Studies on the Preparation of Bioactive Lignans by Oxidative Coupling Reaction. III.[1] Synthesis of Polyphenolic Benzofuran and Coumestan Derivatives by Oxidative Coupling Reaction of Methyl (*E*)-3-(4-Hydroxy-2-methoxyphenyl)propenoate and Their Inhibitory Effect on Lipid Peroxidation

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Three dihydrobenzofuran derivatives 11, 19, 22, a Pummerer's ketone 20 and a dimeric phenylpropanoid 24 were synthesized by oxidative coupling reaction of methyl (*E*)-3-(4-hydroxy-2-methoxyphenyl)propenoate 10, which was prepared from umbelliferone. The major product 11 was converted into its acetate 21 and schizotenuin D analogs 27, 28, 29. A new coumestan derivative 13 was synthesized from 29. Ten synthetic compounds thus obtained were tested for inhibitory effects on lipid peroxidation in rat brain homogenate.

Keywords lignan; oxidative coupling reaction; lipid peroxidation inhibitory effect; umbelliferone; benzofuran; coumestane

Schizotenuin D (**1**) is one of the bioactive lignans which have been isolated from *Schizonepeta tenuifolia* BRIQ. as inhibitors of 3α-hydroxysteroid dehydrogenase. In a previous paper,[2] we reported that an efficient synthesis of **1** could be achieved *via* a dihydrobenzofuran derivative **3**, which was obtained by oxidative coupling reaction of methyl ferulate (**2**), and that compounds **4** and **5**, related to **1**, strongly inhibited lipid peroxidation. Subsequently, in search of new schizotenuin D derivatives with more potent inhibitory activity we examined the oxidative coupling reaction of a hydroxycinnamate derivative **7**, which was prepared by the ring-opening of esculetin (**6**).[1] Contrary to our expectation, the major product was not the dihydrobenzofuran compound but a dihydronaphthalene compound **8**. The inhibitory activity of **8** and related compounds was more potent than that of **4** or **5**.

In connection with the synthesis of bioactive lignans from coumarins, we investigated their synthesis from umbelliferone (**9**). The failure of dihydrobenzofuran formation in the reaction of **7** seems to be attributable to the steric hindrance imposed by the 2-methoxy group, which prevents participation of the C-3 radical in the coupling reaction. In the case of the substrate **10**, derived from **9**, the C-5 radical species would be reactive enough to couple with the C-β radical and the production of a dihydrobenzofuran derivative **11** would be reasonably expected. Dehydrogenation of the product **11** would afford a benzofuran derivative **12** analogous to schizotenuin D. In addition the demethylation of **12** followed by lactone ring formation would afford a new coumestan derivative **13**. There have been many reports on the bioactive natural coumestan derivatives. For instance wedelolactone (**14**) was found to show strong anti-hepatotoxic activity[3] and antihemostatic activity,[4] and coumestrol (**15**) was reported to have strong estrogenic activity.[5] Therefore, examination of the bioactivity of **13** was of interest.

Umbelliferone (**9**) is a common bioactive constituent of several plants used as crude drugs, namely *Foeniculum vulgare* MILLER (Japanese name: uikyo), *Morus alba* LINNE (Japanese name: sohakuhi) and *Angelica pubescens* MAXIM (Japanese name: dokkatu).[6] Since oxidative coupling is a very common reaction in biosynthesis, the occurrence of lignans related to **9** in the crude drugs should be considered.

Results and Discussion

Synthesis The first task was conversion of umbelliferone (**9**) to 4-hydroxy-2-methoxycinnamate **10**, the substrate of the oxidative coupling. Treatment of **9** with sodium hydride and chloromethyl methyl ether in tetrahydrofuran (THF)–dimethyl formamide (DMF) gave a protected product **16** in 88% yield, and this was subjected to opening of the coumarin ring using sodium methoxide in dry MeOH to afford the methyl ester **17** in 89% yield. The phenolic hydroxy group of **17** was methylated with dimethyl sulfate, giving **18** in 84% yield. Cleavage of the methoxymethyl group was performed in the presence of a catalytic amount of acid to give the desired compound **10** in 92% yield.

The oxidative coupling reactions were examined using silver oxide, potassium hexacyanoferrate(III) and iron(III) chloride in the same manner as in the previous paper,[1] which were known as the general one electron oxidizing agents for the reaction of hydroxycinnamic acid derivatives.[7-14] Firstly the oxidative coupling reaction of **10** was carried out with potassium hexacyanoferrate(III)–Na_2CO_3. Treatment of **10** with equimolar potassium hexacyanoferrate(III) and a 1.5 fold molar excess of 1% aqueous Na_2CO_3 solution in $CHCl_3$ at room temperature, followed by separation of the products by chromatography on a silica gel column, afforded three products **11**, **19** and **20**, of which the first one represented the major product and the others were obtained only in minute amounts after rechromatography (see Experimental for details of the separation scheme). The mother liquor from the recrys-

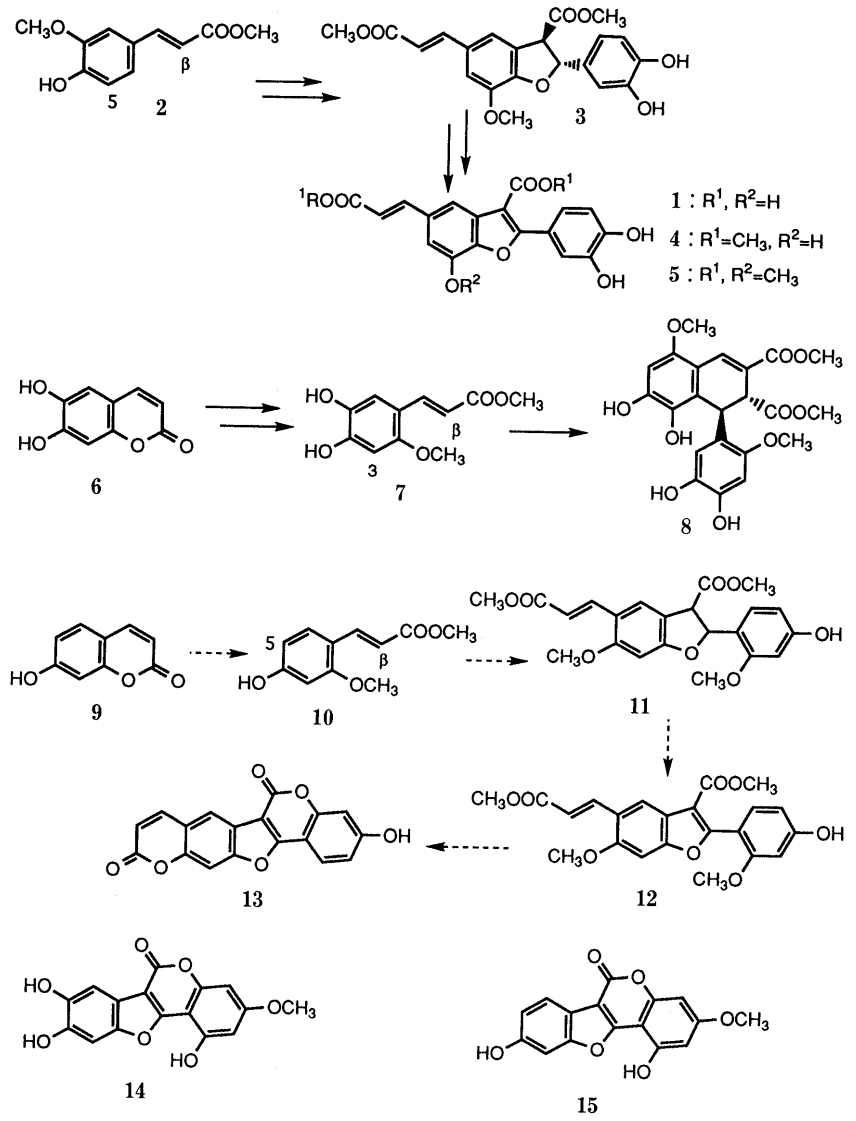

Chart 1

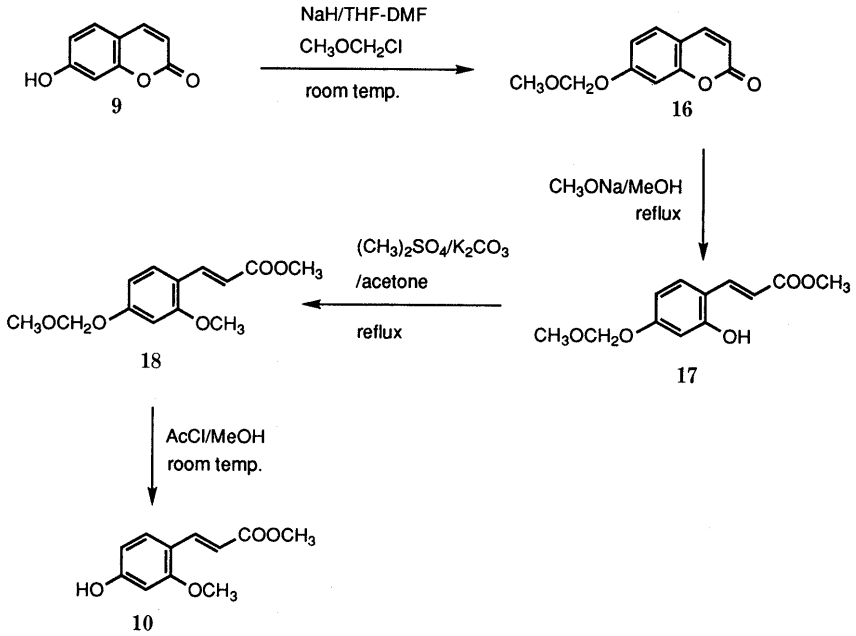

Chart 2

tallization of crude **11** was acetylated and the acetylated product was divided into two parts. The chromatography of one part gave the acetate **23** of an additional coupling product. The other part was treated with sodium methoxide in MeOH at 0 °C and the deacetylated product was chromatographed, giving **24** and **25**. Compound **24** was recognized as a minor product of the oxidative coupling reaction from the presence of the corresponding peak in the HPLC chromatogram of the crude oxidation mixture. No peak corresponding to **25** was detected in the chromatogram, and this compound was presumed to be a decomposition product of **23** generated during the sodium methoxide treatment.

The major product **11** was formulated as $C_{22}H_{22}O_8$ (MS and elemental analysis) and gave a monoacetate **21** upon acetylation. In the ^{1}H-NMR spectrum, **11** exhibited four methoxy singlets ascribed to two methyl ester and two methyl ether groups, an AB quartet typical of the propenoate chain, a pair of vicinal proton signals (δ6.30, d, J=6 Hz, 2-H; δ4.18, dd, J=1, 6 Hz, 3-H), and two sets of aryl proton signals (δ7.41, d, J=1 Hz, 4-H; δ6.48, s, 7-H and δ6.44, d, J=2 Hz, 3′-H; δ6.39, dd, J=2, 8 Hz, 5′-H; δ7.13, d, J=8 Hz, 6′-H). These results indicate that **11** has a dihydrobenzofuran structure formed by coupling in the predicted mode. The ^{13}C-NMR spectrum of **11** corroborates this conclusion. The stereochemistry of the dihydrobenzofuran ring in **11** is assigned to be *trans* on the basis of the coupling constant (J_{H2-H3}=6 Hz) with reference to the previous data.[8] In consonance with this assignment, nuclear Overhauser effect (NOE) was observed between 3-H and 6′-H.

The molecular formula, $C_{33}H_{32}O_{12}$, of the second product **19** suggested that **19** is the trimer of **10**. The ^{1}H-NMR spectrum of **19** closely resembled that of **11** and all of the signals due to protons attached to carbon atoms present in the latter were retained in the former. The additional signals in the spectrum of **19** were due to a methoxy group and a methyl ester group together with an ABC-type resonance due to aromatic protons (δ6.60, d, J=2 Hz, 3″-H; δ6.54, dd, J=2, 9 Hz, 5″-H; δ 7.37, d, J=9 Hz, 6″-H) and a singlet at δ7.88. The data indicated that in the formation of **19** the O-radical of **11** would be appended to the carbon atom next to the methoxycarbonyl group in **10**. Thus the structure **19** was assigned for the trimer, and this assignment was fully compatible with the ^{13}C-NMR data. The remaining problem with respect to the structure was the configuration of the trisubstituted double bond, which was determined based on gated decoupling and long-range spin decoupling (LSPD) experiments. Namely, between the carbonyl carbon of the methoxycarbonyl group (δ164.5) and the vinyl proton of double bond (δ7.88) there was a long-range coupling of J=4 Hz, considerably smaller than the usual $^3J_{CH}$ value for an *E*-double bond (10 Hz). Thus,the double bond in question was concluded to have *Z*-geometry.

The third product **20** has the molecular formula $C_{22}H_{22}O_8$ as revealed by elemental analysis and MS measurement, thus being a dimer of **10**. Notable features in the ^{1}H-NMR spectrum of **20** were two sets of signals ascribed to the methyl (*E*)-propenoate chains and an ABX-type signal (δ2.74, dd, J=4, 18 Hz; δ3.00, dd, J=3, 18 Hz; δ4.90, dd, J=3, 4 Hz), of which the large J_{AB} value suggested the presence of a methylene group adjacent to a ketone carbonyl group. In addition, two singlets due to aromatic protons (δ6.43 and 7.43) and a singlet due to a vinyl proton (δ5.55) were observed. The presence of the ketone group was substantiated by the appearance of a peak at δ193.5 in the ^{13}C-NMR spectrum. In the IR spectrum of **20** a carbonyl absorption peak appeared at 1655 cm^{-1}, which indicated the conjugation of the ketone group with the double bond of the vinyl proton. Thus the presence of a $-O-\underset{|}{C}HCH_2COCH=\underset{|}{C}-$ grouping was inferred. All of the foregoing evidence led to the conclusion that **20** has a structure related to that of Pummerer's ketone, which is formed by the *o–p* coupling of cresol. To our knowledge, **20** represents the first example of a product analogous to Pummerer's ketone formed by the oxidative coupling reaction of hydroxyphenylpropanoid derivatives. The stereochemistry with regard to C-2 and C-3 was determined based on NOE observation. Since irradiation of the H-2 signal caused an NOE increase in the α-vinyl proton signal of the (*E*)-propenoate chain at the 3 position and *vice versa*, the (*E*)-propenoate chain at the 3 position and H-2 were concluded to be in *cis* configuration.

The fourth product, obtained as the acetate **23**, is a dimer with the molecular formula $C_{24}H_{24}O_9$. The ^{1}H-NMR spectrum of **23** closely resembled that of **21**, the acetate of **11**, but there was a marked difference in the aromatic proton region, where a pair of doublets with *ortho* coupling constant (δ6.75, 7.48, J=9 Hz) was observed in the spectrum of **23** instead of two singlets (δ6.53, 7.41) in that of **21**. These facts established the dihydrobenzofuran structure **23**, isomeric with **21**, for the former acetate. The ^{13}C-NMR spectrum gave further support to this assignment. The stereochemistry of the dihydrobenzofuran ring in **23** was assumed to be *trans* from the coupling constant (J_{H2-H3}=7 Hz) in the ^{1}H-NMR spectrum, and this was confirmed by the observation of NOE enhancement between the H-3 signal (δ4.23) and the C-2′ methoxy proton signal (δ3.80).

The fifth product **24**, $C_{22}H_{22}O_8$, is also a dimer of **10**. The ^{1}H-NMR spectrum of **24** revealed four methyl singlets due to two methyl ester and two methoxy groups, and two vinyl protons of a methyl (*E*)-propenoate chain. In addition, two sets of aromatic proton signals both with a 1,2,4-trisubstituted benzene coupling pattern and a low field singlet (δ7.85) were observed, the latter being attributed to the β-proton of a cinnamate moiety. Accordingly, the structure was determined to be **24** and the ^{13}C-NMR spectrum showed distinct signals compatible with this formulation. The configuration of the trisubstituted double bond in **24** was inferred based on gated decoupling and LSPD experiments as in the case of **19** to be *Z*. The observed coupling constant between the carbonyl carbon of the methoxycarbonyl group (δ163.9) and the vinyl proton of the double bond (δ7.85) was 4 Hz.

The sixth compound **25**, which is the product of secondary conversion on treatment with sodium methoxide, has the molecular formula $C_{22}H_{22}O_8$, being isomeric with **24**. The ^{1}H-NMR spectrum of **25** was also very similar to that of **24**, except that one set of the

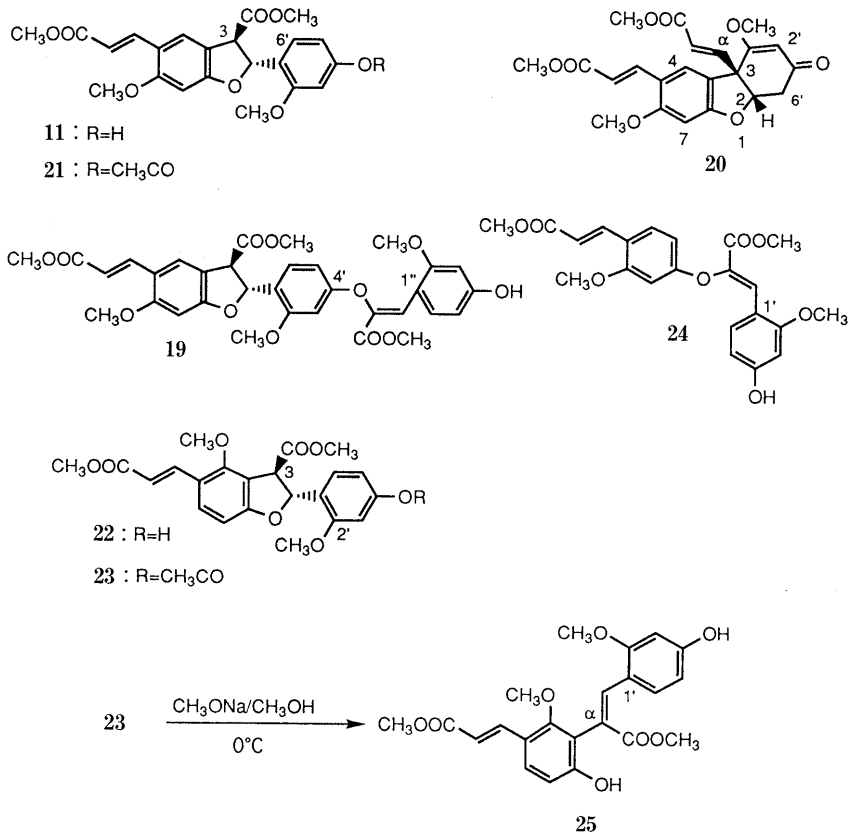

Chart 3

aromatic protons appeared as an AB quartet with an *ortho* coupling constant ($J=9$ Hz), indicating the presence of a 1,2,3,4-tetrasubstituted benzene unit in **25**. The other set of aromatic protons was observed as ABC-type signals (δ 6.37, d, $J=2$ Hz; δ 6.12, dd, $J=2$, 9 Hz; δ 6.78, d, $J=9$ Hz). Thus, **25** was concluded to have the structure shown in Chart 3, and would be formed from **23** or **22** by β-elimination on base treatment. The geometry of the trisubstituted double bond was addressed as before, using gated decoupling and LSPD techniques. The coupling constant ($^3J_{CH}$) between the carbonyl carbon of the methoxycarbonyl group (δ 168.5) and the vinyl proton (δ 8.32) was determined to be 8 Hz, indicating the *trans* relationship of the carbon and hydrogen atoms concerned. Therefore the double bond in **25** was concluded to have *Z*-configuration.

Subsequently we examined the oxidative coupling reaction of **10** with silver oxide. Treatment of **10** with equimolar silver oxide in benzene–acetone at room temperature, followed by silica gel short column chromatography afforded a fraction, which was essentially the same mixture of products as obtained in the oxidation with potassium hexacyanoferrate(III)–Na_2CO_3, containing **11** as the major product. The reactions of **10** with potassium hexacyanoferrate(III)–sodium acetate in acetone–water or iron(III) chloride in acetone–water resulted practically in recovery of the starting material after 48 h at room temperature. In order to examine the product distribution of the oxidative coupling reaction more precisely, HPLC analysis was investigated. Using an octadecyl silica (ODS) column with acetonitrile–water

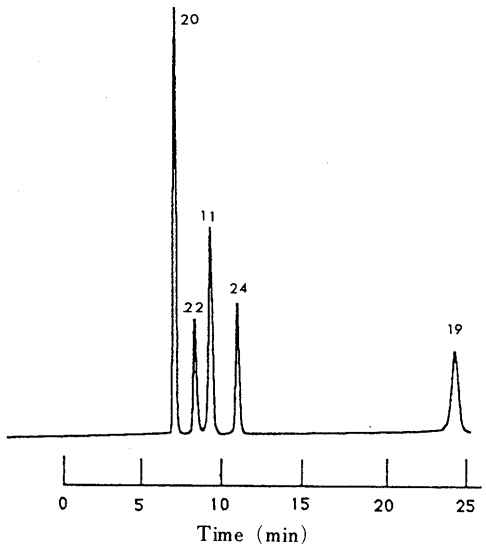

Fig. 1. HPLC Chromatogram of an Authentic Mixture

(1 : 1) containing 1% formic acid as the eluent, clear separation of an authentic mixture of **11**, **19**, **20**, **22** and **24** was achieved as shown in Fig. 1.

Figures 2 and 3 illustrate chromatograms of the product mixtures obtained respectively by oxidation with potassium hexacyanoferrate(III)–Na_2CO_3 and silver oxide, after silica gel column pretreatment to remove unreacted starting material. The ratio of products was calculated using the calibrating factors for the different UV extinction coefficients of the products (Table I), and the results are

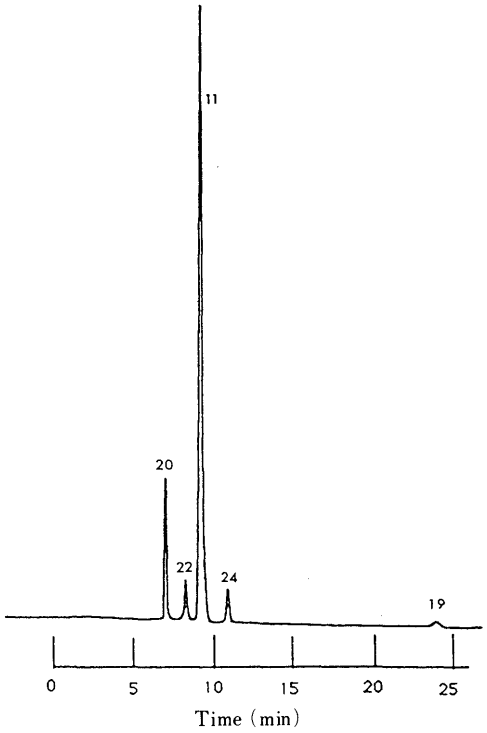

Fig. 2. HPLC Chromatogram of Products Obtained by Oxidative Coupling Reaction with Potassium Hexacyanoferrate–Sodium Carbonate

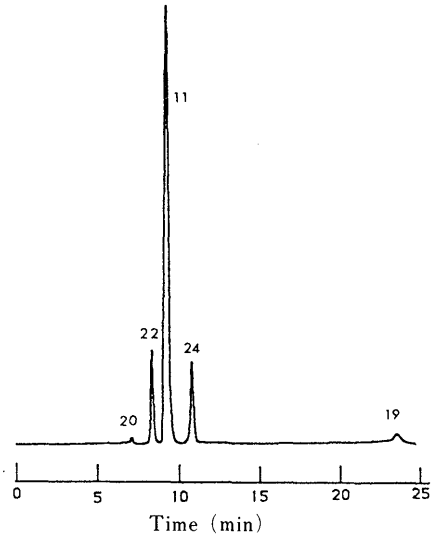

Fig. 3. HPLC Chromatogram of Products Obtained by Oxidative Coupling Reaction with Silver Oxide

summarized in Table II.

The mechanism of the formation of products of the five types obtained in the oxidative coupling reaction could be as illustrated in Chart 4. The RO radical initially formed from **10** by the action of the oxidizing agents can give rise to further mesomeric forms R3, R5, R1 and Rβ by delocalization of the unpaired electron. The major product **11** would be formed by C–C coupling between R5 and Rβ radicals. Coupling of the R3 radical, more hindered than R5, with Rβ would occur to a lesser extent to give the minor product **22**. Combination of the O-radical generated

TABLE I. Relative Peak Area for Authentic Samples of the Oxidation Products on HPLC Analysis[a]

11	19	20	22[b]	24
1	0.84	2.30	0.65	0.78

a) HPLC analysis was conducted for a mixture containing each product at a concentration of 2 mg/ml MeOH. The values were calculated relative to the peak area of **11**. *b*) The sample of **22** was obtained by the deacetylation of **23** (Na_2CO_3/MeOH–H_2O, room temperature).

TABLE II. Total Yield[a] and Ratio[b] of Products Obtained by Oxidative Coupling Reaction

	Total yield	11	19	20	22	24
Potassium hexacyanol ferrate–Na_2CO_3	40%	0.79	0.02	0.07	0.07	0.04
Silver oxide	29%	0.71	0.03	0.002	0.13	0.13

a) The yield denotes the percentage (w/w) of the product mixture obtained by chromatography with respect to the starting material. *b*) The ratio was calculated using the values in Table I.

from **11** with Rβ radical would afford the trimer **19** as a minor product. The Pummerer's ketone-type product **20** would be formed by C–C coupling between R5 and R1 radicals, followed by an intramolecular Michael type addition of the O-radical to the dienone ring. Reaction between RO and Rβ radicals may occur to furnish the minor product **24**.

Next we investigated the conversion of the major product **11** to benzofuran and coumestan derivatives with the aim of employing them for pharmacological tests as described at the outset. On treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dry dioxane the acetate **21** obtained from **11** afforded a benzofuran derivative **26** in quantitative yield. In the ^{1}H-NMR spectrum of **26** the signals due to H-2 and H-3 present in the spectrum of **21** had disappeared. Compound **26** was converted to **27** by hydrolysis with sodium methoxide in 85% yield. On the other hand, **26** was treated with boron tribromide in CH_2Cl_2 at -78 °C to afford **28** in 81% yield. The ^{1}H-NMR spectrum of **28** revealed proton signals due to an acetyl, two methyl ester and a methoxy groups. Therefore it was suggested that the acetyl group remained intact and only one of the two methoxy groups was cleaved in **28**. Since the correlation spectroscopy *via* long-range coupling (COLOC) spectrum of **28** revealed a correlation between the signal of the methyl proton of a methoxy group (δ 3.93) and the aromatic carbon at the 6 position (δ 156.9), the remaining methoxy group was confirmed to be located at the 6 position. When the benzofuran **26** was treated with boron tribromide in CH_2Cl_2 at room temperature, the other product **29** was obtained in 79% yield. The ^{1}H-NMR spectrum of **29** revealed only a methyl singlet due to a methyl ester group (δ 3.79), suggesting the disappearance of one of two methyl ester groups present in **26** in addition to deacetylation and demethylation of the methoxy groups. Moreover in the ^{1}H-NMR spectrum of **29** the coupling constant of the AB type signal due to the propenoate chain had changed from 16 Hz in **26** to 10 Hz, suggesting that the configuration of the double bond

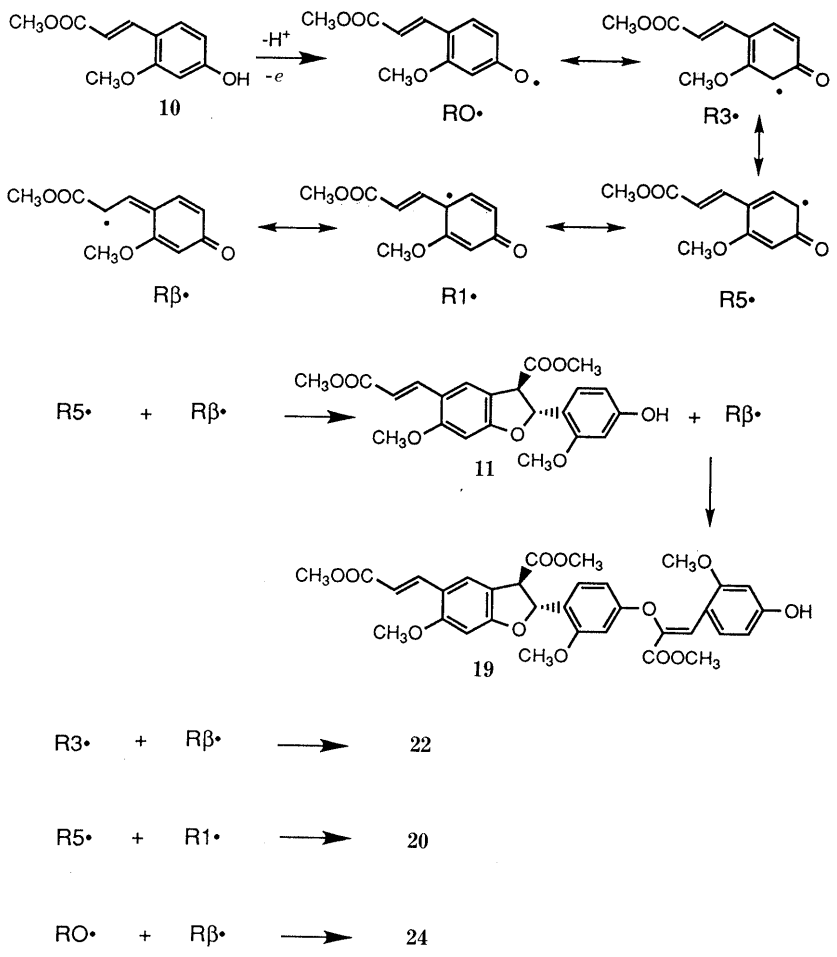

Chart 4

had changed from *E* to *Z*, and the COLOC spectrum of **29** revealed a correlation between the signals of the two vinyl protons (δ 6.47, d, J=10 Hz; δ 8.24, d, J=10 Hz) and the demethylated carboxyl carbon (δ 160.1). Consequently it was concluded that lactone ring formation took place between the (*E*)-propenoate chain and the hydroxyl group of the 6 position, giving a furocoumarin derivative **29**. Treatment of **29** with 50% H_2SO_4 at 100 °C effected hydrolysis and lactonization to afford the desired coumestan derivative **13** in 88% yield. ^{1}H- and ^{13}C-NMR spectra and elemental analysis of **13** gave support to the depicted structure. Compound **13** was acetylated with acetic anhydride in pyridine to gave the corresponding acetate **30** in a quantitative yield. Interestingly, eriocephaloside (**31**) isolated from *Lasiosiphon eriocephalus* has a structure closely related to **13**.[15] In connection with the biosynthesis of **31** our synthesis of **30** using the oxidative coupling reaction of a hydroxycinnamate derived from a naturally occurring coumarin seems significant.

Inhibitory Effect on Lipid Peroxidation We examined compounds **11**, **19**, **20**, **21**, **23**, **24**, **26**, **27**, **28** and **29** for inhibitory activity against lipid peroxidation in rat brain homogenate according to the method described in a previous paper.[2] To our regret, the coumestan compounds **13** and **30** could not be examined, since they were insoluble in all of the solvents examined, even dimethyl sulfoxide (DMSO). The results are summarized in Table III. The inhibitory activities shown by the tested compounds was weaker than that of idebenone, a standard nootropic drug.

Conclusion

The oxidative coupling reaction of methyl (*E*)-3-(4-hydroxy-2-methoxyphenyl)propenoate, readily derivable from umbelliferone, was investigated with the aim of obtaining bioactive lignans. The reactions using potassium hexacyanoferrate(III) and silver oxide afforded the dihydrobenzofuran derivative **11** as the major product. In addition, two benzofuran derivatives **19** and **22**, a Pummerer's ketone-type compound **20** and an open-chain dimer **24** were produced as minor products. The major compound **11**, after acetylation, was converted by dehydrogenation with DDQ into the corresponding benzofuran derivative **26**, from which several compounds **27**—**30** related to schizotenuins were obtained. Compound **30** has a coumestan skeleton akin to that of a natural product. These results demonstrate that our synthetic approach using oxidative coupling is potentially valuable for obtaining bioactive lignans related to natural products. Unfortunately the synthetic products did not exhibit prominent inhibitory activity against lipid peroxidation. Further biological activities of the synthetic lignans are under examination.

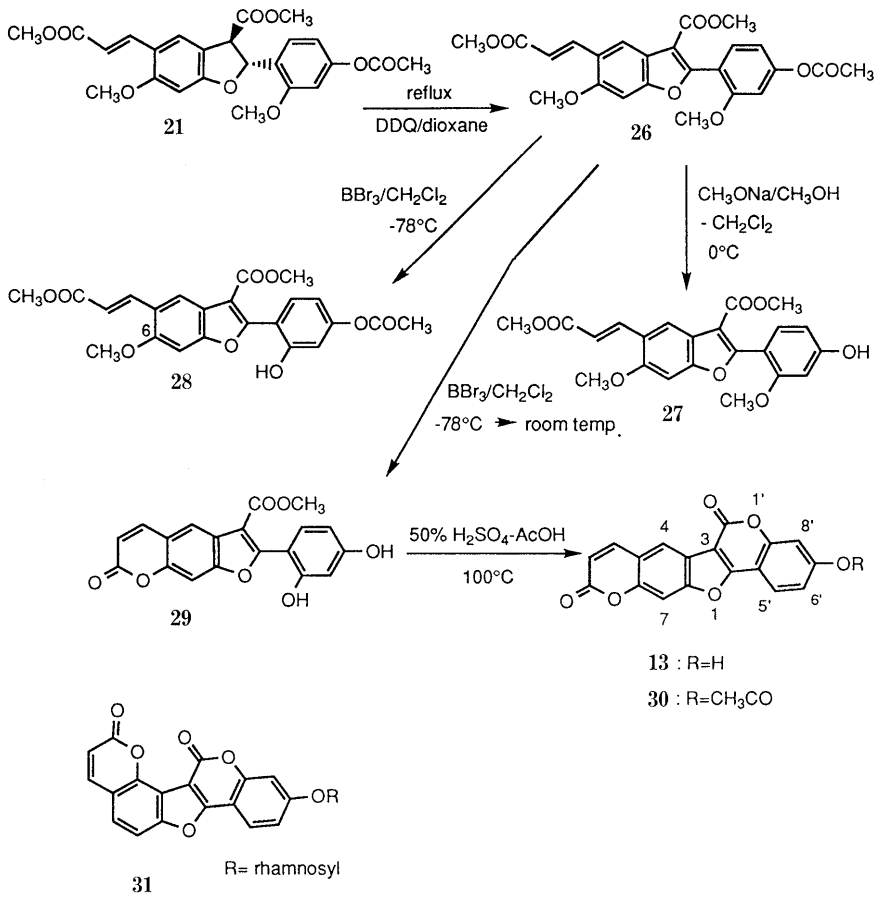

Chart 5

TABLE III. Inhibitory Effect of the Products Obtained by Oxidative Coupling Reaction on Lipid Peroxidation in Rat Brain Homogenate

Compound	Inhibition (%)	
	10^{-4} M	10^{-5} M
11	55	10
19	2	—
20	14	—
21	28	—
23	30	—
24	67	2
26	18	—
27	50	1
28	53	0
29	13	—
Idebenone	93	27

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured with Nicolet 60 SX spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained at 300 and 75 MHz, respectively, using a Brucker AM 300 instrument. Chemical shift values are expressed in ppm downfield from tetramethylsilane as an internal standard. The MS were recorded on a JEOL JMS-AX 500.

Methoxymethylumbelliferone (16) A solution of umbelliferone (**9**) (60.0 g, 0.37 mol) in dry THF–DMF (400 ml, 5:3, v/v) was added dropwise to a suspension of sodium hydride (60%, in oil, 14.8 g, 0.37 mol) in dry THF–DMF (600 ml, 5:1, v/v) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 3 h at room temperature, then chloromethyl methyl ether (29.8 g, 0.37 mol) was added dropwise at 0 °C and the mixture was stirred for 17 h at room temperature. The mixture was concentrated and water was added. The precipitate was collected by filtration, washed with water, and dried. Recrystallization from MeOH gave **16** (67.2 g, 88%) as colorless needles, mp 104—105 °C. IR (KBr): 1716 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.49 (3H, s, $CH_2O\underline{CH}_3$), 5.24 (2H, s, $C\underline{H}_2OCH_3$), 6.27 (1H, d, J=10 Hz, 3-H), 6.95 (1H, d, J=2 Hz, 8-H), 6.99 (1H, dd, J=2, 9 Hz, 6-H), 7.34 (1H, d, J=9 Hz, 5-H), 7.65 (1H, d, J=10 Hz, 4-H). *Anal.* Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.90. Found: C, 64.07; H, 4.91.

Methyl (*E*)-3-[2-Hydroxy-4-(methoxymethoxy)phenyl]propenoate (17) To a solution of **16** (56.9 g, 0.28 mol) in dry MeOH (600 ml) was added sodium methoxide solution (28% in MeOH, 80 ml, 0.42 mol) and the mixture was refluxed for 4 h. It was then concentrated and ice-water was added. After being acidified with 2 M HCl, the precipitate was collected by filtration, washed with water, and dried. Recrystallization from EtOH gave **17** (66.0 g, 89%) as colorless prisms, mp 116—117 °C. IR (KBr): 3367 (OH), 1669 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.47 (3H, s, $CH_2OC\underline{H}_3$), 3.82 (3H, s, $=CHCOOC\underline{H}_3$), 5.16 (2H, s, $C\underline{H}_2OCH_3$), 6.55 (1H, d, J=16 Hz, $=C\underline{H}COOCH_3$), 6.58 (1H, d, J=2 Hz, 3-H),6.60 (1H, dd, J=2, 8 Hz, 5-H), 7.18 (1H, s, OH), 7.39 (1H, d, J=8 Hz, 6-H), 7.98 (1H, d, J=16 Hz, ArCH=). *Anal.* Calcd for $C_{12}H_{14}O_5$: C, 60.49; H, 5.93. Found: C, 60.93; H, 6.20.

Methyl (*E*)-3-[2-Methoxy-4-(methoxymethoxy)phenyl]propenoate (18) A mixture of **17** (60.0 g, 0.25 mol), anhydrous K_2CO_3 (174 g, 1.26 mol) and dimethyl sulfate (60 ml, 0.63 mol) in dry acetone (900 ml) was refluxed for 4 h. An inorganic solid was removed by filtration and the filtrate was concentrated. Excess dimethyl sulfate was decomposed by the addition of 5% ammonia solution, and the mixture was extracted with AcOEt. The organic layer was washed with 2 M HCl and brine, dried over $MgSO_4$, and evaporated to dryness. The residue was recrystallized from MeOH, giving **18** (53.6 g, 84%) as colorless needles, mp 39—40 °C. IR (KBr): 1706 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.48 (3H, s, $CH_2OC\underline{H}_3$), 3.78, 3.86 (each 3H, s, $ArOCH_3$, $=CHCOOC\underline{H}_3$), 5.19 (2H, s, $C\underline{H}_2OCH_3$), 6.44 (1H, d, J=16 Hz, $=C\underline{H}COOCH_3$), 6.59 (1H, d, J=2 Hz, 3-H), 6.64 (1H, dd, J=2, 9 Hz, 5-H), 7.42 (1H, d, J=9 Hz, 6-H), 7.92 (1H, d, J=16 Hz, ArCH=). *Anal.* Calcd for $C_{13}H_{16}O_5$: C, 61.89; H, 6.41. Found: C, 61.86; H, 6.41.

Methyl (*E*)-3-(4-Hydroxy-2-methoxyphenyl)propenoate (10) Acetyl

chloride (4 g) was added to a solution of **18** (52.5 g, 0.21 mol) in dry MeOH (800 ml) and the reaction mixture was stirred at room temperature for 22 h. After being neutralized with saturated $NaHCO_3$ solution, the mixture was concentrated and ice-water was added. The precipitate was collected by filtration, washed with water, and dried.Recrystallization from benzene gave **10** (39.6 g, 92%) as colorless prisms, mp 136—139 °C. IR (KBr): 3391 (OH), 1697, 1674 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.79, 3.81 (each 3H, s, $ArOCH_3$, $=CHCOOCH_3$), 6.42 (1H, d, J=16 Hz, $=CHCOOCH_3$), 6.45 (1H, d, J=2 Hz, 3-H), 6.47 (1H, dd, J=2, 8 Hz, 5-H), 6.90 (1H, s, OH), 7.35 (1H, d, J=8 Hz, 6-H), 7.93 (1H, d, J=16 Hz, ArCH=). *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.44; H, 5.82. Found: C, 63.44; H, 5.78.

Oxidative Coupling Reaction of 10 with Potassium Hexacyanoferrate(III)–Sodium Carbonate To a solution of **10** (40.0 g, 0.19 mol) in $CHCl_3$ (3 l) was added dropwise a solution of potassium hexacyanoferrate(III) (63.2 g, 0.19 mol) and anhydrous Na_2CO_3 (30.6 g, 0.29 mol) in water (3 l) at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h and at room temperature for 3 h, then 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 chromatographed on a silica gel column (SiO_2 1.2 kg, *n*-hexane–AcOEt, 5 : 3, v/v). The first eluate was recrystallized from benzene to give unchanged **10** (1.2 g), and recrystallization of the second eluate from benzene gave methyl (*E*)-3-[(2*R**,3*R**)-2,3-dihydro-2-(4-hydroxy-2-methoxyphenyl)-6-methoxy-3-methoxycarbonylbenzofuran-5-yl]propenoate (**11**) (8.7 g) as colorless prisms, mp 121—123 °C. The third eluate was rechromatographed on a silica gel column (*n*-hexane–AcOEt, 5 : 2, v/v). The first eluate was recrystallized from EtOH to give methyl (*E*)-3-[(2*R**,3*R**)-2,3-dihydro-6-methoxy-3-methoxycarbonyl-2-[2-methoxy-4-[methyl (*Z*)-3-(4-hydroxy-2-methoxyphenyl)propenoate-2-yl]oxyphenyl]-benzofuran-5-yl]propenoate (**19**) (0.2 g) as colorless prisms, mp 165—167 °C, and the second eluate gave, after recrystallization from EtOH, methyl (*E*)-3-[(2*R**,3*R**)-2,3-dihydro-3-(*E*)-methoxycarbovinyl-6-methoxy-3′-methoxy-1′-oxo-2′-cyclohexeno[4′,5′-*b*]benzofuran-5-yl]propenoate (**20**) (0.5 g) as colorless scales, mp 173—175 °C.

11: IR (KBr): 3420 (OH), 1734, 1713, 1677 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.71 (3H, s, Ar-2′-OCH_3), 3.79 (3H, s, $=CH$–$COOCH_3$), 3.80 (3H, s, 3-$COOCH_3$), 3.83 (3H, s, Ar-6-OCH_3), 4.18 (1H, dd, J=1, 6 Hz, 3-H), 6.30 (1H, d, J=6 Hz, 2-H), 6.32 (1H, s, OH), 6.38 (1H, d, J=16 Hz, $=CH$–$COOCH_3$), 6.39 (1H, dd, J=2, 8 Hz, 5′-H), 6.44 (1H, d, J=2 Hz, 3′-H), 6.48 (1H, s, 7-H), 7.13 (1H, d, J=8 Hz, 6′-H), 7.35 (benzene), 7.41 (1H, d, J=1 Hz, 4-H), 7.95 (1H, d, J=16 Hz, Ar-5-CH=). ^{13}C-NMR ($CDCl_3$) δ: 51.6 ($=CHCOOCH_3$), 52.7 (3-$COOCH_3$), 53.6 (C3), 55.3 (Ar-2′-OCH_3), 55.7 (Ar-6-OCH_3), 84.1 (C2), 93.8 (C7), 99.2 (C3′), 106.8 (C5′), 114.7 ($=CHCOOCH_3$), 116.2 (C5), 117.1 (C3a), 120.0 (C1′), 124.9 (C4), 127.4 (C6′), 128.3 (benzene), 140.6 (Ar-5-CH=), 157.6 (C2′, C4′), 160.8 (C6), 162.9 (C7a), 168.8 ($=CHCOOCH_3$), 172.1 (3-$COOCH_3$). *Anal.* Calcd for $C_{22}H_{22}O_8 \cdot 1/2C_6H_6$: C, 66.21; H, 5.59. Found: C, 66.23; H, 5.56.

19: IR (KBr): 3421 (OH), 1712 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.47 (3H, s, 3-$COOCH_3$), 3.66 (3H, s, Ar-2′-OCH_3), 3.78 (3H, s, $=CHCOOCH_3$), 3.79 (3H, s, $=C$–$COOCH_3$), 3.82 (3H, s, Ar-2″-OCH_3), 3.86 (3H, s, Ar-6-OCH_3), 4.06 (1H, dd, J=1, 6 Hz, 3-H), 6.24 (1H, d, J=6 Hz, 2-H), 6.29 (1H, s, OH), 6.34 (1H, dd, J=2, 8 Hz, 5′-H), 6.40 (1H, d, J=2 Hz, 3′-H), 6.41 (1H, d, J=16 Hz, $=CHCOOCH_3$), 6.49 (1H, s, 7-H), 6.54(1H, dd, J=2, 9 Hz, 5″-H), 6.60 (1H, d, J=2 Hz, 3″-H), 7.08 (1H, d, J=8 Hz, 6′-H), 7.37 (1H, d, J=9 Hz, 6″-H), 7.80 (1H, d, J=1 Hz, 4-H), 7.88 (1H, s, Ar-1″-CH=), 7.88 (1H, d, J=16 Hz, Ar-5-CH=). ^{13}C-NMR ($CDCl_3$) δ: 51.6 ($=CHCOOCH_3$), 52.2 (3-$COOCH_3$), 52.4 ($=C$–$COOCH_3$), 53.5 (C3), 55.3 (Ar-2′-OCH_3), 55.5 (Ar-2″-OCH_3), 55.9 (Ar-6-OCH_3), 84.0 (C2), 93.4 (C7), 99.1 (C3′), 99.2 (C3″), 106.8 (C5′), 106.8 (C5″), 113.6 (C3a), 116.1 ($=CHCOOCH_3$), 117.1 (C5), 117.8 (C1″), 119.9 (C1′), 122.3 (Ar-1″-CH=), 126.6 (C4), 127.3 (C6′), 130.4 (C6″), 136.4 ($=C$–$COOCH_3$), 140.1 (Ar-5-CH=), 157.5 (C2′), 157.5 (C4′), 159.6 (C4″), 159.9 (C2″), 160.3 (C6), 162.4 (C7a), 164.5 ($=C$–$COOCH_3$), 168.5 ($=CHCOOCH_3$), 171.8 (3-$COOCH_3$). *Anal.* Calcd for $C_{33}H_{32}O_{12}$: C, 63.86; H, 5.21. Found: C, 63.88; H, 5.22. MS *m/z*: 620 (M^+).

20: IR (KBr): 1712, 1655 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.74 (1H, dd, J=4, 18 Hz, 6′-H), 3.00 (1H, dd, J=3, 18 Hz, 6′-H), 3.69 (3H, s, Ar-3′-OCH_3), 3.79 (6H, s, $=CHCOOCH_3 \times 2$), 3.86 (3H, s, Ar-6-OCH_3), 4.90 (1H, dd, J=3, 4 Hz, 2-H), 5.55 (1H, s, 2′-H), 6.03 (1H, d, J=16 Hz, 3-CH=$CHCOOCH_3$), 6.42 (1H, d, J=16 Hz, Ar-5-CH=$CHCOOCH_3$), 6.43 (1H, s, 7-H), 7.10 (1H, d, J=16 Hz, 3-CH=$CHCOOCH_3$), 7.43 (1H, s, 4-H), 7.93 (1H, d, J=16 Hz, Ar-5-CH=$CHCOOCH_3$). ^{13}C-NMR ($CDCl_3$) δ: 36.5 (C6′), 51.4 (3-CH=$CHCOOCH_3$), 51.9 (Ar-5-CH=$CHCOOCH_3$), 53.7 (C3),55.8 (Ar-6-OCH_3), 56.4 (Ar-3′-OCH_3), 86.0 (C2), 94.4 (C7), 103.1 (C2′), 116.0 (Ar-5-CH=$CHCOOCH_3$), 117.5 (C5), 120.7 (C3a), 124.4 (3-CH=$CHCOOCH_3$), 126.3 (C4), 139.7 (Ar-5-CH=$CHCOOCH_3$), 144.8 (3-CH=$CHCOOCH_3$), 160.8 (C6), 162.0 (C7a), 165.7 (3-CH=$CHCOOCH_3$), 167.9 (Ar-5-CH=$CHCOOCH_3$), 171.2 (C3′), 193.5 (C1′). *Anal.* Calcd for $C_{22}H_{22}O_8$: C, 63.75; H, 5.36. Found: C, 63.74; H, 5.43. MS *m/z*: 414 (M^+).

Methyl (*E*)-3-[(2*R,3*R**)-2,3-Dihydro-2-(4-acetoxy-2-methoxyphenyl)-6-methoxy-3-methoxycarbonylbenzofuran-5-yl]propenoate (21)** A solution of **11** (7.0 g, 16.9 mmol) in dry pyridine (61 ml) and acetic anhydride (48 ml, 0.51 mol) was stirred at room temperature for 20 h. The reaction mixture was poured into 6 M HCl–ice-water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was recrystallized from EtOH, giving **21** (6.9 g, 89%) as colorless prisms, mp 134—136 °C. IR (KBr): 1764, 1731, 1707 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.29 (3H, s, CH_3CO), 3.78 (6H, s, Ar-2′-OCH_3, $=CHCOOCH_3$), 3.82 (3H, s, 3-$COOCH_3$), 3.87 (3H, s, Ar-6-OCH_3), 4.14 (1H, d, J=5 Hz, 3-H), 6.36 (1H, d, J=5 Hz, 2-H), 6.38 (1H, d, J=16 Hz, $=CHCOOCH_3$), 6.53 (1H, s, 7-H), 6.66 (1H, d, J=2 Hz, 3′-H), 6.67 (1H, dd, J=2, 8 Hz, 5′-H), 7.34 (1H, d, J=8 Hz, 6′-H), 7.41 (1H, s, 4-H), 7.94 (1H, d, J=16 Hz, Ar-5-CH=). ^{13}C-NMR ($CDCl_3$) δ: 21.1 (CH_3CO), 51.4 ($=CHCOOCH_3$), 52.6 (3-$COOCH_3$), 53.7 (C3), 55.5 (Ar-2′-OCH_3), 55.7 (Ar-6-OCH_3), 83.5 (C2), 93.8 (C7), 104.9 (C3′), 113.3 (C5′), 115.1 ($=CHCOOCH_3$), 116.6 (C5), 116.8 (C3a), 124.8 (C4), 126.0 (C1′), 126.5 (C6′), 140.0 (Ar-5-CH=), 151.5 (C4′), 156.6 (C2′), 160.7 (C6), 162.6 (C7a), 168.2 ($=CHCOOCH_3$), 169.3 (CH_3CO), 171.7 (3-$COOCH_3$). *Anal.* Calcd for $C_{24}H_{24}O_9$: C, 63.14; H, 5.31. Found: C, 62.99; H, 5.36. MS *m/z*: 456 (M^+).

Methyl (*E*)-3-[(2*R,3*R**)-2,3-Dihydro-2-(4-acetoxy-2-methoxyphenyl)-4-methoxy-3-methoxycarbonylbenzofuran-5-yl]propenoate (23)** The mother liquor of recrystallization of **11** (1.6 g) was dissolved in dry pyridine (20 ml) and acetic anhydride (16 ml, 0.17 mol), and the mixture was stirred at room temperature for 20 h. The reaction mixture was poured into 6 M HCl–ice-water and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. Half (0.7 g) of the residue was purified by chromatography on a silica gel column (*n*-hexane–AcOEt, 5 : 2, v/v) twice and recrystallized from EtOH to afford **23** (0.1 g) as colorless needles, mp 100—102 °C. IR (KBr): 1743, 1728 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s, CH_3CO), 3.77 (3H, s, Ar-4-OCH_3), 3.79 (3H, s, $=CHCOOCH_3$), 3.80 (3H, s, Ar-2′-OCH_3), 3.83 (3-$COOCH_3$), 4.23 (1H, d, J=7 Hz, 3-H), 6.20 (1H, d, J=7 Hz, 2-H), 6.36 (1H, d, J=16 Hz, $=CHCOOCH_3$), 6.67(1H, d, J=2 Hz, 3′-H), 6.69 (1H, dd, J=2, 9 Hz, 5′-H), 6.75 (1H, d, J=9 Hz, 7-H), 7.38 (1H, d, J=9 Hz, 6′-H), 7.48 (1H, d, J=9 Hz, 6-H), 7.86 (1H, d, J=16 Hz, Ar-5-CH=). ^{13}C-NMR ($CDCl_3$) δ: 21.1 (CH_3CO), 51.5 ($=CHCOOCH_3$), 52.6 (3-$COOCH_3$), 53.7 (C3), 55.5 (Ar-2′-OCH_3), 60.8 (Ar-4-OCH_3), 84.3 (C2), 104.7 (C3′), 106.4 (C7), 113.4 (C5′), 116.2 ($=CHCOOCH_3$), 117.7 (C3a), 120.8 (C5), 126.0 (C1′), 126.1 (C6′), 130.5 (C6), 139.5 (Ar-5-CH=), 151.5 (C4′), 156.4 (C2′), 156.7 (C4), 163.3 (C7a), 167.9 ($=CHCOOCH_3$), 169.4 (CH_3CO), 172.3 (3-$COOCH_3$). *Anal.* Calcd for $C_{24}H_{24}O_9$: C, 63.14; H, 5.31. Found: C, 63.24; H, 5.34. MS *m/z*: 456 (M^+).

Methyl (*E*)-3-[2-Methoxy-4-((*Z*)-α-methoxycarbonyl-4-hydroxy-2-methoxystyryl)oxyphenyl]propenoate (24), Methyl (*E*)-3-[4-Hydroxy-2-methoxy-3-((*Z*)-α-methoxycarbonyl-4-hydroxy-2-methoxystyryl)phenyl]-propenoate (25) The rest (0.7 g) of the above residue was dissolved in dry MeOH (70 ml) and sodium methoxide solution (28% in MeOH, 14 ml, 0.07 mol) was added. After the mixture was stirred at 0 °C for 1 h, 6 M HCl–ice-water was added and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was chromatographed on a silica gel column (*n*-hexane–AcOEt, 5 : 1, v/v). The first eluate was recrystallized from EtOH to afford **24** (0.05 g) as colorless scales, mp 204—205 °C, and the second eluate was recrystallized from EtOH, giving **25** (0.12 g) as colorless needles, mp 173—175 °C.

24: IR (KBr): 3392 (OH), 1714, 1692 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.77 (6H, s, $COOCH_3 \times 2$), 3.85 (3H, s, Ar-2′-OCH_3), 3.88 (3H, s, Ar-2-OCH_3), 6.37 (1H, dd, J=2, 9 Hz, 5′-H), 6.41 (1H,d, J=16 Hz, $=CHCOOCH_3$), 6.42 (1H, d, J=2 Hz, 3′-H), 6.52 (1H, dd, J=2, 9 Hz,

5-H), 6.61 (1H, d, J=2 Hz, 3-H), 7.39 (1H, d, J=9 Hz, 6-H), 7.44 (1H, s, OH), 7.71 (1H, d, J=9 Hz, 6'-H), 7.85 (1H, s, Ar-1'-CH=), 7.88(1H, d, J=16 Hz, Ar-1-CH=). ^{13}C-NMR ($CDCl_3$) δ: 51.0, 51.8 ($COO\underline{C}H_3 \times 2$), 55.1, 55.2 (Ar-$OCH_3 \times 2$), 98.8 (C3'), 98.9 (C3), 106.5 (C5), 107.9 (C5'), 111.8 (C1'), 115.7 (=$\underline{C}$HCOOCH$_3$), 117.3 (C1), 121.7 (Ar-1'-CH=), 129.8 (C6), 131.1 (C6'), 135.5 (=$\underline{C}$–COOCH$_3$), 139.4 (Ar-1-CH=), 159.2 (C2'), 159.4 (C4), 159.5 (C2), 160.6 (C4'), 163.9 (=C–$\underline{C}$OOCH$_3$), 167.6 (=CH–$\underline{C}$OOCH$_3$). *Anal.* Calcd for $C_{22}H_{22}O_8$: C, 63.75; H, 5.36. Found: C, 63.43; H, 5.39. MS m/z: 414 (M^+).

25: IR (KBr): 3397 (OH), 1684 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.58 (3H, s, Ar-2-OCH_3), 3.74 (3H, s, =C–$COOCH_3$), 3.77 (3H, s, =CHCOO$\underline{C}$H$_3$), 3.82 (3H, s, Ar-2'-OCH_3), 6.12 (1H, dd, J=2, 9 Hz, 5'-H), 6.34 (1H, d, J=16 Hz, =C$\underline{H}$COOCH$_3$), 6.37 (1H, d, J=2 Hz, 3'-H), 6.74 (1H, d, J=9 Hz, 5-H), 6.78 (1H, d, J=9 Hz, 6'-H), 7.45 (1H, d, J=9 Hz, 6-H), 7.87 (1H, d, J=16 Hz, Ar-1-CH=), 8.32 (1H, s, Ar-1'-CH=), 8.80, 9.21 (each 1H, s, OH). ^{13}C-NMR ($CDCl_3$) δ: 51.1 (=CHCOO$\underline{C}$H$_3$), 51.7 (=CCOO$\underline{C}$H$_3$), 55.2 (Ar-2'-OCH_3), 61.3 (Ar-2-OCH_3), 98.4 (C3'), 107.5 (C5'), 112.2 (C5), 114.7 (=$\underline{C}$H-COOCH$_3$), 114.9 (C1'), 118.4 (C3), 119.1 (C1), 119.4 (=$\underline{C}$–COOCH$_3$), 128.0 (C6), 129.3 (C6'), 136.1 (Ar-1'-CH=), 139.8 (Ar-1-CH=), 158.0 (C4), 158.6 (C2), 159.9 (C2'), 160.2 (C4'), 167.7 (=CH$\underline{C}$OOCH$_3$), 168.5 (=C–$\underline{C}$OOCH$_3$). MS m/z: 414 (M^+).

Oxidative Coupling Reaction with Silver Oxide Silver oxide (1.67 g, 7.2 mmol) was added to a solution of **10** (1.5 g, 7.2 mmol) in benzene–acetone (45 ml, 2 : 1, v/v) under nitrogen atmosphere and the mixture was stirred at room temperature for 24 h. The suspension was filtered and the filtrate was evaporated to dryness. The residue was chromatographed on a silica gel column (SiO_2 45 g, *n*-hexane–AcOEt, 5 : 3, v/v), giving unchanged **10** (0.24 g) in the first eluate and a resinous solid (0.44 g) from the second eluate, of which the product ratio was analyzed by means of HPLC.

Oxidative Coupling Reaction with Potassium Hexacyanoferrate(III)–Sodium Carbonate (for Measurement of the Product Ratio) The reaction was conducted essentially in the same way as the preparative experiment, except that the stirring of the reaction mixture at room temperature was stopped after 1h. After chromatography (SiO_2 30 g, *n*-hexane–AcOEt, 5 : 3, v/v), the resinous product mixture (0.40 g) with unchanged **10** (0.09 g) was obtained from 1.0 g of the starting material.

Product Analysis of Oxidative Coupling Reaction by HPLC HPLC analysis was performed on a column (Shiseido Capcell Pak C_{18}, 6 × 250 mm) with a solvent system of acetonitrile–water (1 : 1, v/v) containing 1% formic acid, at a flow rate of 1 ml/min (Waters model 6000A delivery system). A Sowa S-310 UV detector was used, set at 254 nm.

Methyl (*E*)-3-[2-(4-Acetoxy-2-methoxyphenyl)-6-methoxy-3-methoxycarbonylbenzofuran-5-yl]propenoate (26) To a solution of **21** (6.0 g, 13.1 mmol) in dry dioxane (100 ml) was added a solution of DDQ (3.9 g, 17 mmol) in dry dioxane (100 ml) and the mixture was refluxed for 40 h. After cooling, the precipitate formed was filtered and washed with CH_2Cl_2. The filtrate and the washing were combined and evaporated to dryness, and the residue was recrystallized from AcOEt to afford **26** (6.0 g, 100%) as pale yellow needles, mp 172—173 °C. IR (KBr): 1755, 1718 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s, CH_3CO), 3.80, 3.82, 3.85, 3.93 (each 3H, s, Ar-$OCH_3 \times 2$, $COOCH_3 \times 2$), 6.61 (1H, d, J=16 Hz, =C$\underline{H}$COOCH$_3$), 6.78 (1H, d, J=2 Hz, 3'-H), 6.84 (1H, dd, J=2, 8 Hz, 5'-H), 7.04 (1H, s, 7-H), 7.55 (1H, d, J=8 Hz, 6'-H), 8.12 (1H, d, J=16 Hz, ArCH=), 8.14 (1H, s, 4-H). *Anal.* Calcd for $C_{24}H_{22}O_9$: C, 63.42; H, 4.89. Found: C, 63.41; H, 4.93. MS m/z: 454 (M^+).

Methyl (*E*)-3-[2-(4-Hydroxy-2-methoxyphenyl)-6-methoxy-3-methoxycarbonylbenzofuran-5-yl]propenoate (27) Sodium methoxide solution (28% in MeOH, 10 ml, 52 mmol) was added to a solution of **26** (0.5 g, 1.1 mmol) in dry MeOH–CH_2Cl_2 (100 ml, 1 : 1, v/v) and the mixture was stirred at 0 °C for 1 h, then poured into 6 M HCl–ice-water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was recrystallized from acetone to afford **27** (0.4 g, 85%) as pale yellow scales, mp 218—219 °C. IR (KBr): 3385 (OH), 1692 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.73, 3.74, 3.78, 3.93 (each 3H, s, Ar-$OCH_3 \times 2$, $COOCH_3 \times 2$), 6.51 (1H, dd, J=2, 8 Hz, 5'-H), 6.55 (1H, d, J=2 Hz, 3'-H), 6.61 (1H, d, J=16 Hz, =C$\underline{H}$COOCH$_3$), 7.36 (1H, d, J=8 Hz, 6'-H), 7.41 (1H, s, 7-H), 7.97 (1H,d, J=16 Hz, ArCH=), 8.07 (1H, s, 4-H), 10.10 (1H, s, OH). MS m/z: 412 (M^+).

Methyl (*E*)-3-[2-(4-Acetoxy-2-hydroxyphenyl)-6-methoxy-3-methoxycarbonylbenzofuran-5-yl]propenoate (28) To a solution of **26** (0.5 g, 1.1 mmol) in dry CH_2Cl_2 (30 ml) was added dropwise a solution of boron tribromide (1.6 ml, 17 mmol) in dry CH_2Cl_2 (15 ml) at −78 °C. The mixture was stirred at −78 °C for 4 h and then poured into ice-water. 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 recrystallized from MeOH, giving **28** (0.4 g, 81%) as yellow needles, mp 192—193 °C. IR (KBr): 3422 (OH), 1764, 1707 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.32 (3H, s, CH_3CO), 3.75 (3H, s, =CHCOOC$\underline{H}_3$), 3.81 (3H, s, 3-$COOCH_3$), 3.93 (1H, s, Ar-6-OCH_3), 6.60 (1H, d, J=16 Hz, =C$\underline{H}$COOCH$_3$), 6.74 (1H, dd, J=2, 8 Hz, 5'-H), 6.79 (1H, d, J=2 Hz, 3'-H), 7.38 (1H, s, 7-H), 7.51 (1H, d, J=8 Hz, 6'-H), 7.96 (1H, d, J=16 Hz, Ar-CH=), 8.07 (1H, s, 4-H), 10.46 (1H, s, OH). ^{13}C-NMR (DMSO-d_6) δ: 20.9 ($\underline{C}H_3CO$), 51.4 (=CHCOO$\underline{C}$H$_3$), 51.5 (3-COO$\underline{C}$H$_3$), 56.3 (Ar-6-OCH_3), 95.2 (C7), 109.5 (C3'), 110.1 (C3), 112.3 (C5'), 114.3 (C1'), 117.4 (=$\underline{C}$HCOOCH$_3$), 119.3 (C3a), 119.9 (C5), 120.8 (C4), 131.7 (C6'), 139.7 (ArCH=), 152.8 (C2), 155.8 (C7a), 156.8 (C2'), 156.9 (C6), 157.4 (C4'), 163.2 (3-$\underline{C}$OOCH$_3$), 166.9 (=CH$\underline{C}$OOCH$_3$), 168.9 ($CH_3\underline{C}O$). MS m/z: 440 (M^+).

6-Hydroxy-2-(2,4-dihydroxyphenyl)-3-methoxycarbonylbenzofuran-5-yl]propenoic Acid-δ-lactone (29) To a solution of **26** (2.0 g, 4.4 mmol) in dry CH_2Cl_2 (150 ml) was added dropwise a solution of boron tribromide (6.1 ml, 66 mmol) in dry CH_2Cl_2 (50 ml) at −78 °C. The mixture was stirred at room temperature for 16 h and then poured into ice-water. The precipitate formed was collected by filtration and dissolved in AcOEt. The solution was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was recrystallized from acetone, giving **29** (1.2 g, 79%) as yellow needles, mp >300 °C. IR (KBr): 3366, 3276 (OH), 1698 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.79 (3H, s, $COOCH_3$), 6.39 (1H, dd, J=2, 8 Hz, 5'-H), 6.46 (1H, d, J=2 Hz, 3'-H), 6.47 (1H, d, J=10 Hz, =CHCOO), 7.35 (1H, d, J=8 Hz, 6'-H), 7.75 (1H, s, 7-H), 8.16 (1H, s, 4-H), 8.24 (1H, d, J=10 Hz, ArCH=), 9.93 (1H, s, 4'-OH), 10.05 (1H, s, 2'-OH). ^{13}C-NMR (DMSO-d_6) δ: 51.4 (COO$\underline{C}$H$_3$), 99.3 (C7), 102.6 (C3'), 106.9 (C5'), 107.4 (C1'), 108.4 (C3), 114.4 (=$\underline{C}$HCOO), 116.0 (C5), 120.3 (C4), 123.9 (C3a), 131.9 (C6'), 145.0 (ArCH=), 151.6 (C6), 154.4(C7a), 157.5 (C2'), 160.1 (=CH$\underline{C}$OO), 160.5 (C2), 160.9 (C4'), 163.4 (3-$\underline{C}$OOCH$_3$). *Anal.* Calcd for $C_{19}H_{12}O_7$: C, 64.77; H, 3.44. Found: C, 64.70; H, 3.41.

7',6-Dihydroxycoumarino[3',4'-*b*]benzofuran-5-yl-propenoic Acid-δ-lactone (13) A mixture of **29** (0.5 g, 1.4 mmol), AcOH (30 ml) and 50% H_2SO_4 (30 ml) was stirred at 100 °C for 2 h. The reaction mixture was poured into ice-water and the precipitate formed was collected by filtration, washed with water, and dried. Recrystallization from DMSO gave **13** (0.4 g, 88%) as colorless prisms, mp >300 °C. IR (KBr): 3259 (OH), 1725, 1698, 1682 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.55 (1H, d, J=10 Hz, =CHCOO), 6.94 (1H, d, J=2 Hz, 8'-H), 6.98 (1H, dd, J=2, 9 Hz, 6'-H), 7.94 (1H, d, J=9 Hz, 5'-H), 8.03 (1H, s, 7-H), 8.30 (1H, s, 4-H), 8.33 (1H, d, J=10 Hz, Ar-5-CH=). *Anal.* Calcd for $C_{18}H_8O_6$: C, 67.50; H, 2.52. Found: C, 67.28; H, 2.53.

7'-Acetoxy-6-hydroxycoumarino[3',4'-*b*]benzofuran-5-yl-propenoic Acid-δ-lactone (30) Compound **13** (0.20 g, 0.62 mmol) was dissolved in dry pyridine (6 ml) and acetic anhydride (5 ml, 53 mmol), and the mixture was stirred at room temperature for 18 h. The reaction mixture was poured into 6 M HCl–ice-water and the precipitate was collected by filtration, washed with water, and dried. Recrystallization from DMF gave **30** (0.22 g, 99%) as colorless needles, mp >300 °C. IR (KBr): 1736 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.35 (3H, s, CH_3CO), 6.59 (1H, d, J=10 Hz, =CHCOO), 7.38 (1H, dd, J=2, 9 Hz, 6'-H), 7.56 (1H, d, J=2 Hz, 8'-H), 8.12 (1H, s, 7-H), 8.18 (1H, d, J=9 Hz, 5'-H), 8.36 (1H, d, J=10 Hz, Ar-5-CH=), 8.41 (1H, s, 4-H). *Anal.* Calcd for $C_{20}H_{10}O_7$: C, 66.30; H, 2.79. Found: C, 66.30; H, 2.66. MS m/z: 362 (M^+).

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