Studies on the Preparation of Bioactive Lignans by Oxidative Coupling Reaction. V.[1] Oxidative Coupling Reaction of Methyl (*E*)-3-(2-Hydroxyphenyl)propenoate Derivatives and Lipid Peroxidation Inhibitory Effects of the Produced Lignans

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The oxidative coupling reactions of 2-hydroxycinnamates were investigated as a continuation of our previous studies on 4-hydroxy derivatives. The reaction of 2-hydroxycinnamate 1 and 2-hydroxy-4-methoxycinnamate 3 with silver oxide afforded polymerized lignin-like products, while that of 2-hydroxy-bis(methoxymethoxy)cinnamates 5 and 6, after acetylation, gave the enol acetates, 8 and 14, of oxotetrahydrobenzoxanthene derivatives, respectively. These two products were also obtained by the oxidation of 5 and 6 with potassium hexacyanoferrate(III). In the reactions of 5 and 6 with iron(III) chloride, the major products were the partially demethoxymethoxylated compounds 9 and 15, respectively. Thus, the course of the reactions in the oxidation of 2-hydroxycinnamates is quite different from that in the case of 4-hydroxy derivatives. The product 8 and the corresponding oxotetrahydrobenzoxanthene derivative were found to show moderate inhibitory effects upon lipid peroxidation.

Key words lignan; oxidative coupling reaction; 2-hydroxycinnamate derivative; benzoxanthene derivative; lipid peroxidation inhibitory effect

In the previous papers,[1-4] we dealt with the synthesis of lignans by the oxidative coupling of hydroxycinnamates and with screening of the products for inhibitory activity on lipid peroxidation. A feature of our work is that coumarins are utilized as the source of the hydroxycinnamates. A number of polyphenolic coumarins are synthetically easily accessible, and they are often themselves biologically active.[5-12] The oxidative coupling reactions of three 2-methoxy-4-hydroxycinnamate derivatives obtained from coumarins were found to give a dihydronaphthalene derivative or dihydrobenzofuran derivatives as the major products, of which some exhibited prominent lipid peroxidation-inhibitory activities.

As a continuation of our studies on the synthesis of bioactive lignans from coumarins we have investigated the oxidative coupling of 2-hydroxycinnamate derivatives obtained from coumarins. Whereas the oxidative coupling of 4-hydroxycinnamates has been extensively investigated, that of the 2-hydroxycinnamate derivatives has never been reported, to our knowledge. The mode of oxidative coupling is greatly affected by the environment of the radical formed by oxidation,[1-4,13] and so the purpose of this paper is to disclose the reaction pattern of polyphenolic substrates of a new type.

Results and Discussion

Oxidative Coupling Reactions of Methyl (*E*)-3-(2-Hydroxyphenyl)propenoate (1) and Methyl (*E*)-3-(2-Hydroxy-4-methoxyphenyl)propenoate (3) Oxidation of methyl (*E*)-3-(2-hydroxyphenyl)propenoate (**1**) obtained from coumarin was examined. Treatment of **1** with silver oxide resulted in the formation of **2** as a brownish yellow powder. The average molecular weight of **2** was determined by means of gel permeation chromatography (GPC) to be around 11000, which is comparable with those of common natural lignins. The ^{1}H-NMR spectrum of **2** exhibited a large proton signal due to methyl esters (δ 3.00—4.50), and a broad signal in the aromatic proton region (δ 6.00—8.30). In the IR spectrum of **2** a strong carbonyl absorption peak appeared at 1712 cm^{-1} while no appreciable hydroxy peak was noted. This fact suggested that the formation of the ether linkage might play an important part in the chain propagation. Compound **2** is presumed to contain a 2-oxyphenylpropanoic acid unit in place of the 4-hydroxyphenyl propanol unit of natural lignin,[14,15] and its structure will be examined in the future.

On the other hand, when methyl (*E*)-3-(2-hydroxy-4-methoxyphenyl)propenoate (**3**) obtained from 7-methoxycoumarin was treated with silver oxide and the products were separated from unreacted **3** by chromatography on silica gel, **4** was obtained as a yellow powder, of which the average molecular weight was measured to be about 2000 by GPC. The ^{1}H-NMR spectrum of **4** resembled that of **2** and a large proton signal due to methyl esters and methoxy groups (δ 3.00—4.00), and a broad signal due to aromatic protons (δ 5.50—8.20) were observed. The IR spectrum of **4** exhibited a strong carbonyl absorption peak at 1709 cm^{-1} and a broad hydroxy absorption at 3328 cm^{-1}. Thus, **4** is a lignin closely related to **2**. However the presence of the 4-methoxy group in the substrate **3** greatly suppresses the polymerization and the molecular weight of the oxidation product **4** is only one-fifth of that of **2**. The formation of a lignin from **3** contrasts to the oxidative coupling reaction of the 4-hydroxy-2-methoxy analogue, which produced a dihydrobenzofuran compound as the major product.[4] The reactions of **3** with potassium hexacyanoferrate(III)–Na_2CO_3 in $CHCl_3$ or iron(III) chloride (5% on silica gel) in CH_2Cl_2, manganese acetylacetonate in acetonitrile, and $[Fe(DMF)_3Cl_2]$-$[FeCl_4]$[16] in ether did not give any lignan-type product, and the treatment of **3** with horseradish peroxidase–H_2O_2

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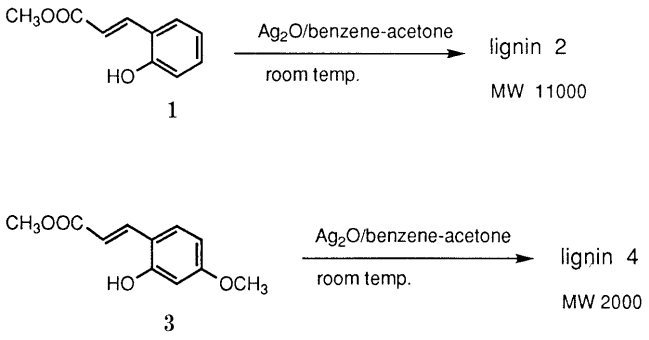


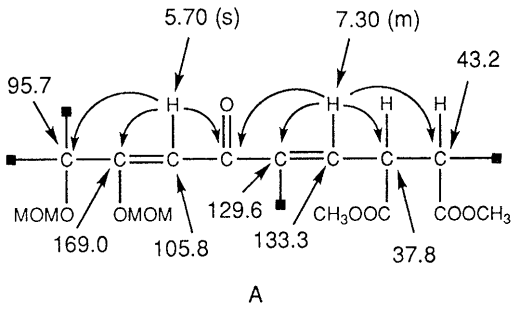
Chart 1. Oxidative Coupling Reaction of Simple 2-Hydroxycinnamates **1** and **3** with Silver Oxide

in phosphate buffer resulted in no reaction.

Oxidative Coupling Reaction of Methyl (*E*)-3-[2-Hydroxy-4,5-bis(methoxymethoxy)phenyl]propenoate (5) and Methyl (*E*)-3-[2-Hydroxy-3,4-bis(methoxymethoxy)-phenyl]propenoate (6) From the above results, it was considered that the presence of an additional bulky group in the substrate might interfere with the polymerization, so our attention was directed toward the reactions of the substrates **5**[3] and **6**[1] derived from esculetin and daphnetin, respectively.

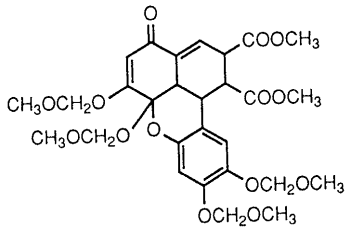
Treatment of the bis(methoxymethoxy)phenol derivative **5** with silver oxide followed by purification of the crude product by chromatography on silica gel afforded a crystalline product **7** in 56% yield.

The molecular formula, $C_{28}H_{34}O_{14}$ as determined by elemental analysis and MS measurement revealed that **7** was a dimer of **5**. In survey of the ^{1}H-NMR with reference to that of **5**, disappearance of typical AB-type vinyl proton signals due to two (*E*)-propenate chain and a pair of aromatic protons, and retention of all of the signals due to methoxymethyl (MOM) and the methoxy groups were noted. These observations suggested that **7** might have a 1-arylhydronaphthalene structure, which would be formed by β–β coupling of the radicals derived from **5** and subsequent formation of the hydronaphthalene ring through intramolecular *o*–α linkage. In the IR spectrum of **7** no hydroxyl absorption was observed and an absorption due to a conjugated ketone group was observed instead at 1672 cm^{-1}. These spectral data, in conjunction with the molecular formula, suggested that one of two phenolic hydroxy groups of the intermediate dimer had been oxidized to a ketone group and the other had participated in the formation of an ether ring, so that the product **7** is a tetracyclic ring compound. The additional signals in the ^{1}H-NMR spectrum were those due to four methine protons (δ 3.16, 3.18, 3.99, 4.04, each m), attached to the four contiguous sp^3 carbon atoms, and two vinyl protons (δ 5.70, s; δ 7.30, m). The positional relationship of two vinyl protons with the ketone group was investigated by ^{1}H-, ^{13}C-NMR correlation spectroscopy *via* long-range coupling (COLOC), and the presence of the partial structure A in **7** was revealed. In consequence, the gross structure **7′** was assigned to the product. The relative configuration of the four contiguous stereogenic centers in **7** was examined by means of selective spin decoupling in the ^{1}H-NMR, with reference to the results obtained for compound **8** where coupling constant values



A

Fig. 1



7′

Fig. 2

among H-1, H-11b and H-11c could be obtained directly from the spectrum (*vide infra*). The constants $J_{H1-H11b}$ and $J_{H11b-11c}$ thus determined were 3.5 and 5.7 Hz, respectively, the values being similar to those found in the case of **8**. The coupling constants J_{H1-H2} and J_{H2-H3} were revealed to be 5.5 and 2.2 Hz, respectively. The inspection of a molecular model indicated that these values were more consonant with *cis*-disposition of the H-1 and H-2 protons than with *trans*. Thus, the *r*-1, *cis*-2, *trans*-11c configuration is assigned for the product **7**.

When the crude product of the above reaction was acetylated and purified by chromatography on silica gel, an acetate **8**, $C_{30}H_{36}O_{15}$, was obtained. Inspection of the IR spectrum indicated the appearance of the absorption peaks at 1768, 1735 and 1700 cm^{-1}, assignable to the carbonyl groups of enol acetate, saturated ester and conjugated ester, respectively. This result suggested that **8** would be the dienol acetate corresponding to **7**. In consonance with this formulation, ^{1}H–^{1}H shift correlation spectroscopy (COSY) experiments on **8** showed long-range ^{1}H–^{1}H correlations between 11c-H (δ 3.41) and 3-H (δ 7.37) as well as between H-11b (δ 3.98) and H-11 (δ 6.97). Comparison of the ^{13}C-NMR spectra of **7** and **8** also corroborated the dienol acetate formation.

With respect to the conformation of **8**, appreciable allylic coupling was observed between the signals of H-3 and H-11c but not between those of H-1 and H-3 in the COSY experiment. Therefore the H-1 and H-11c bonds were assignable as *quasi*-equatorial and *quasi*-axial, respectively. The H-11b bond was inferred to be *quasi*-equatorial, since the observed coupling constants $J_{H1-H11b}$ and $J_{H11b-H11c}$ were 2 and 5 Hz, respectively. Therefore **8** has the *r*-1, *trans*-11b, *trans*-11c configuration and takes the conformation depicted in **B**. The observation of nuclear Overhauser effect (NOE) enhancements between the signals of H-1 and H-11, H-1 and H-11b, H-11b and H-11c corroborates this conformation.

On oxidation with potassium hexacyanoferrate(III) and

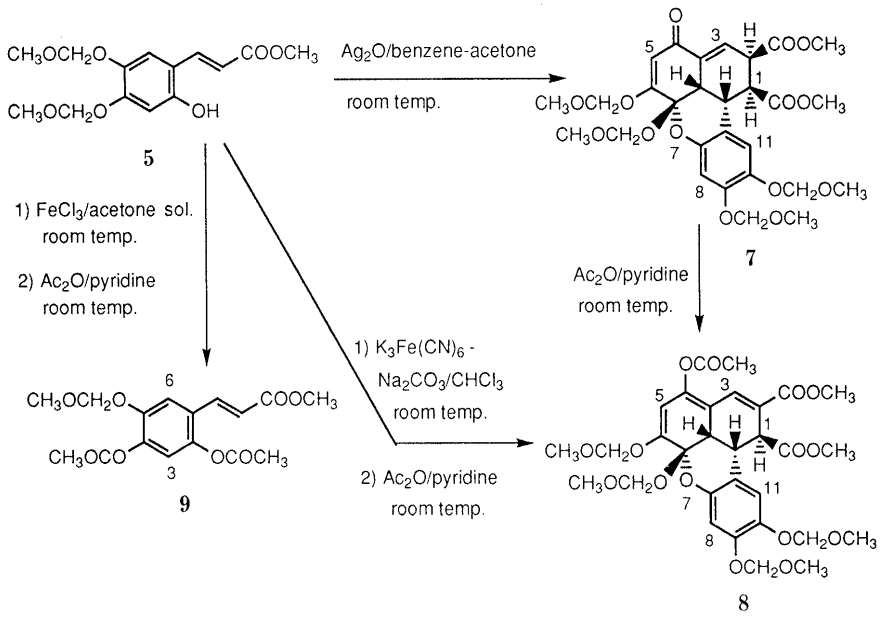
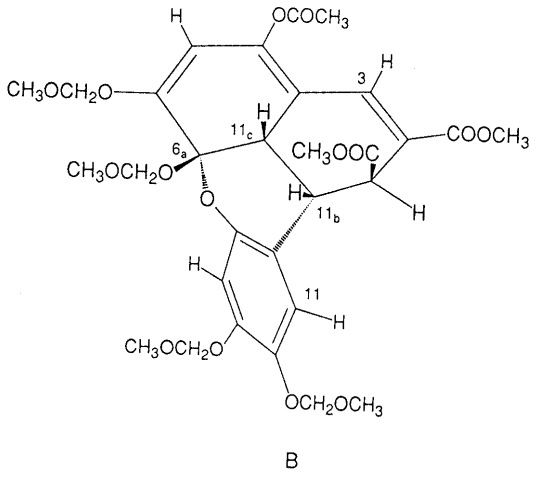


Chart 2. Oxidative Coupling Reaction of Methyl 2-Hydroxy-4,5-bis(methoxymethoxy)cinnamate **5**



B

Fig. 3

aqueous 1% Na_2CO_3 in $CHCl_3$ **5** afforded, after acetylation and subsequent purification by chromatography on silica gel, the enol acetate **8** in 65% yield. When **5** was treated with iron(III) chloride in aqueous acetone and the product was purified in the same way, an acetate **9** was obtained in a low yield (11%). The acetate **9** showed the molecular ion peak (M^+) at *m/z* 338 in the MS. The ^{1}H-NMR spectrum of **9** exhibited methyl and methylene proton signals due to only one MOM group, and two methyl proton signals due to two acetyl groups, which indicated that **9** is the diacetate of a product derived from **5** by partial demethoxymethylation. The position of the removed MOM group was identified by the comparison of the ^{13}C-NMR chemical shifts with the values calculated from the substituent parameters.[17,18] In the case of the 4-acetoxy-5-methoxymethoxy derivative, the calculated chemical shifts of C-3 and C-6 were δ 115.0 and 112.4, respectively, while in the case of the 4-methoxymethoxy-5-acetoxy derivative they were δ 107.1 and 120.3, respectively. The observed chemical shift values, 117.9 and 114.1, correspond more closely to the former case. Thus compound **9** was concluded to be 2,4-diacetoxy-5-(methoxymethoxyphenyl)propenoate.

The oxidative coupling reaction of the 2-hydroxycinnamate derivative **5** with two bulky methoxymethoxy groups at the 4 and 5 positions using silver oxide or potassium hexacyanoferrate(III) afforded the lignan **7**, as expected. As reported previously,[3] the oxidation of the 4,5-dihydroxy-2-methoxycinnamate gave a benzo[*kl*]xanthene derivative **13** as a minor product, of which formation is comparable with that of **7**. A possible mechanism for the formation of **7** is shown in Chart 3. The mutual coupling of the R-β radical, produced from the initially formed RO radical, would yield a dimer **10**, of which partial aromatization gives a phenolic intermediate **11**. Its cyclization *via* the hetero Diels–Alder type reaction or the Michael reaction followed by bond formation between the resultant enolate and the alkoxy carbocation affords the dienol **12**, which isomerizes to **7**.

The oxidative coupling reaction of **6** (obtained from daphnetin) treated with silver oxide afforded, after acetylation and purification by chromatography on silica gel, a product **14** in a low yield. The molecular formula $C_{30}H_{36}O_{15}$ of the acetate **14** as determined by elemental analysis and MS measurement was the same as that of the acetate **8**. The ^{1}H-NMR spectrum of **14** closely resembled that of **8**, which suggested a tetrahydrobenzoxanthene structure. In the ^{1}H-NMR spectrum of **14**, double doublets with $J=5$ and 1 Hz were observed at δ 5.02. From analysis of the COSY spectrum, this proton signal was correlated with the 11c-H and 3-H proton signals and it was assigned as 6a-H. Thus, the product was formulated as **14**. The H-1 bond was assumed to be *quasi*-equatorial on the basis of the lack of allylic coupling between H-1 and H-3. NOE effects were observed between the signals of H-1 and H-11, H-1 and H-11b, H-11b and H-11c, H-11c and H-6a, respectively. Thus, the H-11b and H-6a bonds are *quasi*-equatorial, and the H-11c bond is *quasi*-axial. The dihedral angles between the C-1–H-1 and

C-11b–H-11b bonds (around 70°), the C-11b–H-11b and C-11c–H-11c bonds (around 50°), and the C-11c–H-11c and C-6a–H-6a bond (around 50°) are consistent with the observed coupling constants ($J_{H1-H11b}=2$ Hz, $J_{H11b-H11c}=5$ Hz, $J_{H11c-H6a}=5$ Hz), respectively. Consequently compound **14** was concluded to have the *r*-1, *trans*-11b, *trans*-11c, *trans*-6a configuration.

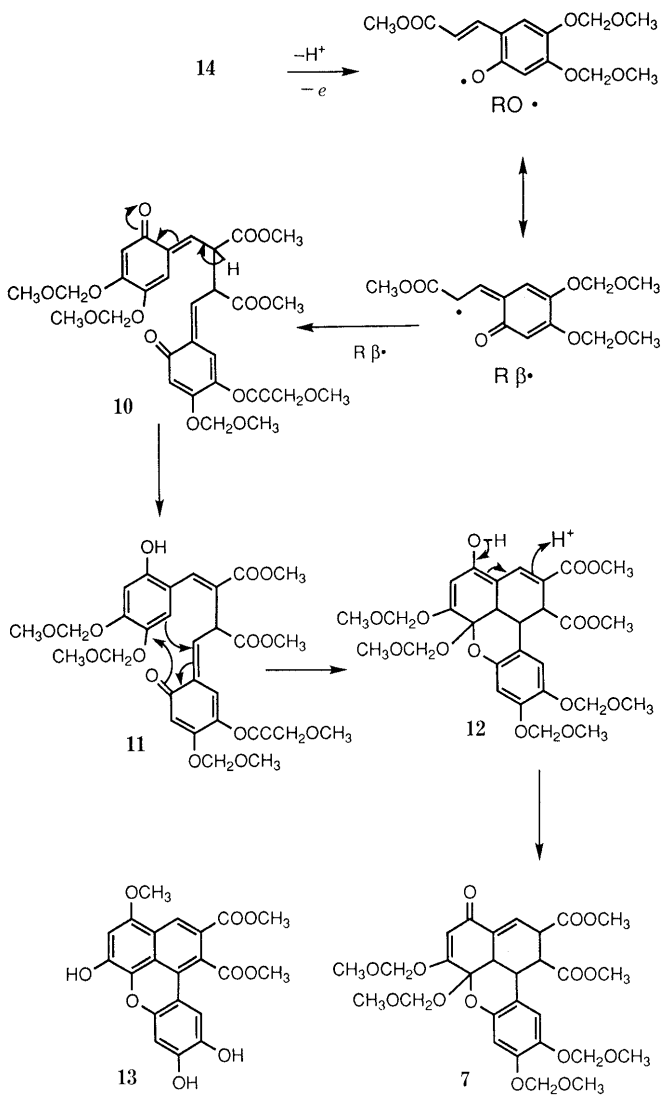


Chart 3. Proposed Mechanism for the Formation of **7**

Subsequently the oxidative coupling reaction of **6** was carried out using potassium hexacyanoferrate(III) and iron(III) chloride. Treatment of **6** with potassium hexacyanoferrate(III) and aqueous 1% Na_2CO_3 in $CHCl_3$, followed by acetylation and purification of the acetate by chromatography on silica gel, also afforded the tetrahydrobenzoxanthene **14** in 21% yield. On the other hand, when **6** was exposed to iron(III) chloride in aqueous acetone and the product was purified by chromatography on silica gel, **15** was obtained in 33% yield. The results of MS measurement and ^{1}H-NMR analysis indicated that **15** was merely a product of partial demethoxymethoxylation, as observed in the iron(III) chloride oxidation of **5**. Since the COLOC spectrum of **15** revealed a correlation between the signals of one hydroxy proton (δ 6.25) and the aromatic carbon at the 2 position (δ 144.8) bearing another hydroxy group, the remaining MOM group was confirmed to be

Table 1. Inhibitory Effects of Benzoxanthene Derivatives on Lipid Peroxidation in Rat Brain Homogenate

Compound	Inhibition (%)	
	10^{-4} M	10^{-5} M
7	96	50
8	85	30
14	57	7
Idebenone	93	27

Table 2. Inhibitory Effects of Benzoxanthene Derivatives on Lipid Peroxidation in Rat Liver Microsome

Compound	IC_{50} (10^{-6} M)[a]
7	31.4 (29.4—33.7)
8	43.1 (41.4—44.8)
13	0.95 (0.87—1.04)[b]
Schizotenuin A	36.3 (33.5—39.8)[c]
(±)-α-Tocopherol	976 (880—1149)

a) IC_{50} values and their 95% confidence limits were calculated through probit analysis by using set of 4 determinations at 3—4 different concentrations (geometric ratio = 1.4) for each compound. *b*) Ref. 3. *c*) Ref. 2.

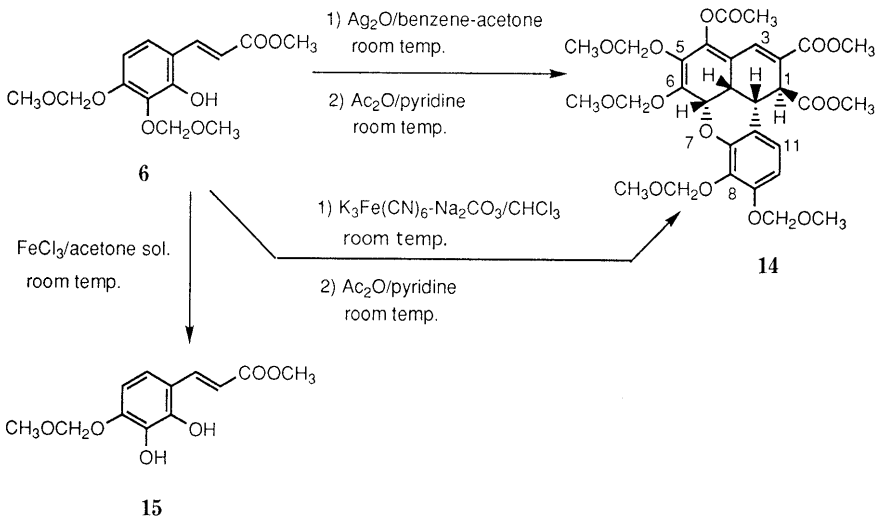


Chart 4. Oxidative Coupling Reaction of Methyl 2-Hydroxy-3,4-bis(methoxymethoxy)cinnamate **6**

located at the 4 position.

Inhibitory Effect on Lipid Peroxidation We tested compounds **7**, **8** and **14** for inhibitory activity on lipid peroxidation in rat brain homogenate and rat liver microsomes according to the method described in a previous paper.[2] The results are summarized in Tables 1 and 2.

Among the three compounds tested in rat brain homogenate, **7** and **8** showed similar inhibitory activities to that of idebenone, a standard nootropic drug. When the former two compounds were further tested in rat liver microsomes, their activity was found to be more potent than that of (±)-α-tocopherol and comparable to that of schizotenuin A[2] (a major bioactive component of *Schizonepeta tenuifolia* BRIQ.), but lower than that of the benzoxanthene derivative **13**.[3]

In summary, the oxidative coupling reaction of 2-hydroxycinnamate derivatives, obtained from coumarins, was investigated. It was found that the reactivity contrasted markedly to that of 4 hydroxycinnamates. Although simple derivatives such as 3-(2-hydroxyphenyl)- or 3-(2-hydroxy-4-methoxyphenyl)cinnamates afforded lignin-like polymers, the oxidation of the 2-hydroxyphenylcinnamates with 4,5- or 3,4-bismethoxymethoxy groups was controlled in such a way that the oxotetrahydrobenzoxanthene derivatives or, after acetylation, the corresponding enol acetates were generated. These products exhibited moderate inhibitory activity against lipid peroxidation. Further examination of the biological activities of the synthetic lignans is in progress.

Experimental

Details of the analytical procedures used and the evaluation method for inhibitory effects on lipid peroxidation are given in Parts I and III of this series of papers.[2,3]

Oxidative Coupling Reaction of Methyl (*E*)-3-(2-Hydroxyphenyl)-propenoate (1) Silver oxide (3.9 g, 16.8 mmol) was added to a solution of **1**[19] (5.0 g, 28.1 mmol) in benzene–acetone (150 ml, 2 : 1) under nitrogen atmosphere and the mixture was stirred at room temperature for 4 d. The suspension was filtered and the filtrate was evaporated to dryness. The residue was dissolved in MeOH, then concentrated, and the precipitate formed was collected by filtration and dried to give **2** (4.2 g) as a brownish yellow powder, mp 180—186 °C. Average molecular weight determined by means of GPC ($\bar{M}w$): 10995. IR ($CHCl_3$): 1712 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.00—4.50 (br s), 6.00—8.30 (m).

Oxidative Coupling Reaction of Methyl (*E*)-3-(2-Hydroxy-4-methoxyphenyl)propenoate (3) Compound **3**[20] (5.0 g, 24.0 mmol) was dissolved in benzene–acetone (150 ml, 2 : 1) and the solution was stirred with silver oxide (5.6 g, 24.2 mmol) under nitrogen atmosphere at room temperature for 4 d. The suspension was filtered and the filtrate was evaporated to leave a residue, which was chromatographed on silica gel. The *n*-hexane–AcOEt (3 : 1) eluate afforded unchanged **3**. The CH_2Cl_2–EtOH (95 : 5) eluate was concentrated, and ether was added. The precipitate was collected by filtration and dried, giving **4** (2.5 g) as a yellow powder, mp 186—193 °C, average molecular weight determined by means of GPC ($\bar{M}w$): 1972. IR ($CHCl_3$): 3328 (OH), 1709 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.00—4.00 (br s), 5.50—8.20 (m).

Oxidative Coupling Reaction of Methyl (*E*)-3-[2-Hydroxy-4,5-bis-(methoxymethoxy)phenyl]propenoate (5) with Silver Oxide To a solution of **5**[3] (3.0 g, 10.1 mmol) in benzene–acetone (90 ml, 2 : 1) was added silver oxide (1.4 g, 6.0 mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 24 h, then filtered and the precipitate was sufficiently washed with acetone. The filtrate and the washing were combined, and evaporated to dryness. The residue was purified by chromatography on silica gel (*n*-hexane–AcOEt, 5 : 2 then 1 : 1) and recrystallized from ether, giving dimethyl 6,6a,9,10-tetramethoxymethoxy-4-oxo-*r*-1,*c*-2,4,6a,*t*-11b,*t*-11c-hexahydrobenzo(*kl*)-xanthene-1,2-dicarboxylatec (**7**) (1.7 g, 56%) as yellow-white needles, mp 116—117 °C. IR (KBr): 1743 (C=O), 1672 (conjugated C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.08 (3H, s, 6a-$OCH_2OC\underline{H}_3$), 3.16 (1H, m, 11c-H), 3.18 (1H, m, 2-H), 3.48 (3H, s, 10-$OCH_2OC\underline{H}_3$), 3.52 (3H, s, 9-$OCH_2OC\underline{H}_3$), 3.53 (3H, s, 6-$OCH_2OC\underline{H}_3$), 3.72 (3H, s, 1-$COOCH_3$), 3.76 (3H, s, 2-$COOCH_3$), 3.99 (1H, m, 1-H), 4.04 (1H, m, 11b-H), 5.13 (2H, ABq, J=10 Hz, 6a-$OC\underline{H}_2OCH_3$), 5.13 (2H, s, 9-$OC\underline{H}_2OCH_3$), 5.14 (2H, s, 10-$OC\underline{H}_2OCH_3$), 5.20 (2H, s, 6-$OC\underline{H}_2OCH_3$), 5.70 (1H, s, 5-H), 6.70 (1H, s, 8-H), 7.10 (1H, s, 11-H), 7.30 (1H, m, 3-H). ^{13}C-NMR ($CDCl_3$) δ: 31.4 (C11b), 37.8 (C2), 39.4 (C11c), 43.2 (C1), 52.4 (1, 2-$COO\underline{C}H_3$), 56.2 (9, 10-$OCH_2O\underline{C}H_3$), 56.3 (6a-$OCH_2O\underline{C}H_3$), 57.3 (6-$OCH_2O\underline{C}H_3$), 92.8 (6a-$O\underline{C}H_2OCH_3$), 95.0 (6-$O\underline{C}H_2OCH_3$), 95.1 (10-$O\underline{C}H_2OCH_3$), 95.7 (C6a), 96.5 (9-$O\underline{C}H_2OCH_3$), 105.5 (C8), 105.8 (C5), 112.6 (C11a), 114.8 (C11), 129.6 (C3a), 133.3 (C3), 142.5 (C9), 147.2 (C7a), 147.8 (C10), 169.0 (C6), 171.2 (2-$\underline{C}OOCH_3$), 171.9 (1-$\underline{C}OOCH_3$), 184.9 (C4). *Anal.* Calcd for $C_{28}H_{34}O_{14}$: C, 56.55; H, 5.78. Found: C, 56.56; H, 5.93. MS *m/z*: 594 (M^+).

Dimethyl 4-Acetoxy-6,6a,9,10-tetramethoxymethoxy-*r*-1,6a,*t*-11b,*t*-11c-tetrahydrobenzo(*kl*)xanthene-1,2-dicarboxylate (8) Silver oxide (0.47 g, 2.03 mmol) was added to a solution of **5** (1.0 g, 3.35 mmol) in benzene–acetone (30 ml, 2 : 1) at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h and at room temperature for another 3 h, then filtered and the precipitate was sufficiently washed with acetone. The filtrate and the washing were combined, and the mixture was evaporated to dryness. The residue was dissolved in dry pyridine (6 ml) and acetic anhydride (5 ml, 0.05 mol), and the mixture was stirred at room temperature for 22 h, then poured into ice-water. The precipitate formed was dissolved in AcOEt. The solution was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by chromatography on silica gel (*n*-hexane–AcOEt, 5 : 3 then 1 : 1) and recrystallized from MeOH, giving **8** (0.56 g, 53%) as yellow white needles, mp 134—136 °C. IR (KBr): 1768 (CH_3CO_2C=C–), 1735 (CO_2CH_3), 1700 (–C=C–CO_2CH_3) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s, CH_3CO), 3.18 (3H, s, 6a-$OCH_2OC\underline{H}_3$), 3.41 (1H, br d, J=5 Hz, 11c-H), 3.45 (3H, s, 9-$OCH_2OC\underline{H}_3$), 3.48 (3H, s, 10-$OCH_2OC\underline{H}_3$), 3.51 (3H, s, 6-$OCH_2OC\underline{H}_3$), 3.74 (3H, s, 1-$COOCH_3$), 3.76 (3H, s, 2-$COOCH_3$), 3.98 (1H, ddd, J=1, 2, 5 Hz, 11b-H), 4.61 (1H, d, J=2 Hz, 1-H), 5.07 (2H, s, 10-$OC\underline{H}_2OCH_3$), 5.08 (2H, ABq, J=7 Hz, 6a-$OC\underline{H}_2OCH_3$), 5.13 (2H, s, 9-$OC\underline{H}_2OCH_3$), 5.14 (2H, s, 6-$OC\underline{H}_2OCH_3$), 5.45 (1H, s, 5-H), 6.67 (1H, s, 8-H), 6.97 (1H, br s, 11-H), 7.37 (1H, d, J=1 Hz, 3-H). ^{13}C-NMR ($CDCl_3$) δ: 20.6 ($\underline{C}H_3CO$), 32.0 (C11c), 37.3 (C11b), 42.3 (C1), 51.9 (2-$COO\underline{C}H_3$), 52.6 (1-$COO\underline{C}H_3$), 56.1 (10-$OCH_2O\underline{C}H_3$), 56.2 (9-$OCH_2O\underline{C}H_3$), 56.4 (6a-$OCH_2O\underline{C}H_3$), 56.9 (6-$OCH_2O\underline{C}H_3$), 92.7 (6a-$O\underline{C}H_2OCH_3$), 94.9 (6-$O\underline{C}H_2OCH_3$), 95.2 (9-$O\underline{C}H_2OCH_3$), 96.4 (10-$O\underline{C}H_2OCH_3$), 97.1 (C6a), 99.3 (C5), 104.7 (C8), 112.7 (C3a), 112.9 (C11a), 115.0 (C11), 121.6 (C2), 131.1 (C3), 141.6 (C10), 146.6 (C4), 147.2 (C9), 149.0 (C7a), 157.6 (C6), 166.9 (2-$\underline{C}OOCH_3$), 168.2 ($CH_3\underline{C}O$), 172.3 (1-$\underline{C}OOCH_3$). *Anal.* Calcd for $C_{30}H_{36}O_{15}$: C, 56.59; H, 5.71. Found: C, 56.60; H, 5.78. MS *m/z*: 636 (M^+).

Oxidative Coupling Reaction of 5 with Potassium Hexacyanoferrate(III) To a solution of **5** (1.0 g, 3.35 mmol) in $CHCl_3$ (200 ml) at 0 °C under nitrogen atmosphere was added dropwise a solution of potassium hexacyanoferrate(III) (1.1 g, 3.34 mmol), and Na_2CO_3 (0.53 g, 5.00 mmol) in water (50 ml). The mixture was stirred at 0 °C for 1 h and at room temperature for another 1 h, then the organic layer was separated and the water layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was dissolved in dry pyridine (6 ml) and acetic anhydride (5 ml, 0.05 mol), and the mixture was stirred at room temperature for 17 h, then poured into ice-water. The precipitate formed was dissolved in AcOEt. This solution was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was recrystallized from MeOH, giving **8** (0.70 g, 65%).

Oxidative Coupling Reaction of 5 with Iron(III) Chloride A solution of iron(III) chloride heptahydrate (1.8 g, 6.66 mmol) in water (30 ml) was added dropwise to a solution of **5** (2.0 g, 6.70 mmol) in acetone–water (90 ml, 2 : 1) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 47 h, and then water was added. The whole was extracted with AcOEt and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was dissolved in dry pyridine (12 ml) and acetic anhydride (10 ml, 0.1 mol), and the mixture was stirred at room temperature for 18 h, then poured into ice-water. The precipitate formed was dissolved in AcOEt. This solution was washed with brine, dried over $MgSO_4$, and evapo-

rated to dryness. The residue was chromatographed on silica gel (CH_2Cl_2–EtOH, 99.5:0.5) and the first eluate was recrystallized from MeOH, giving methyl (*E*)-3-(2,4-diacetoxy-5-methoxymethoxyphenyl)-propenoate (**9**) (0.24 g, 11%) as colorless needles, mp 124—125 °C. IR (KBr): 1767, 1753, 1708 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.31, 2.35 (each 3H, s, $CH_3CO \times 2$), 3.48 (3H, s, CH_2OCH_3), 3.80 (3H, s, $=CHCOOCH_3$), 5.17 (2H, s, CH_2OCH_3), 6.41 (1H, d, J=16 Hz, $=CHCOOCH_3$), 6.91 (1H, s, 3-H), 7.45 (1H, s, 6-H), 7.68 (1H, d, J=16 Hz, Ar-CH=). ^{13}C-NMR ($CDCl_3$) δ: 20.5, 20.8 ($CH_3CO \times 2$), 51.8 ($COOCH_3$), 56.2 (OCH_2OCH_3), 95.2 (OCH_2OCH_3), 114.1 (C6), 117.9 (C3), 120.0 ($=CHCOOCH_3$), 125.3 (C1), 137.4 (Ar-CH=), 142.0 (C4), 143.4 (C2), 147.1 (C5), 166.9 ($=CHCOOCH_3$), 168.2, 169.0 ($CH_3CO \times 2$). MS *m/z*: 338 (M^+).

Oxidative Coupling Reaction of Methyl (*E*)-3-[2-Hydroxy-3,4-bis-(methoxymethoxy)phenyl]propenoate (6) with Silver Oxide Silver oxide (0.65 g, 2.80 mmol) was added to a solution of **6**[4] (1.4 g, 4.69 mmol) in benzene–acetone (45 ml, 2:1) at 0 °C under nitrogen atmosphere and the mixture was stirred at room temperature for 48 h, then filtered. The precipitate was sufficiently washed with acetone. The filtrate and the washing were combined, and the mixture was evaporated to dryness. The residue was dissolved in dry pyridine (12 ml) and acetic anhydride (10 ml, 0.10 mol), and the mixture was stirred at room temperature for 17 h, then poured into ice-water. The precipitate formed was dissolved in AcOEt. The solution was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was chromatographed on silica gel (*n*-hexane–AcOEt, 5:3) and the first eluate gave the acetate of **6** (0.34 g), and the second eluate was recrystallized from ether to give dimethyl 4-acetoxy-5,6,8,9-tetramethoxymethoxy-*r*-1,*t*-6a,*t*-11b,*t*-11c-tetrahydrobenzo(*kl*)xanthene-1,2-dicarboxylate (**14**) (0.23 g, 15%) as yellow prisms, mp 110—112 °C. IR (KBr): 1779, 1734 (C=O), 1700 (CH=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s, CH_3CO), 3.22 (1H, t, J=5 Hz, 11c-H), 3.46 (3H, s, 6-OCH_2OCH_3), 3.51 (3H, s, 5-OCH_2OCH_3), 3.55 (each 3H, s, 8 and 9-OCH_2OCH_3), 3.75 (3H, s, 1-$COOCH_3$), 3.78 (3H, s, 2-$COOCH_3$), 3.91 (1H, ddd, J=1, 2, 5 Hz, 11b-H), 4.66 (1H, d, J=2 Hz, 1-H), 4.96 (2H, ABq, J=6 Hz, 5-OCH_2OCH_3), 5.02 (1H, dd, J=1, 5 Hz, 6a-H), 5.03 (2H, ABq, J=6 Hz, 8-OCH_2OCH_3), 5.13 (2H, d, J=1 Hz, 9-OCH_2OCH_3), 5.22 (2H, ABq, J=6 Hz, 6-OCH_2OCH_3), 6.62 (1H, d, J=9 Hz, 10-H), 6.81 (1H, br d, J=9 Hz, 11-H), 7.32 (1H, m, 3-H). ^{13}C-NMR: ($CDCl_3$) δ: 20.3 (CH_3CO), 32.3 (C11c), 34.3 (C11b), 42.9 (C1), 52.0 (2-$COOCH_3$), 52.7 (1-$COOCH_3$), 56.1 (6-OCH_2OCH_3), 56.8 (9-OCH_2OCH_3), 57.0 (8-OCH_2OCH_3), 57.2 (5-OCH_2OCH_3), 71.3 (C6a), 95.2 (6-OCH_2OCH_3), 95.7 (9-OCH_2OCH_3), 98.2 (5-OCH_2OCH_3), 98.6 (8-OCH_2OCH_3), 108.4 (C10), 114.3 (C11a), 114.4 (C3a), 120.4 (C11), 123.1 (C2), 130.6 (C3), 133.7 (C5), 134.3 (C8), 143.4 (C6), 144.3 (C4), 149.3 (C7a), 149.9 (C9), 166.8 (2-$COOCH_3$), 167.7 (CH_3CO), 172.4 (1-$COOCH_3$). *Anal.* Calcd for $C_{30}H_{36}O_{15}$: C, 56.59; H, 5.71. Found: C, 56.50; H, 5.71. MS *m/z*: 636 (M^+).

Oxidative Coupling Reaction of 6 with Potassium Hexacyanoferrate(III) A solution of potassium hexacyanoferrate(III) (1.1 g, 3.34 mmol) and anhydrous Na_2CO_3 (0.53 g, 5.00 mmol) in water (50 ml) was added dropwise to a solution of **6** (1.0 g, 3.35 mmol) in $CHCl_3$ (200 ml) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 28 h, then a further amount of potassium hexacyanoferrate(III) (0.55 g, 1.67 mmol) and anhydrous Na_2CO_3 (0.53 g, 5.00 mmol) dissolved in water (50 ml) was added and the whole was stirred at room temperature for 17 h. The organic layer was separated and the water layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was dissolved in dry pyridine (6 ml) and acetic anhydride (5 ml, 0.05 mol), and the mixture was stirred at room temperature for 18 h, then poured into ice-water. The precipitate formed was dissolved in AcOEt. This solution was washed with brine, dried over $MgSO_4$, and evaporated to leave a residue, which was chromatographed on silicagel (*n*-hexane–AcOEt, 5:3). The first eluate gave the acetate of **6** (0.28 g), and the second eluate was recrystallized from ether, giving **14** (0.22 g, 21%).

Oxidative Coupling Reaction of 6 with Iron(III) Chloride To a solution of **6** (2.0 g, 6.70 mmol) in acetone–water (80 ml, 3:1) was added dropwise a solution of iron(III) chloride heptahydrate (1.1 g, 4.07 mmol) in water (20 ml) at 0 °C under nitrogen atmosphere and the mixture was stirred at room temperature for 26 h. Water was added, then the whole was extracted with AcOEt and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was chromatographed on silica gel (*n*-hexane–AcOEt, 5:3). The first eluate gave unchanged **6** (0.64 g), and the second eluate was recrystallized from benzene to give methyl (*E*)-3-[2,3-bis(hydroxy-4-methoxymethoxy)-phenyl]propenoate (**15**) (0.56 g, 33%) as colorless prisms, mp 92—94 °C. IR (KBr): 3401 (OH), 1697 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.52 (3H, s, CH_2OCH_3), 3.80 (3H, s, $=CHCOOCH_3$), 5.19 (2H, s, CH_2O-CH_3), 6.25 (1H, s, 2-OH), 6.49 (1H, s, 3-OH), 6.57 (1H, d, J=16 Hz, $=CHCOOCH_3$), 6.66 (1H, d, J=9 Hz, 5-H), 6.96 (1H, d, J=9 Hz, 6-H), 7.89 (1H, d, J=16 Hz, Ar-CH=). ^{13}C-NMR ($CDCl_3$) δ: 51.6 ($COOCH_3$), 56.5 (OCH_2OCH_3), 95.9 (OCH_2OCH_3), 107.9 (C5), 116.5 (C1), 117.0 ($=CHCOOCH_3$), 120.5 (C6), 133.4 (C3), 140.2 (Ar-CH=), 144.8 (C2), 146.1 (C4), 168.4 ($=CHCOOCH_3$). *Anal.* Calcd for $C_{12}H_{14}O_6$: C, 56.68; H, 5.56. Found: C, 56.78; H, 5.53. MS *m/z*: 254 (M^+).

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