

Regio- and Diastereo-selective Synthesis of Dimeric Lignans Using Oxidative Coupling

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The oxidative dimerization of monolignols such as (*E*)-isoeugenol (**1**), (*E*)-methyl ferulate (**2**) and (*E*)-coniferyl alcohol (**3**) has been performed using two catalytic systems: horseradish peroxidase (HRP)–H₂O₂ and tetraphenylporphyrinato-manganese(III) acetate or chloride–iodosylbenzene or H₂O₂. The kinetically controlled diastereoselective formation of *trans* β-5 dimers was obtained in both cases. No diastereoselection between *threo* and *erythro* β-O-4 dimers was observed in the HRP-catalyzed reaction. The *trans* stereochemistry of dehydrodiferulic acid methyl ester (**5**) was assigned by X-ray diffractometric analysis. The nature of the enzyme–substrate complex and the influence of pH and methanol content in the HRP-catalyzed reaction were also studied.

The biosynthesis of lignin from phenolic phenylpropenoids occurs via oxidative processes catalyzed by enzymes such as peroxidase, which converts the phenols into phenoxyl radicals by an electron abstraction which is followed by carbon–carbon and carbon–oxygen bond formation.¹ In this step, chiral centers are formed.

Tuning the enzymatic reaction to give dimers, and the use of metal complexes which mimic the enzymatic reaction allows the observation of the stereochemical course at the stereocenters and gives information related to the mechanism of lignin formation in nature. In this work an enzymatic system, horseradish peroxidase (HRP)–hydrogen peroxide and a synthetic system, tetraphenylporphyrinatomanganese(III) (MnTPPX, X = OAc, Cl)–iodosylbenzene or hydrogen peroxide, were used as catalysts for the synthesis of dimers from propenyl substituted phenols.

Results and discussion

The enzyme–substrate complex. The first approach to the enzymatic reaction was the study of the enzyme–substrate complex. Previous work has shown² that the enzyme in the native form interacts with aromatic donors and forms 1 : 1 complexes. Moreover, the addition of the substrate causes very little change in the electronic spectrum of HRP. This indicates that the binding site is quite distant from the ferric center. The influence of an *R* group attached to a vinyl chain in compounds **1–3** and ferulic acid was studied by measuring the binding constants of

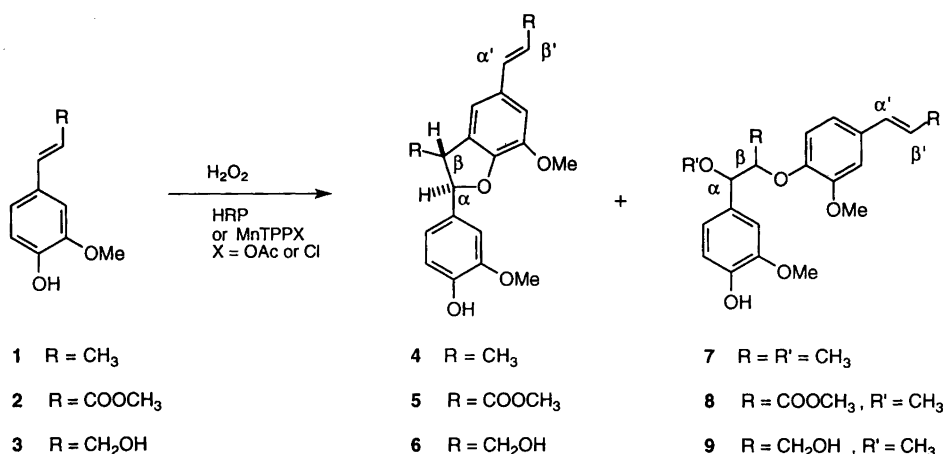
the compounds to HRP. The binding constants K_B were obtained by spectrophotometric titration. A Hill plot³ gave the number *n* of the sites of binding (Table 1). These were very similar to those obtained by other authors for simpler phenolic compounds^{2,4–6} and this suggests that the binding site for phenolic phenylpropenoids is the same as that suggested for simpler phenols and involving a tyrosine residue.⁶ The similarity of the binding constants suggests a very similar reactivity for these substrates.

Oxidation of (E)-isoeugenol (1), (E)-methyl ferulate (2) and (E)-coniferyl alcohol (3) with HRP in water–methanol mixtures. Compounds **1–3** were subjected to reaction with hydrogen peroxide with the HRP catalysis in mixtures containing aqueous buffer (pH 3–7.4) and methanol from 10% to 90% (v/v). The reaction was interrupted after one hour and the mixture was analyzed by HPLC. The reaction products were also separated using preparative LC and analyzed by ¹H and ¹³C NMR and MS techniques. The major products in all cases were the phenylcoumaran (β-5) dimers **4–6**.⁷

Table 1. Binding constant K_B and number of binding sites *n* for the reaction of phenolic phenylpropenoids with horseradish peroxidase.

Substrate	K_B	<i>n</i>
Coniferyl alcohol	0.135	1.02
Methyl ferulate	0.157	1.03
Ferulic acid	0.286	1.08
Isoeugenol	0.492	1.06

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Scheme 1.

Two chiral centers are present in these compounds. The β -5 dimer (**4**) obtained from isoeugenol (**1**) had the same ¹H NMR spectrum as dehydrodiisoeugenol isolated previously⁸ and has been shown to have the *trans* stereochemistry at the five-membered ring by X-ray crystallography.⁹ The β -5 dimer (**5**) from methyl ferulate (**2**) has now been analyzed by X-ray crystallography and shown to have the same *trans* stereochemistry. The phenyl and the carboxymethoxy group bonded to the hetero ring are in a *gauche* conformation, the torsion angle being 91.3(5)°. The hetero ring presents an envelope configuration [⁵E, $q = 0.233(4) \text{ \AA}^2$, $\phi = 141(1)^\circ$]. The phenolic hydroxy group forms two hydrogen bonds, one intermolecular [2.850(5) Å] and one intramolecular to the adjacent methoxy oxygen [2.655(5) Å].

Reduction of (**5**) with LiAlH₄ led to the *trans* β -5 dimer (**6**), identical with that obtained in the HRP-catalyzed dimerization of coniferyl alcohol (**3**). The minor products, β -O-4 dimers, were obtained from **1** and **3** as nearly 1 : 1 mixtures of *erythro* and *threo* diastereomers (for nomenclature, see Scheme 2) and were identified by comparison with reference samples. In the case of methyl ferulate (**2**) the amount of β -O-4 dimer **8** was too small for positive identification. The dimer **7** was identified by comparison with a sample obtained by reacting isoeugenol with silver(I) oxide,¹⁰ and dimer **9** by comparison with compounds synthesized according to Ref. 11.

The β - β or resinol structure **10** was found in ca. 10% yield only in the reaction of coniferyl alcohol.

A CD examination of all these dilignols showed that they were not optically active. This indicated that HRP did not induce enantioselectivity in these reactions.

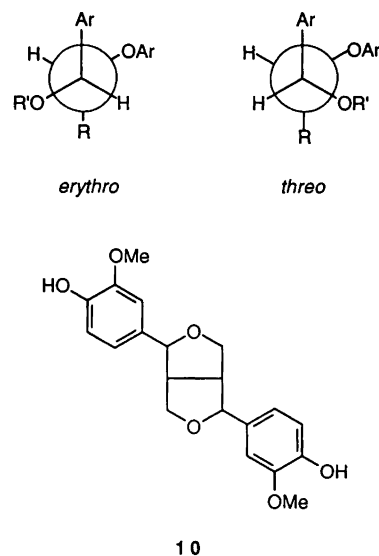
Concerning the diastereoselection observed in the formation of β -5 dimers, some preliminary calculations on the stability of the diastereoisomeric β -5 dimers were performed using DISCOVER and the energy minima were further refined using the program DO-RANDOM. A difference as low as 4 kcal mol⁻¹ between the *trans* and *cis* stereochemistry of the β -5 dimer **5** was obtained. Hence, the diastereoselection is under kinetic control.

The results of changing the pH of the buffer is shown in Fig. 1. For all three substrates the yields of dimeric products are highest at pH 3, the lowest pH at which the enzyme seemed to be active. At pH values close to 7 considerable amounts of oligomeric products were formed. Thus by keeping the pH as low as possible a cleaner production of dimeric products was achieved.

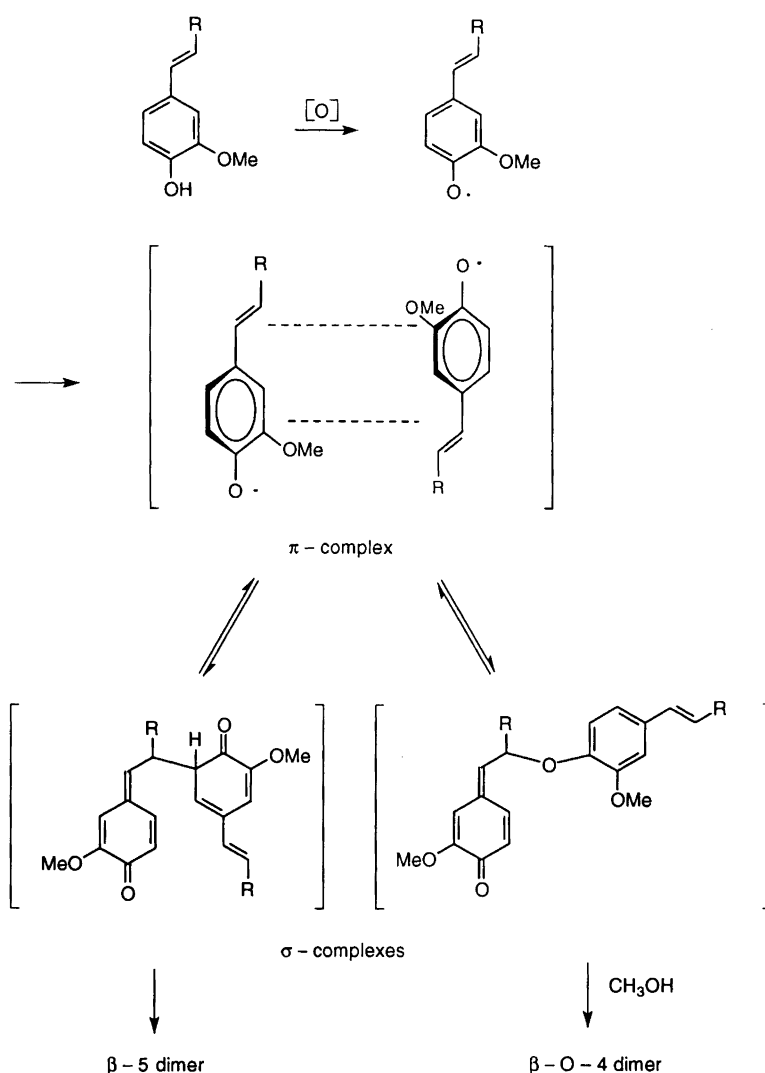
The results of varying the water content are shown in Fig. 2. For isoeugenol (**1**) and methyl ferulate (**2**) a distinct minimum in the yield of dimers **4** and **5** is observed at 50% water content. For coniferyl alcohol (**3**) no such minimum was observed.

The yields of β -O-4 dimers (**7** and **9**) formed from isoeugenol (**1**) and coniferyl alcohol (**3**) increased with increasing methanol content in the solvent mixture, suggesting that these compounds were formed by addition of methanol to a quinone methide intermediate, Fig. 3.

The dimerization of these three phenylpropenoidic phenols is due to the formation of phenoxyl radicals by



Scheme 2.



Scheme 3.

reaction with the active form of HRP.^{8,12} The influence of the solvent composition and the pH of the reaction on the regioselectivity can be explained by assuming that the intermediate π -complex^{12d} undergoes reversible bond formation to give two isomeric quinone methides. In a non-enzymatic step, one gives rise to the β -5 dimer, and the other reacts with methanol to form the β -O-4 dimers, Scheme 3. Both reactions are catalyzed by acid but the β -O-4 dimer formation is favored by the presence of methanol. It is remarkable that methanol addition predominates over water addition, even in the presence of excess water. The regioselectivity in these reactions is not determined by the enzyme, but by non-enzymatic reactions leading to stable products.

Oxidation with iodosylbenzene or hydrogen peroxide catalyzed by tetraphenylporphyrinatomanganese(III) [Mn(III)TPP] acetate or chloride. Further experiments were devoted to mimicking the enzymatic reaction with a synthetic catalyst. Tetraphenylporphyrinatometal complexes such as Mn(III)TTP-OAc or -Cl have been widely

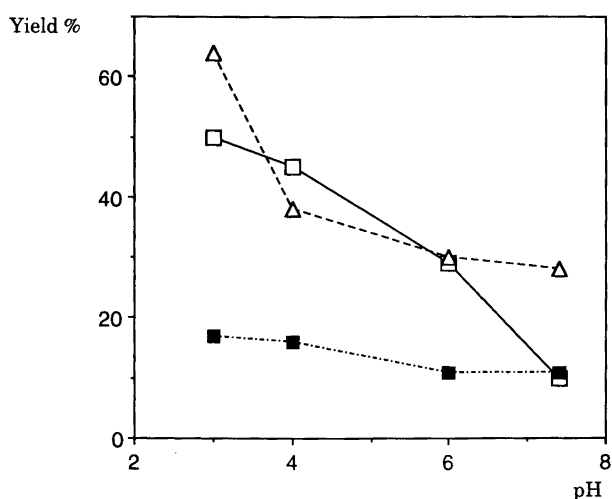


Fig. 1. The yields of dimeric products of the phenyl coumaran type on oxidation of (a) (*E*)-isoeugenol (--- Δ ---); (b) (*E*)-methyl ferulate (— \square —); (c) (*E*)-coniferyl alcohol (--- \blacksquare ---) with HRP and H₂O₂ in 10% aqueous MeOH at different pH-values.

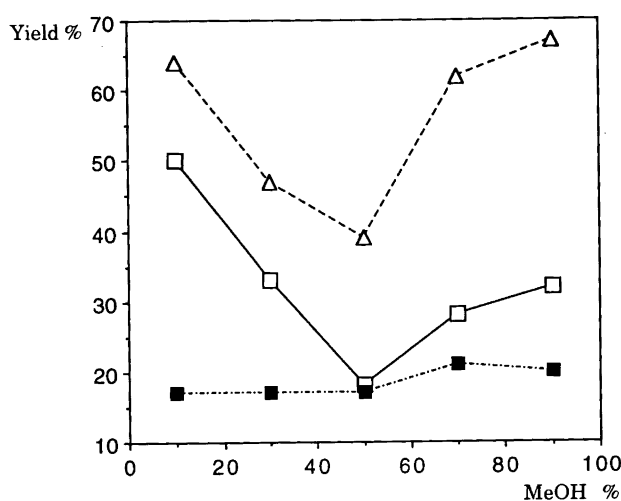


Fig. 2. The yields of dimeric products of the phenyl coumaran or β -5 type on oxidation of (a) (*E*)-isoeugenol (--- Δ ---); (b) (*E*)-methyl ferulate (— \square —); (c) (*E*)-coniferyl alcohol (--- \blacksquare ---) with HRP and H_2O_2 in different methanol-water mixtures at pH 3.

used as catalysts for the epoxidation of simple olefins with sodium hypochlorite, iodosylbenzene, *N,N*-dimethylaniline *N*-oxide, hydrogen peroxide, or *tert*-butylperoxide.¹³ They have been suggested to react via the resonance-stabilized octahedral oxomanganese intermediate,¹⁴ very similar to that acting in HRP¹⁰ and cytochrome P-450 catalyzed¹⁵ reactions. An example of Mn(III)TPPOAc-catalyzed oxidative phenol coupling is the formation of the alkaloid glaziovine from *N*-methylcoclaurine.¹⁶

The *trans* β -5 dimers **4** and **5** were produced by oxidation of isoeugenol (**1**) and methyl ferulate (**2**) with an excess of iodosylbenzene in the presence of Mn(III)TPPOAc as a catalyst. The yield of the products (**4**) and (**5**) was 5% and 22%, respectively. These com-

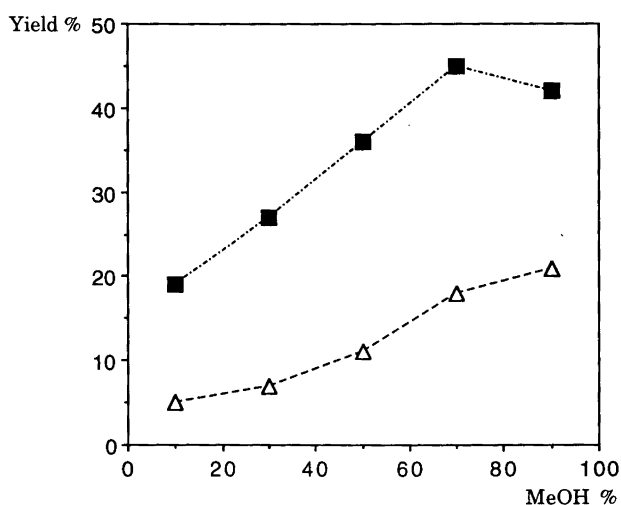


Fig. 3. The yields of dimeric products of the β -O-4 type on oxidation of (a) (*E*)-isoeugenol (--- Δ ---); (b) (*E*)-coniferyl alcohol (--- \blacksquare ---) with HRP and H_2O_2 in different methanol-water mixtures at pH 3.

pounds were isolated by silica gel chromatography. Iodosylbenzene was ineffective in promoting the reaction in the absence of Mn(III)TPPOAc. Similar oxidations with MnTPPCl using stoichiometric amounts of iodosylbenzene gave 10% of the dimer **4** and 36% of the dimer **5** as analyzed by HPLC. Oxidation of methyl ferulate was also performed using excess hydrogen peroxide as the oxidant together with MnTPPCl in a mixture of dichloromethane and acetonitrile (1 : 1). This method yielded ca. 25% of the β -5 dimer **5** (HPLC).

These results demonstrate the versatility of HRP-promoted reactions in organic solvents and show that the regioselectivity can be influenced by changing the solvent system. Tetraphenylporphyrinometal complexes mimic efficiently the enzymatic system.

Experimental

General. Horse radish peroxidase (HRP, EC 1.11.1.7) was obtained from Cultor Co (430 U ml⁻¹, in 0.1 M, pH 6, phosphate buffer). HRP for enzyme-substrate complex studies was a Boehringer grade II product. Stock solutions (for enzyme-substrate studies) of HRP in 50% phosphate buffer and 50% MeOH were obtained by dissolving 20 mg of HRP (Boehringer) in 25 ml buffer (the concentration was determined by using $\epsilon = 102 \text{ mM}^{-1} \text{ cm}^{-1}$ at 403 nm). 25 ml MeOH were added and the solution was kept overnight at 18°C after which it was purified by centrifugation. The activity measurements of enzymes were always based on the purpurogallin method.

Hydrogen peroxide (30% in water) was obtained from Merck. TLC was performed on Merck Kieselgel 60 F₂₅₄ plates, visualizing with a 254 nm UV lamp. Silica gel 60 (ϕ 0.040–0.063 mm) used for flash chromatography was purchased from Merck. HPLC analyses were performed on Waters 990 equipment with a photodiode array detector at 280 nm, with a Nova-Pak[®] C-18 column (ϕ 3.9 \times 150 mm, particle size 5 μ m), or on semipreparative Perkin-Elmer equipment with detection at 254 nm, with a Lichrosorb RP-18 column (ϕ 4 \times 250 mm, particle size 7 μ m). Water-methanol was used as the eluent in both cases. The pH of the water was adjusted to 3 with phosphoric acid. Preparative scale LC was performed on PVK-31A equipment with a Lichrosorb 600 column (ϕ 28 \times 300 mm, particle size 10 μ m), detection at 280 nm and hexane-ethyl acetate as the eluent, or on a semipreparative Perkin-Elmer instrument with a Supelcosil PLC18 column (ϕ 21.2 \times 250 mm, particle size 18 μ m), detection at 254 nm and methanol-water as the eluent. ¹H NMR (200 MHz or 300 MHz) and ¹³C NMR (50 MHz) spectra were recorded on a Varian Gemini-200 or a Bruker AC 300 spectrometer in deuteriochloroform (CDCl₃) with chloroform (7.26 ppm ¹H, 77.70 ppm ¹³C) as an internal reference. Signal assignments for NMR were based on COSY and HETCOR experiments. The assignments of the diastereomers of **7** and **9** were based on spectra of analogous compounds of which crystal

structures were available.¹⁷ MS was performed with a Jeol JMS-SX102 or a VG 7070 EQ instrument. Melting points are uncorrected.

Optical difference spectroscopy. Enzyme–substrate binding measurements were made by adding small amounts of concentrated solutions of the substrates (0.1 M in MeOH) to the enzyme solution (10^{-5} M in 1 : 1 aqueous buffer–MeOH). The same amount of substrate was added to a reference cell containing the solvent. This allowed us to subtract the absorption of the substrate which is close to the Soret region. All the spectra were then corrected for the small variation of volume. The difference spectra were obtained subtracting the spectra of HRP from those of the enzyme–substrate complexes. The binding constants were evaluated by a least-squares fit of the data using the expression given in eqn. (1) where ΔA is the variation in

$$1/\Delta A = [1/(K_b \times \Delta A_\infty)] \times (1/S^\circ) + 1/\Delta A_\infty \quad (1)$$

absorbance of the enzyme caused by the addition of the substrate, ΔA_∞ the variation in absorbance caused by the complete formation of the enzyme–substrate complex, K_b is the binding constant and S° is the ligand concentration.

Crystal structure determination of (5).¹⁸ $C_{22}H_{22}O_8$, $M_r = 414.41$; $a = 17.113(2)$, $b = 6.585(1)$, $c = 19.122(2)$ Å, $\beta = 107.41(1)$; $Z = 4$; monoclinic, space group $P2_1/n$; $d_{\text{calc}} = 1.337 \text{ g cm}^{-3}$; graphite monochromated Mo K radiation ($\lambda = 0.71073$ Å), $\mu(\text{Mo K}\alpha) = 10 \text{ mm}^{-1}$, $\theta/2\theta$ scan mode, $\theta_{\text{max}} 24^\circ$, hkl limits: $0 \leq h \leq 19$, $0 \leq k \leq 7$, $-21 \leq l \leq 21$, Lorentz and polarization corrections, 3225 independent reflections, of which 1448 with $I > 2\sigma(I)$ were observed. The structure was solved by direct methods (MULTAN routine): the 30 heavy atoms were obtained by the best E -map; hydrogen atoms were partly derived from a subsequent difference Fourier map, the remainder were calculated and included in structure factor calculations, but not refined. The refinement was carried out by full-matrix least-squares, minimizing the function $\sum w(|F_o| - k|F_c|)^2$, with weight $w = 1/\sigma^2(I)$. All heavy atoms were refined anisotropically. Final agreement factors were $R = 0.056$ and $R_w = 0.056$. The maximum Δ/σ in the last cycle was ≤ 0.04 . The final Fourier difference map shows three peaks of $0.3\text{--}0.5 \text{ e \AA}^{-3}$ near the ethylenecarboxylate group; this fact, the quite high atomic displacement parameters of the same residue and the abnormally short distance C23–C24 [$1.252(2)$ Å] suggest that this group may be affected by partial disorder. No attempt was made to rationalize this disorder because of the low data/parameters ratio. The phenol and the methoxy-carbonyl group bonded to the heteroring are in a *gauche* conformation, the torsion angle being $91.3(5)^\circ$. The hetero ring presents an envelope configuration¹⁹ [3E , $q = 0.233(4) \text{ \AA}^2$, $\phi = 141(1)^\circ$]. The phenolic hydroxy group forms two hydrogen bonds, one intermolecular [$2.850(5) \text{ \AA}$] and one intramolecular to the adjacent methoxy oxygen [$2.655(5) \text{ \AA}$].

Mn(III)TPPX-catalyzed reactions. (a) To 0.275 mmol of substrate in 6 ml of dichloromethane were added 0.0075 mmol of MnTPPOAc and 0.375 mmol of iodosylbenzene. The resulting suspension was stirred at room temperature for 24 h and then filtered and the residue was chromatographed through silica gel eluting with dichloromethane.

(b) To 0.50 mmol of methyl ferulate in 9 ml of acetonitrile–dichloromethane (1 : 1) were added 0.10 mmol benzoic acid,²⁰ 0.10 mmol 4-dimethylaminopyridine and 0.015 mmol MnTPPCI. Hydrogen peroxide (1.0 ml, 1.3 M) was gradually added over 30 min. The reaction mixture was stirred at room temperature for 20 h, then extracted with ether, dried and evaporated.

(c) To 0.50 mmol of substrate in 10 ml of dichloromethane were added 0.016 mmol of MnTPPCI and 0.68 mmol of iodosylbenzene. The resulting suspension was stirred at room temperature for 0.5 to 20 h, then filtered and evaporated.

(d) Reaction conditions were as above except that a stoichiometric amount (0.26 mmol) of iodosylbenzene was used, and the reaction time was 3 h. In all cases the products were analyzed by HPLC and/or by ^1H NMR spectroscopy.

General procedure for oxidative coupling of phenols using HRP. **Analytical scale reactions.** The phenol in organic solvent (overall conc 10 mM), citrate–phosphate buffer (20 mM, pH 3–7.4) and HRP (Cultor) in buffer (43 U) were added in an Erlenmeyer flask and the reaction was started by adding H_2O_2 (overall conc 5 mM). The flask was shaken in a reciprocal shaker at 25°C and the reaction was interrupted after 1 h (complete conversion in all cases). The mixture was filtered and the filtrate was diluted with methanol (1 : 9) and analyzed by HPLC. Quantitative estimation of β -5 dimers **4**, **5** and **6** was performed using synthesized products as external standards. These β -5 dimers were prepared as described later.

Preparative-scale synthesis of the dilignols. The syntheses of the dilignols were carried out under optimized conditions (from HPLC measurements). The reactions were performed in methanol–buffer solution mixtures. The amount of methanol (v/v) was 10% or 90% for methyl ferulate (**2**) and 90% for isoeugenol (**1**) and coniferyl alcohol (**3**). The water pool was always 20 mM citrate–phosphate buffer, pH 3, and the reaction temperature was 20°C . The phenol (4.90–10.0 mmol) was dissolved in 300–500 ml of the methanol–buffer solution. Hydrogen peroxide (2.45–5.0 mmol) and HRP (2150–4300 U) were added over ca. 10 min. The reaction mixture was stirred for 1 h at room temperature. The mixture was filtered, most of the methanol was evaporated off and the residue was extracted with ethyl acetate. The extract was washed with brine and dried with Na_2SO_4 and the solvent was evaporated off. The crude product was acetylated with an excess of acetic anhydride

and pyridine (1 : 1) overnight at room temperature and purified by chromatography.

Preparation of the model compounds: (E)-1-[(2RS,3SR)-2,3-Dihydro-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methyl-1-benzofuran-5-yl]-1-propene (**4**). The β -5 model compound **4** was a gift from Dr. K. Lundquist, Chalmers University of Technology, Göteborg, Sweden. The NMR spectrum of the acetate was identical with published data.²¹

(E)-Methyl 3-[(2RS,3SR)-2,3-dihydro-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-methoxycarbonyl-1-benzofuran-5-yl]propenoate (**5**). Compound **5** was prepared from methyl ferulate (**2**) as described in the general procedure and purified by flash chromatography eluting with ethyl acetate-hexane (3 : 2). The yield of β -5 dimer after recrystallization from methanol was 306 mg (30%), m.p. 158–159°C (lit.²² 151–152°C). ¹H NMR and MS values were as in Refs. 8 and 22.

The acetate was obtained by acetylation of the crude product and purified by flash chromatography (ethyl acetate-hexane, 2 : 3). Recrystallisation from ethanol gave white crystals, m.p. 122–123°C (lit.²³ 122–124°C). ¹H NMR and MS spectra were as in Ref. 23.

(E)-3-[(2RS,3SR)-2,3-Dihydro-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-3-hydroxymethyl-1-benzofuran-5-yl]-2-propenol (**6**). LiAlH₄ (187 mg, 4.93 mmol) was weighed into a 200 ml flask and 50 ml dry THF were added. The suspension was cooled to –20°C in an ice-NaCl bath. The β -5 dimer **5** (510 mg, 1.23 mmol) was dissolved in 50 ml dry THF. This solution was added slowly over 30 min to the reaction flask. The contents were stirred for 2 h after which 10 ml aq. 80% THF were added slowly ($T < 0^\circ\text{C}$) and then 50 ml 0.1 M aqueous ammonium chloride. The product was extracted twice with 200 ml ethyl acetate. The organic solution was washed with water and brine and dried with Na₂SO₄ and the solvent was evaporated off. The product was recrystallized from dichloromethane-petrol ether. The yield was 410 mg (93%), m.p. 155–157°C (lit.²⁴ 155–156°C). ¹H NMR and MS values for compound **6** and its acetate were as in Refs. 25 and 26.

1-(4-Hydroxy-3-methoxyphenyl)-1-methoxy-2-(2-methoxy-4-(1-propenyl)phenoxy)propane (**7**).¹⁰ Isoeugenol (**1**) (900 mg, 5.47 mmol) was dissolved in 100 ml of anhydrous dichloromethane, and 3.0 g of silver(I) oxide were added. The suspension was shaken vigorously at room temperature. When the reaction was complete [TLC: hexane-ethyl acetate (1 : 1), R_f (**1**) 0.50, R_f (quinone methide) 0.25], the mixture was filtered. The clear, yellow solution was added to 50 ml dry methanol together with 5 mg TsOH, and stirred until the reaction was complete (10 min, TLC). The solution was washed twice with brine, 5% sodium hydrogen carbonate, and once with brine, dried with Na₂SO₄ and evaporated. The product mixture

was acetylated and purified as described for compound (**4**). The overall yield of β -O-4 dimer **7** was 650 mg (59%). The *erythro* : *threo* ratio was 1 : 1 as analyzed by ¹H NMR spectroscopy. ¹H NMR of the acetates, *erythro*-**7**: δ 1.29 (3 H, d, $J = 6.1$ Hz, γ -Me), 1.85 (3 H, dd, $J = 6.4, 1.3$ Hz, γ' -Me), 2.30 (3 H, s, ArOAc), 3.36 (3 H, s, α -OMe), 3.80, 3.82 (2 \times 3 H, s, ArOMe), 4.36 (2 H, m, α - and β -H), 6.09 (1 H, dq, $J = 15.7, 6.4$ Hz, β' -H), 6.32 (1 H, dd, $J = 15.8, 1.3$ Hz, α' -H), 6.71–7.03 (6 H, m, ArH). ¹³C NMR, *erythro*-**7**: δ 15.5 (γ -Me), 19.0 (γ' -Me), 21.4 (OMe), 56.5 (2 \times ArOAc), 58.3 (α -OMe), 80.4 (β -C), 85.8 (α -C), 110.3, 112.0, 118.5, 119.3, 120.4, 122.9 (arom. CH), 124.8 (β' -C), 131.2 (α' -C), 133.1, 138.7, 139.7, 146.9, 151.5, 151.6 (arom. C), 169.7 (CO).

¹H NMR, *threo*-**7**: δ 1.12 (3 H, d, $J = 6.3$ Hz, γ -Me), 1.87 (3 H, dd, $J = 6.4$ and 1.3 Hz, γ' -Me), 2.32 (3 H, s, ArOAc), 3.33 (3 H, s, α -OMe), 3.84, 3.85 (2 \times 3 H, s, ArOMe), 4.36 (1 H, d, $J = 5.9$ Hz, α -H), 4.49 (1 H, quintet, $J = 6.2$ Hz, β -H), 6.11 (1 H, dq, $J = 15.7$ and 6.4 Hz, β' -H), 6.35 (1 H, dd, $J = 15.7$ and 1.3 Hz, α' -H), 6.81–7.05 (6 H, m, ArH). ¹³C NMR, *threo*-**7**: δ 17.0 (γ -Me), 19.0 (γ' -Me), 21.4 (OMe), 56.5 (2 \times ArOMe), 58.1 (α -OMe), 79.4 (β -C), 86.8 (α -C), 110.2, 112.2, 117.6, 119.3, 120.8, 122.9 (arom. CH), 124.7 (β' -C), 131.3 (α' -C), 132.8, 138.2, 140.0, 147.5, 151.2, 151.7 (arom. C), 169.6 (CO). MS (70 eV, m/z and intensities for *erythro*/*threo*): 400 (M^+ , 41/13), 237 (32/14), 209 (21/14), 195 (100/50), 167 (92/70), 164 (77/100).

1-(4-Hydroxy-3-methoxyphenyl)-1-methoxy-2-(2-methoxy-4-(3-hydroxy-1-propenyl)phenoxy)-3-hydroxypropane (**9**). Compound (**9**) was prepared from coniferyl alcohol (**3**), as described in the general procedure, and purified as described for compound **5**. The overall yield of β -O-4 dimer **9** was 505 mg (36%). ¹H NMR, *erythro*-**9**: δ 2.00 (3 H, s, γ -OAc), 2.09 (3 H, s, γ' -OAc), 2.30 (3 H, s, ArOAc), 3.31 (3 H, s, α -OMe), 3.77, 3.79 (2 \times 3 H, s, ArOMe), 4.44 (4 H, m, α -, β - and γ -H), 4.69 (2 H, dd, $J = 6.5, 1.0$ Hz, γ' -H), 6.14 (1 H, dt, $J = 15.8, 6.5$ Hz, β' -H), 6.55 (1 H, d, $J = 16.0$ Hz, α' -H), 6.63–7.01 (6 H, m, ArH). ¹³C NMR, *erythro*-**9**: δ 21.4, 21.5, 21.7 (3 \times OAc), 56.4, 56.6 (2 \times ArOMe), 58.3 (α -OMe), 64.0 (γ -C), 65.8 (γ' -C), 82.7 (α - or β -C), 83.0 (α - or β -C), 110.7, 112.1, 119.2, 120.4, 120.4, 123.1 (arom. CH), 122.5 (β' -C), 134.6 (α' -C), 131.9, 137.8, 140.1, 148.3, 151.5, 151.7 (arom. C), 169.6, 171.5 (CO).

¹H NMR, *threo*-**9**: δ 1.95 (3 H, s, γ -OAc), 2.07 (3 H, s, γ' -OAc), 2.29 (3 H, s, ArOAc), 3.31 (3 H, s, α -OMe), 3.80 (2 \times 3 H, s, ArOMe), 4.07 (1 H, m, α -H), 4.26 (1 H, m, β -H), 4.47 (2 H, m, γ -H), 4.69 (2 H, dd, $J = 6.6, 1.1$ Hz, γ' -H), 6.14 (1 H, dt, $J = 15.9, 6.6$ Hz, β' -H), 6.56 (1 H, d, $J = 16.0$ Hz, α' -H), 6.87–7.05 (6 H, m, ArH). ¹³C NMR, *threo*-**9**: δ 21.2, 21.3, 21.6 (3 \times OAc), 56.3, 56.5 (2 \times ArOMe), 58.1 (α -OMe), 64.0 (γ -C), 65.7 (γ' -C), 81.8 (α - or β -C), 83.4 (α - or β -C), 110.5, 112.9, 118.4, 120.3, 120.3, 123.1 (arom. CH), 122.3 (β' -C), 134.6 (α' -C), 131.6, 137.2, 140.1, 148.8, 151.2, 151.8 (arom. C), 169.4, 171.2 (CO). MS (70 eV, m/z and intensities for *erythro*/*threo*):

516 (M^+ , 14), 456 (12), 235 (90/80), 209 (27/42), 193 (16/14), 167 (100).

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