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FULL PAPER

Biomass-Based and Oxidant-Free Preparation of Hydroquinone from Quinic Acid

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Abstract: A biomass-based route for preparation of hydroquinone starting from renewable starting material quinic acid is described. Amberlyst 15 in the dry form promotes the one-step formation of hydroquinone from quinic acid in toluene without any oxidants or metal catalysts in 72% yield. Several acid polymer-based resins and organic acids as promoters including a variety of reaction conditions were screened taking into account other solvents of low or high boiling points, temperature and different concentrations. A 1:4 (w/w) ratio of quinic acid/amberlyst 15 was determined to be optimal to promote hydroquinone formation, with only traces of dimeric side product. A mechanistic proposal based on decarbonylation of protonated quino-1,5-lactone is supported by experimental and computational calculations data.

Introduction

Enormous efforts of the chemical industry in waste minimisation and use of less toxic and/or hazardous reagents to develop safer and greener processes have been made in the last decades. However, most of the raw materials used in the chemical industry have been generally obtained from fossil resources totalling 10 % of the crude oil consumption.[1] In order to accomplish sustainable methods for production of commodity chemicals and liquid fuels, non-renewable fossil resources (crude oil, coal and natural gas) should be replaced by sustainable feedstocks. Despite the intensive interest and the accomplished methods in the large scale industrial conversion of biomass to chemicals and materials in the second half of the 19th century, such investments suffered a drawback in the 20th century due to the much cheaper products synthesised by conventional routes from abundantly available fossil resources.[2] Fossil raw materials are irrevocably decreasing and the environmental consciousness of the chemical industry and the regulating agencies has led to an enormous research activity in a progressive shift of the chemical industry to renewable feedstocks in the last decade.[3] The selective defunctionalisation of highly functionalised molecules derived from renewable feedstocks is probably the biggest challenge in such shift, considering that sugars and polyols platforms can be highly exploited.[4] The production of aromatic compounds continues to be highly dependent on the non-renewable fossil feedstocks. Despite the enormous achievements in the depolymerisation of lignin, the only renewable source of high-volume aromatic compounds,[5] the industrial application of any of the reported methods has not yet been achieved.

Hydroquinone is prepared industrially by hydroperoxidation of *p*-diisopropylbenzene, hydroxylation of phenol, and oxidation of aniline. World production of hydroquinone is 40,000 – 50,000 ton yearly and mainly used in the rubber industry, monomer inhibitors, dyes and pigments, antioxidants, agricultural and photographic applications.[6] It is mostly used as a water soluble reducing agent in photography film development and in the rubber industry for production of antioxidants and antiozonants. It is also used as inhibitor of acrylic acid, methyl methacrylate, cyanoacrylate and other monomers commonly used in adhesives, glue and other type of bonding applications and in cosmetic applications in skin whitening compositions.

Preparation of hydroquinone from non-fossil sources has been reported by Frost and co-workers, after the seminal work of Woskresensky[7] on isolation of hydroquinone by dry distillation of quinic acid **1** (Scheme 1). Frost reported the preparation of hydroquinone from glucose in a two enzyme-catalysed steps and two chemical steps via 2-deoxy-*scyllo*-inosose synthase.[8] The construction of a transgenic *Escherichia coli* strain able to synthetize quinic acid from glucose under shake-flask condition was coupled to oxidation with stoichiometric amounts of MnO_2 of the obtained quinic acid to hydroquinone.[9] Other oxidative systems such as NaOCl, $(NH_4)_2Ce_2(SO_4)_3$, V_2O_5, and $K_2S_2O_8$ in presence of catalytic amounts of Ag_3PO_4 were reported to induce the same transformation in up to 91 % yield.[10] Quinic acid[11] is readily available from the bark of cinchona tree[12] as a side product during the extraction of cinchona alkaloids, and the principal constituent in coffee beans and other plant products.[13] Taking the dry distillation of quinic acid for preparation of hydroquinone,[7] it was hypothesised that the same transformation could be achieved under aerobic strongly acidic conditions. Besides formation of hydroquinone, other products expected in the acid promoted decomposition of quinic acid are bicyclic quino-1,5-lactone,[14] benzoic acid,[15] and quinone.[10]

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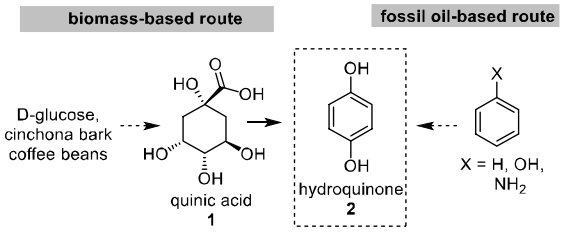


Scheme 1. Alternative biomass-based route to hydroquinone.

Results and Discussion

Versatile and robust polymer based resins were screened as promoters for the quinic acid conversion to hydroquinone.[16] Preliminary reaction of quinic acid was carried out with different forms of polystyrene macroreticular amberlyst resins; amberlyst 15 (dry and wet), amberlyst 16 and amberlyst 35 in toluene at 100°C (Table 1). Delightfully, amberlyst 15 in the dry form resulted in formation of hydroquinone **2** in 62% yield accompanied by ether **3**, resulting from condensation of hydroquinone (entry 1). Despite presence of quino-1,5-lactone in the reaction mixture, a likely reaction intermediate, benzoquinone formation was not observed. Amberlyst 15 has been reported in many instances as a mild and selective heterogeneous polymeric material for routine acid catalysed transformation in organic synthesis.[17] Other amberlysts tested showed inferior activity, leading to traces formation of the desired hydroquinone (entries 2-4). Acidic ion exchange resins Amberlite IRC86, IRC120/H and Dowex 50WX4 also failed to provide hydroquinone **2** in decent yields (entries 5-7). Despite the high moisture content (64-72%), Dowex 50WX4 proved to be superior to the other ion exchange resins, providing 12% of hydroquinone after 17 h (entry 7). After identification of amberlyst 15 in the dry form as being the best reaction promoter amongst the ones tested, and being a polymer supported sulfonic acid resin, we tested the ability of *para*-toluenesulfonic acid – *p*TSA - (entries 8-9) and sulphuric acid (entry 10) as reaction promoters. While sulphuric acid and monohydrate *p*TSA resulted in traces of hydroquinone (entries 8 and 10), use of molecular sieves and anhydrous *p*TSA resulted in recovery of the starting materials after 17 h (entry 9). Better conversions of the starting quinic acid were achieved by employing grinded amberlyst 15, sieved over a 106 µm sieve. Previous studies on the acid site accessibility of amberlyst 15 showed similar strengths of acid sites for the bead and powder forms of amberlyst 15 and the higher activity of powder resin should be associated with the exposed external surface of the resin.[18] Despite the 71 % yield of hydroquinone, use of grinded amberlyst led to considerable formation of ether side product **3** (entry 13).

Table 1. Screening of acid promoters for the formation of hydroquinone [a]

Entry	Acid	**2** Yield [%][b]	**3** Yield [%][b]
1	Amberlyst 15 (dry)	62	3
2	Amberlyst 15 (wet)	6	ND[c]
3	Amberlyst 16 (wet)	4	ND
4	Amberlyst 36 (wet)	5	ND
5	Amberlite IRC86	ND	ND
6	Amberlite IR120/H	6	ND
7	Dowex 50WX4	12	<3
8	*p*TSA.H_2O[d]	<3	ND
9	*p*TSA, 4Å MS[d]	NR[e]	
10	H_2SO_4[f]	<3	ND
11	Acetic acid[g]	ND	ND
12	None	NR	
13	Amberlyst 15 (dry) grinded	71	7

[a] Reaction conditions: Unless otherwise stated, the reaction was carried out with quinic acid (0.5 mmol), resin (0.3 g) and toluene (15 mL) at 100 °C for 17 h in an open vessel. [b] Determined by analysis of ^{1}H NMR spectrum of reaction mixture using bromobenzene as an internal standard. [c] ND – not detected. [d] 0.5 mmol of acid in 7 mL heated for 24 h. [e] NR – no reaction. [f] 1.5 mL of H_2SO_4 in toluene (15 mL). [g] 3 mL of AcOH.

In an attempt to optimize the reaction conditions and to allow the dissolution of quinic acid into the reaction solvent, other several solvents were screened. Using amberlyst 15 as the reaction promoter in refluxing THF, 1,4-dioxane, CH_2Cl_2, 1,2-dichloroethane, CCl_4, chlorobenzene, and methanol, or glycerol, sulfolane and polyethylene glycol at 125 °C for 24 h did not improve the selectivity towards hydroquinone formation. Besides toluene, only chlorinated solvents allowed detection of hydroquinone **2** in the reaction crude mixtures. From the abovementioned solvents, chlorobenzene allowed the higher formation of hydroquinone by running reaction in a sealed tube resulting in a mixture of **2** and **3** in a 4:3 ratio (68 % conversion). Taking toluene as the reaction solvent for this two-phase reaction, the influence of temperature in the reaction outcome was assessed (Figure 1). While very low conversions were achieved under 100 °C, the temperature interval 100-110 °C allows formation of hydroquinone in higher yields, while higher temperatures induce dimerisation of **2** into ether **3**. This process was verified by exclusive formation of **3** in 48 % isolated yield after heating hydroquinone **2** in toluene in presence of amberlyst 15 for 6 days.

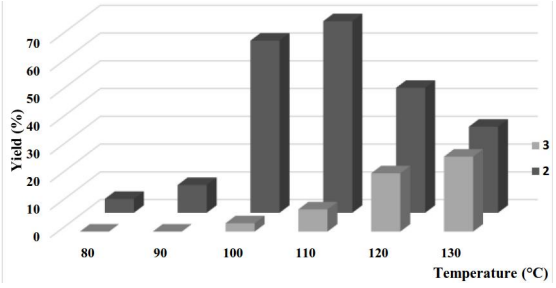
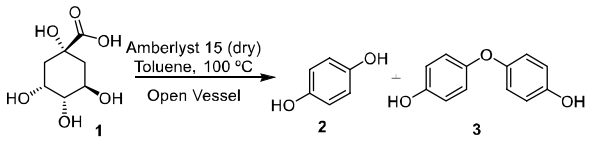


Figure 1. Effect of temperature on hydroquinone formation. Reactions conditions: quinic acid (0.5 mmol), Amberlyst 15 (0.3 g) in toluene (15 mL) at 100 °C, 17 h.

With these optimised conditions, we shifted our attention to the effect of amberlyst/quinic acid ratio on the reaction (Table 2). It was observed that, the yield of hydroquinone increased with only traces of ether **3** or none at all, as the amberlyst/ quinic acid ratio (w/w) was increased from 0.5 to 4 (entries 1-7). Further increase of the amount of amberlyst did not show any improvement when running reaction at 100 °C for 17 h (entries 7-9). Further tuning of the reaction conditions, namely amount of solvent and reaction time (see Supporting Information), resulted in formation of the desired hydroquinone in 72 % together with 5 % of ether **3** after 25 h (entry 10) and isolated by chromatography. Expansion of the reaction time to 48 h was showed beneficial for ether **3** formation, while formation of hydroquinone was kept the same (entry 11).

Table 2. Effect of amberlyst/quinic acid ratio on reaction performance.[a]



1 2 3

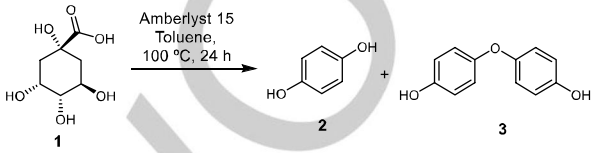
Entry	Amberlyst 15/**1** ratio (w/w)	Time (h)	**2** Yield [%][b]	**3** Yield [%][b]
1	0.5	17	9	ND[c]
2	1	17	17	ND
3	2	17	29	ND
4	3	17	43	<3
5	3.125	17	48	<3
6	3.5	17	56	<3
7	4	17	55	<3
8	5	17	55	<3
9	10	17	59	<3
10[d]	4	25	72 (71)[e]	5
11[d]	4	48	72	9

[a] Reaction conditions: Unless otherwise stated, the reaction was carried out with quinic acid (0.5 mmol), Amberlyst 15 (dry) in toluene (15 mL) at 100 °C in an open vessel. [b] NMR yield calculated from ^{1}H NMR spectrum of reaction mixture using bromobenzene as an internal standard. [c] ND – not detected. [d] 10 mL of toluene as solvent. [e] Isolated yield after flash chromatography.

Being a formal oxidation, the influence of oxygen and other oxidative conditions were also tested (Table 3). Absence of air or presence of water had a detrimental effect in the hydroquinone formation and the presence of oxygen or copper salts[19] were not effective catalysts in the putative aerobic oxidation process.

In order to get further insight into the reaction mechanism, two possible reaction intermediates **4** and **5** were prepared and reacted under similar reaction conditions (Scheme 2). Lactone **4** was converted into hydroquinone in 52 % yield, as previously observed for the reaction of quinic acid. As previously demonstrated by Frost,[10] ketone **5** is converted into the hydroquinone through the two possible enone intermediates. In such strongly acidic medium, the dehydration of **5** is a very fast process and such intermediates were not visible in the NMR spectrum of the quinic acid dehydration reaction mixture. It was nevertheless possible to detect and isolate a mixture of the enones **7** in 25 % yield when running the reaction in dioxane.

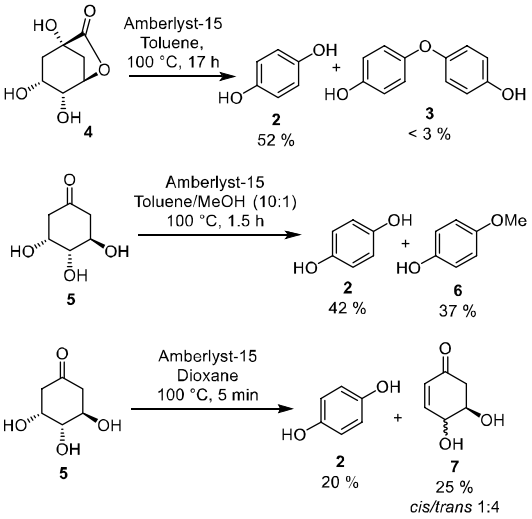
Table 3. Effect of oxidation conditions on reaction performance.[a]



1 2 3

Entry	Reaction conditions	**2** Yield [%][b]	**3** Yield [%][b]
1	Open vessel	72	5
2	O_2 atmosphere	64	6
3	Argon atmosphere	46	<3
4	1.5 equiv. of H_2O	62	3
5	5 mol % CuBr	58	4
6	5 mol % CuI	51	4
7	5 mol % $CuBr_2$	43	3
8	5 mol % $CuCl_2.H_2O$	47	4

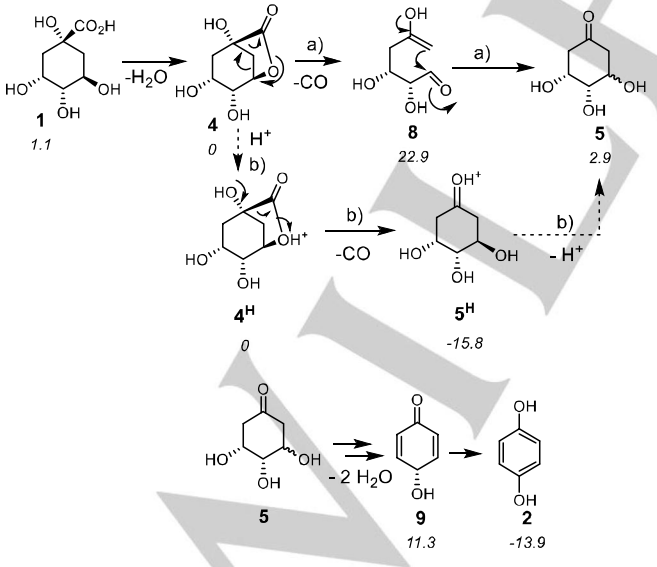
[a] Reaction conditions: Quinic acid (0.5 mmol), Amberlyst 15 (1:4 ratio (w/w)) in toluene (10 mL) at 100 °C, 24 h in an open vessel, except entries 2 and 3. [b] Determined by analysis of ^{1}H NMR spectrum of reaction mixture using bromobenzene as an internal standard.



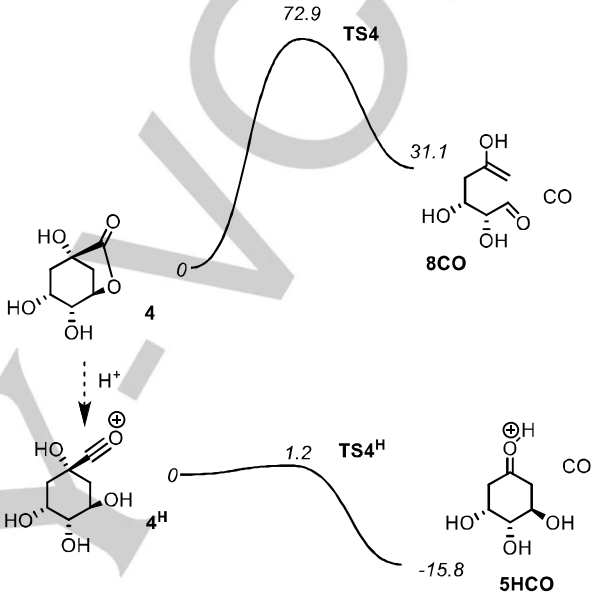
Scheme 2. Reactivity of reaction intermediates

Adding TEMPO, BHT, styrene and azodicarboxylates to the reaction mixture did not allow to isolate any intermediates derived from a single-electron-transfer pathway. Curiously, TEMPO inhibited the formation of the hydroquinone, and only starting material and lactone **4** were detected. Additionally, the use of *tert*-butyl peroxide as radical initiator did not improve hydroquinone formation or reduce reaction rate. The carbon atom lost in converting quinic acid to hydroquinone occurs through liberation of carbon monoxide. Such event was confirmed by reduction of palladium chloride to palladium when a filter paper soaked in $PdCl_2$ aqueous solution (1:500 w/v) was placed on the top of the reaction condenser (see supporting information).[20]

DFT calculations[21] were performed to compare ionic and radical mechanisms, through the optimisation of likely intermediates. The free energy values obtained for the diradical intermediates considered in single-electron-transfer processes clearly preclude a radical pathway for the reaction (ΔG = 80–84 kcal/mol, see Supporting Information for details). Furthermore, the high acidity of amberlyst should favour ionic mechanisms as it would be expectable by the favourable protonation of the starting material and reaction intermediates. Two ionic mechanisms were considered for the decarbonylation step both having lactone **4** as a starting point: a) a pericyclic decarbonylation of the lactone, with concomitant formation of the enol aldehyde **8** and b) ring opening of protonated lactone $\mathbf{4^H}$ (Scheme 3). From a thermodynamic point of view, formation of enol aldehyde **8** seems to be unlikely due to its high free energy (ΔG = 22.9 kcal/mol) while decarbonylation of protonated lactone $\mathbf{4^H}$ should be a spontaneous process towards formation of protonated ketone $\mathbf{5^H}$ (ΔG = –15.8 kcal/mol). This is further confirmed by the energy barriers calculated for both processes clearly indicating preference for the ring opening of protonated lactone over the pericyclic process (Scheme 4). While a large energy barrier of 72.9 kcal/mol needs to be overcome for the pericyclic process, the energy barrier for decarbonylation of $\mathbf{4^H}$ is only of 1.2 kcal/mol. Under the highly acidic reaction conditions, **9** should be formed after double protonation and dehydration of **5**, resulting in formation of more stable hydroquinone. The overall reaction from quinic acid to hydroquinone, is a thermodynamically favourable process, with ΔG = –14.9 kcal.



Scheme 3. Proposed ionic reaction mechanisms. Calculated free energies of the intermediates are indicated in italics (kcal/mol).



Scheme 4. Energy profiles calculated for two alternative decarbonylation steps. Free energies of the intermediates and transition states are indicated in italics (kcal/mol).

Conclusions

In conclusion, a mild and efficient method for conversion of naturally available quinic acid into hydroquinone is herein disclosed. By using Amberlyst 15 in its dry form as an acid promoter it is possible to obtain the hydroquinone in up to 72 % yield with only slight formation of the dimeric ether compound after 24 h. This method does not rely on the use of any oxidants or high temperatures as the previously reported ones. An ionic decarbonylation mechanism is proposed, supported by experimental and computational calculations data.

Experimental Section

General methods: Polymer based resins were used as received from suppliers. Amberlyst 15 (dry), 20-50 mesh from Fluka (06423) and Aldrich (216380), Amberlyst 15 (wet) from Aldrich (216399), Amberlyst 16 (wet) from Aldrich (86317), Amberlyst 36 (wet) from Fluka (06455), Amberlite IRC86 from Aldrich (10322), Amberlite IR120/H from Aldrich (216534), Dowex 50WX4 from Aldrich (422096). Quinic acid was obtained from Sigma-Aldrich and sieved over a 106 µm sieve prior to use. Retsch ZM200 and Retsch AS200 were used as grinder and sieve, respectively. Other

reagents were used as obtained from the suppliers (Sigma-Aldrich and Fluka). The reactions were monitored by thin-layer chromatography carried out on pre-coated (Merck TLC silica gel 60 F254) aluminium plates by using UV light as visualizing agent and cerium molybdate solution as developing agent. Flash column chromatography was performed on silica gel 60 (Merck, 0.040 - 0.063 mm). NMR spectra were recorded with Varian Mercury 300 MHz instrument using $CDCl_3$, DMSO-d_6 or D_2O as solvents and calibrated using tetramethylsilane as internal standard. Chemical shifts are reported in ppm relative to TMS and coupling constants are reported in Hz. ^{1}H NMR yields were determined by adding a known amount of bromobenzene to the reaction mixture after work-up.

Hydroquinone 2: Quinic acid (0.5 mmol) was added to a suspension of Amberlyst-15 dry (0.38 g) in toluene (10 mL) in a round bottomed flask equipped with a magnetic stirrer bar and condenser open to air. The mixture was heated at 100 °C for 24 h. After cooling to room temperature, methanol (5 mL) was added and the mixture stirred vigorously for 5 min. The mixture was filtered and the solid residue resuspended in methanol (20 mL) and stirred for an additional 5 min. After filtration and washings with more methanol (10 mL), the solvents were removed under reduced pressure. The residue was either dissolved in DMSO-d_6 for ^{1}H NMR yield determination (72%) or purified by flash chromatography with toluene/ethyl acetate (3:1) affording pure hydroquinone (39 mg, 71% yield) with similar spectral data as commercial samples. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.64 (s, 2 H), 6.55 (s, 4 H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 149.8, 115.8 ppm.

4,4-Dihydroxydiphenyl ether 3: Hydroquinone (1.0 mmol) was added to a suspension of Amberlyst-15 dry (0.77 g) in toluene (20 mL) in a round bottomed flask equipped with a magnetic stirrer bar and condenser. The mixture was heated at 100 °C for 6 days. After cooling to room temperature, methanol (10 mL) was added and the mixture stirred vigorously for 5 min. The mixture was filtered and the solid residue resuspended in methanol (40 mL) and stirred for an additional 5 min. After filtration, and washings with more methanol (20 mL) the solvents were removed under reduced pressure. The residue was purified by preparative TLC with toluene/ethyl acetate (3:1) to afford pure 49 mg (48 % yield) of **3,** with similar spectral data as previously reported.[22] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.70-6.83 (m, 8 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.9, 150.8, 120.1, 119.4, 115.9 ppm.

Quino-1,5-lactone 4: Amberlyst 15 dry (0.69 g) was added to a suspension of quinic acid (3 mmol) in acetonitrile (150 mL) and the mixture stirred at 50 °C for 24 h. After cooling, the reaction mixture was filtered over celite and washed with methanol. Solvent removal under reduced pressure yielded the desired lactone **4** in quantitative yield (0.52 g), with similar spectral data as previously reported.[23] ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.90 (s, 1 H), 5.24 (d, *J*=3.8 Hz, 1 H), 4.84 (d, *J*=6.7 Hz, 1 H), 4.61 (t, *J*=5.3 Hz, 1 H), 3.81 (d, *J*=4.1 Hz, 1 H), 3.49 (dd, *J*=11.0, 4.8 Hz, 1 H), 2.27 - 2.24 (m, 1 H), 2.13 - 2.07 (m, 1 H), 1.87 - 1.82 (m, 1 H), 1.75 - 1.66 (m, 1 H) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 177.8, 76.0, 71.6, 65.6, 65.3, 39.4, 36.8 ppm.

3(*R*), 5(*R*)-trihydroxycyclohexanone 5: Prepared according to previously reported procedure.[10] To a stirred solution of quinic acid (10 mmol) in water (7 mL) was added NaOCl 14% aqueous solution (30 mmol) and H_2SO_4 (8 mmol) dropwise for 30 minutes. The reaction was left stirring at room temperature for 2.5 h. The reaction was quenched with *iso*-propanol (30 mmol) and left stirring for 30 min. After pH neutralisation with aqueous saturated solution of Na_2CO_3 the solvent was removed under reduced pressure. The obtained residue was resuspended in acetone (55 mL) and left stirring overnight at room temperature. After filtration and solvent removal under reduced pressure, the residue obtained was purified by flash chromatography with eluent gradient from ethyl acetate/hexane (9:1) to methanol/ethyl acetate (1:9). Desired ketone **5** was obtained in 75 % yield (1.03 g), with similar spectral data as previously reported.[10] ^{1}H NMR (D_2O, 300 MHz) δ 4.83 (s, 3 H), 4.29 (ddd, *J*=6.3, 3.7, 2.9 Hz, 1 H), 4.15 (td, *J*=8.2, 5.3 Hz, 1 H), 3.97 (dd, *J*=7.8, 2.8 Hz, 1 H), 2.83 – 2.80 (m, 1 H), 2.78 - 2.75 (m, 1 H), 2.65 - 2.50 (m, 2 H) ppm; ^{13}C NMR (D_2O, 75 MHz): δ 212.8, 73.0, 68.7, 45.7 ppm.

4-Methoxyphenol 6: Ketone **5** (0.5 mmol) was dissolved in methanol (1 mL) and dispersed in toluene (10 mL) in a round bottomed flask equipped with a magnetic stirrer bar. Amberlyst-15 dry (384 mg) was added and the mixture stirred at 100 °C until disappearance of the starting material as judged by TLC (1.5 h). After cooling to room temperature, methanol (5 mL) was added, the mixture filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography with gradient ethyl acetate/Hexane (1:9 to 1:1), to afford 42 % (23 mg) of hydroquinone **2** and 37 % (23 mg) of **6** with similar spectral data as previously reported.[24] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.78 (d, *J*=1.8 Hz, 4 H), 4.93 (br. s., 1 H), 3.77 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.6, 149.4, 116.0, 114.8, 55.8 ppm.

Dihydroxy-2-cyclohexen-1-one 7: Amberlyst 15 dry (0.38 g) was added to a solution of ketone 5 (1 mmol) in 1,4-dioxane (10 mL) and the mixture stirred at 100 °C for 5 min. After cooling to room temperature, the mixture was filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography with eluent gradient from ethyl acetate/hexane (4:1) to methanol/ethyl acetate (1:9). gradient ethyl acetate/Hexane (1:9 to 1:1), to afford 20 % (20 mg) of hydroquinone **2** and 25 % (31 mg) of **7** in a *cis/trans* 1:4 ratio as determined by ^{1}H NMR, and compared with previous reports.[10] ^{1}H NMR (D_2O, 300 MHz) δ 6.96 (dd, *J*=10.1, 2.2 Hz, 1 H), 6.92 - 6.87 (m, 0.2 H), 6.73 - 6.72 (m, 0.2 H), 6.06 (dd, *J*=2.2, 1.0 Hz, 0.2 H), 6.03 – 5.98 (m, 1 H), 4.64 - 4.61 (m, 0.2 H), 4.39 - 4.30 (m, 1.2 H), 3.99 - 3.91 (m, 1 H), 2.78 – 2.76 (m, 0.5 H), 2.73 - 2.71 (m, 1 H), 2.68 (dd, *J*=5.1, 1.0 Hz, 0.2 H), 2.55 - 2.46 (m, 1.3 H) ppm; ^{13}C NMR (D_2O, 75 MHz): δ 204.8, 204.4, 156.2, 154.2, 151.8, 131.6, 131.5, 119.2, 74.4, 74.3, 72.5, 70.3, 68.8, 63.3, 57.8, 46.5, 45.7ppm.

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Keywords: Cyclitols • Sustainable Chemistry • Heterogeneous catalysis • Natural Products

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