[23,24] To our delight, α-glucose turned out to be stable in DMSO, not showing notable mutarotation at room temperature over several hours.[25,26] Apparently the hydroxyl groups of the glucose itself are not sufficient to catalyze mutarotation to an appreciable extent, even up to a glucose concentration of 1.5 M.

In the event, it turned out that α-glucose **2** is rapidly and with excellent selectivity oxidized at C3 with Waymouth's catalyst **1** and benzoquinone as co-oxidant in DMSO. By NMR, no gluconolactone (the product resulting from oxidation at the anomeric center) could be detected. The reaction is exceptionally fast, reaching full conversion within 1 h with catalyst loadings as low as 0.5 mol% (Scheme 1).

Scheme 1. Regioselective oxidation of α-glucose and N-acetyl α-glucosamine.



2: R = OH
3: R = NHAc

4: R = OH
5: R = NHAc

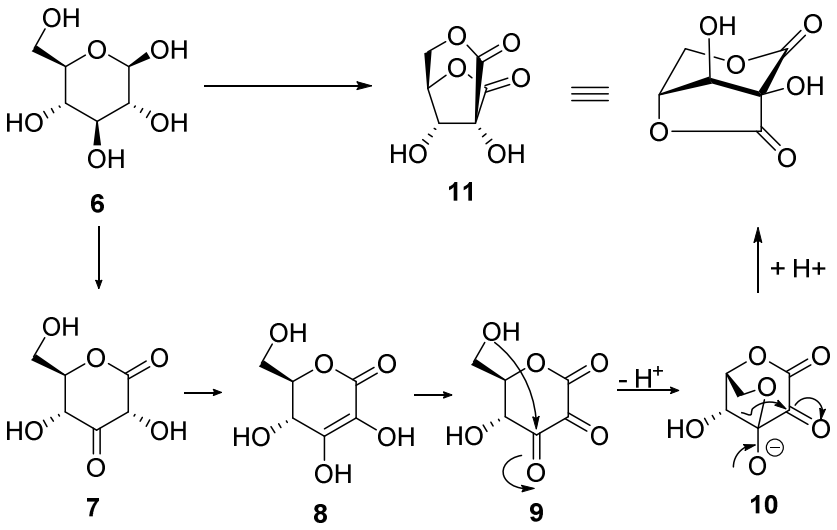
Reaction conditions: $[(neocuproine)PdOAc]_2OTf_2$ (**1**) (0.5 mol %), benzoquinone (1.25 eq), 1.5 M in DMSO, r.t., 1 h

Even a catalyst loading of 0.05 mol% resulted in 95% conversion after 1 h (see SI). It is remarkable that the involved chelation control of the catalyst overrules both the better accessibility of the primary hydroxyl group and the enhanced reactivity of the anomeric hydroxyl group. Only prolonged reaction times at elevated temperature induced further oxidation of the product at the anomeric center (vide infra). To determine whether α-glucose is unique in this reaction, we applied N- acetyl-α-D-glucosamine **3** in the same reaction and obtained the same highly selective oxidation at the C3 position.

To confirm our hypothesis that oxidation of α-glucose is selective because of the axial hydroxyl group at the anomeric center, we also studied the oxidation of β-glucose **6**, which can be obtained by crystallization of glucose from pyridine.[27] Since the anomeric hydroxyl

group is now in equatorial position we predicted oxidation at this center. In the palladium-catalyzed oxidation reaction we indeed observed a mixture of products, likely formed by either oxidation at C3 or at C1. In an attempt to drive the reaction to the doubly oxidized product, the reaction was heated to 40 °C for a prolonged time (~12 h). Although one product was indeed formed, it turned out not to be the expected ketolactone! In addition, prolonged reaction times and elevated temperatures in the oxidation of both α-glucose and gluconolactone, in the presence of excess benzoquinone, led selectively to the same compound (see SI). Initially, extensive NMR-studies did not provide a conclusive answer, until we realized that glucose is available in its all-^{13}C labeled form. Upon oxidation of glucose-$^{13}C_6$, the ^{1}H- and ^{13}C-NMR spectra in combination with 2D-NMR techniques led unambiguously to compound **11.** Apparently, ketolactone **7** is formed, but rapidly tautomerizes

Scheme 2. Oxidation of β-D-glucose leads to rearranged bislactone 11.



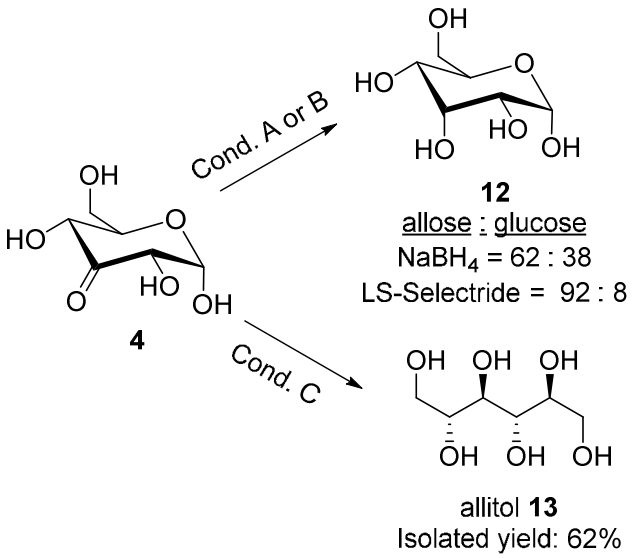
Reaction conditions: $[(neocuproine)PdOAc]_2OTf_2$ (**1**) (2.5 mol %), benzoquinone (3 eq), 0.3 M in DMSO, 40 °C, 18 h

to the corresponding enediol **8**, which in turn is rapidly oxidized to the diketolactone **9**. This intermediate subsequently undergoes intramolecular lactol formation followed by α-ketol rearrangement leading to **11** (Scheme 2). None of the intermediate stages could be observed by NMR. Although **11** as such has not been described in literature, products of this α-ketol rearrangement in pyranoses have been reported and the skeleton is present in the antibiotic ashimycin A. [28–31]

In order to study the implications of this regioselective oxidation of α-D-glucose on the interconversion of hexoses, we aimed at the reduction of 3-ketoglucose with sodium borohydride to D-allose. Noteworthy, the synthesis of this rare sugar currently takes several steps.[2] Treatment of aqueous solutions of the parent carbohydrate glucose with sodium borohydride is used to produce glucitol (sorbitol), as the minute amount of the open form, the aldehyde, is rapidly reduced.[32] In the reduction of α-D-3-keto glucose to D-allose, this reduction of the open form has to be effectively suppressed as both the starting material 3-ketoglucose and the product allose are vulnerable to the reduction of the open form. In addition, the axial hydroxyl group at the anomeric center is required to induce the desired stereoselectivity in the reduction of the keto group by hampering the approach of the borohydride from the bottom face. Any mutarotation to the β-anomer would eradicate this stereoselectivity. We were pleased to see that treatment of the crude 3-ketoglucose in DMSO with an aqueous solution of

sodium borohydride at 0 °C cleanly effected the reduction. The resulting 3:2 mixture of allose and glucose could be effectively separated by chelation chromatography on a calcium-loaded ion-exchange resin affording pure D-allose in 54% yield from glucose over just two steps.[33–36] The ratio of allose to glucose was somewhat disappointing as we had shown that this reduction carried out on 3-keto α-methyl glucoside produces α-methyl alloside with high selectivity.[19] Variation in the reducing agent (see scheme 3 and SI) showed that the bulky LS-selectride produces D-allose in high selectivity, though at the expense of a more complicated work up and purification.

Scheme 3. Selective reduction of 3-ketoglucose to allose and allitol.



Reaction conditions: A: $NaBH_4$ (0.75 eq), DMSO/H_2O (1:1), 0 °C B: LS-Selectride (3 eq), DMSO/THF (2:1), 0 °C. C: $NaBH_4$ (6 eq), DMSO/H_2O (1:1), r.t. 12 h

With these results established, a two-steps-one-pot conversion of glucose to allitol, was envisioned. Allitol and galactitol (dulcitol), being meso compounds, play a central role in Izumoring as the bridges between D- and L-hexoses. Currently, allitol is produced by a combination of enzymatic transformations (Figure 2). [37,38] The envisioned chemical method to interconvert glucose to allitol would not only be a drastic shortcut in the Izumoring scheme, but would also demonstrate that homogeneous catalysis is complementary to the existing biotechnological methods and that can be used to fill blank spots in the Izumoring. Treatment of the crude 3-keto glucose with aqueous sodium borohydride at room temperature led smoothly to a mixture of allitol and glucitol (3:2) (scheme 3) from which allitol was readily purified by calcium chelation chromatography. This synthesis of allitol from glucose in a two-steps-one-pot sequence is more efficient than the current enzymatic route. Furthermore, with LS-selectride as the reducing agent, up to 90% selectivity to allitol would be obtained.

Apart from the conversion into platform chemicals, the field of transition metal catalysis has kept a distance to unprotected carbohydrates as substrates for selective transformations. We show that in addition to biotechnology, also homogeneous catalysis can make an important contribution to the selective conversion and interconversion of unprotected carbohydrates. This is demonstrated in the palladium-catalyzed regioselective oxidation of glucose and N-acetyl glucosamine. Chelation-control overrules in this case both steric hindrance and the reac-

tivity of the anomeric hydroxyl group. Subsequent reduction under controlled conditions leads directly to either allose or allitol. This strategy provides not only ground for the straightforward synthesis of rare sugars but also for their potential applications in chemical biology.

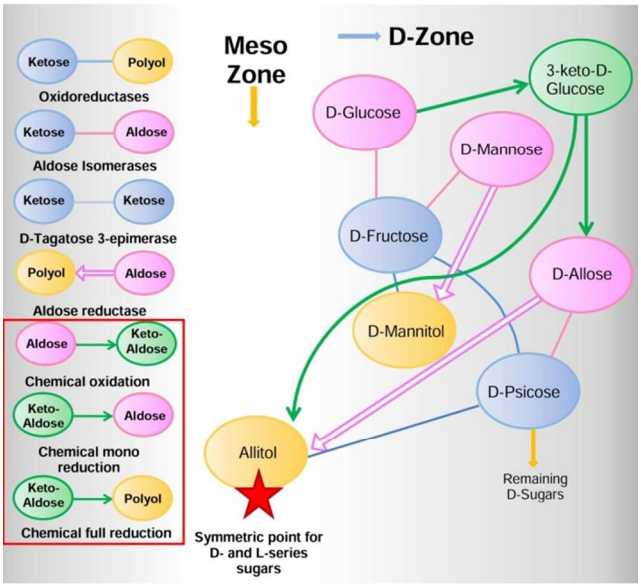


Figure 2. Chemical conversion of D-glucose to D-allose and allitol, complementary to the current enzymatic conversions.

EXPERIMENTAL SECTION

General Information

All solvents used for reaction, extraction, filtration and chromatography were of commercial grade, and used without further purification. $[(neocuproine)PdOAc]_2OTf_2$ Was prepared according to the literature procedure.[39]. TLC was performed on silica gel TLC plates and visualization was done by staining with anisaldehyde reagent (a mixture of acetic acid (300 ml), H_2SO_4 (6 ml), anisaldehyde (3 ml)) or potassium permanganate stain (a mixture of $KMnO_4$ (3 g), K_2CO_3 (10 g), water (300 mL)).^{1}H-, ^{13}C-, APT-, COSY-, HMBC- and HMQC-NMR were performed on at 400, 100 MHz, respectively) using D_2O or DMSO-d_6 as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (DMSO-d_6: δ 2.50 for 1H, δ 39.5 for 13C; D_2O: δ 4.80 for 1H)). Data are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, appt = apparent triplet, q = quartet, m = multiplet), coupling constants J (Hz), and integration.

Exchange of the resin to Ca2+

Dowex 50WX8 (200-400 mesh) resin in either the H^+ or the Na^+ form was exchanged to the Ca^{2+} form by stirring the resin with 4 M aqueous $CaCl_2$ (3 ml : 1 g resin) for at least 3 h. The aqueous layer was decanted, the resin washed with water and decanted once more. This washing step was repeated till there was a negative result for chlorides in the aqueous layer with $AgNO_3$ (1 M).

General procedure Ion exchange column

Dowex 50WX8 (200-400 mesh) in the Ca^{2+} form was loaded into a thin and long cylindrical glass column (column diameter 3.2 cm, filled to 24 cm). The crude material was loaded in 1-2 ml of water on top of the column and was eluted with water. The effluent was fractionated every 1.5–2.0 ml with a FRAC-100 fraction collector maintaining the flow rate between 0.6 to 0.8 ml/min.

For separation of glucose and allose

Glucose elutes first, followed by allose. Fractions were collected roughly on the basis of intensity of the spots on the TLC stained with anisaldehyde.

For separation of sorbitol and allitol

Allitol elutes first followed by sorbitol. TLC separation is visible between allitol and sorbitol (20% H_2O/acetonitrile as TLC eluens)

3-keto-α-D-glucose (4)

To a mixture of α-D-glucose **2** (35 mg, 0.19 mmol, 1 eq) and benzoquinone (60 mg, 0.58 mmol, 3 eq) in DMSO-d_6 (650 µL, 0.3 M) was added [(2,9-dimethyl-1,10-phenanthroline)-Pd(µ-OAc)]$_2$(OTf)$_2$ (5 mg, 45 µmol, 2.5 mol%). The reaction mixture was left at r.t. for 30 min. The product was left crude and characterized by NMR.

^{1}H NMR (400 MHz, DMSO-d_6) δ 5.30 (d, J = 4.1 Hz, 1H), 4.21 (dd, J = 4.2, 1.5 Hz, 1H), 4.06 (dd, J = 9.7, 1.6 Hz, 1H), 3.74 (ddd, J = 9.6, 4.7, 1.9 Hz, 1H), 3.68 (dd, J = 11.8, 2.0 Hz, 1H), 3.61 (dd, J = 11.9, 4.7 Hz, 1H) ^{13}C NMR (101 MHz, DMSO-d6) δ 207.2, 95.3, 75.3, 75.1, 72.2, 61.0.

Characterization matches literature[40]

D-allose (12) from 3-keto-α-D-glucose (4)

To a mixture of α-D-glucose **2** (120 mg, 0.67 mmol, 1 eq) and benzoquinone (90 mg, 0.83 mmol, 1.25 eq) in DMSO (450 µL, 1.5 M) was added [(2,9-dimethyl-1,10-phenanthroline)-Pd(µ-OAc)]$_2$(OTf)$_2$ (3.5 mg, 3.33 µmol, 0.5 mol%). The reaction mixture was stirred at r.t. for 1.5 h. Upon complete conversion (monitored by TLC 20% H2O/acetonitrile or ^{1}H-NMR), the reaction mixture was directly used for the successive reduction step. The reaction mixture was diluted with water (DMSO/H_2O 2:1). A cold solution of $NaBH_4$ (19 mg, 0.5 mmol, 0.75 eq) in water (225 µL) was added dropwise to the reaction at 0 ° C and stirred for 1.5 h. When the reaction showed complete conversion as indicated by TLC, methanol and acetone (1 : 1, 2 ml) were added to quench the reaction. The reaction mixture was concentrated in vacuo, and the remaining DMSO was diluted with dichloromethane to the point of precipitation. To this suspension, activated carbon (1 g) was added, the solution was filtered and the charcoal washed multiple times with dichloromethane till TLC indicated complete elution of the DMSO. Upon complete elution of DMSO, the charcoal was dried with a stream of air, and water was added to elute off the products. Concentration in vacuo resulted in a mixture of **12** and **2**. The mixture was further purified on an ion exchange column Dowex DVB WX8 Ca^{2+} (180 g of dry resin) and resulted in pure allose (65 mg, 0.36 mmol, 54%).

^{1}H NMR (400 MHz, D_2O) (assignment of the major configuration: β-D-allose) δ 4.89 (d, J = 8.2 Hz, 1H), 4.17 (t, J = 3.0 Hz, 1H), 3.89 (dd, J = 12.1, 2.0 Hz, 1H), 3.83 – 3.76 (m, 1H), 3.70 (dd, J = 12.0, 5.9 Hz, 1H), 3.64 (dd, J = 10.0, 2.9 Hz, 1H), 3.42 (dd, J = 8.3, 3.0 Hz, 1H). ^{13}C NMR (101 MHz, D_2O) (assignment of the major configuration: β-D-allose) δ 94.2, 74.4, 72.0, 71.9, 67.5, 61.9.

Characterization matches literature.[41]

Allitol (13) from 3-keto-α-D-glucose (4)

To a mixture of α-D-glucose **2** (120 mg, 0.666 mmol, 1 eq) and benzoquinone (90 mg, 0.833 mmol, 1.25 eq.) in DMSO (450 µL, 1.5 M) was added [(2,9-dimethyl-1,10-phenanthroline)-Pd(µ-OAc)]$_2$(OTf)$_2$ (3.5 mg, 3.33 µmol, 0.5 mol%). The reaction mixture was stirred at rt for 1.5 h. Upon complete conversion (monitored by TLC, 20% H_2O/ACN, or ^{1}H-NMR), the reaction mixture was directly used for the successive reduction step. To this end, the reaction mixture was diluted with water (DMSO/H_2O 2:1). A cold solution of $NaBH_4$ (150 mg, 4 mmol 6 eq) in water (1 ml) was added dropwise to the reaction at 0 °C and stirred for 18 h. When the reaction showed complete conversion as indicated by TLC, methanol and acetone (1 : 1, 2 ml) were added to quench the reaction. The reaction mixture was concentrated in vacuo. The residue in DMSO was diluted with dichloromethane to the point of precipitation. To this suspension, activated carbon (1 g) was added, the solution was filtered and the charcoal washed multiple times with dichloromethane till TLC (20% H_2O/ACN) indicated complete elution of the DMSO. Upon complete elution of DMSO, the charcoal was dried with a stream of air, and water was added to elute the product. Concentration in vacuo resulted in a mixture of **13** and **14**. The mixture was separated on an ion exchange column Dowex DVB WX8 Ca^{2+} (180 g of dry resin) and resulted in pure allitol **13** (76 mg, 0.419 mmol, 62%) (contains ~40% DMSO by NMR integration, isolated yield corrected for the presence of DMSO). ^{1}H NMR (400 MHz, D2O) δ 3.92 – 3.84 (m, 2H), 3.82 – 3.73 (m, 4H), 3.69 – 3.58 (m, 2H). ^{13}C NMR (101 MHz, D2O) δ 73.0, 72.8, 63.0.

Characterization matches literature.[42]

Oxidation of D-glucose-$^{13}C_6$

To a mixture of D-glucose-$^{13}C_6$ (34 mg, 0.18 mmol, 1 eq) and benzoquinone (58 mg, 0.54 mmol, 3 eq) in DMSO-d_6 (600 µL, 0.3 M) was added [(2,9-dimethyl-1,10-phenanthroline)-Pd(µ-OAc)]$_2$(OTf)$_2$ (4.7 mg, 45 µmol, 2.5 mol%). The reaction mixture was left at 40 °C for 4 h. The product was left crude and the structure was elucidated by NMR. ^{1}H NMR (400 MHz, DMSO-d_6) (decoupled for 13C) δ 4.97 (d, J =5.2 Hz, 1H, H5), 4.66 – 4.58 (m, 2H,H6a + H4), 4.44 (d, J =12.2 Hz, 1H, H6b). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.2 (dd, J = 55.0, 1.6 Hz, C1), 166.2 (d, J = 51.4 Hz, C3), 79.9 (ddd, J = 54.9, 51.5, 36.5 Hz, C2), 78.9 (appt, J = 35.0 Hz, C5), 71.6 (appt, J = 35.9 Hz, C4), 70.2 (d, J = 35.0 Hz, C6). HRMS (ESI) calculated for $C_6H_7O_6$ ([M+H]+): 175.024, found: 175.024

Oxidation of N-acetyl-α-D-glucosamine (3)

To a mixture of N-acetyl-α-D-glucosamine (40 mg, 0.18 mmol, 1 eq) and benzoquinone (58 mg, 0.54 mmol, 3 eq) in DMSO-d_6 (600 µL, 0.3 M) was added [(2,9-dimethyl-1,10-phenanthroline)-Pd(µ-OAc)]$_2$(OTf)$_2$ (4.7 mg, 45 µmol, 2.5 mol%). The reaction mixture was left at r.t. for 1.5 h. The crude product was characterized by NMR. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 8.2 Hz, 1H), 5.34 (d, J = 4.0 Hz, 1H), 4.69 (ddd, J = 8.2, 4.0, 1.3 Hz, 1H), 4.15 (dd, J = 9.7, 1.3 Hz, 1H), 3.82 (ddd, J = 9.6, 4.7, 2.0 Hz, 1H), 3.70 (dd, J = 11.9, 2.1 Hz, 1H), 3.64 (dd, J = 11.9, 4.7 Hz, 1H), 1.92 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 204.0, 169.8, 93.8, 75.3, 72.5, 61.0, 59.5, 22.4.

Characterization matches literature.[43]

ASSOCIATED CONTENT

The associated analytical data (^{1}H-NMR, ^{13}C-NMR and APT spectra for all compounds) can be found in the supporting information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

All authors have given approval to the final version of the manuscript.

‡ Varsha R. Jumde and Niek N. H. M. Eisink contributed equally.

Notes

The authors hereby declare no competing financial interests.

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