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Studies on the Preparation of Bioactive Lignans by Oxidative Coupling Reaction. II.[1] Oxidative Coupling Reaction of Methyl (*E*)-3-(4,5-Dihydroxy-2-methoxyphenyl)propenoate and Lipid Peroxidation Inhibitory Effects of the Produced Lignans

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The oxidative coupling reaction of methyl (*E*)-3-(4,5-dihydroxy-2-methoxyphenyl)propenoate (10), obtainable from esculetin, has been studied using silver oxide and potassium hexacyanoferrate(III). The products were separated, after acetylation, by silica gel column chromatography. 1-Aryl-1,2-dihydronaphthalene derivative 12 was obtained as a major product, accompanied by the benzo[*kl*]xanthene derivative 13. In the oxidation with silver oxide, a benzodioxane compound 14a was produced additionally in a minor amount. Thus, the course of the reaction differed notably from those of ferulic or caffeic acid derivatives.

The compounds 11, 12, 13 and 14a were tested for their inhibitory effects on lipid peroxidation in rat brain homogenate and rat liver microsomes. They showed activities more effective than that of idebenone in rat brain homogenate, and were found to be more potent than benzofuran lignans 4 and 5, and much more potent than (±)-α-tocopherol in rat liver microsomes.

Keywords lignan; oxidative coupling reaction; lipid peroxidation inhibitor; dihydronaphthalene; benzoxanthene; benzodioxane

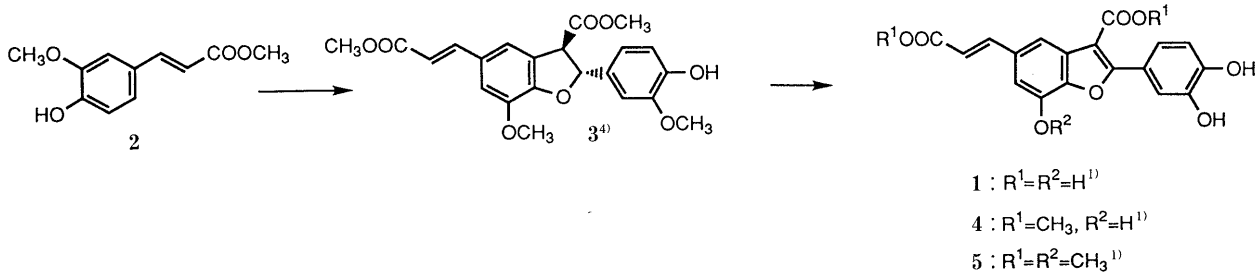
In the previous paper,[1] we reported that an efficient synthesis of benzofuran lignan **1**, the parent compound of schizotenuin A, C_1, C_2 was achieved *via* a dihydrobenzofuran derivative **3**, obtained by the oxidative coupling reaction of methyl ferulate (**2**), and that its derivatives **4** and **5** possessed the strong inhibitory effect on lipid peroxidation.

On the basis of these results, we decided to synthesize the polyphenolic lignans by the oxidative coupling of hydroxycinnamic acid derivatives and to provide them for biological screening, thereby contributing to the search for compounds with more potent activity. As a source of the requisite polyhydroxycinnamic acid derivatives we focused on the coumarins,[2] which represent a prevailing group of natural polyphenols and for which a number of synthetic methods have been established. A ring opening of the latter compound would provide the former. Although there have been many reports on the oxidative coupling reaction of hydroxycinnamic acid derivatives, *e.g.* methyl ferulate,[3,4] methyl *p*-hydroxycinnamate,[5] ferulic acid,[6] sinapic acid,[7] methyl caffeate,[8,9] and methyl sinapiate,[10] to our best knowledge, the oxidative reaction of those with 2-oxy-substituents has never been reported. Thus, it would be significant to examine the type of the lignans formed and to test their biological activity. Since oxidative coupling is a general reaction in plants and its linkage with the biosynthesis of coumarins is possible, our synthetic products might prove in the future to be minor biologically active constituents in plants containing coumarins. Our first candidate was esculetin (**6**), a representative of biologically active coumarins in Chinese crude drugs,[11] from which the hydroxycinnamic acid derivative **10**, related to caffeic acid, would be obtained.

Synthesis

Esculetin (**6**)[12] was treated with sodium hydride and chloromethyl methyl ether in tetrahydrofuran (THF)–dimethylformamide (DMF) to give bismethoxymethyl esculetin (**7**) in 90% yield. Compound **7** was subjected to the opening of the coumarin ring using sodium methoxide in dry MeOH to afford the methyl ester **8** in 90% yield. The phenolic hydroxy group of **8** was then methylated, and the product **9**, obtained in 97% yield, was deprotected by treatment with a catalytic amount of acid to give the desired substrate **10** in 76% yield.

The oxidative coupling reaction has been studied with various one electron oxidizing agents such as potassium hexacyanoferrate(III), iron(III) chloride, silver oxide,



1 : $R^1=R^2=H$[1]

4 : $R^1=CH_3$, $R^2=H$[1]

5 : $R^1=R^2=CH_3$[1]

Chart 1

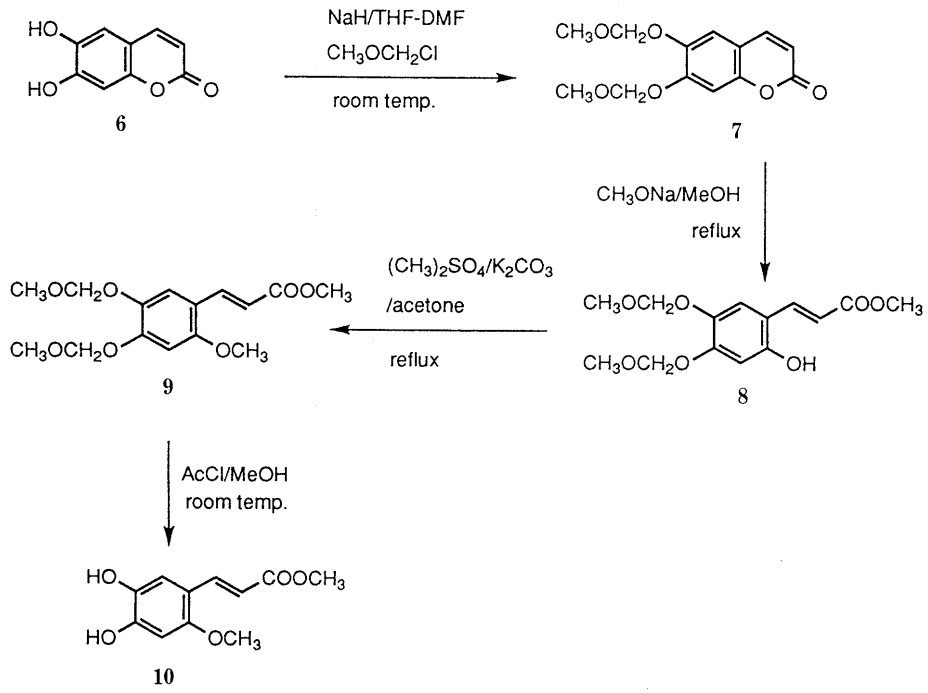


Chart 2

manganese oxide, lead tetraacetate, hydrogen peroxide and peroxidases (horseradish peroxidase).[13] We examined the reaction with silver oxide, potassium hexacyanoferrate(III) and iron(III) chloride, because these are generally used for the reaction of hydroxycinnamic acid analogues.[3-10] Firstly, **10** was treated with 0.6-fold molar eq of silver oxide in benzene–acetone at room temperature. The crude products were then acetylated with acetic anhydride in pyridine, and separated by chromatography on silica gel to afford **12**, **13**, **14a** and **15** in 28%, 10%, 3% and 2% yields, respectively. When the products of the above reaction were chromatographed on silica gel without acetylation, **11** was obtained in 22% yield.

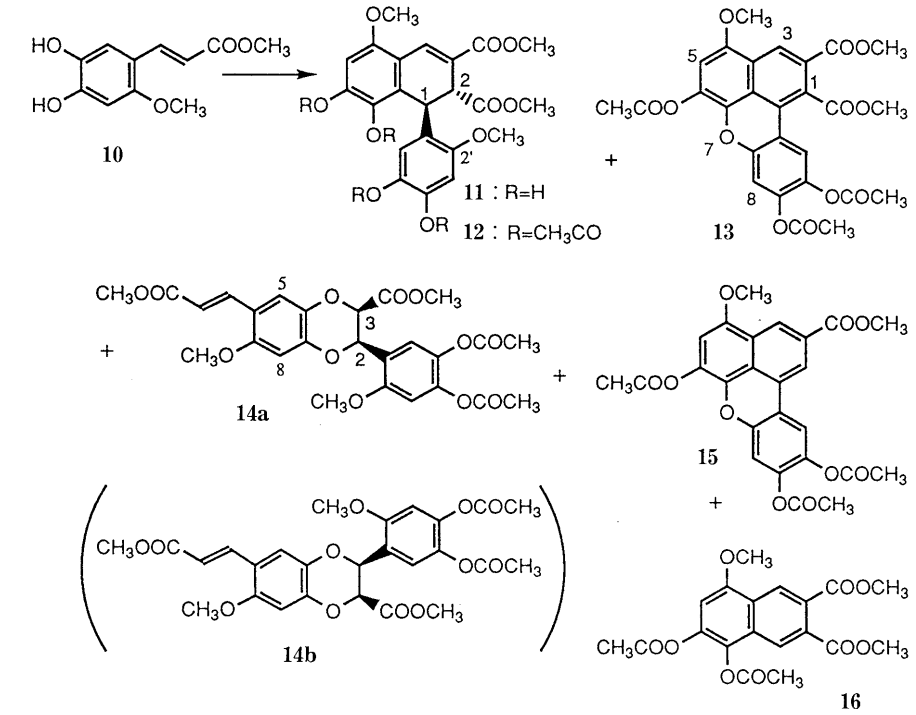
The molecular formula of **11** was determined to be $C_{22}H_{22}O_{10}$ by elemental analysis and MS measurement [*m/z*: 446 (M^+)], indicating that **11** is a dimer of **10**. In the ^{1}H-NMR spectrum of **12**, the acetate of **11**, in which a typical AB type signal due to protons of the (*E*)-propenoate chain disappeared, the presence of proton signals due to four acetyl (δ 2.09, 2.15, 2.22, 2.23), two methyl ester (δ 3.63, 3.75) and two methoxy (δ 3.88, 3.90) groups were indicated. These spectral data suggested that **11** would represent the dimer formed by the mutual combination of **10** at 2 positions on (*E*)-propenoate chains and that the oxygen radical did not participate in the dimerization reaction. Moreover, **11** was deduced to be tricyclic from the molecular formula, provided that one additional double bond is present other than those of the two aryl groups, as revealed by the ^{1}H- and ^{13}C-NMR spectra of **11** and **12**. The presence of only three aromatic protons indicated one bonding site located on an aryl ring, and the other was presumed to be the β carbon of a propenoate chain. Thus, the oxidation product **11** was inferred to have a 1-phenyl-1,2-dihydronaphthalene ring, and this deduction was fully supported by the ^{1}H- and ^{13}C-NMR data. The ^{1}H-NMR spectrum of **11** exhibited signals due to the vicinal protons at C-1 and C-2 at δ 5.31 and 3.99, respectively, and a vinyl proton signal at a highly deshielded position (δ 8.02). The coupling constant of the former signals (J = 1 Hz) indicates that the configuration of the aryl and the methoxycarbonyl groups is *trans*.[9,14,15] There have been many reports about the naturally occurring analogs of **11**. Magnoshinin (**17**) was isolated from *Magnolia salicifolia* Maxim. (Japanese name: shin-i)[14] which is used in traditional Chinese medicine. Thomasic acid (**18**)[16] and thomasidioic acid (**19**)[17] were isolated from *Ulmus thomasil* Sarg. And rabdosiin (**20**)[9] was isolated from *Rabdosia japonica* Hara (Japanese name: enmeiso) which is used as a common household medicine.

The molecular formula of the second acetate **13** was assigned to be $C_{27}H_{22}O_{12}$ from elemental analysis and MS measurement [*m/z*: 538 (M^+)], suggesting that **13** is the acetate of a dimer, similar to the first one **12**. When the ^{1}H-NMR spectra of **12** and **13** were compared, that of **13** contained fewer signals due to acetyl protons and methoxy protons both by one signal, and to a lack of the alicyclic protons of the dihydronaphthalene ring present in **12**. Thus, the aromatization of the dihydronaphthalene and the formation of an ether ring between the hydroxy group of 8 position and the methoxy group of 2′ position in **11** was suggested to occur during oxidative treatment. The benzoxanthene structure for **13** is in consonance with the quantity of hydrogen deficiency in the molecular formula. The ^{13}C-NMR spectrum was also compatible with the structure.

The third acetate **14a** showed a molecular ion peak (M^+) at *m/z* 530 in MS, suggesting it is again the acetate of a dimerized product. The ^{1}H-NMR spectrum of **14a** exhibited proton signals due to two acetyl groups (δ 2.24,

2.28), two methoxy groups (δ 3.82, 3.84) and two vinyl protons of a methyl (*E*)-propenoate chain (δ 6.39, 7.91, both d, $J=16$ Hz). Therefore, the vicinal phenolic hydroxy groups of **10** were assumed to join oxidatively to the double bond of the (*E*)-propenoate chain in the other molecule, forming a benzodioxane ring. In agreement with this assumption, the ^{1}H-NMR spectrum of **14a** showed resonances due to the protons of two methyl ester groups (δ 3.70, 3.78), two methoxy groups (δ 3.82, 3.84), vicinal methine groups and two aromatic protons of the benzodioxane ring (δ 5.73, 4.87 each d, $J=4$ Hz, 2-H and 3-H respectively; δ 7.17, s, 5-H; δ 6.53, s, 8-H), as well as two additional aromatic protons (δ 6.78, s, 3′-H; δ 7.07, s, 6′-H). The ^{13}C-NMR spectrum also corroborated the 2-arylbenzodioxane structure. Discrimination of structure **14a** from the isomeric formula **14b** was secured by the application of ^{1}H–^{13}C-NMR gated decoupling and long-range spin decoupling (LSPD) techniques, in which were observed coupling between signals due to the methine proton of C-2 and the aromatic carbon (C-8a, δ 144.9), and between signals due to the methine proton of C-3 position and the aromatic carbon of (C-4a, δ 135.5). The stereochemical assignment of the dioxane ring in **14a** was possible with reference to the reported ^{1}H-NMR data[18] for the isomeric lignans **23**. The coupling constants of the vicinal methine protons at C-2 and C-3 are 2.9 and 8.2 Hz respectively for *cis* and *trans* derivatives.[18] Accordingly, the stereochemistry of **14a** was reasonably assigned to be *cis* from the coupling constant ($J_{H2-H3}=4$ Hz).

The fourth compound **15** showed a molecular ion peak (M^+) at *m/z* 480 in MS, suggesting it to be the acetyl derivative of a dimerized product. Although the ^{1}H-NMR



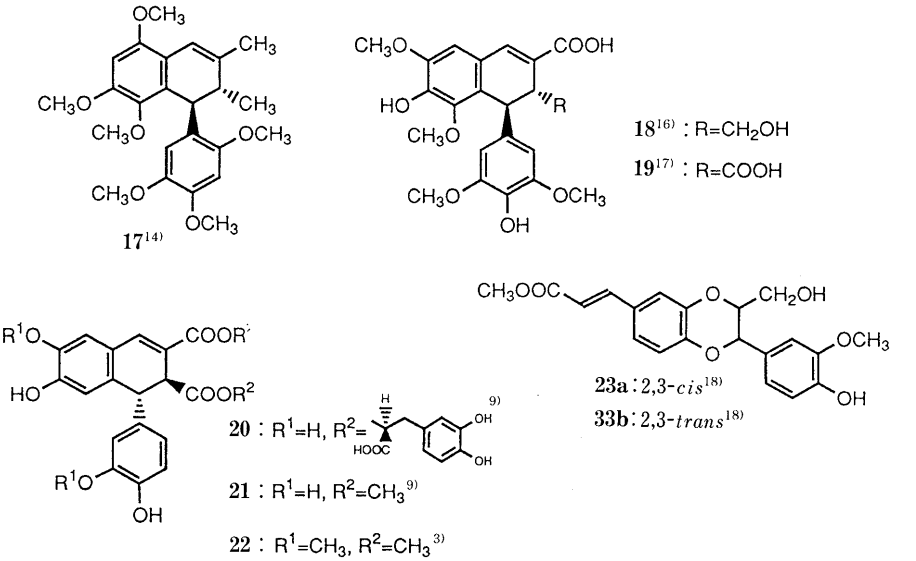


Chart 3

spectrum of **15** closely resembled that of **13**, in the spectrum of the former the disappearance of a signal due to methyl protons of the methoxycarbonyl group joined at C-1, and the presence of a signal due to an additional aromatic proton (1-H) with an *m*-coupling constant (δ 8.06, J=1.4 Hz) were indicated. Thus, **15** was concluded to be a decarbomethoxylation product of **13**.

Next, we examined the oxidative coupling reactions of **10** with potassium hexacyanoferrate(III) in the presence of sodium acetate or sodium carbonate. When **10** was exposed to the agency of 1.2 molar eq of potassium hexacyanoferrate(III) and 5 molar eq of sodium acetate in acetone solution at room temperature, and the products were separated by chromatography on silica gel after acetylation, there were obtained **12**, **13** and **15** in 20%, 2% and 2% yields, respectively. On the other hand, when **10** was treated with the same molar equivalent of potassium hexacyanoferrate(III) and 1.5 molar eq of 1% Na_2CO_3 solution in $CHCl_3$ at room temperature, and the products were separated in the same way as above, they afforded **12**, **13** and **16** in 13%, 2% and 2% yields, respectively.

The molecular formula of **16** was determined to be $C_{19}H_{18}O_9$ by elemental analysis and MS measurement [*m/z*: 390 (M^+)]. The ^{1}H-NMR spectrum of **16** exhibited signals due to two acetyl groups (δ 2.36, 2.46), two methoxycarbonyl groups and a methoxy group (δ 3.95, 3.95, 4.00), and three aromatic protons (δ 6.79, 8.09 and 8.71). In conjunction with the ^{13}C-NMR data, the above evidence suggested **16** should be formulated as a naphthalene derivate **16**, formed from **11** *via* dearylation and acetylation. The treatment of **10** with the same molar equivalent of iron(III) chloride in acetone solution resulted in no reaction at all, even after 48 h. The ^{1}H-NMR and ^{13}C-NMR chemical shift of the dihydronaphthalene derivatives **11**, **12**, and the benzoxanthene derivatives **13**, **15** are summarized in Tables I and II. The product distribution in the oxidative coupling reactions of **10** under various conditions is summarized in Table III.

As for the oxidative coupling reaction of methyl caffeate (**24**), reactions with silver oxide[8] and iron(III) chloride[9] have been reported to give a dihydrobezofuran compound **25** and a dihydronaphthalene compound **21**, respectively. Similarly, in the reaction of methyl ferulate (**2**), the silver oxide[4] gives a dihydrobezofuran compound **3** in 38% yield, and iron(III) chloride[3] is known to afford **3** and a dihydronaphthalene compound **22** in 37% and 31% yields, respectively. In contrast, the salient feature in the oxidative coupling reaction with **10** was the formation of the dihydronaphthalene derivative **11** as the major product, irrespective of the oxidizing agents.

The proposed mechanism for the formation of compounds **3** and **25** by silver oxide oxidation[3,8] and our mechanism for the production of **11** are shown in Charts

TABLE I. ^{13}C-NMR and ^{1}H-NMR Data for Compounds **11** and **12** in $CDCl_3$

Position	**11**	**12**	
	^{1}H-NMR	^{13}C-NMR	^{1}H-NMR
1	5.31 (1H, d, 1)	33.3	5.28 (1H, d, 1)
2	3.99 (1H, d, 1)	43.5	4.02 (1H, d, 1)
3		130.7	
4	8.02 (1H, s)	130.7	8.06 (1H, s)
4a		119.5	
5		154.5	
6	6.54 (1H, s)	105.3	6.79 (1H, s)
7		144.8	
8		133.5	
8a		123.8	
1′		125.8	
2′		154.0	
3′	6.49 (1H, s)	106.0	6.74 (1H, s)
4′		141.4	
5′		134.9	
6′	6.00 (1H, s)	122.9	6.18 (1H, s)
OCO$\underline{CH_3}$		19.8, 20.5, 20.7, 20.8	2.09, 2.15, 2.22, 2.23 (each, 3H, s)
5-OCH$_3$	3.61, 3.70, 3.77, 3.83 (each 3H, s)	55.9	3.88, 3.90 (each, 3H, s)
2′-OCH$_3$		56.1	
2-COO$\underline{CH_3}$		52.5	3.63 (3H, s)
3-COO$\underline{CH_3}$		51.9	3.75 (3H, s)
O$\underline{C}$OCH$_3$		167.5, 167.7, 168.0, 168.0	
2-$\underline{C}$OOCH$_3$		171.6	
3-$\underline{C}$OOCH$_3$		166.7	

TABLE II. ^{13}C-NMR and ^{1}H-NMR Data for Compounds **13** and **15** in $CDCl_3$

Position	**13**		**15**	
	^{13}C-NMR	^{1}H-NMR	^{13}C-NMR	^{1}H-NMR
1	123.8		115.4	8.06 (1H, d, 1.4)
2	124.3		123.7	
3	125.2	8.61 (1H, s)	124.1	8.63 (1H, d, 1.4)
3a	122.2		123.2	
4	149.9		150.3	
5	103.4	6.67 (1H, s)	102.6	6.63 (1H, s)
6	134.0		133.2	
6a	134.8		134.7	
7a	150.2		149.3	
8	112.3	7.01 (1H, s)	112.4	6.99 (1H, s)
9	143.5		143.3	
10	137.9		138.3	
11	120.2	7.55 (1H, s)	117.7	7.66 (1H, s)
11a	116.6		118.0	
11b	123.6		126.2	
11c	126.1		127.8	
11d	123.6		123.6	
OCO$\underline{CH_3}$	20.5, 20.5, 20.6	2.30, 2.30, 2.37 (each, 3H, s)	20.6, 20.7, 20.7	2.31, 2.34, 2.41 (each, 3H, s)
OCH$_3$	55.9	3.92 (3H, s)	55.9	3.96 (3H, s)
1-COO$\underline{CH_3}$	52.6	3.94 (3H, s)		
2-COO$\underline{CH_3}$	53.1	4.00 (3H, s)	52.4	3.98 (3H, s)
O$\underline{C}$OCH$_3$	167.5, 168.1, 168.3		167.8, 168.4, 146.5	
1-$\underline{C}$OOCH$_3$	170.6			
2-$\underline{C}$OOCH$_3$	166.0		166.8	

TABLE III. Product Distribution in the Oxidative Coupling Reaction of **10**

	Silver oxide (%)	Potassium hexacyanoferrate/ sodium acetate (%)	Potassium hexacyanoferrate/ sodium carbonate (%)
12	28	20	13
13	10	2	2
14a	3	—	—
15	3	2	—
16	—	—	2

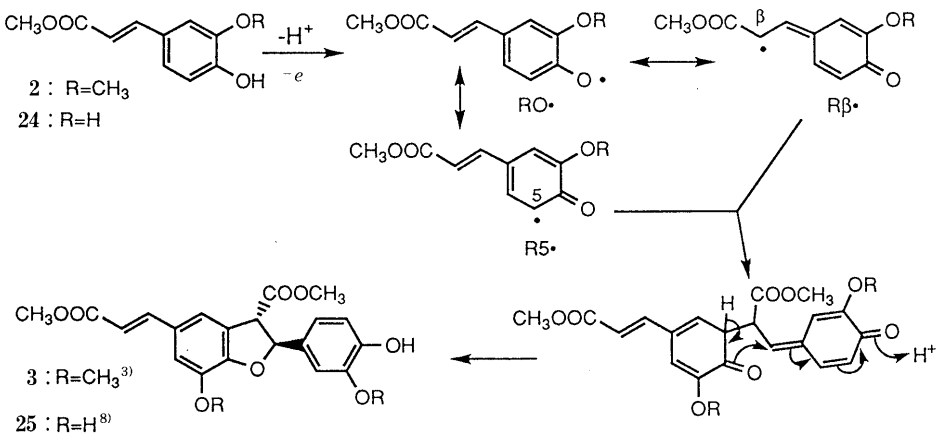


Chart 4

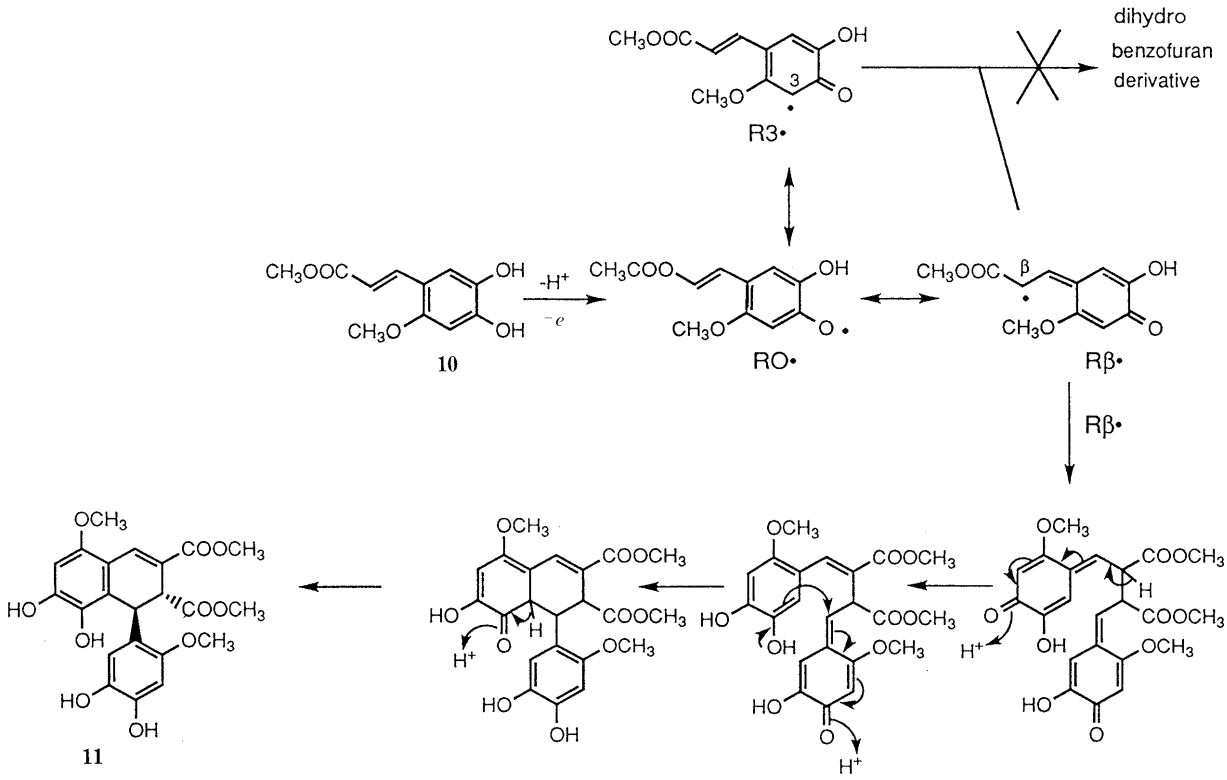


Chart 5

4 and 5, respectively. In the case of the substrates **2** and **24**, the formed radicals R5· and Rβ· coupled with each other to yield the benzofuran derivatives **3** or **25**.[3,8] However, in the case of the substrate **10**, the coupling of the Rβ radical with the R3 *ortho* radicals derived from compound **10** would be interrupted sterically by the presence of a methoxy group at the C-2 position of the latter. Consequently, the mutual coupling of two Rβ radicals would result, alternatively leading to the exclusive formation of **11** and its related compounds, which are all the products of Cβ–Cβ coupling.

To our best knowledge, benzoxanthene derivatives such as **13** and **15**, and a naphthalene compound like **16** have never been reported as the products in an oxidative coupling reaction. The conceivable mechanism for the formation of these products is shown in Chart 6. The bis-*O*-radical **26** formed initially would isomerize to a biradical **27** which would collapse to 28 through intramolecular O–C coupling, and the ensuing prototropy and elimination of a methanol molecule would yield compound **30** (educt of triacetate **13**) *via* **29**. If the methyl ester group of C-2 position in the intermediate **29** would then undergo hydrolysis to **31**, the decarboxylative elimination of a methanol would occur to afford **32** (an educt of triacetate **15**). Furthermore, compound **33** (the educt of diacetate **16**) would be formed from the radical **26** with the elimination of a phenol molecule. The driving force for this rather unusual reaction would be relief from the strain doubly imposed by the *peri*-interaction with a hydroxyl group on one side and the gauche interaction with a neighboring methoxycarbonyl group on the other, as well as the subsequent energy gain by aromatization.

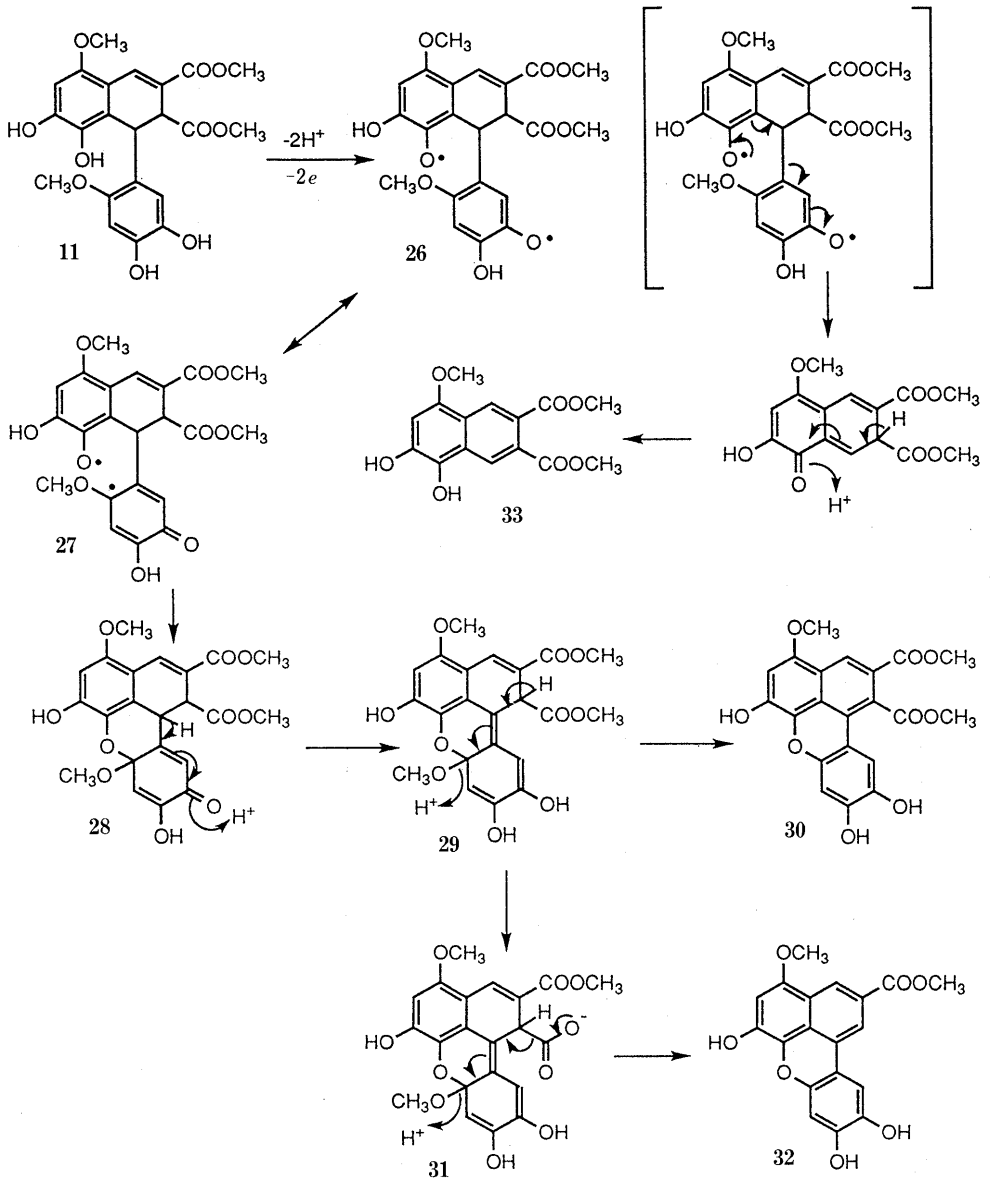


Chart 6

TABLE IV. Inhibitory Effects of Naphthalene Derivatives, Benzoxanthene Derivatives and Benzodioxane Derivative on Lipid Peroxidation in Rat Brain Homogenate[a]

Compound	Inhibition (%)[b]			IC_{50} (10^{-6} M)[c]
	10^{-4} M	10^{-5} M	10^{-6} M	
11	94	95	100	0.32 (0.30—0.34)
12	60	73	33	—
13	93	92	50	1.02 (0.98—1.07)
14a	96	94	54	0.58 (0.53—0.65)
4	97	100	56	0.77 (0.73—0.79)
5	97	100	52	1.20 (1.15—1.26)
Idebenone	93	27	—	23.7 (20.5—27.0)

a) Malondialdehyde (MDA) productions of control were 250—300 nmol/g wet tissue. *b*) The inhibition % values were the average of three to four experiments. *c*) IC_{50} values and their 95% confidence limits were calculated by probit analysis by using 4 determinations of 5 different concentrations for each compound.

TABLE V. Inhibitory Effects of Naphthalene Derivatives, Benzoxanthene Derivatives and Benzodioxane Derivative on Lipid Peroxidation in Rat Liver Microsomes[a]

Compound	IC_{50} (10^{-6} M)[b,c]
11	1.13 (1.05—1.21)
12	1.20 (1.16—1.25)
13	0.95 (0.87—1.04)
14a	0.89 (0.84—0.95)
4	4.49 (4.31—4.70)
5	3.66 (3.48—3.83)
(±)-α-Tocopherol	976 (880—1149)

a) MDA productions of control were 20—28 nmol/g protein. *b*) IC_{50} values and their 95% confidence limits were calculated by probit analysis by using 4 determinations of 3—4 different concentrations (geometric ratio = 1.4) for each compound. *c*) The inhibitory effect of esculetin (**6**) was reported to be IC_{50} 13.0×10^{-6} M.[19]

Inhibitory Effect on Lipid Peroxidation We have performed tests on synthetic lignans **11**, **12**, **13** and **14a** regarding their inhibitory activity on lipid peroxidation in rat brain homogenate and then rat liver microsomes, according to the method described in a previous paper.[1] The results are summarized in Tables IV and V.

All four compounds tested in rat brain homogenate

showed inhibitory activities more potent than idebenone, a nootropic drug. Especially, the activity of **11** was the highest, and more potent than that of the benzofuran lignans **4** and **5** synthesized in a previous work.[1] Since the activity of the acetate **12** did not differ significantly from that of the corresponding phenol **11**, the acetyl groups in **12**, **13** and **14a** are presumed to be hydrolyzed during incubation. Furthermore, when the above four compounds were tested in rat liver microsomes, their activity was found to be more potent than that of **4** and **5**, and thus much more potent than that of (±)-α-tocopherol.

In summary, an oxidative coupling reaction of the hydroxycinnamic acid derivative **10**, obtained from esculetin (**6**), a bioactive coumarin,has been investigated using silver oxide and potassium hexacyanoferrate(III) with the aim of seeking products which might have a potent inhibitory effect on lipid peroxidation. In contrast to the prediction, the major product obtained after acetylation was the 1-aryldihydronaphthalene derivative **12**, accompanied by the corresponding benzoxanthene derivative **13**. In the oxidation reaction with silver oxide, a benzodioxane derivative **14a** was obtained in a minor amount. Formation of a dihydrobenzofuran derivative such as **3**, the major product in the oxidation of methyl ferulate, was not detected. Thus, the presence of the oxy substituent at an *ortho* position of the substrate was found to cause a profound effect on the course of the oxidative coupling reaction. Tests of the synthetic lignans for lipid peroxidation inhibiting activity have been carried out in rat brain homogenate and then in rat liver microsomes. All of the compounds tested were found to exhibit prominent activities. Significantly, the bioactive lignan derivatives have been demonstrated to be provided from the appropriately designed substrate by biomimetic oxidation. Further evaluation of the biological activities of the synthetic lignans are now under examination.

Experimental

Details of the analytical procedures used and the evaluation method for inhibitory effects on lipid peroxidation were given in Part I of the series of papers.[1]

Bis(methoxymethyl)esculetin (7) To a suspension of sodium hydride (60%, in oil) (12.0 g, 0.30 mol) in dry THF–DMF (350 ml, 5:1) was added dropwise a solution of esculetin (**6**) (25.0 g, 0.14 mol) dissolved in dry THF–DMF (200 ml, 5:3) at 0 °C under nitrogen atmosphere. After the reaction mixture had been stirred for 3 h at room temperature, chloromethyl methyl ether (24.0 g, 0.30 mol) was added dropwise at 0 °C, and the mixture was stirred for another 19 h at room temperature. The mixture was concentrated and ice water was added. The precipitate was collected by filtration, washed with water, and dried. Recrystallization from MeOH gave **7** (33.7 g, 90%) as pale yellow needles, mp 99—101 °C. IR (KBr): 1708 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.53, 3.54 (each 3H, s, $CH_2OC\underline{H}_3 \times 2$), 5.26, 5.32 (each 2H, s, $C\underline{H}_2OCH_3 \times 2$), 6.29 (1H, d, J=10 Hz, 3-H), 7.15, 7.26 (each 1H, s, ArH), 7.66 (1H, d, J=10 Hz, 4-H). *Anal.* Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.31. Found: C, 58.62; H, 5.39.

Methyl (*E*)-3-[2-Hydroxy-4,5-bis(methoxymethoxy)phenyl]propenoate (8) To a solution of **7** (60.0 g, 0.23 mol) in dry MeOH (600 ml) was added sodium methoxide (28% MeOH solution) (87 ml, 0.45 mol), and the reaction mixture was refluxed for 5 h. The mixture was concentrated and ice water was added. After acidification with 6 M HCl, the product was extracted with AcOEt. The organic layer was washed with sat. NaCl sol., dried over $MgSO_4$, and evaporated to dryness. The residue was recrystallized from benzene, giving **8** (60.8 g, 90%) as pale yellow prisms, mp 104—105°C. IR (KBr): 3409(OH), 1673(C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.47, 3.54 (each 3H, s, $CH_2OC\underline{H}_3 \times 2$), 3.81 (3H, s, $COOCH_3$), 5.15, 5.20 (each 2H, s, $C\underline{H}_2OCH_3 \times 2$), 6.46 (1H, d, J=16 Hz, $=C\underline{H}COOCH_3$), 6.72, 7.24 (each 1H, s, ArH), 7.12 (1H, s, OH), 7.95 (1H, d, J=16 Hz, ArCH=). *Anal.* Calcd for $C_{14}H_{18}O_7$: C, 56.36; H, 6.09. Found: C, 56.63; H, 6.11.

Methyl (*E*)-3-[2-Methoxy-4,5-bis(methoxymethoxy)phenyl]propenoate (9) A mixture of **8** (50.0 g, 0.17 mol), anhydrous K_2CO_3 (116 g, 0.84 mol) and dimethyl sulfate (40 ml, 0.42 mol) in dry acetone (800 ml) was refluxed for 4 h. The insoluble inorganic material was removed by filtration and the filtrate was concentrated. After the excess dimethyl sulfate was decomposed by the addition of 5% ammonia solution, the mixture was extracted with ether. The organic layer was washed with sat.NaCl sol., dried over $MgSO_4$, and evaporated to dryness. The residue was recrystallized from ether, giving **9** (51.0 g, 97%) as colorless needles, mp 65—66°C. IR (KBr): 1720 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.52, 3.53 (each 3H, s, $CH_2OC\underline{H}_3 \times 2$), 3.79, 3.85 (each 3H, s, $ArOCH_3$ and $COOCH_3$), 5.16, 5.27 (each 2H, s, $C\underline{H}_2OCH_3 \times 2$), 6.41 (1H, d, J=16 Hz, $=C\underline{H}COOCH_3$), 6.79, 7.32 (each 1H, s, ArH), 7.92 (1H, d, J=16 Hz, ArCH=). *Anal.* Calcd for $C_{15}H_{20}O_7$: C, 57.68; H, 6.47. Found: C, 57.68; H, 6.51.

Methyl (*E*)-3-(4,5-Dihydroxy-2-methoxyphenyl)propenoate (10) To a solution of **9** (49.0 g, 0.16 mol) in dry MeOH (700 ml) was added acetyl chloride (3 g), and the reaction mixture was stirred at room temperature for 18 h. After the solution was neutralized with sat. $NaHCO_3$ sol., it was concentrated and ice water was added, and then the mixture was extracted with ether. The organic layer was washed with sat. NaCl sol. and dried over $MgSO_4$, and evaporated to give a crude product. Recrystallization from ether gave **10** (26.8 g, 76%) as pale yellow prisms, mp 127—129 °C. IR (KBr): 3440, 3252 (OH), 1680 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.77, 3.78 (each 3H, s, $ArOCH_3$ and $COOCH_3$), 6.30 (1H, d, J=16 Hz, $=C\underline{H}COOCH_3$), 6.51, 7.04 (each 1H, s, ArH), 7.62, 8.00 (each 1H, s, OH), 7.91 (1H, d, J=16 Hz, ArCH=). *Anal.* Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.41. Found: C, 58.94; H, 5.39.

Oxidative Coupling Reaction with Silver Oxide Silver oxide (0.62 g, 2.7 mmol) was added to a solution of **10** (1.0 g, 4.5 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 2 h. The suspension was filtered and the precipitate was sufficiently washed with hot 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, 53 mmol), and the mixture was stirred at room temperature for 17 h. The reaction mixture was poured into 6 M HCl–ice water and extracted with AcOEt. The organic layer was washed with sat. NaCl sol., dried over $MgSO_4$, and evaporated to dryness. The residue was chromatographed on silica gel (*n*-hexane–AcOEt, 5:2). The first eluate was recrystallized from EtOH to give the acetate of unreacted **10** (0.02 g), and the second eluate was recrystallized from MeOH to give methyl 6,9,10-triacetoxy-4-methoxybenzo[*kl*]xanthene-2-carboxylate (**15**) (0.02 g, 2%) as yellow needles, mp 185—188 °C. The third eluate was recrystallized from EtOH, giving methyl (*E*)-3-[(2*R**,3*R**)-2-(4,5-diacetoxy-2-methoxyphenyl)-7-methoxy-3-methoxycarbonyl-1,4-benzodioxan-6-yl]propenoate (**14a**) (0.03 g, 3%) as colorless needles, mp 204—206 °C and the fourth eluate was recrystallized from acetone, giving dimethyl 6,9,10-triacetoxy-4-methoxybenzo[*kl*]xanthene-1,2-dicarboxylate (**13**) (0.12 g, 10%) as yellow needles, mp 256—258 °C, and the fifth eluate was recrystallized from acetone–EtOH, giving dimethyl (1*S**,2*R**)-7,8-diacetoxy-1-(4,5-diacetoxy-2-methoxyphenyl)-1,2-dihydro-5-methoxynaphthalene-2,3-dicarboxylate (**12**) (0.38 g, 28%) as colorless needles, mp 241—243 °C.

Methyl (*E*)-3-(4,5-Diacetoxy-2-methoxyphenyl)propenoate [Acetate of Unreacted **10**]: ^{1}H-NMR ($CDCl_3$) δ: 2.28, 2.30 (each 3H, s, $CH_3CO \times 2$), 3.79, 3.86 (each 3H, s, $ArOCH_3$ and $COOCH_3$), 6.44 (1H, d, J=16 Hz, $=C\underline{H}COOCH_3$), 6.76, 7.31 (each 1H, s, ArH × 2), 7.90 (1H, d, J=16 Hz, ArCH=).

12: IR (KBr): 1769, 1725, 1703 (C=O) cm^{-1}. *Anal.* Calcd for $C_{30}H_{30}O_{14}$: C, 58.62; H, 4.93. Found: C, 58.66; H, 4.92. **13**: IR (KBr): 1766, 1723 (C=O) cm^{-1}. *Anal.* Calcd for $C_{27}H_{22}O_{12}$: C, 60.22; H, 4.13. Found: C, 60.23; H, 4.09. MS *m/z*: 538 (M^+). **14a**: IR (KBr): 1759, 1711, 1691 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.24, 2.28 (each 3H, s, $CH_3CO \times 2$), 3.70 (3H, s, 3-$COOCH_3$), 3.78 (3H, s, $=CHCOOC\underline{H}_3$), 3.82 (3H, s, Ar-7-OCH_3), 3.84 (3H, s, Ar-2-OCH_3), 4.87 (1H, d, J=4 Hz, 3-H), 5.73 (1H, d, J=4 Hz, 2-H), 6.39 (1H, d, J=16 Hz, $=C\underline{H}COOCH_3$), 6.53 (1H, s, 8-H), 6.78 (1H, s, 3′-H), 7.07 (1H, s, 6′-H), 7.17 (1H, s, 5-H), 7.91 (1H, d, J=16 Hz, ArCH=). ^{13}C-NMR ($CDCl_3$) δ: 20.5, 20.6 ($\underline{C}H_3CO \times 2$), 51.5 ($=CHCOO\underline{C}H_3$), 52.6 (3-$COO\underline{C}H_3$), 55.9 (Ar-7-

OCH_3), 56.1 (Ar-2'-OCH_3), 71.1 (C2), 74.5 (C3), 100.4 (C8), 106.2 (C3'), 116.6 (=$\underline{C}HCOOCH_3$), 116.8 (C5), 117.3 (C6), 122.1 (C6'), 122.5 (C1'), 135.5 (C4a, C5'), 139.4 (ArCH=), 142.8 (C4'), 144.9 (C8a), 154.1 (C7), 154.3 (C2'), 167.9, 168.4 ($CH_3\underline{C}O \times 2$), 168.0 (=$CH\underline{C}OOCH_3$), 168.0 (3-$\underline{C}OOCH_3$). MS *m/z*: 530 ($M^+$). **15**: IR (KBr): 1764, 1720 (C=O) cm^{-1}. MS *m/z*: 480 (M^+).

Dimethyl (1*S,2*R**)-1-(4,5-Dihydroxy-2-methoxyphenyl)-1,2-dihydro-7,8-dihydroxy-5-methoxynaphthalene-2,3-dicarboxylate (11)** To a solution of **10** (5.0 g, 22.3 mmol) in benzene–acetone (150 ml, 2:1) was added silver oxide (3.1 g, 13.4 mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h and at room temperature for another 2 h. The suspension was filtered and the precipitate was sufficiently washed with hot acetone. The filtrate and the washing were combined, and the solvent was evaporated to leave a residue, which was chromatographed on silica gel. The CH_2Cl_2–MeOH (49:1 then 9:1) eluate was recrystallized from acetone–EtOH, giving **11** (1.1 g, 22%) as white brown scales, mp 229—231 °C. IR (KBr): 3486, 3381 (OH), 1704, 1681 (C=O) cm^{-1}. *Anal.* Calcd for $C_{22}H_{22}O_{10} \cdot H_2O$: C, 56.89; H, 5.21. Found: C, 56.96; H, 5.32. MS *m/z*: 446 (M^+).

Oxidative Coupling Reaction with Potassium Hexacyanoferrate–Sodium Acetate A solution of potassium hexacyanoferrate(III) (1.8 g, 5.5 mmol) and sodium acetate (1.7 g, 21 mmol) in water (100 ml) was added dropwise to a solution of **10** (1.0 g, 4.5 mmol) in acetone–water (100 ml, 1:1) at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h and at room temperature for another 2 h, and then extracted with AcOEt. The organic layer was washed with sat. NaCl sol.and dried over $MgSO_4$, and evaporated to dryness. The residue was dissolved in dry pyridine (6 ml) and acetic anhydride (5 ml, 53 mmol), and the mixture was stirred at room temperature for 17 h. The reaction mixture was poured into 6 M HCl–ice water and extracted with AcOEt. The organic layer was washed with sat.NaCl sol., dried over $MgSO_4$, and evaporated to dryness. The residue was chromatographed on silica gel (*n*-hexane–AcOEt, 5:2). The first eluate was recrystallized from EtOH to give the acetate of unreacted **10** (0.05 g), and the second eluate was recrystallized from MeOH to give **15** (0.02 g, 2%). The third eluate was recrystallized from acetone, giving **13** (0.03 g, 2%), and the fourth eluate was recrystallized from acetone–EtOH, giving **12** (0.28 g, 20%).

Oxidative Coupling Reaction with Potassium Hexacyanoferrate–Sodium Carbonate To a solution of **10** (2.0 g, 8.9 mmol) in $CHCl_3$ (800 ml) at 0 °C under nitrogen atmosphere was added dropwise a solution of potassium hexacyanoferrate(III) (2.9 g, 8.8 mmol) and Na_2CO_3 (1.4 g, 13.2 mmol) in water (140 ml). After the mixture was stirred at 0 °C for 1 h, the organic layer was separated and then the water layer was extracted with CH_2Cl_2. The combined organic layer was washed with sat.NaCl sol., 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 16 h. The reaction mixture was poured into 6 M HCl–ice water and extracted with AcOEt. The organic layer was washed with sat.NaCl sol., dried over $MgSO_4$, and evaporated to leave a residue, which was chromatographed on silica gel (*n*-hexane–AcOEt, 5:1 then 1:1). The first eluate was recrystallized from EtOH, giving the acetate of unreacted **10** (0.14 g),the second eluate was recrystallized from EtOH, giving dimethyl 5,6-diacetoxy-8-methoxynaphthalene-2,3-dicarboxylate (**16**) (0.03 g, 2%) as yellow brown scales, mp 140—141 °C, and the third eluate was recrystallized from acetone, giving **13** (0.06 g, 2%). Recrystallization of the fourth eluate from acetone–EtOH gave **12** (0.37 g, 13%). **17**: IR (KBr): 1776, 1754, 1732, 1719 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.36, 2.46 (each 3H, s, $CH_3CO \times 2$), 3.95, 3.95, 4.00 (each 3H, s, $COOCH_3 \times 2$ and Ar-OCH_3), 6.79 (1H, s, 7-H), 8.09 (1H, s, 4-H), 8.71 (1H, s, 1-H). ^{13}C-NMR ($CDCl_3$) δ: 20.4, 20.8 ($\underline{C}H_3CO \times 2$), 52.7, 52.8 ($COO\underline{C}H_3 \times 2$), 56.1 ($ArOCH_3$), 102.8 (C7), 122.8 (C4), 123.9 (C8a), 125.4 (C1), 127.4 (C4a), 128.4 (C2), 130.7 (C5), 130.8 (C3), 141.7 (C6), 154.4 (C8), 167.4, 168.0, 168.3 ($CH_3\underline{C}O \times 2$ and $\underline{C}OOCH_3 \times 2$). *Anal.* Calcd for $C_{19}H_{18}O_9$: C, 58.45; H, 4.66. Found: C, 58.48; H, 4.63. MS *m/z*: 390 (M^+).

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