ELECTROCHEMICAL OXIDATIVE COUPLING OF 4-HYDROXY-CINNAMIC ESTER DERIVATIVES: A CONVENIENT METHODOLOGY FOR THE BIOMIMETIC SYNTHESIS OF LIGNIN PRECURSORS

Anne NEUDORFFER[a1], Brigitte DEGUIN[b], Céline HAMEL[a], Maurice-Bernard FLEURY[a2] and Martine LARGERON[a3,*]

[a] *Laboratoire de Chimie Analytique et Electrochimie, UMR 8638 CNRS – Université Paris 5, Faculté des Sciences Pharmaceutiques et Biologiques, 4 Avenue de l'Observatoire, 75270 Paris Cedex 06, France; e-mail:* [1] *neudorff@pharmacie.univ-paris5.fr,* [2] *fleury@pharmacie.univ-paris5.fr,* [3] *largeron@pharmacie.univ-paris5.fr*

[b] *Laboratoire de Pharmacognosie, UMR 8638 CNRS – Université Paris 5, Faculté des Sciences Pharmaceutiques et Biologiques, 4 Avenue de l'Observatoire, 75270 Paris Cedex 06, France; e-mail: deguin@pharmacie.univ-paris5.fr*

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We are delighted to dedicate this paper to Professor Sergio Roffia for his major contribution to the field of molecular and physical electrochemistry.

Based on the electrochemical oxidative coupling of 4-hydroxycinnamic ester derivatives, a straightforward biomimetic synthesis of lignin precursors is reported. This one-pot procedure leads to various naturally occurring coupling products whose distribution depends on aromatic substituents.

Keywords: Biomimetic synthesis; Dimerization; Electrochemistry; Lignans; Oxidation; Radical coupling; Cyclic voltammetry; Reaction mechanism.

Lignin, the second most important biopolymer in plant cell walls of higher plants, next to cellulose, results from cross-coupling between many phenylpropenoid units[1,2]. This dehydrogenative polymerization requires the single-electron oxidation of 4-hydroxycinnamic acid derivatives to the corresponding phenoxyl radical, which dimerizes after delocalization in position 5 or 8. *In vivo*, various "guiding" enzymes determine the outcome of the bimolecular radical process[1]. The main monolignols identified in native lignin possess 8-O ether, 8-5 benzofuran and 8-8 skeletons[3,4], while the 5-5 units are less abundant (Fig. 1). *In vitro*, a wide range of enzymatic, chemical and electrochemical methods has been used to mimic the initial steps of the lignin biosynthesis. Although radical coupling involving the 8 position

also predominated, the distribution of the resulting 8-coupling products strongly depended on the nature of both the oxidant and solvent used.

Thus, in the case of ferulate ester, when utilizing the peroxidase–hydrogen peroxide aqueous system[5,6], the 8-5 benzofuran product was isolated as the main primary dimer, while similar enzymatic oxidation afforded, in water containing a quaternary ammonium salt as a surfactant[7], a mixture of 8-8, 8-5 and 5-5 dehydrodimers. With methyl sinapate, oxidative coupling using hydrogen peroxide and horse radish peroxidase in aqueous acetone gave an 8-8 dihydronaphthol derivative[8], whereas in aqueous methanol the main product was the 8-8 spiro compound[9].

Chemical oxidation of ferulate esters, utilizing a range of single-electron oxidants[5,10,11] such as Ag_2O in acetone–benzene 40:60 v/v, afforded the 8-5

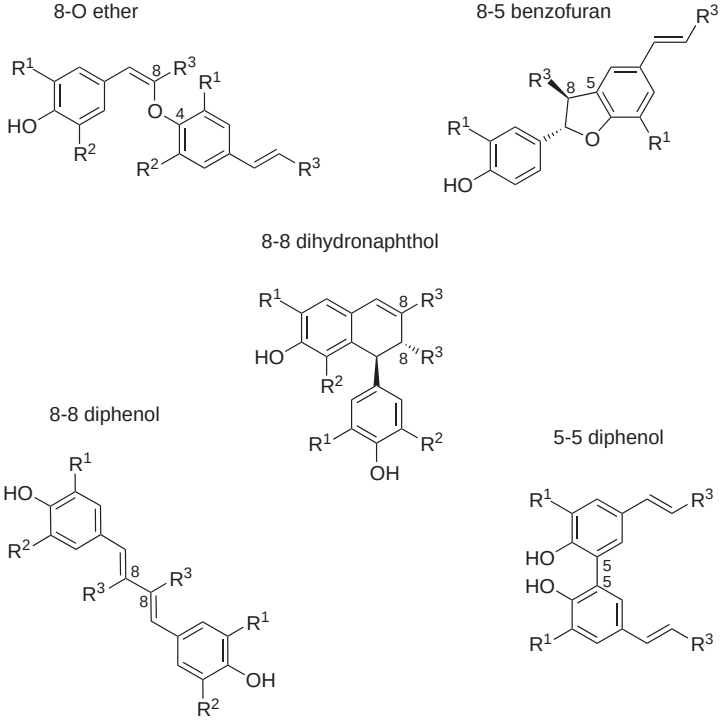
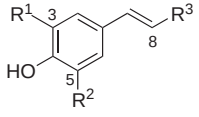


FIG. 1
General chemical structure of 4-hydroxycinnamic dehydrodimers identified in plant cell walls

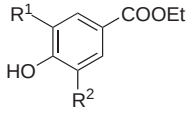
benzofuran dimer as the sole product. Comparatively, it was recently shown by NMR studies that through bulky, water-soluble Mn-salen in water–dioxane buffered solutions[12], the well-known 8-O ether dimer of coniferyl alcohol could be generated together with other common 8-8 and 8-5 benzofuran dimers. Oxidation of 3,5-di-*tert*-butyl-4-hydroxycinnamate[13] or of 4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)butan-2-one[14], using alkaline potassium hexacyanoferrate(III), yielded the stable 8-8 bis-quinomethide derivative along with 8-8 spiro-dimer as the minor product. Last, dehydrogenation of 3,5-di-*tert*-butyl-4-hydroxystilbene with 2,3-dichloro-5,6-dicyanobenzoquinone led to 8-8 bis-quinomethide, which spontaneously dissociates in methanolic solution into its monomeric radical precursors[15].

In the course of electrochemical oxidation of 2,6-di-*tert*-butyl-4-isopropylphenol[16] in acetonitrile, 8-8 coupling products (8-8 diphenol and 8-8 bis-quinomethide) were characterized by cyclic voltammetry and thin layer chromatography, but not isolated. Surprisingly, the anodic controlled-potential electrolysis of sinapic or ferulic acid in methanol produced asatone-type dimers through a two-electron oxidative step followed by a Diels–Alder reaction[17,18].

Due to diversity of the experimental conditions used, we thought that an electrochemical investigation of such reactions, using a unique oxidant/solvent system, could be worthwhile to provide additional information about the competing reaction pathways that led to the various coupling products. Herein, we report the results of a study devoted to electrochemical oxidation of 4-hydroxycinnamic ester derivatives **1a**–**1c** and ethyl vanillate **1d** (Fig. 2), in acetonitrile medium at a graphite carbon electrode.



Ethyl ester	R^1	R^2
Ferulate **1a**	MeO	H
Sinapate **1b**	MeO	MeO
4-Hydroxy-3,5-di-*tert*-butylcinnamate **1c**	*t*-Bu	*t*-Bu



Vanillate **1d**	MeO	H

FIG. 2
Chemical structure of 4-hydroxycinnamic esters **1a**–**1c** and ethyl vanillate **1d**

Through anodic controlled-potential electrolysis, which is a convenient procedure for biomimetic synthesis of lignin precursors, we endeavour to demonstrate that the distribution of different 8-coupling products depends primarily on the nature of aromatic substitution.

RESULTS AND DISCUSSION

The phenoxyl radical was electrogenerated using controlled-potential electrolysis at a graphite carbon electrode, in acetonitrile solution containing lithium perchlorate as the supporting electrolyte and a stoichiometric amount of tetramethylammonium hydroxide (TMAOH). Under such experimental conditions, **1a**–**1d** derivatives essentially exist as the corresponding phenolate ions $\mathbf{1a}^-$–$\mathbf{1d}^-$, as indicated by UV-VIS spectrophotometry (Fig. 3). The voltammogram of the ferulate ion $\mathbf{1a}^-$ exhibited an oxidation peak P_a due to a diffusion-controlled one-electron process at +400 mV *vs* SCE, the sweep rate *v* being 0.2 V s^{-1} (Fig. 4). This peak could be assigned to the formation of phenoxyl radical $\mathbf{1a}^{\bullet}$. No cathodic peak was recorded in the reverse sweep, suggesting that a dimerization reaction rapidly occurred after the electron transfer. Accordingly, it has been previously reported that 4-hydroxycinnamic alcohol such as coniferyl alcohol also exhibited, at low sweep rates, an irreversible behavior in cyclic voltammetry. Only the use of fast linear sweep voltammetry with ultramicroelectrodes allowed to measure the one-electron oxidation standard potential E'° of the phenolate anion/phenoxyl radical couples[19–22].

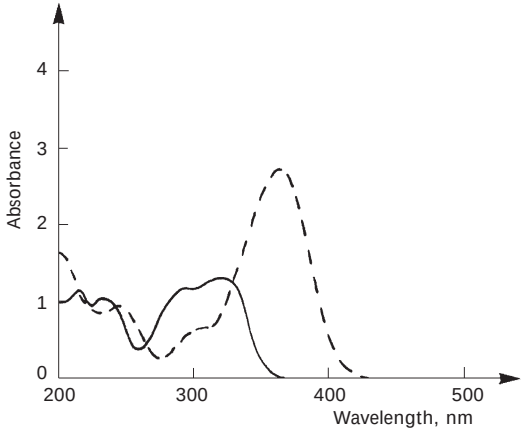


FIG. 3
UV-VIS absorption spectrum of 2 mM ethyl ferulate **1a** in acetonitrile (——); after addition of 2 mM TMAOH (– – – –). Cell thickness 0.1 cm

When the controlled potential *E* of the graphite carbon electrode was fixed at +500 mV *vs* SCE, *i.e.* at a potential immediately following the peak P_a, a coulometric value of 0.7 ± 0.1 was found for the number of electron (*n*) involved in the oxidation of one molecule of **1a**$^-$. As the electrolysis proceeded, the anodic peak P_a intensity decreased (Fig. 4). The anodic process ceased after the consumption of 0.7 F mol^{-1} due to a passivation phenomenon of the working graphite carbon electrode. Accordingly, four products were isolated, together with 28% of the starting phenol **1a**: 8-8 diphenol **4a** (8%), 8-8 dihydronaphthol **5a** (15%), 8-5 benzofuran **6a** (13%) and 8-O ether **7a** (10%) (Scheme 1).

The cyclic voltammogram of ethyl sinapate ion **1b**$^-$ was identical to that described for **1a**$^-$. When *E* was fixed at +500 mV *vs* SCE, a coulometric value of 0.8 ± 0.1 was found for *n*. Finally, preparative scale electrolysis allowed the isolation of dihydronaphthol **5b** (Scheme 2), in 42% yield, as the sole coupling product, along with 12% of the starting material.

To clarify the role of aromatic substitution on the distribution of different 8-coupling products, we examined the electrochemical oxidation of **1c**$^-$ ion, which bears two bulky *tert*-butyl groups in the *ortho* positions. The voltammogram of **1c**$^-$ ion showed an anodic peak P_a at +65 mV *vs* SCE due to the irreversible one-electron oxidation (Fig. 5). Furthermore, a cathodic peak P_c appeared in the reverse sweep, at –1100 mV *vs* SCE, indicating that

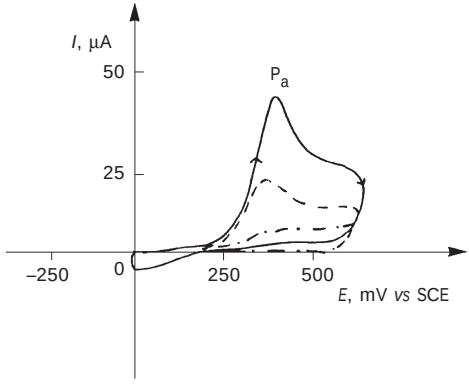
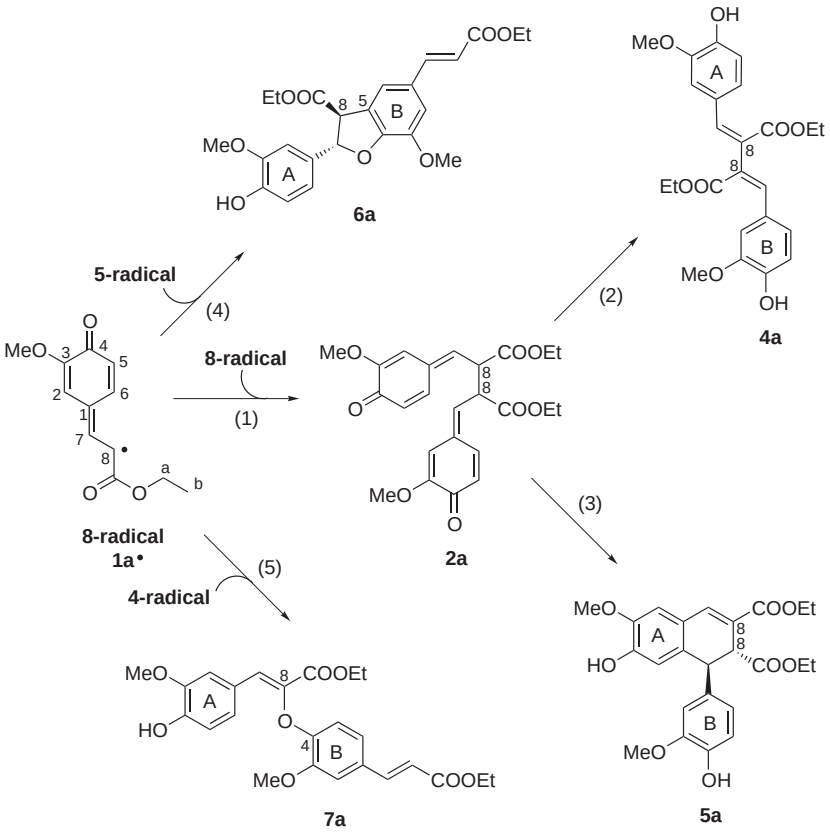
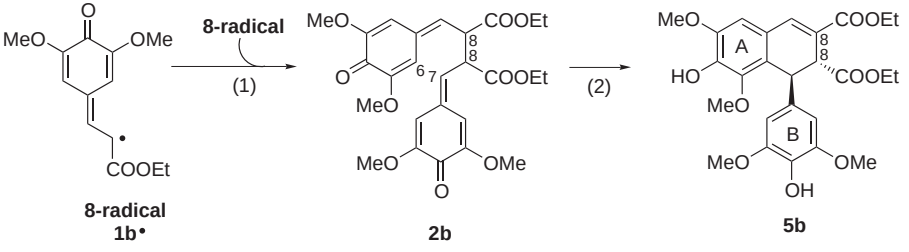


FIG. 4

Progress of the cyclic voltammogram in the course of anodic controlled-potential electrolysis of 2 mM ethyl ferulate **1a**, at a graphite carbon working electrode (*E* = +500 mV *vs* SCE), in deaerated acetonitrile containing 20 mM $LiClO_4$ and 2 mM TMAOH: before electrolysis (——); after consumption of 0.5 F mol^{-1} (– – – –); after consumption of 0.7 F mol^{-1} (– · – ·). Arrowheads indicate the direction of the potential sweep; v = 0.2 V s^{-1}



SCHEME 1
Oxidative coupling modes of ethyl ferulate **1a**



SCHEME 2
Dimerization reaction of ethyl sinapate **1b**

the dimerization product could be reduced. When *E* was fixed at +150 mV *vs* SCE, a coulometric value of 0.8 ± 0.1 was found for *n*. As the electrolysis proceeded, a decrease in the P_a intensity was observed while the P_c intensity increased simultaneously (see Fig. 5). Finally, preparative anodic electrolysis produced compounds **2c** (30%) and **3c** (22%) as the major products, together with **4c** (10%) as the minor product and 22% of the recovered starting phenol (Scheme 3). By comparison with a reference sample of **2c**, the peak P_c could be assigned to the reduction of the quinone methide moiety of **2c**.

In the last experiment aimed at evaluating the role of the propenoic chain in the dimerization pathways of 4-hydroxycinnamic ester derivatives, we studied the oxidation of ethyl vanillate ion **1d**$^-$, the benzoic homologous derivative of ethyl ferulate ion **1a**$^-$. The cyclic voltammogram of **1d**$^-$ anion exhibited an anodic peak P_{a1} at +525 mV *vs* SCE due to its single-electron irreversible oxidation, followed by a second anodic peak P_{a2}, at +765 mV *vs* SCE (Fig. 6). This corresponded to the oxidation of the 5-5 diphenol dimer **8** (Scheme 4), as further confirmed after recording a cyclic voltammogram of an authentic sample. When *E* was fixed at +600 mV *vs* SCE, *i.e.* at a potential for which the phenolate ion of ethyl vanillate could be oxidized exclusively to the dimer product, a coulometric value of 1.1 F mol^{-1} was found for *n*. As the electrolysis proceeded, a decrease in the P_{a1} intensity was observed, while the P_{a2} intensity remained unchanged over a long

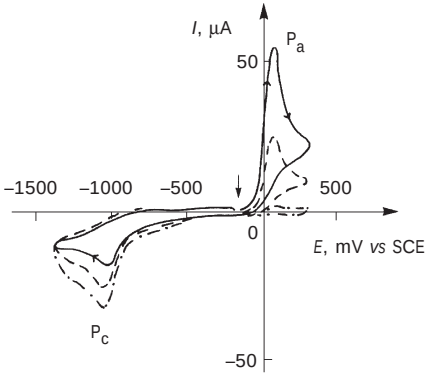
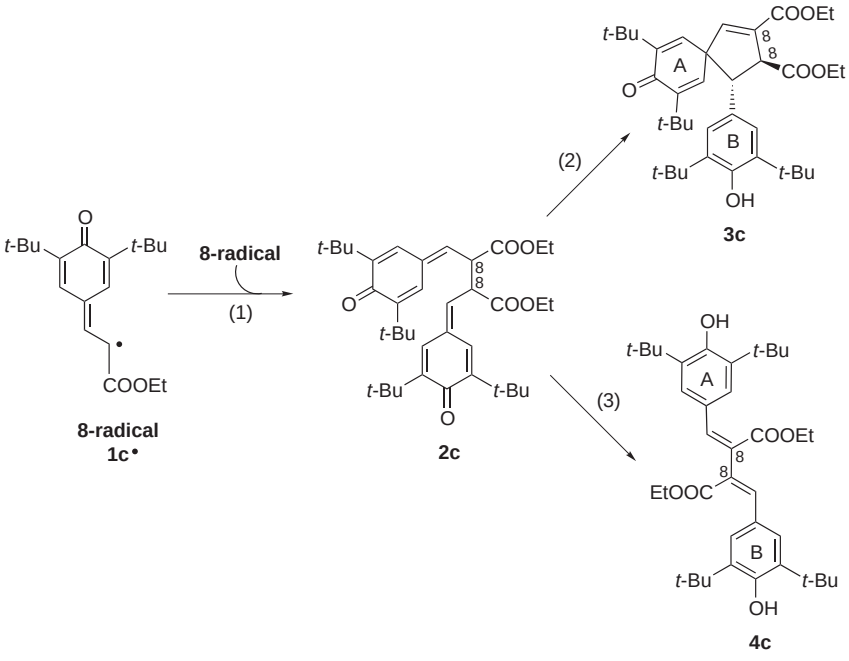
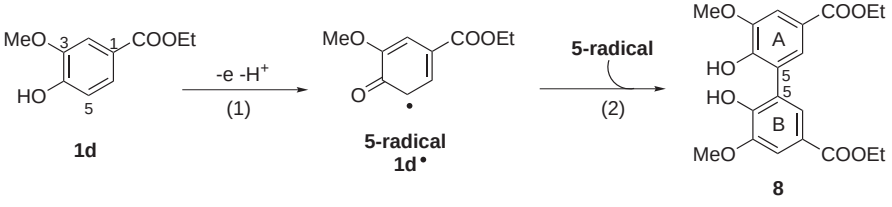


FIG. 5

Progress of the cyclic voltammogram in the course of anodic controlled-potential electrolysis of 2 mM ethyl 3,5-di-*tert*-butyl-4-hydroxycinnamate **1c**, at a graphite carbon working electrode (*E* = +150 mV *vs* SCE), in deaerated acetonitrile containing 20 mM $LiClO_4$ and 2 mM TMAOH: before electrolysis (——); after consumption of 0.5 F mol^{-1} (– – –); after consumption of 0.8 F mol^{-1} (– · – ·). Arrowheads indicate the direction of the potential sweep; v = 0.2 V s^{-1}. The vertical arrow indicates the initial potential point



SCHEME 3
Oxidative coupling modes of 4-hydroxy-3,5-*tert*-butylcinnamate **1c**



SCHEME 4
Dimerization reaction of ethyl vanillate **1d**

time. Preparative scale electrolysis allowed the isolation of 5-5 phenol dimer **8** (83%) as the sole dehydrogenation product, along with a small proportion of the starting material (7%).

MECHANISTIC DEDUCTIONS

Previous results underline the determining role of steric hindrance in the outcome of the dimerization process. It is well established that **1a**$^-$–**1c**$^-$ anions are oxidized into the corresponding phenoxyl radical **1a**$^\bullet$–**1c**$^\bullet$, whose

electrons are delocalized. Depending on the aromatic substitution of the produced intermediates, different coupling modes are favored.

When **1c**$^-$ anion was the starting material, the dimerization reactions implicating positions 5 and 3 were prevented by *tert*-butyl substituents. The presence of the propenoic chain ensures stabilization of the electrogenerated phenoxyl radical. Accordingly, the 3,5-di-*tert*-butylcinnamate ester radical **1c**$^\bullet$ underwent exclusively 8-8 coupling (Scheme 3, step 1). As earlier reported for hindered quinone species[23], the resulting 8-8 bisquinomethide **2c** was stable enough to be characterized by cyclic voltammetry (E_{P_c} = –1100 mV *vs* SCE) and isolated after anodic electrolysis. However, on silica gel, the corresponding fraction was transformed into 8-8 diphenol derivative **4c** and 8-8 spiro compound **3c**. The formation of the latter required migration of proton in position 8, followed by intramolecular cyclization in position 7 (Scheme 3, step 2). Comparatively, the 8-8 diphenol compound **4c** resulted from migration of both protons 8, which restored the phenolic aromaticity (Scheme 3, step 3).

In the case of ethyl sinapate radical **1b**$^\bullet$, the replacement of the *tert*-butyl groups in the 3 and 5 positions by the methoxy substituents induced a noticeable decrease in crowding and, consequently, in stability of 8-8 bisquinomethide, which could not be detected in the course of electrolysis. Once formed, this unstable species led directly to dihydronaphthol compound **5b** *via* migration of proton 7 and subsequent intramolecular cyclization in position 6 (Scheme 2, step 2).

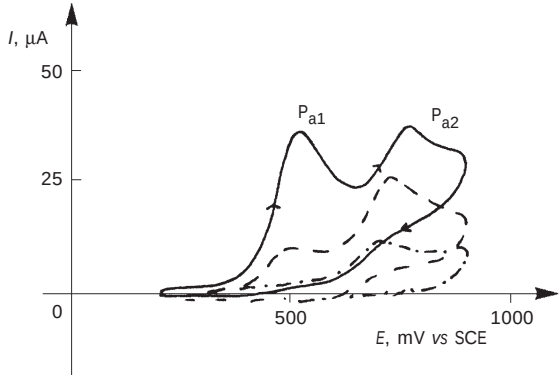


FIG. 6

Progress of the cyclic voltammogram in the course of anodic controlled-potential electrolysis of 2 mM ethyl vanillate **1d**, at a graphite carbon working electrode (E = +600 mV *vs* SCE), in deaerated acetonitrile containing 20 mM $LiClO_4$ and 2 mM TMAOH: before electrolysis (——); after consumption of 0.5 F mol^{-1} (– – – –); after consumption of 1.1 F mol^{-1} (– · – ·). Arrowheads indicate the direction of the potential sweep; v = 0.2 V s^{-1}

In the case of ethyl ferulate radical **1a**$^{\bullet}$, the lack of substitution in position 5 had two consequences. First, unstable, less substituted 8-8 bis-quinomethide **2a** underwent two successive tautomerization reactions, leading to mixed coupling products **4a** (Scheme 1, step 2) and **5a** (Scheme 1, step 3). Second, radicals in positions 4 and 5 could be generated in addition to the radical in position 8. Coupling of 8- and 5- radicals afforded **6a**, after intramolecular rearrangement of the quinone methide moiety (Scheme 1, step 4), while the well-known 8-O-dimer **7a** resulted from the condensation reaction of 8-radical and phenoxyl 4-radical (Scheme 1, step 5).

Last, in the case of ethyl vanillate radical **1d**$^{\bullet}$, the lack of the propenoid chain prevented electron delocalization[24,25], so that oxidative dimerization generated in high yield the 5-5 diphenol compound **8** as the sole coupling product (Scheme 4).

CONCLUDING REMARKS

Anodic electrolysis of 4-hydroxycinnamic ester derivatives, in acetonitrile at a graphite carbon working electrode, turned out to be a straightforward access to lignans, precursors in the lignin biosynthesis. In contrast to chemical methods, which generated exclusively the 8-5 dimer **6a** [5,10,11], electrochemical oxidation of ethyl ferulate afforded, in a one-pot synthesis, the natural 8-8, 8-O and 8-5 coupling products, in roughly similar proportions, as observed in plants. Note that compound **7a**, possessing the predominant 8-O-ether inter-unit linkage in native lignin, was essentially isolated from saponified plant material[26]. To the best of our knowledge, the sole organic synthesis reported as yet required numerous successive protection and deprotection steps of phenol and aldehyde groups, so that the overall yield did not exceed 10% [3]. For this purpose, our electrochemical procedure appears to be of particular interest. Likewise, electrochemical oxidation of ethyl sinapate leading to **5b** could be regarded as an easy access to the dihydronaphthol skeleton[27] common with thomasoic acid and podophyllotoxin derivatives. Note that dimers **5a**, **5b** and **6a s**howed *trans* configuration as reported for natural *threo* coupling mode.

As part of our continuing research efforts to find safe and effective antioxidants[28–30], studies are currently under way to evaluate the antioxidant activity of **1c** and its dimer **4c** as low-density lipoprotein protectors against Cu^{II}-catalyzed oxidation[27,31].

EXPERIMENTAL

Materials and Methods

UV-VIS spectra were recorded on a Varian Cary 100 UV spectrometer. ^{1}H NMR and ^{13}C NMR spectra were performed on a Bruker AC 300 spectrometer operating at 300 and 75 MHz for ^{1}H and ^{13}C NMR observations, respectively. Deuteriochloroform was used as the solvent. Chemical shifts (in ppm) are given relative to internal tetramethylsilane, *J* values are given in Hz. The measurements were carried out using the standard pulse sequences. The carbon type (methyl, methylene, methine or quaternary) was determined by DEPT experiments. The relative stereochemistry of compounds **3c**, **5a**, **5b**, **6a** and **7a** were determined by ^{1}D and ^{2}D NMR experiments and compared with that of natural products[8–11,32,33]. NOE, NOESY, COSY, HMBC and HMQC experiments were realized on a Bruker AMX-400 spectrometer. The atom numbering shown in Schemes 1 – 4 are for NMR assignments only and does not correspond to the IUPAC naming. Melting points were determined on a Köfler block and are uncorrected. Infrared spectra were recorded on a Nicolet FT-IR 510 spectrometer in dichloromethane. Mass spectra were recorded on a ZQ 2000 Waters spectrometer, equipped with the positive electrospray mode (ES+), or on a Nermag R 10-10C spectrometer equipped with desorption chemical ionization mode (DCI/NH_3).

Controlled-potential electrolysis was carried out in a cylindrical, three-electrode divided cell. In the main compartment, a cylindrical graphite carbon electrode (area 64.5 cm^2) served as anode (working electrode). A platinum sheet was placed in the concentric cathodic compartment (counter-electrode), which was separated from the main compartment with a glass frit. The reference electrode was an aqueous saturated calomel electrode (SCE), which was isolated from the bulk solution in a glass tube with fine-porosity frit. The electrolyte solution (20 mM lithium perchlorate in acetonitrile) was poured into the cathodic compartment, as well as into the glass tube containing the SCE electrode. A Tacussel PJT 120-1 potentiostat and a Tacussel IG6-N electronic integrator were included in the circuit.

For cyclic voltammetry, a Radiometer-Tacussel PRG 5 multipurpose polarograph was used as a rapid-response potentiostat, triangular wave forms being supplied by a Tacussel GSTP 4 function generator. Current–potential curves were recorded on a Schlumberger SI 8312 instrument. The cell was a Radiometer-Tacussel CPRA water-jacketed cell working at a temperature of 25 °C. The reference electrode and counter-electrode were mentioned above. The working electrode was a glassy carbon disk, carefully polished before each voltammogram with an aqueous alumina suspension.

Acetonitrile (SDS-anhydrous analytical grade) was freshly distilled before use. Lithium perchlorate was obtained from Fluka (purum purity grade). Tetramethylammonium hydroxide (TMAOH), 25 wt.% solution in methanol, was supplied by Aldrich. Compounds **1a**–**1d** were prepared by a classic esterification procedure[34], using ethanolic solution of commercially available acids and concentrated sulfuric acid. Macherey–Nagel Silica Gel polygram UV_{254} and Macherey–Nagel Silica Gel 60 (lot No. 815381) were used for thin-layer chromatography and flash chromatography, respectively.

Electrochemical Oxidative Coupling of Ethyl 3,5-Di-*tert*-butyl-4-hydroxycinnamate (**1c**). General Procedure

A solution of ethyl 3,5-di-*tert*-butyl-4-hydroxycinnamate **1c** (152 mg, 0.5 mmol), lithium perchlorate (530 mg, 5 mmol) and tetramethylammonium hydroxide (0.25 ml, 0.5 mmol)

in acetonitrile (250 ml) was oxidized under nitrogen, at room temperature, at a graphite carbon electrode (E = +150 mV *vs* SCE). After exhaustive oxidation, *i.e.* when a steady-state minimum value of the current was recorded, the solution was poured into a 0.5 M citrate-buffered aqueous solution of pH 6.0 (150 ml). The resulting mixture was concentrated to 150 ml under reduced pressure at 50 °C and extracted with ethyl acetate (150 ml). The organic phase was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure, at 50 °C. Flash chromatography on silica gel with a toluene–acetone gradient ((100:0) 100 ml, (98.5:1.5) 100 ml) as the eluent afforded 8-8 bis-quinomethide **2c** (45 mg, 30%), 8-8 spiro compound **3c** (34 mg, 22%) and 8-8 diphenol **4c** (15 mg, 10%), together with the starting phenol **1c** (34 mg, 22%).

Diethyl (2RS,3SR)-2,3-bis[(3,5-di-tert-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl]succinate (**2c**): orange oil. ^{1}H NMR: 1.25 s, 18 H and 1.35 s, 18 H (*t*-Bu-A_5, -B_5 and -A_3, -B_3); 1.30 t, 6 H, J(a,b) = 7 (H-A_b and -B_b); 4.20 q, 4 H, J(a,b) = 7 (H-A_a and -B_a); 4.35 d, 2 H, J(7,8) = 8 (H-A_8 and -B_8); 5.95 d, 2 H, J(7,8) = 8 (H-A_7 and -B_7); 6.75 s, 2 H and 7.30 s, 2 H (H-A_6, -B_6 and H-A_2, -B_2). ^{13}C NMR: 14.05 (CH_3-A_b and -B_b); 29.30 and 29.50 (CH_3-*t*-Bu-A_3, -B_3 and -A_5, -B_5); 34.90 and 35.50 (Cq-*t*-Bu-A_3, -B_3 and -A_5, -B_5); 47.30 (CH-A_8 and -B_8); 62.05 (CH_2O-A_a and -B_a); 125.70 (CH-A_7 and -B_7); 133.75 and 135.90 (CH-A_2, -B_2 and -A_6, -B_6); 135.15 (Cq-A_1 and -B_1); 148.10 and 149.70 (Cq-A_3, -B_3 and -A_5, -B_5); 170.40 (CO-A_8 and -B_8); 186.20 (CO-A_4 and -B_4). IR (CH_2Cl_2): 2958, 2858, 1738, 1625, 1618, 1574, 1456, 1389, 1363, 1255, 1182, 1025. For $C_{38}H_{54}O_6$ (606.9) calculated: 75.21% C, 8.97% H; found: 75.43% C, 8.87% H. MS (DCI), *m/z*: 607 [MH^+], 624 [M – NH_4^+].

Diethyl 7,9-di-tert-butyl-1-(3,5-di-tert-butylphenyl-4-hydroxy)-8-oxospiro[4.5]deca-3,6,9-triene-2,3-dicarboxylate (**3c**): yellow oil. ^{1}H NMR: 0.95 s, 9 H (*t*-Bu-A_3); 1.25 t, 3 H, J(a,b) = 7 (H-B_b); 1.30 s, 9 H (*t*-Bu-A_5); 1.35 t, 3 H, J(a,b) = 7 (H-A_b); 1.40 s, 18 H (*t*-Bu-B_3 and -B_5); 3.95 d, 1 H, J(B_7,B_8) = 10 (H-B_7); 4.20 m, 2 H (H-B_a); 4.30 m, 2 H (H-A_a); 4.50 dd, J(B_7,B_8 and A_7,B_8) = 10 and 2 (H-B_8); 5.10 s, 1 H, D_2O exchanged (HO-B_4); 6.05 d, 1 H, J(A_2,A_6) = 2 (H-A_2); 6.40 d, 1 H, J(A_7,B_8) = 2 (H-A_7); 6.75 d, 1 H, J(A_2,A_6) = 2 (H-A_6); 6.90 s, 2 H (H-B_2 and -B_6). ^{13}C NMR: 14.05 (CH_3-B_b); 14.15 (CH_3-A_b); 28.95 (CH_3-*t*-Bu-A_3); 29.60 (CH_3-*t*-Bu-A_5); 30.20 (CH_3-*t*-Bu-B_3 and -B_5); 34.20 (Cq-*t*-Bu-B_3 and -B_5); 34.50 (Cq-*t*-Bu-A_5); 35.00 (Cq-*t*-Bu-A_3); 52.25 (CH-B_8); 56.80 (Cq-spiro); 59.30 (CH-B_7); 61.05 (CH_2O-A_a); 61.17 (CH_2O-B_a); 123.50 (CH-B_2 and -B_6); 126.15 (Cq-B_1); 135.40 (Cq-B_3 and -B_5); 136.90 (Cq-A_8); 138.00 (CH-A_2); 141.70 (CH-A_6); 146.10 (CH-A_7); 147.90 (Cq-A_3); 148.60 (Cq-A_5); 152.90 (Cq-B_4); 163.70 (CO-A_8); 173.35 (CO-B_8); 185.85 (CO-A_4). IR (CH_2Cl_2): 3646, 2958, , 2862, 1721, 1658, 1644, 1440, 1391, 1367, 1251, 1124, 1025. For $C_{38}H_{54}O_6$ (606.9) calculated: 75.21% C, 8.97% H; found: 74.98% C, 9.01% H. MS (ES+), *m/z*: 629 [M + Na]$^+$.

Nuclear overhauser effects (NOE) and NOESY cross-peaks were observed between H-B_7 and H-A_6 on one hand, and between H-B_8 and H-A_2 on the other. The relative trans configuration of the bond C-B_7–C-B_8 was confirmed by the measurement of the $^3J_{C-H}$ coupling constants between aromatic Cq-B_1 and H-B_8 (3 Hz) and between CO-B_8 and H-B_7 (3 Hz).

Diethyl (E,E)-2,3-bis(3,5-di-tert-butyl-4-hydroxybenzylidene)succinate (**4c**): white solid recrystallized from a diethyl ether–pentane mixture, m.p. 126 °C. ^{1}H NMR: 1.10 t, 6 H, J(a,b) = 7 (H-A_b and -B_b); 1.35 s, 36 H (*t*-Bu-A_3, -A_5, -B_3 and -B_5); 4.15 m, 4 H (H-A_a and -B_a); 5.40 br s, 2 H, D_2O exchanged (HO-A_4 and -B_4); 7.40 s, 4 H (H-A_2, -A_6, -B_2 and -B_6); 7.90 s, 2 H (H-A_7 and -B_7). ^{13}C NMR: 14.05 (CH_3-A_b and -B_b); 30.10 (CH_3-*t*-Bu-A_3, -A_5, -B_3 and -B_5); 34.35 (Cq-*t*-Bu-A_3, -A_5, -B_3 and -B_5); 60.65 (CH_2O-A_a and -B_a); 124.40 (Cq-A_8 and -B_8); 126.60 (Cq- A_1 and -B_1); 127.65 (CH-A_2, -A_6, -B_2 and -B_6); 135.70 (Cq-A_3, -A_5, -B_3 and -B_5); 142.85 (CH-A_7 and -B_7); 155.25 (Cq-A_4 and -B_4); 167.40 (CO-A_8 and -B_8). IR (CH_2Cl_2): 3627,

2958, 2870, 1699, 1595, 1438, 1421, 1392, 1364, 1242, 1197, 1105, 1040. For $C_{38}H_{54}O_6$ (606.9) calculated: 75.21% C, 8.97% H; found: 75.12% C, 9.03% H. MS (DCI), *m/z*: 607 [MH^+], 624 [M – NH_4^+].

Electrochemical Oxidative Coupling of Ethyl Sinapate **1b**

When ethyl 3,5-di-*tert*-butylcinnamate was replaced by ethyl sinapate **1b** (126 mg, 0.5 mmol), the above described procedure with *E* = +500 mV *vs* SCE afforded, after flash chromatography on silica gel with a toluene–acetone gradient ((90:10) 100 ml, (80:20) 100 ml) as the eluent, 8-8 dihydronaphthol **5b** (53 mg, 42%) along with the starting phenol **1b** (15 mg, 12%).

Diethyl 7-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-6,8-dimethoxy-1,2-dihydronaphthalene-2,3-dicarboxylate (**5b**): white solid recrystallized from a diethyl ether–petroleum ether mixture, m.p. 97 °C. ^{1}H NMR: 1.20 t, 3 H, *J*(a,b) = 7 (H-B_b); 1.30 t, 3 H, *J*(a,b) = 7 (H-A_b); 3.70 s, 3 H (CH_3O-A_5); 3.80 s, 6 H (CH_3O-B_3 and -B_5); 3.95 s, 3 H (CH_3O-A_3); 4.00 s, 1 H (H-B_8); 4.10 q, 2 H, *J*(a,b) = 7 (H-B_a); 4.20 m, 2 H (H-A_a); 5.00 s, 1 H (H-B_7); 5.35 and 5.75 2 × br s, 2 H, D_2O exchanged (HO-A_4 and -B_4); 6.30 s, 2 H (H-B_2 and -B_6); 6.70 s, 1 H (H-A_2); 7.65 s, 1 H (H-A_7). ^{13}C NMR: 14.05 (CH_3-B_b); 14.25 (CH_3-A_b); 39.35 (CH-B_7); 46.50 (CH-B_8); 56.25 (CH_3-O-A_3, -B_3 and -B_5); 60.60 (CH_3-O-A_5); 60.65 (CH_2-O-A_a); 61.10 (CH_2-O-B_a); 104.40 (CH-B_2 and -B_6); 107.30 (CH-A_2); 123.45 (Cq-A_1 and -A_8); 123.90 (Cq-A_6); 133.55 (Cq-B_1); 133.75 (Cq-B_4); 137.05 (CH-A_7); 140.80 (Cq-A_4); 144.95 (Cq-A_5); 146.70 and 146.80 (Cq-A_3, -B_3 and -B_5); 166.60 (CO-A_8); 171.90 (CO-B_8). IR (CH_2Cl_2): 3419, 2979, 2839, 1724, 1698, 1608, 1575, 1516, 1499, 1457, 1369, 1265, 1212, 1101, 1047. For $C_{26}H_{30}O_{10}$ (502.5) calculated: 62.15% C, 6.02% H; found: 62.30% C, 6.04% H. MS (DCI), *m/z*: 503 [MH^+], 520 [M – NH_4^+].

Electrochemical Oxidative Coupling of Ethyl Ferulate **1a**

When ethyl 3,5-di-*tert*-butylcinnamate was replaced by ethyl ferulate **1a** (111.0 mg, 0.5 mmol), the above described procedure with *E* = +500 mV *vs* SCE afforded, after flash chromatography on silica gel with a toluene–acetone gradient ((95:5) 100 ml, (90:10) 100 ml) as the eluent, 8-8 diphenol **4a** (9.0 mg, 8%), 8-8 dihydronaphthol **5a** (16.5 mg, 15%), 8-5 benzofuran **6a** (14.5 mg, 13%) and 8-O-ether **7a** (11.0 mg, 10%) together with the starting phenol **1a** (30.5 mg, 28%).

Diethyl (E,E)-2,3-bis(3,5-dimethoxy-4-hydroxybenzylidene)succinate (**4a**): yellow oil. ^{1}H NMR: 1.15 t, 6 H, *J*(a,b) = 7 (H-A_b and -B_b); 3.75 s, 6 H (CH_3O-A_3 and -B_3); 4.15 q, 4 H, *J*(a,b) = 7 (H-A_a and -B_a); 5.70 br s, 2 H, D_2O exchanged (HO-A_4 and -B_4); 6.85 d, 2 H, *J*(5,6) = 8 (H-A_5 and -B_5); 7.05 dd, 2 H, *J*(2,6 and 5,6) = 2 and 8 (H-A_6 and -B_6); 7.10 d, 2 H, *J*(2,6) = 2 (H-A_2 and -B_2); 7.85 s, 2 H (H-A_7 and -B_7). ^{13}C NMR: 14.10 (CH_3-A_b and -B_b); 55.75 (CH_3-O-A_3 and -B_3); 61.00 (CH_2O-A_a and -B_a); 111.35 (CH-A_2 and -B_2); 114.50 (CH-A_5 and -B_5); 124.85 (Cq-A_8 and -B_8); 125.10 (CH-A_6 and -B_6); 127.40 (Cq-A_1 and -B_1); 142.15 (CH-A_7 and -B_7); 146.40 (Cq-A_3 and -B_3); 147.30 (Cq-A_4 and -B_4); 167.30 (CO-A_8 and -B_8). IR (CH_2Cl_2): 3396, 2979, 1699, 1593, 1514, 1464, 1428, 1367, 1254, 1223, 1184, 1125, 1101, 1033. For $C_{24}H_{26}O_8$ (442.5) calculated: 65.15% C, 5.92% H; found: 64.88% C, 5.90% H. MS (DCI), *m/z*: 443 [MH^+], 460 [M – NH_4^+].

Diethyl 7-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-6-methoxy-1,2-dihydronaphthalene-2,3-dicarboxylate (**5a**): white solid recrystallized from diethyl ether–petroleum ether, m.p. 153 °C. ^{1}H NMR: 1.15 t, 3 H, *J*(a,b) = 7 (H-B_b); 1.30 t, 3 H, *J*(a,b) = 7 (H-A_b); 3.80 s, 3 H (CH_3O-B_3); 3.95 s, 3 H (CH_3O-A_3); 4.00 d, 1 H, *J*(B_7,B_8) = 4 (H-B_8); 4.10 m, 2 H (H-B_a); 4.20 q, 2 H,

J(a,b) = 7 (H-A_a); 4.55 d, 1 H, *J*(B_7,B_8) = 4 (H-B_7); 5.50 and 5.80 2 × br s, 2 H, D_2O exchanged (HO-A_4 and -B_4); 6.45 dd, 1 H, *J*(B_2,B_6 and B_5,B_6) = 2 and 8 (H-B_6); 6.65 d, 1 H, *J*(B_2,B_6) = 2 (H-B_2); 6.70 s, 1 H (H-A_5); 6.75 d, 1 H, *J*(B_5,B_6) = 8 (H-B_5); 6.85 s, 1 H (H-A_2); 7.65 s, 1 H (H-A_7). ^{13}C NMR: 14.00 (CH_3-B_b); 14.20 (CH_3-A_b); 45.80 (CH-B_7); 47.40 (CH-B_8); 55.85 (CH_3-O-B_3); 56.00 (CH_3-O-A_3); 60.60 (CH_2-O-B_a); 61.00 (CH_2-O-A_a); 110.25 (CH-B_2); 111.15 (CH-A_2); 114.15 (CH-B_5); 115.45 (CH-A_5); 120.50 (CH-B_6); 123.15 (Cq-A_8); 123.95 (Cq-A_1); 131,35 (Cq-A_6); 134.40 (Cq-B_1); 137.20 (CH-A_7); 144.45 (Cq-B_4); 145.70 (Cq-A_3); 146.40 (Cq-B_3); 147.55 (Cq-A_4); 166.70 (CO-A_8); 172.50 (CO-B_8). IR (CH_2Cl_2): 3406, 2978, 2842, 1729, 1699, 1574, 1513, 1464, 1370, 1267, 1238, 1206, 1032. For $C_{24}H_{26}O_8$ (442.5) calculated: 65.15% C, 5.92% H; found: 65.00% C, 5.93% H. MS (DCI), *m/z*: 443 [MH^+], 460 [M – NH_4^+].

Ethyl 5-[(E)-2-(ethoxycarbonyl)vinyl]-2-(4-hydroxy-3-methoxyphenyl)-7-methoxy-2,3-dihydro-1-benzofuran-3-carboxylate (**6a**): white solid recrystallized from a diethyl ether–pentane mixture, m.p. 155 °C. Spectroscopic data of **6a** have been reported earlier[3].

Ethyl (Z)-4-{[(E)-1-(ethoxycarbonyl)-2-(4-hydroxy-3-methoxyphenyl)vinyl]oxy}-3-methoxycinnamate (**7a**): colorless oil. ^{1}H NMR: 1.25 t, 3 H, *J*(a,b) = 7 (H-A_b); 1.35 t, 3 H, *J*(a,b) = 7 (H-B_b); 3.80 s, 3 H (CH_3O-A_3); 4.00 s, 3 H (CH_3O-B_3); 4.25 q, 2 H, *J*(a,b) = 7 (H-A_a); 4.30 q, 2 H, *J*(a,b) = 7 (H-B_a); 5.85 br s, 1 H, D_2O exchanged (HO-A_4); 6.35 d, 1 H, *J*(B_7,B_8) = 16 (H-B_8); 6.80 d, 1 H, *J*(B_5,B_6) = 9 (H-B_5); 6.90 d, 1 H, *J*(A_5,A_6) = 8 (H-A_5); 7.00 dd, 1 H, *J*(B_2,B_6 and B_5,B_6) = 2 and 9 (H-B_6); 7.15 s, 1 H, *J*(B_2,B_6) = 2 (H-B_2); 7.20 dd, 1 H, *J*(A_2,A_6 and A_5,A_6) = 2 and 8 (H-A_6); 7.35 s, 1 H (H-A_7); 7.45 d, 1 H, *J*(A_2,A_6) = 2 (H-A_2); 7.60 d, 1 H, *J*(B_7,B_8) = 16 (H-B_7). ^{13}C NMR: 14.10 (CH_3-A_b); 14.30 (CH_3-B_b); 55.50 (CH_3-O-A_3); 56.20 (CH_3-O-B_3); 60.40 (CH_2-O-B_a); 61.40 (CH_2-O-A_a); 111.20 (CH-B_2); 112.00 (CH-A_2); 114.15 (CH-B_5); 114.45 (CH-A_5); 116.80 (CH-B_8); 122.05 (CH-B_6); 124.75 (Cq-A_1); 125.50 (CH-A_6); 127.75 (CH-A_7); 129.40 (Cq-B_1); 137.75 (Cq-A_8); 144.10 (CH-B_7); 146.40 (Cq-A_3); 147.40 (Cq-A_4); 147.70 (Cq-B_4); 149.15 (Cq-B_3); 163.40 (CO-A_8); 167.05 (CO-B_8). IR (CH_2Cl_2): 3408, 2980, 2935, 2852, 1713, 1635, 1597, 1506, 1465, 1429, 1368, 1340, 1259, 1177, 1161, 1134, 1094, 1033. For $C_{24}H_{26}O_8$ (442.5) calculated: 65.15% C, 5.92% H; found: 64.91% C, 5.90% H. MS (DCI), *m/z*: 443 [MH^+], 460 [M – NH_4^+].

Electrochemical Oxidative Coupling of Ethyl Vanillate **1d**

When ethyl 3,5-di-*tert*-butylcinnamate was replaced by ethyl vanillate **1d** (98 mg, 0.5 mmol), the above described procedure with *E* = +600 mV *vs* SCE afforded, after flash chromatography on silica gel with a toluene–acetone gradient ((95:5) 100 ml, (90:10) 100 ml) as the eluent, 5-5 diphenol **8** (81 mg, 83%) along with the starting phenol **1d** (7 mg, 7%).

Diethyl 6,6′-dihydroxy-5,5′-dimethoxybiphenyl-3,3′-dicarboxylate (**8**)**:** white solid recrystallized from a diethyl ether–hexane mixture, m.p. 170 °C. ^{1}H NMR: 1.40 t, 6 H, *J*(a,b) = 7 (H-A_b and -B_b); 4.00 s, 6 H (CH_3O-A_3 and -B_3); 4.35 q, 4 H, *J*(a,b) = 7 (H-A_a and -B_a); 6.30 br s, 2 H, D_2O exchanged (HO-A_4 and -B_4); 7.65 s, 2 H (H-A_2 and -B_2); 7.75 s, 2 H (H-A_6 and -B_6). ^{13}C NMR: 14.40 (CH_3-A_b and -B_b); 56.30 (CH_3-O-A_3 and -B_3); 60.85 (CH_2O-A_a and -B_a); 111.15 (CH-A_2 and -B_2); 122.25 and 122.90 (Cq-A_1, -B_1, -A_5 and -B_5); 125.85 (CH-A_6 and -B_6); 146.55 and 147.25 (Cq-A_3, -B_3, -A_4 and -B_4); 166.30 (CO-A_1 and -B_1). IR (CH_2Cl_2): 3434, 2989, 1704, 1594, 1463, 1378, 1237, 1050, 763. For $C_{20}H_{22}O_8$ (390.4) calculated: 61.53% C, 5.68% H; found: 61.37% C, 5.90% H. MS (DCI), *m/z*: 391 [MH^+], 408 [M – NH_4^+].

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