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Deoxygenation of Polyhydroxybenzenes: An Alternative Strategy for the Benzene-Free Synthesis of Aromatic Chemicals

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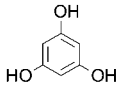
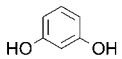
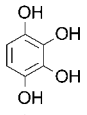
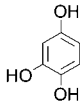
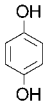
Benzene-free syntheses of mono-,[1a] di-,[1b,c] and trihydroxy benzenes[1d] have primarily been based on the shikimate pathway. A completely different route to aromatic chemicals involving intermediacy of polyhydroxyaromatics derived from glucose is described in this report. The centerpiece of this strategy is the discovery that catalytic hydrogenation of polyhydroxybenzenes followed by acid-catalyzed dehydration of the dihydro intermediates results in loss of one oxygen atom from the starting polyhydroxybenzene. The result (Table 1) is a new synthesis of pyrogallol (**4**) from glucose, a new benzene-free synthesis of hydroquinone (**6**), and the first benzene-free synthesis of resorcinol (**2**).

Reduction of phloroglucinol (**1a**) with $NaBH_4$ followed by azeotropic removal of H_2O is known to lead to resorcinol (**2**).[2a] As for catalytic reduction, formation of the sodium salt of dihydrophloroglucinol has been reported when phloroglucinol is hydrogenated using 5% Rh on Al_2O_3 although dehydration of this intermediate was not examined.[2b] Phloroglucinol was thus an ideal substrate to test the viability of polyhydroxybenzene deoxygenation as a route for synthesis of aromatic chemicals. Phloroglucinol (**1a**) was hydrogenated over 5% Rh on Al_2O_3 under basic conditions. Subsequent acid-catalyzed dehydration led to the formation of resorcinol (**2**, Table 1) in 82% isolated yield after distillation. Use of Rh on Al_2O_3 gave somewhat higher yields of resorcinol (**2**) than use of activated C as the support. Successively lower yields of **2** were obtained for use of Rh, Pt, and Pd as hydrogenation catalysts (Table 1). 1,2,3,4-Tetrahydroxybenzene (**3**) and hydroxyhydroquinone (**5**) were then similarly reacted to test the generality of the deoxygenation strategy for polyhydroxybenzenes that can be synthesized from glucose.

In route to 1,2,3,4-tetrahydroxybenzene (**3**), *myo*-inositol (**8a**) was microbially synthesized from glucose and then oxidized by a second microbe (Scheme 1).[3] As previously reported,[3] acid-catalyzed dehydration of the resulting *myo*-2-inosose (**9**) was used to obtain 1,2,3,4-tetrahydroxybenzene (**3**, Scheme 1). Catalytic hydrogenation of 1,2,3,4-tetrahydroxybenzene (**3**) using Rh on Al_2O_3 led to a 44% yield of pyrogallol (**4**, Table 1). Changing the metal or its solid support had little impact on the yield of pyrogallol (**4**, Table 1). Synthesis of pyrogallol by way of *myo*-2-inosose (**9**) required only 4 enzyme-catalyzed steps and 2 chemical steps (Scheme 1). By comparison, synthesis of pyrogallol (**4**) by way of gallic acid (**10**) and the shikimate pathway (Scheme 1) required at least 20 enzyme-catalyzed steps.[1d] Phytic acid (**8b**, Scheme 1), which constitutes about 8% of the dry weight of corn steeping liquor, is an abundant alternative source of *myo*-inositol.[4a,b] Established methods are available for the isolation of phytic acid (**8b**) and its dephosphorylation.[4c]

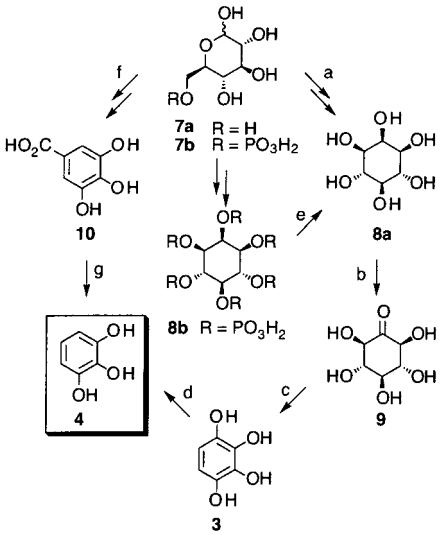
A more direct derivation of an inosose is possible using 2-deoxy-*scyllo*-inosose synthase, which catalyzes the conversion of glucose 6-phosphate (**7b**) into 2-deoxy-*scyllo*-inosose (**11**, Scheme 2). Reaction of inosose **11** with Ac_2O under acidic conditions produces

Table 1. Products, Isolated Yields, and Reaction Conditions for Deoxygenation of Polyhydroxybenzenes

polyhydroxybenzene	[a]reaction conditions	product	[b]yield
 **1a**	Rh/Al_2O_3	 **2**	82
	Rh/C		74
	Pt/C		60
	Pd/C		32
 **3**	Rh/Al_2O_3	 **4**	44
	Rh/C		43
	Pt/C		42
	Pd/C		41
 **5**	Rh/Al_2O_3	 **6**	53
	Rh/C		47
	Pt/C		46
	Pd/C		18

[a] Polyhydroxybenzene (1 M) in degassed, aqueous 1 M NaOH was reacted with 0.012 equiv of Rh, Pt, or Pd (5 wt %, metal/solid support) in a Parr hydrogenation apparatus at room temperature under 50 psi H_2 for 12 h. After filtration, acidification to pH 6.0, and concentration, the residue (0.25 M) was refluxed in 0.5 M H_2SO_4 under Ar for 9 h. [b] Yields (mol/mol) are of purified product after distillation.

Scheme 1 [a]



[a] Key: (a) *E. coli* JWF1/pAD1.88A, 11%, see ref 3; (b) *G. oxydans* ATCC 621, 95%, see ref 3; (c) H_2SO_4, H_2O, reflux, 66%, see ref 3; (d) 44%, see Table 1; (e) phytase; (f) *E. coli* KL7/pSK6.161, 12%, see ref 1d; (g) *E. coli* RB791 *serA*::*aroB*/pSK6.234, 93%, see ref 1d.

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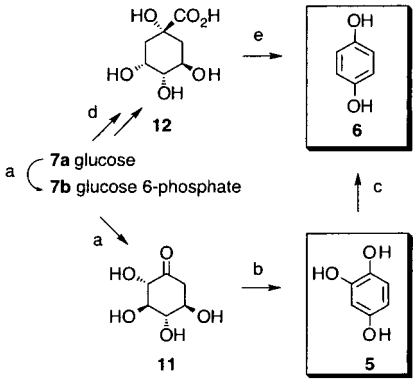
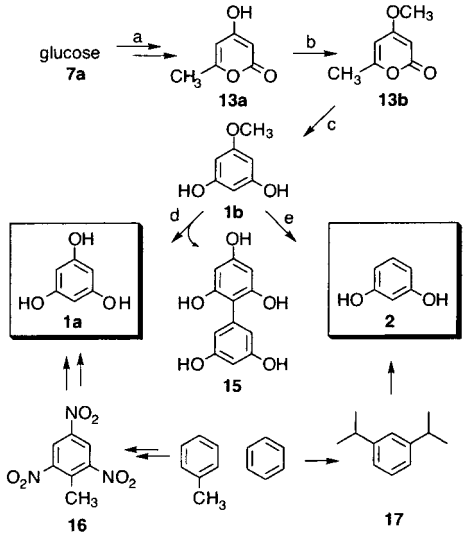
Scheme 2 [a]



[a] Key: (a) i. hexokinase, ii. 2-deoxy-*scyllo*-inosose synthase, 38%, see ref 5a; (b) 0.5 M H_3PO_4, reflux, 39%; (c) 53%, see Table 1; (d) *E. coli* QP1.1/pKD12.138, 20% (from glucose), see ref 1b; (e) i. NaOCl, ii. reflux, 87%, see ref 1b.

Scheme 3 [a]



[a] Key: (a) see ref 6; (b) $(CH_3O)_2SO_2$, K_2CO_3, acetone, reflux, 85%; or $(CH_3O)_3PO$ (neat), K_2CO_3, 79%; or Dowex 50 (H^+), MeOH 43%; (c) Na, MeOH, 185 °C, 85%; (d) 12 N HCl, 56% **1a**, 15% **15**; (e) 80%, see Table 1.

a 29% yield of hydroxyhydroquinone triacetate.[5] We find that hydroxyhydroquinone (**5**) can be directly obtained (Scheme 2) by acid-catalyzed dehydration of an aqueous solution of chemically synthesized[5b] 2-deoxy-*scyllo*-inosose (**11**). Hydrogenation of hydroxyhydroquinone with Rh on Al_2O_3 (Table 1) produced hydroquinone (**6**) in 53% yield. While similar yields of **6** were obtained with Rh and Pt as the hydrogenation catalysts, a substantially lower yield was realized with Pd (Table 1). The 2 enzyme-catalyzed steps and 2 chemical steps required for the conversion of glucose into hydroquinone via 2-deoxy-*scyllo*-inosose (**11**) contrast with the 18 enzyme-catalyzed steps and 1 chemical step required for the synthesis of hydroquinone (**6**) from glucose (**7a**) via quinic acid (**12**) and the shikimate pathway (Scheme 2).[1b]

The report[6] of microbe-catalyzed synthesis of triacetic acid lactone (**13a**) and the reported[7] conversion of **13b** into phloroglucinol (**1a**, Scheme 3) allowed advantage to be taken of the highest yielding deoxygenation of a polyhydroxybenzene (Table 1). Literature-based[7a] alkylation of triacetic acid lactone (**13a**) by $(CH_3O)_2SO_2$ afforded the corresponding methyl ether (**13b**) (Scheme 3). Reaction of triacetic acid lactone methyl ether (**13b**) as a melt in Na and MeOH gave an excellent yield of phloroglucinol methyl ether (**1b**, Scheme 3).[7a] To circumvent the toxicity of $(CH_3O)_2SO_2$, triacetic acid lactone (**13a**) was converted to its methyl ether **13b** by using $(CH_3O)_3PO$ or by refluxing in MeOH with Dowex 50 (H^+) (Scheme 3). Hydrolysis of the phloroglucinol methyl ether (**1b**) afforded phloroglucinol (**1a**) along with substantial amounts of 2,4,6,3′,5′-pentahydroxybiphenyl (**15**, Scheme 3).[7b] Fortuitously, hydrogenation of phloroglucinol methyl ether (**1b**) followed by acid-catalyzed dehydration of the intermediate dihydrophloroglucinol proved to be highly regioselective with formation of resorcinol (**2**) in 80% yield (Scheme 3). The syntheses of phloroglucinol (**1**) and resorcinol (**2**) from glucose contrast with the synthesis (Scheme 3) of these aromatics from toluene-derived TNT[8] (**16**) and benzene-derived 1,3-diisopropylbenzene[9] (**17**), respectively.

New synthetic connections have been made between glucose and aromatic chemicals by recruiting biosynthetic pathways other than the shikimate pathway. To fully exploit these syntheses in the future, a microbe that directly synthesizes *myo*-2-inosose from glucose (**7a**) or phytic acid (**8b**) remains to be constructed. A microbe capable of synthesizing 2-deoxy-*scyllo*-inosose (**11**) from glucose is also needed[5a] along with a microbe that synthesizes triacetic acid lactone (**13a**) in high yield. Compelling reasons for surmounting these biocatalytic challenges can be found in the drastic reductions in the numbers of enzymes required to synthesize pyrogallol and hydroquinone. The access gained to resorcinol is comparably important. With polyhydroxybenzene deoxygenation, benzene-free syntheses have now been established for all of the "building block" hydroxybenzenes including phenol,[1a] resorcinol, catechol,[1c,5a] hydroquinone,[1b] pyrogallol,[1d] hydroxyhydroquinone, and phloroglucinol.

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Supporting Information Available: Syntheses of **1a**,**b**, **2**, **4**, **5**, **6**, and **13b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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