Mechanistic Studies of Selective Catechol Formation from *o*-Methoxyphenols using a Copper(II)–Ascorbic Acid–Dioxygen System

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Mechanistic details of selective conversion of *o*-methoxyphenols to the corresponding catechols using a Cu^{2+}–ascorbic acid–O_2 system, were studied. 2,5-Dimethoxyphenol was converted predominantly to the *o*-demethylated compound and partially to the *m*-demethylated one. Anisole with no phenolic hydroxy group was much less reactive. When guaiacol (**1**), [Me-$^2H_3$]guaiacol and 2-[$^2H_3$]methoxy-6-methoxyphenol were used as substrates, moderate intermolecular and intramolecular kinetic isotope effects were observed (1.4–1.9). [^{18}O]Catechol was derived from **1** in nine-fold excess over [^{16}O]catechol when the reaction was run in an $^{18}O_2$ atmosphere with natural water as a solvent, though no [^{18}O]catechol was formed when using natural O_2 and $H_2{}^{18}O$. It was determined that the Cu^{2+}–ascorbic acid–O_2 system operates in a monooxygenase mode because the oxygen atom of dioxygen (not water) was incorporated into the products, and this oxidative conversion proceeded mainly *via* ipso-substitution at the methoxy position, probably with hydroxyl radical coordinated to the cupric ion as the active oxygen species.

We have already reported that oxidative conversion of *o*-methoxyphenols to catechols can be conducted with high selectivity by use of a Cu^{2+}–ascorbic acid–O_2 system (Scheme 1).[1] This

1 2

Scheme 1

reaction seems unique in that oxido-labile products can be obtained without undergoing further oxidation.

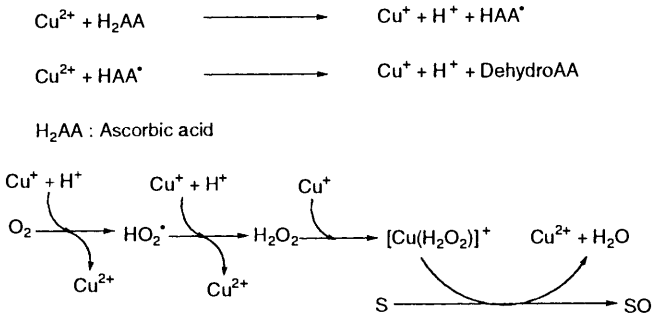
While oxidative O-dealkylation of alkyl aryl ethers is catalyzed effectively *in vivo* by cytochrome P-450s,[2] this reaction has been very difficult to achieve with the use of chemical oxidation couples.[3]

The Cu^{2+}–ascorbic acid–O_2 system serves as a hydroxyl radical-generating system, analogous to the Fenton system (Fe^{2+}–H_2O_2),[4] for studies on oxidative damage to biomolecules such as amino acids, proteins, and DNA.[5] However, it seems necessary to investigate the real active species in the Cu^{2+}–ascorbic acid–O_2 system, becuase it has been questioned whether or not hydroxyl radicals are produced in Cu^+–H_2O_2 systems[6] including the Cu^{2+}–ascorbic acid–O_2 one. These circumstances prompted our mechanistic studies of the reaction.

Results and Discussion

As our previous report shows,[1] substrate, cupric salt, ascorbic acid and dioxygen are all indispensable for this reaction (Table 1). There was little difference in reactivity among copper(II) salts having various counter anions and a copper(I) salt was also capable of conducting the reaction, though less effectively. Other metal salts were inferior to copper(II) salts in yield and selectivity. Hydrogen peroxide under anaerobic conditions could substitute for dioxygen, and the reaction rate increased, though the selectivity somewhat decreased.

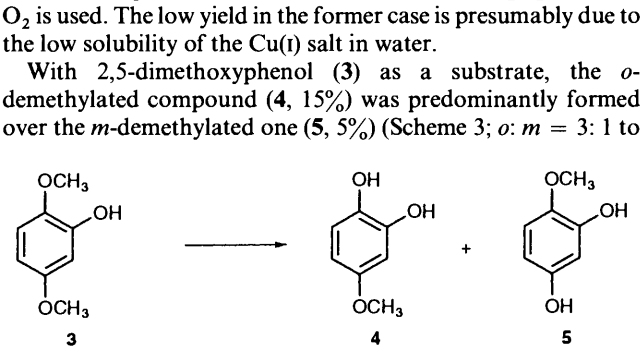
The oxygenation by the Cu^{2+}–ascorbic acid–O_2 system is generally believed to proceed as shown in Scheme 2.[5] Ascorbic acid or ascorbic acid semiquinone radical reduces a Cu^{2+} ion to a Cu^+ ion, either of which successively reduces O_2 to H_2O_2.



Scheme 2

Then the cuprous ion and the hydrogen peroxide combine to afford the active species, tentatively represented by $Cu^I(H_2O_2)$, which oxygenates the substrate, and the other oxygen atom is converted to water. The Scheme is supported by the fact that the reaction can proceed if Cu^+ instead of Cu^{2+} or H_2O_2 in lieu of O_2 is used. The low yield in the former case is presumably due to the low solubility of the Cu(I) salt in water.

With 2,5-dimethoxyphenol (**3**) as a substrate, the *o*-demethylated compound (**4**, 15%) was predominantly formed over the *m*-demethylated one (**5**, 5%) (Scheme 3; *o*: *m* = 3: 1 to



3 4 5

O_2	76	:	24
H_2O_2	82	:	18

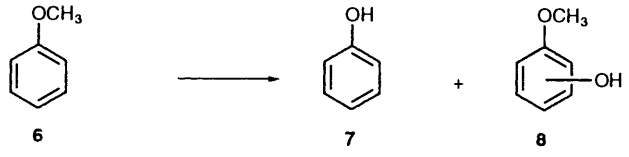
Scheme 3

4: 1) by using either O_2 or H_2O_2 under an Ar atmosphere. When anisole (**6**) having no hydroxy group was used as a substrate, formation of the demethylated compound markedly decreased (**7**, 2.7%) and the reaction selectivity was also lowered because a small amount of aromatic hydroxylation occurred (**8**, ca. 2.5%)

Table 1 Oxidative catechol formation from *o*-methoxyphenol (**1**) by a Cu^{2+}–ascorbic acid–O_2 system.

Run	1/mmol	Cu^{2+}/mmol	AA/mmol	Gas phase	H_2O_2/mmol	*t*/h	Yield (%)	Selectivity (%)
1	1	1	10	O_2	—	24	26	96
2	1	1	10	O_2	—	6	14	100
3	0	1	10	O_2	—	17	0	—
4	1	0	10	O_2	—	17	< 0.5	—
5	1	1	0	O_2	—	17	0	—
6	1	1	10	Ar	—	17	0	—
7	1	1	10	Ar	10	1.5	28	85
8	1	1 (Cu^{+})	10	O_2	—	24	2	—
9	1	1 (Fe^{2+})	10	O_2	—	24	4	—
10	1	1 (Ni^{2+})	10	O_2	—	24	< 0.1	—

(Scheme 4). Therefore, the *ortho*-hydroxy group seemed to



Scheme 4

enhance reaction efficiency.

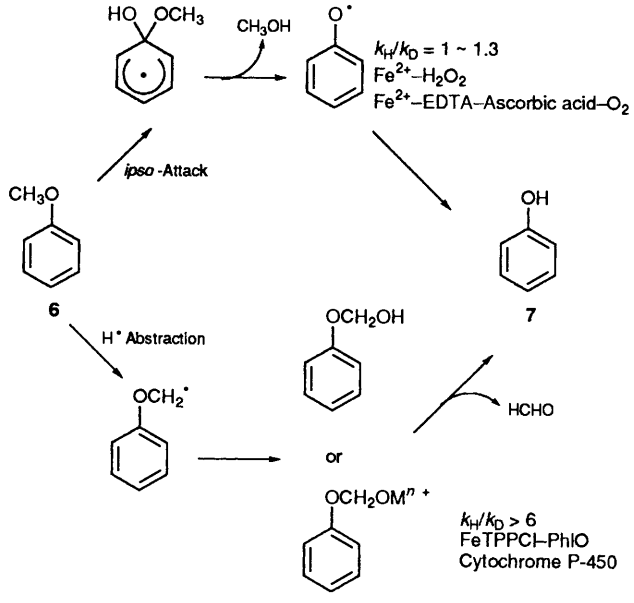
We think these results depend on the substrate properties. One possible explanation is that an active oxy-radical preferentially causes hydrogen atom abstraction from the phenolic hydroxy group rather than *ipso*-substitution taking place at the 2- or 5-position followed by hydrogen abstraction from the methoxy groups, and that the catechol (**4**) can be formed *via* all the routes but the resorcinol (**5**) cannot arise *via* the first main route.

The Cu^{2+}–ascorbic acid–O_2 system is comparable with a monooxygenase system (*e.g.* cytochrome P-450) *in vivo*. An iron–heme chelate is an active centre in the P-450 system, while in the Cu^{2+}–ascorbic acid–O_2 system, a copper–ascorbate complex is. The reductant is NADPH in the enzyme system and ascorbic acid in the chemical system. Dioxygen is a common oxidant. Ascorbate serves to reduce a cupric ion, to coordinate to the copper ion, to scavenge excess free oxidants, thus protecting the catechol products against further oxidation, and possibly also to reduce *o*-quinone to catechol. The reason why catechol formation and *o*-methoxyphenol consumption in this oxidation reached a ceiling at the halfway point may be that ascorbic acid is a highly oxidizable competitive substrate and that almost all cuprous ions are rendered insoluble and inert by carbon monoxide, oxalate, *etc.* produced in the reaction.[7]

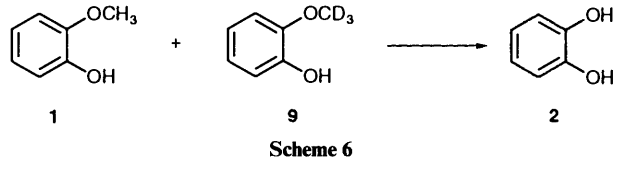
As Scheme 5 shows, oxidative O-demethylation of aryl methyl ethers can be roughly divided into two pathways.[3b] In one, hydroxy moiety is added at the methoxy position in the *ipso* manner and then methanol is liberated. This type of reaction, which has little isotope effect (k_H/k_D = 1–1.3), occurs in the Fenton system[3b,4] and the Udenfriend system (Fe^{2+}–ascorbic acid–EDTA–O_2).[8] The other involves hemiacetal formation, followed by elimination of formaldehyde ($k_H/k_D \geqslant 6$), and operates in the cytochrome P-450 system[2] and an iron porphyrin complex–oxidant model system,[3b,9] though the latter type of reaction couple provided less than 1% yield.

We examined intermolecular and intramolecular isotope effects in the Cu^{2+}–ascorbic acid–O_2 system using **1**, **9** and **10** as substrates (Schemes 6 and 7). The k_H/k_D values obtained were 1.6–1.8 in the intermolecular cases and 1.4–1.9 in the intramolecular cases, being intermediate between those expected for the above two pathways, so we presume both routes operate simultaneously.

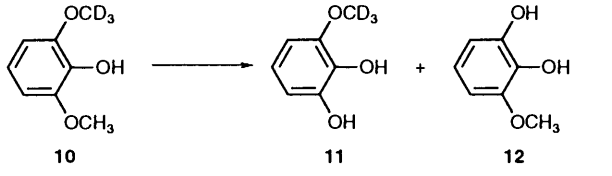
Next, ^{18}O incorporation experiments were conducted.[3b] In the *ipso* type of reaction, the product contains the oxygen atom



Scheme 5



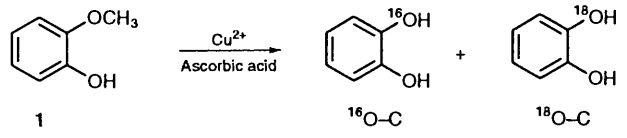
Scheme 6



Scheme 7

derived from the active species, unless the oxygen atom of the reaction intermediates is exchanged for that of the solvent, water. In contrast, in the hydrogen atom abstraction type reactions, the oxygen atom derived from the active oxidant is eliminated as formaldehyde, so that the oxygen atom of the substrate remains in the product.

In the reaction using $^{18}O_2$ and $H_2{}^{16}O$, the catechol which contained an ^{18}OH group in the aromatic ring, abbreviated as ^{18}O–C, was formed in preference to ^{16}O–C (Scheme 8). Correction of these data to a 100 atom% of $^{18}O_2$ basis gave an ^{18}O-C:^{16}O-C ratio of 9:1. On the other hand, ^{18}O-C was not produced at all when $^{16}O_2$ and $H_2{}^{18}O$ were used. The latter result shows that the solvent, water, does not react with reaction intermediates, and that the oxygen atom in the active species undergoes no exchange with that in the solvent. Hence, in the oxidative conversion of guaiacol (**1**) to catechol (**2**) by the



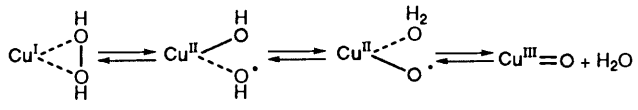
	^{16}O–C	^{18}O–C
under Ar–$^{18}O_2$[a] in H_2O	31% (10%)[b]	69% (90%)[b]
under air in $H_2{}^{18}O$[c]	100%	0%

[a] The isotopic purity was estimated from phenol oxygenation under the same conditions. [b] The yields in parentheses are corrected for the isotopic purity of the $^{18}O_2$ used. [c] H_2O:$H_2{}^{18}O$ (98.4 atom%) = 1:1.

Scheme 8

Cu^{2+}–ascorbic acid–O_2 system, the *ipso* type of reaction occurs preferentially, and the '*ipso* substitution route' and the 'H atom abstraction route' are thought to operate in the ratio of 9:1. These results can account for the intermediate k_H/k_D values. It was clarified that the Cu^{2+}–ascorbic acid–O_2 system catalyzes a monooxygenase type of reaction such that the oxygen atom derived from dioxygen is introduced into the substrate.

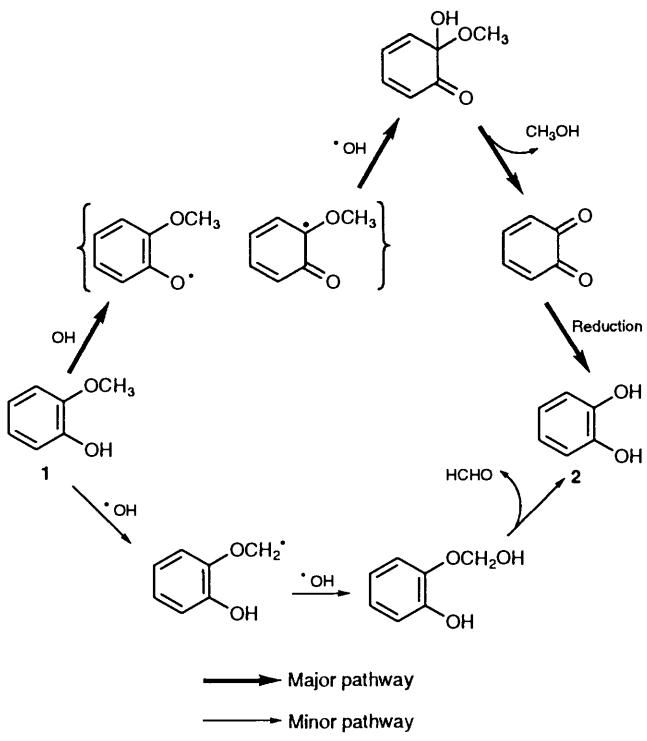
Because there is no attack of the solvent on the intermediates, we consider that no ionic intermediates are generated and that an oxy-radical species directly attacks the aromatic ring or the hydrogen atom of the methyl group. The $Cu^{I}(H_2O_2)$ active species mentioned above may take various forms (Scheme 9).



Scheme 9

Cupryl oxenoid (Cu^{III}=O), however, seems irrelevant because it would suffer oxygen exchange with water as a solvent, considering that Fe^{V}=O does.[10] Therefore, we assume that the ultimate active oxidant is $Cu^{II}(OH^-)(^{\bullet}OH)$ or $Cu^{II}(O^{\bullet})(H_2O)$, which is equivalent to *crypto* $^{\bullet}OH$, *i.e.*, $^{\bullet}OH$ coordinated to the cupric ion. From the above results, we propose the reaction mechanisms shown in Scheme 10.

In concluion, we have revealed by means of experiments using stable isotopes that the *ipso* substitution route is the main one in the conversion of *o*-alkoxyphenols to the corresponding catechols with the Cu^{2+}–ascorbic acid–O_2 system. Since this is a biomimetic oxidation system, the results imply that similar reactions occur in the oxidative metabolism of substituted phenols, such as alkoxyphenols, in various biological systems. So, studies on metabolism of phenols with a rat liver microsome are currently in progress.



Scheme 10

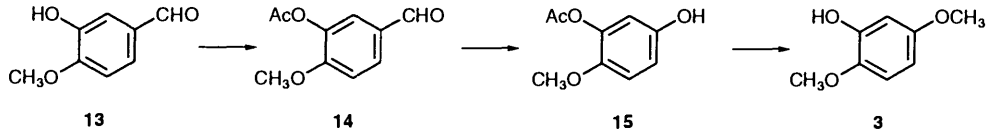
Experimental

Materials.—All the materials were of commercial reagent grade unless otherwise stated, and were obtained from Aldrich Chemical Company, Tokyo Kasei Kogyo, Nacalai Tesque, Wako Pure Chemical Industries and MSD Isotopes. [$^2H_3$]Iodomethane was 99.5% deuteriated. [^{18}O]Dioxygen and [^{18}O]water had isotopic purities of 97 and 98.4 atom %, respectively.

Triethylamine (Et_3N) was distilled over lithium aluminium hydride. Benzyl chloride was distilled over calcium hydride (CaH_2) under vacuum. Tetrahydrofuran (THF) was distilled under an argon atmosphere in the presence of sodium wire and benzophenone ketyl immediately before use. Ether was distilled over CaH_2 and a small amount of ferrous ion salt and stored with molecular sieves 4Å. Chloroform and dichloromethane were distilled over CaH_2 and stored with molecular sieves 4Å. Hexane and ethyl acetate were distilled over calcium chloride. Ethanol and methanol were distilled in the presence of magnesium ribbon and a minute quantity of iodine and stored with molecular sieves 3Å. *N*,*N*-Dimethylformamide (DMF) was distilled with no additives and stored with molecular sieves 4Å.

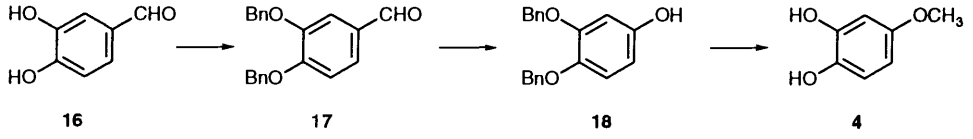
Synthesis of 2,5-*Dimethoxyphenol* **3** (Scheme 11).—(i) *Preparation of* 3-*acetoxy*-4-*methoxybenzaldehyde* **14**. To a mixed solution of isovanillin **13** (4.564 g, 30.0 mmol), 4-*N*,*N*-dimethylaminopyridine (DMAP) (367 mg, 3.0 mmol), and Et_3N (4.55 g, 45.0 mmol) in a mixed solvent of THF (20 cm^3) and ether (20 cm^3) was added dropwise a solution of acetic anhydride (4.00 g, 39.2 mmol) in ether (10 cm^3) over 10 min with stirring in an iced water bath. After stirring for 14 h at room temp., the reaction mixture was diluted with ether, washed with saturated aq. sodium hydrogen carbonate, water, aq. hydrochloric acid (2 mol dm^{-3}), water, and brine, successively, and then dried (Na_2SO_4 anhyd.). Filtration, removal of the solvents, and then vacuum drying afforded **14** as a colourless powder (5.535 g, 95%). Recrystallization from $CHCl_3$–hexane gave colourless blocks, m.p. 86–87 °C (Found: C, 61.8; H, 5.2. $C_{10}H_{10}O_4$ requires C, 61.58; H, 5.19%); ν_{max}(KBr)/cm^{-1} 3420 (OH), 3060–2860 (CH), 1768 (ester C=O), 1683 (aldehyde C=O), 1604, 1578 and 1507; δ_H(60 MHz, $CDCl_3$) 2.3 (3 H, s, CH_3CO_2), 3.85 (3 H, s, CH_3O), 7.0 [1 H, d, J_{56} 9, Ph(5)–H], 7.5 [1 H, d, J_{26} 2.5, Ph(2)–H], 7.7 [1 H, dd, J_{62} 2.5, J_{65} 9, Ph(6)–H] and 9.8 (1 H, s, CHO); *m*/*z* 194 (M^+), 152, 137, 123 and 109.

(ii) *Preparation of* 3-*acetoxy*-4-*methoxyphenol* **15**. A clear solution of **14** (2.912 g, 15.0 mmol) and *m*-chloroperbenzoic acid (mCPBA) (5.18 g, 30.0 mmol) in dry CH_2Cl_2 (35 cm^3) was refluxed with stirring for 2.5 h. Filtration and evaporation under vacuum afforded oily products, which were diluted with AcOEt and washed with 5% aq. $NaHCO_3$ (× 3) and brine, successively. The products were dissolved in EtOH (50 cm^3), and after addition of 5% $NaHCO_3$ aq. (75 cm^3) the solution was stirred for 18 h at room temp. The reaction mixture was acidified to pH 2 with HCl aq. (2 mol dm^{-3}), salted out and extracted with AcOEt. The organic layer was washed with brine, 5% $NaHCO_3$ aq., and brine successively, dried (Na_2SO_4 anhyd.) and filtered. After removal of the solvent, the residual solid was chroma-



13 14 15 3

Scheme 11



16 17 18 4

Scheme 12

tographed on a silica gel column with CH_2Cl_2–AcOEt (19:1) to yield **15** as slightly yellow crystals (2.39 g, 87.5%). Recrystallization from $CHCl_3$–hexane for instrumental analyses furnished colourless needles, m.p. 111–112 °C (Found: C, 59.2; H, 5.6. $C_9H_{10}O_4$ requires C, 59.34; H, 5.53%); ν_{max}(KBr)/cm^{-1} 3420, 2950–2830 (CH), 1740 (ester C=O), 1624, 1594 and 1511; δ_H(60 MHz; $CDCl_3$) 2.3 (3 H, s, CH_3CO_2), 3.7 (3 H, s, CH_3O), 5.65 (1 H, br s, exch. D_2O, PhOH) and 6.4–6.9 (3 H, PhH × 3); *m/z* 182 (M^+), 140, 125 and 111.

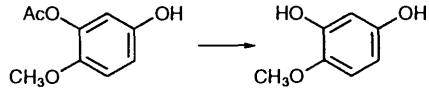
(iii) *Preparation of* 2,5-*dimethoxyphenol* **3**. To a mixture of **15** (60.9 mg, 0.33 mmol) and anhyd. dicesium carbonate (136 mg, 0.42 mmol) in DMF (1.0 cm^3) was added iodomethane (30 cm^3, 0.48 mmol), and the whole was stirred vigorously for 5 h at room temp. To the reaction mixture was then added 25% aq. ammonia (1.0 cm^3), and stirring was continued for a further 30 min. After acidification to pH 2 with HCl aq. (2 mol dm^{-3}) and extraction with ether, the organic layer was washed with 5% $NaHCO_3$ aq. and brine successively, dried (Na_2SO_4 anhyd.), filtered, and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography with hexane–CH_2Cl_2 (1:1) as the eluent to give **3** as a pale yellow solid, which was recrystallized from ether–hexane to provide colourless crystals (50 mg, 97%), m.p. *ca.* 25 °C (hygroscopic); ν_{max}(KBr)/cm^{-1} 3420 (OH), 3000–2830 (CH), 1621, 1596 and 1507; δ_H(60 MHz; $CDCl_3$) 3.75 (3 H, s, CH_3O), 3.85 (3 H, s, CH_3O), 5.7 (1 H, s, exch. D_2O, PhOH), 6.4 [1 H, dd, J_{43} 10, J_{46} 3, Ph(4)–H], 6.6 [1 H, d, J_{64} 3, Ph(6)–H] and 6.8 [1 H, d, J_{34} 9, Ph(3)–H]; *m/z* 154 (M^+), 139, 125 and 111.

Synthesis of 4-*Methoxycatechol* **4** (Scheme 12).—(i) *Preparation of* 3,4-*dibenzyloxybenzaldehyde* **17**. After addition of benzyl chloride (3.00 g, 23.7 mmol) to a mixed solution of protocatechuic aldehyde **16** (1.00 g, 7.24 mmol) and Cs_2CO_3 anhyd. (9.44 g, 29.0 mmol) in DMF (5 cm^3), the suspension was stirred vigorously for 48 h under an argon atmosphere. The reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with water, 15% aq. dipotassium carbonate (× 2), water, HCl aq. (2 mol dm^{-3}), and brine, successively, followed by drying (Na_2SO_4 anhyd.), filtration, and removal of the solvents to furnish a pale yellow powder. Chromatography on a silica gel column with CH_2Cl_2–AcOEt (3:2→2:3) as the eluent yielded **17** as colourless plates (1.548 g, 67%), m.p. 87 °C (Found: C, 79.1; H, 5.7. $C_{21}H_{18}O_3$ requires C, 79.23; H, 5.70%); ν_{max}(KBr)/cm^{-1} 3430, 3080–2720 (CH), 1676 (aldehyde C=O), 1595, 1580 and 1510; δ_H(60 MHz; $CDCl_3$) 5.05 (2 H, s, PhCH_2O), 5.1 (2 H, s, PhCH_2O), 6.95 [1 H, d, J_{56} 9, Ph(5)–H], 7.1–7.5 [12 H, m, Ph(2)–H, PhCH$_2$ × 2 and Ph(6)–H] and 9.7 (1 H, s, CHO); *m/z* 318 (M^+), 290, 243, 227, 209, 198 and 182.

(ii) *Preparation of* 3,4-*dibenzyloxyphenol* **18**. A clear solution of **17** (1.200 g, 3.77 mmol) and mCPBA (1.300 g, 7.55 mmol) in dry CH_2Cl_2 (10 cm^3) was refluxed for 2.5 h with stirring. The precipitates were filtered off, and the filtrate was evaporated under reduced pressure, followed by dilution with AcOEt. The mixture was washed with 5% $NaHCO_3$ aq. (× 3) and brine, successively, dried (Na_2SO_4 anhyd.), filtered, and then evaporated to dryness. Chromatography on silica gel with CH_2Cl_2 as the eluent provided **18** as a slightly orange powder (1.039 g, 90.0%), which was recrystallized from $CHCl_3$–hexane for instrumental analyses to give colourless needles with m.p. 111–112 °C; ν_{max}(KBr)/cm^{-1} 3290 (OH), 3060–2870 (CH), 1606 and 1503; δ_H(60 MHz; $CDCl_3$) 4.6 (1 H, br s, exch. D_2O, PhOH), 5.0 (2 H, s, PhCH_2O), 5.05 (2 H, s, PhCH_2O), 6.2 [1 H, dd, J_{62} 3, J_{65} 9, Ph(6)–H], 6.4 [1 H, d, J_{26} 3, Ph(2)–H], 6.75 [1 H, d, J_{56} 9, Ph(5)–H] and 7.25 (10 H, m, *Ph*CH$_2$ × 2); *m/z* 306 (M^+) and 215.

(iii) *Preparation of* 4-*methoxycatechol* **4**. A mixed suspension of **18** (854 mg, 2.8 mmol), Cs_2CO_3 anhyd. (1.82 g, 5.59 mmol) and iodomethane (1.0 cm^3, 16.2 mmol) in DMF (10 cm^3) was vigorously stirred for 4 h at room temp., followed by addition of aq. sodium hydroxide (2 mol dm^{-3}) to the reaction mixture and extraction with CH_2Cl_2. The combined extracts were washed with HCl aq. (2 mol dm^{-3}), and brine successively, dried (Na_2SO_4 anhyd.), and then evaporated to dryness. The residue was chromatographed on silica gel with CH_2Cl_2–hexane (1:1) as the eluent. A mixed suspension of the given oil and 10% palladium carbon (400 mg) in EtOH (40 cm^3) and HCl aq. (2 mol dm^{-3}; 8 cm^{-3}); was stirred under a hydrogen atmosphere for 19 h at 40 °C. Then AcOEt and HCl aq. (2 mol dm^{-3}) were added and the mixture was shaken. The organic solution was separated, washed with brine, dried (Na_2SO_4 anhyd.), and evaporated to dryness. The residue was chromatographed on a silica gel column with CH_2Cl_2–AcOEt (6:1) as the eluent to give **4** as a pale yellow solid (350 mg, 90%), which was recrystallized from CH_2Cl_2–hexane and dried *in vacuo* to provide a colourless powder, m.p. 44.5–45 °C; ν_{max}(KBr)/cm^{-1} 3370 (OH), 3000–2830 (CH), 1608 and 1520; δ_H(60 MHz; $CDCl_3$) 3.7 (3 H, s, CH_3O), 5.0 (2 H, br s, exch. D_2O, Ph–OH × 2), 6.35 [1 H, dd, J_{53} 3 J_{56} 9, Ph(5)–H], 6.5 [1 H, d, J_{35} 3, Ph(3)–H] and 6.75 [1 H, d, J_{65} 9, Ph(6)–H]; *m/z* 140 (M^+), 125 and 111.

Synthesis of 4-*Methoxyresorcinol* **5** (Scheme 13).—A mixed



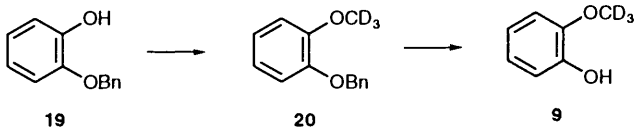
15 5

Scheme 13

solution of 3-acetoxy-4-methoxyphenol **15** (250 mg, 1.37 mmol) in MeOH (2 cm^3) was combined with 25% aq. ammonia (3 cm^3), and then stirred under an argon atmosphere for 2 h at room temp. The reaction mixture was acidified with HCl aq. to pH 2, salted out, and extracted with AcOEt. The combined organic layer was washed with brine, dried (Na_2SO_4 anhyd.), filtered, and evaporated to give an orange oil, which was

chromatographed on a silica gel column with $CHCl_3$–AcOEt (3:1→3:2) as the eluent to yield **5** as a colourless powder (190 mg, 99%). Recrystallization from CH_2Cl_2–hexane furnished colourless plates, m.p. 70.5–71 °C (Found: C, 60.0; H, 5.7. $C_7H_8O_3$ requires C, 60.00; H, 5.75%); ν_{max}(KBr)/cm^{-1} 3330 (OH), 3000–2830 (CH), 1611 and 1509; δ_H(60 MHz; $CDCl_3$) 3.8 (3 H, s, CH_3O), 4.8 [1 H, br s, exch. D_2O, Ph–OH] 5.7 [1 H, br s, exch. D_2O, Ph(3)–OH], 6.3 [1 H, dd, J_{65} 9, J_{62} 3, Ph(6)–H], 6.5 [1 H, d, J_{26} 3, Ph(2)–H] and 6.7 [1 H, d, J_{56} 9, Ph(5)–H]; *m/z* 140 (M^+), 125 and 97.

Synthesis of 2-[$^2H_3$]*Methoxyphenol* **9** (Scheme 14).—(i)



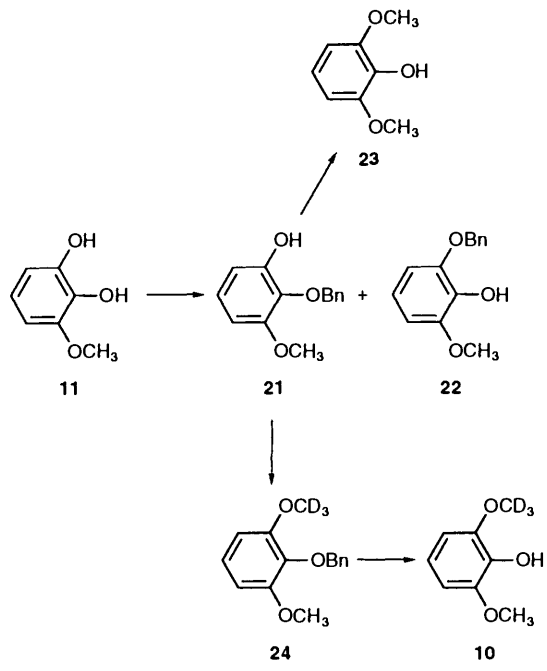
19 **20** **9**

Scheme 14

Preparation of 1-*benzyloxy*-2-[$^2H_3$]*methoxybenzene* **20**. A mixed suspension of 2-benzyloxyphenol **19** (2.00 g, 10.0 mmol), Cs_2CO_3 anhyd. (6.52 g, 20.0 mmol), and [$^2H_3$]iodomethane (1.0 cm^3, 15.7 mmol) in DMF (10 cm^3) was stirred vigorously for 2 h at room temp. After addition of water, the mixture was extracted with CH_2Cl_2. The combined extracts were successively washed with 10% aq. disodium carbonate and brine, dried (Na_2SO_4 anhyd.), filtered and evaporated to dryness. The residue was purified by silica gel column chromatography with CH_2Cl_2–hexane (1:1) as the eluent to yield **20** as pale yellow crystals (2.04 g, 94%), which were recrystallized from hexane to provide colourless needles, having m.p. 56.5–57 °C; ν_{max}(KBr)/cm^{-1} 3050–2870 (CH), 2210 and 2060 (CD), 1588 and 1501; δ_H(60 MHz; $CDCl_3$) 5.15 (2 H, s, PhCH_2O) 6.85 (4 H, s, PhH × 4) and 7.35 (5 H, m, *Ph*CH_2O); *m/z* 217 (M^+), 126, 91 and 65.

(ii) *Preparation of* 2-[$^2H_3$]*methoxyphenol* **9**. A mixed suspension of **20** (1.80 g, 8.3 mmol) and 10% palladium carbon (400 mg) in MeOH (20 cm^3) and HCl aq. (2 mol dm^{-3}; 1.0 cm^3) was stirred under a hydrogen atmosphere for 22 h at room temp. The catalyst was filtered off, then the filtrate was concentrated under reduced pressure, diluted with CH_2Cl_2, and washed with HCl aq. (2 mol dm^{-3}) and brine successively. The organic layer was dried (Na_2SO_4 anhyd.), filtered, evaporated *in vacuo*, and stored in a refrigerator to give **9** as colourless crystals (0.85 g, 81%), m.p. < 25 °C; ν_{max}(cap)/cm^{-1} 3500 (OH), 3050 (Ar CH), 2260–2070(CD), 1611 and 1595; δ_H(60 MHz; $CDCl_3$) 5.65 (1 H, s, exch. D_2O, PhOH) and 6.85 (4 H, m, PhH × 4); *m/z* = 127 (M^+).

Synthesis of 2-[$^2H_3$]*Methoxy*-6-*methoxyphenol* **10** (Scheme 15.—(i) *Preparation of* 2-*benzyloxy*-3-*methoxyphenol* **21**. A mixed suspension of 3-methoxycatechol **11** (7.01 g, 50.0 mmol), Cs_2CO_3 anhyd. (16.30 g, 50 mmol) and benzyl chloride (6.0 g, 50.0 mmol) in DMF (20 cm^3) was stirred vigorously for 21 h at room temp. The reaction mixture was diluted with NaOH aq. (2 mol dm^{-3}), washed and acidified with HCl aq. (2 mol dm^{-3}) to pH 2. After extraction with $CHCl_3$, the organic layer was successively washed with water, 5% $NaHCO_3$ aq., HCl aq. (2 mol dm^{-3}), water and brine, dried (Na_2SO_4 anhyd.), filtered, and evaporated under vacuum to give oily products. Chromatography on silica gel with hexane–CH_2Cl_2 (1:1→1:4) as the eluent yielded both **21** as a slightly yellow oil (3.90 g, 34%); R_f = 0.5 (hexane–CH_2Cl_2); ν_{max}(cap)/cm^{-1} 3510–3400 (OH), 3100–2800 (CH), 1607, 1595, 1497 and 1479; δ_H(60 MHz; $CDCl_3$) 3.85 (3 H, s, CH_3O), 5.0 (2 H, s, PhCH_2O), 5.5 (1 H, br s, PhO*H*), 6.45 [1 H, dd, Ph (4 or 6)–H], 6.5 [1 H, dd, Ph(4 or 6)–H], 6.85 [1 H, dd, Ph(5)–H] and 7.3 (5 H, m, *Ph*CH_2);



Scheme 15

m/z 230 (M^+), and 2-benzyloxy-6-methoxyphenol **22** as a slightly yellow oil (0.95 g, 8.2%); R_f = 0.3; ν_{max}(cap)/cm^{-1} 3520–3440 (OH) and 3110–2840 (CH); δ_H(60 MHz; $CDCl_3$) 3.85 (3 H, s, CH_3O), 5.1 (2 H, s, PhCH_2O), 5.5 (1 H, br s, PhO*H*), 6.4–6.7 (3 H, m, PhH × 3) and 7.35 (5 H, m, *Ph*CH_2); *m/z* 230 (M^+), 140 and 91. Characterization of **21** was conducted by methylation and debenzylation to give 2,6-dimethoxyphenol **23**.

(ii) *Preparation of* 2-*benzyloxy*-1-[$^2H_3$]*methoxy*-3-*methoxybenzene* **24**. A mixed suspension of **21** (2.178 g, 9.47 mmol), Cs_2CO_3 anhyd. (3.085 g, 9.47 mmol), and [$^2H_3$]iodomethane (600 mm^3; 9.43 mmol) was stirred vigorously for 20 h at room temp. After dilution with NaOH aq. (2 mol dm^{-3}), and extraction with AcOEt, the combined extracts were washed with NaOH aq. (2 mol dm^{-3}), water, and brine successively, dried (Na_2SO_4 anhyd.), and then filtered. Removal of the solvent yielded **24** as a pale yellow oil (1.75 g, 75% based on [$^2H_3$]iodomethane), δ_H(60 MHz; $CDCl_3$) 3.8 (3 H, s, CH_3O), 5.0 (2 H, s, PhCH_2O), 6.5 [2 H, dd × 2, Ph(4)–H and Ph(6)–H], 6.95 [1 H, dd, Ph(5)–H] and 7.6–7.2 (5 H, m, *Ph*CH_2).

(iii) *Preparation of* 2-[$^2H_3$]*methoxy*-6-*methoxyphenol* **10**. A mixed suspension of **24** (1.636 g, 6.62 mmol) and 10% palladium carbon (400 mg) in MeOH (5 cm^3) was stirred under a hydrogen atmosphere for 19.5 h at room temp. Filtration and removal of the solvent gave oily products, which were purified by silica gel column chromatography (hexane–CH_2Cl_2 = 1:2→100% CH_2Cl_2) to afford **10** as colourless crystals (1.020 g, 98%). Recrystallization from hexane provided colourless needles with m.p. 55–55.5 °C; ν_{max}(KBr)/cm^{-1} 3490 and 3450 (OH), 3110–2830 (CH), 2260–2070 (CD), 1612 and 1507; δ_H(400 MHz; $CDCl_3$) 3.88 (3 H, s, CH_3O), 5.53 (1 H, s, PhO*H*), 6.58 [2 H, d, *J* 8.1, Ph(3)–H and Ph(5)–H] and 6.80 [1 H, t, *J* 8.1, Ph(4)–H]; *m/z* 157 (M^+), 142 and 139.

Analysis.—Elemental analyses were performed by the Microanalytical Laboratory at the University of Tokyo. M.p.s were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO DS-701G spectrophotometer. NMR spectra were recorded on a JEOL GSX-400 (400 MHz) pulse Fourier-transform NMR spectrometer and a Hitachi R-24-B (60 MHz, CW type) NMR spectrometer. Chemical shifts are expressed in units (ppm) downfield of internal tetramethylsilane and *J* values in Hz. Mass

spectra were measured on a JEOL DX-300 mass spectrometer operating in the direct injection–electron impact mode. HPLC was performed with a reversed-phase column (Partisil-5 ODS-3, 4.3 × 150 mm unless otherwise stated).

General Oxidation Procedure in the Cu^{2+}*–Ascorbic Acid–*O_2 *System.*—Unless otherwise mentioned in the text or Tables, a mixed solution of 2-methoxyphenol (**1**, *x* mmol), copper(II) salt (*y* mmol), and ascorbic acid (*z* mmol) in water with or without a co-solvent (acetone or acetic acid) was stirred vigorously under an oxygen atmosphere at room temp. for an appropriate time, followed by silica gel chromatographic isolation and/or reversed-phase HPLC analysis; eluent [acetonitrile–0.1% aq. phosphoric acid, 1 : 3], flow rate 1.0 cm^3 min^{-1}, detection UV (276 nm), retention time **2**, 3.0 min; **1**, 5.5 min; *p*-methoxyacetophenone (internal standard) 10 min.

Regioselective Oxidation of 2,5-*Dimethoxyphenol* **3**.—(i) Cu^{2+} *–Ascorbic Acid–*O_2 *System.* Aq. **3** (1 equiv.), $Cu(ClO_4)_2 \cdot 6H_2O$ (1 equiv.), and ascorbic acid (10 equiv.) in a mixed solution of acetone and water was stirred vigorously under an oxygen atmosphere at room temp. for 3.5 h. The products were analyzed by HPLC; eluent acetonitrile–0.1% aq phosphoric acid, 1:3, flow rate 0.8 cm^3 min^{-1}, detection UV (289 nm), retention time **5**, 3.3 min; **4**, 4.1 min; *p*-methoxyphenol (internal standard), 6.7 min; **3**, 8.7 min.

(ii) Cu^{2+}*–Ascorbic Acid–*H_2O_2 *System.* To aq. **3** (1 equiv.), $Cu(ClO_4)_2 \cdot 6H_2O$ (1 equiv.), and ascorbic acid (10 equiv.) in a mixed solution of acetone–water, 30% hydrogen peroxide (10 equiv.) was added gradually over 5 min under an argon atmosphere, and then the mixture was stirred vigorously at room temp. for 1 h. The products were analyzed by HPLC.

Oxidation of Anisole **6**.–Aq. **6** (1 mmol), $Cu(ClO_4)_2 \cdot 6H_2O$ (1 mmol), and ascorbic acid (10 mmol) in acetone–water (1:1) were stirred vigorously under an oxygen atmosphere at room temp. for 1 day. The products were analyzed by HPLC; column LiChrosorb (4.3 × 150 mm), eluent acetonitrile–water, 7:93, flow rate 1.5 cm^3 min^{-1}, detection UV (290 nm), retention time **7**, 6.8 min; *p*-**8**, 8.2 min; *o*-**8**, 11.1 min; *m*-**8**, 11.7 min, *p*-nitrophenol (internal standard), 16 min.

Kinetic Isotope Effect Experiments.—(i) *Intermolecular experiment A.* A mixed solution of 2-methoxyphenol (**1**, 1 equiv.), 2-[$^2H_3$]methoxyphenol (**9**, 1 equiv.), $Cu(ClO_4)_2 \cdot 6H_2O$ (0.1 equiv.), and ascorbic acid (1 equiv.) in water was stirred vigorously under pure oxygen at 30 °C for 3 h. The kinetic isotope effect was calculated from the consumption of substrates as analyzed by GC-MS.

(ii) *Intermolecular experiment B.* A mixed solution of **1** or **9** (1 equiv.), $Cu(ClO_4)_2 \cdot 6H_2O$ (0.1 equiv.), and ascorbic acid (0.2 equiv.) in acetone–water was stirred vigorously under pure oxygen at 50 °C for 0.5 h. The kinetic isotope effect was estimated from the catechol **2** formation in the respective reactions by ^1H NMR.

(iii) *Intramolecular experiments.* A mixed solution of 2-[$^2H_3$]methoxy-6-methoxyphenol (**10**, 1 equiv.), $Cu(ClO_4)_2 \cdot 6H_2O$ (1 or 2 equiv.), and ascorbic acid (10 or 20 equiv.) in water was stirred vigorously at room temp. for 24 or 3 h, respectively. The kinetic isotope effects were calculated from the products (**11**, **12**) formed evaluated by ^1H NMR.

^{18}O *Incorporation Experiments.*—(i) *Preparation of* $^{18}O_2$ *mixed gas* (Ar: $^{18}O_2$ = 9:1). After connection of one tube on a commercially available Pyrex 2-necked flask sealing 97 atom% $^{18}O_2$ gas (100 cm^3) and a deaerated gas-sealed pack (1 dm^3), the other tube of the Pyrex flask was connected to an argon gas cylinder, followed by deaeration of the connections. First, the pack-side tube was opened, then the cylinder-side tube was opened, and $^{18}O_2$ gas was pushed into the pack by argon until full, resulting in the desired mixed gas composed of Ar: $^{18}O_2$ = 9:1.

(ii) *Preparation of deaerated water.* Argon gas was bubbled into distilled water under an argon atmosphere for 1 h to afford the deaerated water, which was taken as required.

(iii) $^{18}O_2$ *Reaction.* The gas phase of a flask containing **1**, $Cu(ClO_4)_2 \cdot 6H_2O$, and ascorbic acid was replaced with argon, then deaerated distilled water was added by injection, and the reagents were dissolved under argon. The reaction was started by introduction of $^{18}O_2$ mixed gas, and stopped by injection of AcOEt. The combined extracts were evaporated to dryness, and the residue was subjected to preparative TLC (Merck No. 5715; CH_2Cl_2–AcOEt = 9:1) to yield the catechols (^{18}O-C, ^{16}O-C). The formation ratios were determined by calculation from the peak ratios of 112 and 110 (M^+) in the GC–MS and corrected for natural abundance.

(iv) $H_2{}^{18}O$ *Reaction.* Aq. **1**, $Cu(ClO_4)_2 \cdot 6H_2O$, and ascorbic acid in diluted [^{18}O]water (distilled water:purchased $H_2{}^{18}O$ = 1:1) was stirred vigorously under an air atmosphere at room temp. Work-up and determination were performed as above.

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