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

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The oxidative coupling reaction of the hydroxycinnamate 11 derived from daphnetin has been investigated. The reaction with silver oxide afforded, after acetylation, a dihydrobenzofuran derivative 17 and a benzodioxane derivative 16a as major products accompanied with a small amount of a bis(benzylidene)succinate 18 and a dihydronaphthalene 19, while the oxidation with iron(III) chloride gave the dihydronaphthalene derivative 20 corresponding to 19. The reaction with potassium hexacyanoferrate(III) and Na_2CO_3 produced, after acetylation, 16a and 19 in lower yields. The propensity for product formation in the reaction of 11 is discussed in relation to data for the reactions of hydroxycinnamate derivatives studied so far.

The obtained compounds were tested for inhibitory effects on lipid peroxidation in rat brain homogenate and rat liver microsomes. In the rat brain homogenate the five compounds showed inhibitory activity more potent than that of idebenone. Compounds 17 and 20 were then tested in rat liver microsomes, and found to be more potent than schizotenuin A and much more potent than (±)-α-tocopherol.

Keywords lignan; oxidative coupling reaction; lipid peroxidation inhibitor; daphnetin

In the first paper of this series we reported efficient synthesis of schizotenuin D (**1**) and related compounds, which showed potent inhibitory effects on lipid peroxidation, by using the oxidative coupling reaction of methyl ferulate (**2**) as the key reaction.[2] In a continuation of our search for lipid peroxidation inhibitors, the similar reactions of hydroxycinnamate derivatives obtained from coumarins have been investigated. A dihydronaphthalene derivative **6**[3] was synthesized as a major product by the oxidative coupling reaction of the hydroxycinnamate derivative **5** obtained from esculetin (**4**), whereas a dihydrobenzofuran derivative **9**[1] was produced as the major product by the reaction of **8** obtained from umbelliferone (**7**). Thus the coupling mode appears to be dependent on the substrate structure.

In a series of studies on the synthesis of bioactive lignans from coumarins, our attention was directed toward their synthesis from daphnetin (**10**), which is synthetically easily accessible. With regard to the reaction mode of the hydroxycinnamate derivatives **2**, **8** and **5**, the β position and the 5 position radicals derived from the two substrates **2** and **8** are capable of coupling with each other to yield the dihydrobenzofuran derivatives **3** and **9**, respectively. Contrastingly, in the case of substrate **5** the coupling between the β position and the 3 position radical species would fail to occur due to the steric hindrance imposed by the 2-methoxy group, and the mutual coupling of two β position radicals would result in the formation of the dihydronaphthalene derivative **6**. We considered that the hydroxycinnamate derivative **11** obtained from daphnetin (**10**), without the steric interference by the methoxy group, would afford a dihydrobenzofuran derivative **12** analogous to **3** and **9** on oxidation.

Daphnetin (**10**) is a major biologically active constituent of *Daphne giraldii* NITSCHE, which is used as a Chinese crude drug.[4] From this viewpoint, investigation of the products obtained by the oxidative coupling reaction of **11** derived from daphnetin would be interesting, since the compounds obtained synthetically could be as yet undetected biologically active plant constituents.

Results and Discussion

Preparation of the Hydroxycinnamate Substrate 11 from Daphnetin and Its Oxidative Coupling Reaction Daphnetin (**10**)[5] was first converted to the bismethoxymethyl derivative (**13**) in 73% yield by treatment with sodium hydride and chloromethyl methyl ether in tetrahydrofuran (THF)–dimethylformamide (DMF). The protected compound **13** was subjected to opening of the coumarin ring using sodium methoxide in dry MeOH to afford the methyl ester **14** in 77% yield. The phenolic hydroxy group of **14** was then methylated with dimethyl sulfate and the product **15** (obtained in 85% yield) was deprotected by treatment with a catalytic amount of acid to give the desired compound **11** in quantitative yield.

The oxidative coupling reaction of **11** was examined with silver oxide, potassium hexacyanoferrate(III) and iron(III) chloride, as in the previous papers.[1-3] Firstly **11** was treated with 0.6-fold molar eq of silver oxide in benzene–acetone at room temperature. After acetylation of the crude products with acetic anhydride in pyridine, the separation was performed by chromatography on silica gel to afford **16a**, **17**, **18** and **19** in 7%, 15%, 1% and 1% yields, respectively.

The molecular formula $C_{26}H_{26}O_{12}$ of the acetate **16a** as determined by elemental analysis and MS measurement [*m/z*: 530 (M^+)] indicated that **16a** is the diacetate of a dimer of **11**. The ^{1}H-NMR spectrum of **16a** closely resembled that of a benzodioxane compound **21**, which was obtained previously[3] as a minor product in the

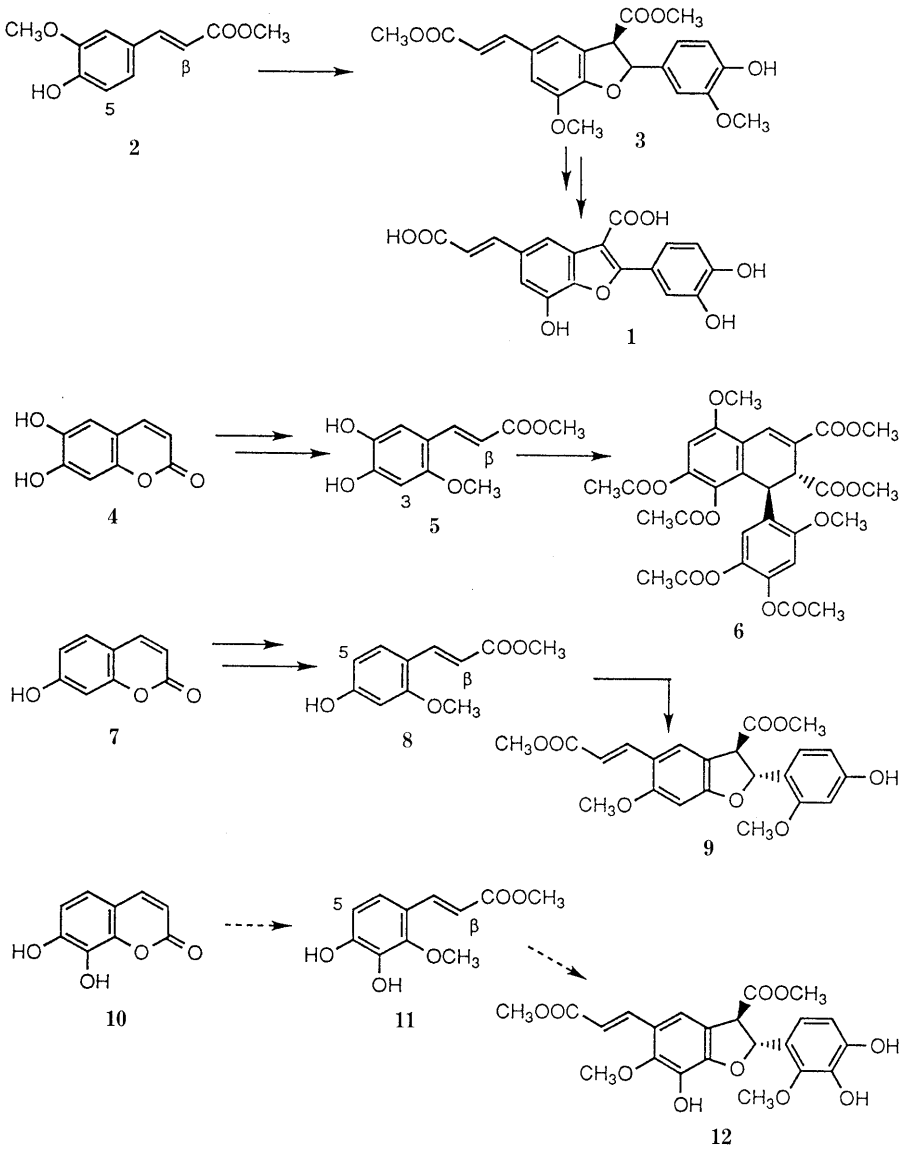


Chart 1

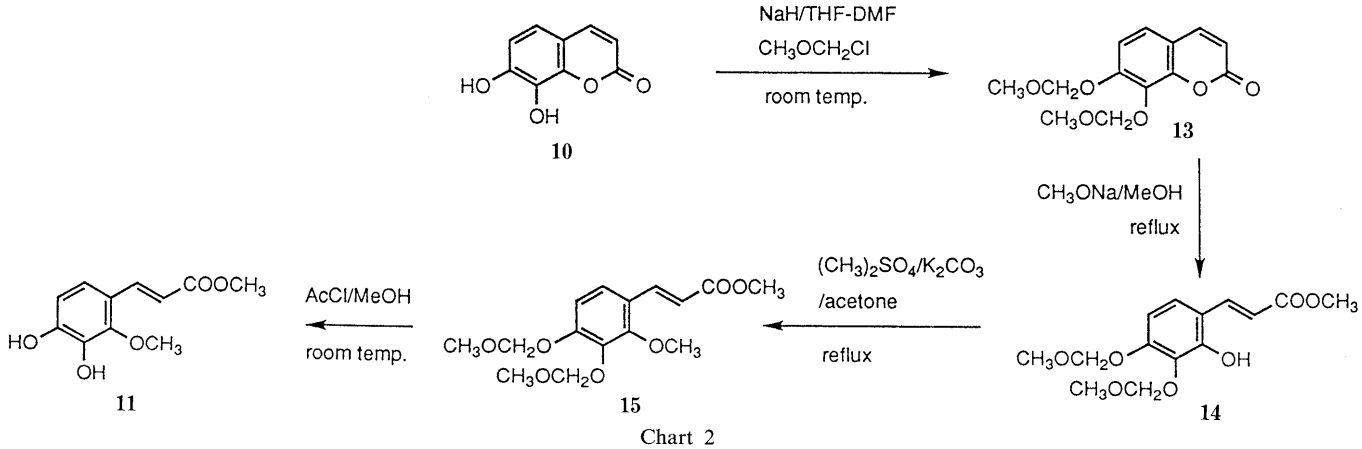


Chart 2

oxidation of the hydroxycinnamate **5** derived from esculetin (**4**). When the ^{1}H-NMR spectra of compounds **16a** and **21** were compared, the only marked difference lay in the aromatic proton region, where two AB type signals with *ortho* coupling constants (δ 6.72, 7.13, J=9 Hz; δ 6.96, 7.23, J=9 Hz) were observed in the spectrum of **16a** instead of two pairs of singlets in that of **21** (δ 6.53, 7.17; δ 6.78, 7.07). From these facts, the acetate

TABLE I. ^{13}C-NMR and ^{1}H-NMR Data for Compounds **16a** and **21** in $CDCl_3$

Position	**16a**		**21**[a]	
	^{13}C-NMR	^{1}H-NMR	^{13}C-NMR	^{1}H-NMR
2	71.0	5.65 (1H, d, 5)	71.1	5.73 (1H, d, 4)
3	74.6	4.95 (1H, d, 5)	74.5	4.87 (1H, d, 4)
4a	135.6		135.5	
5	148.3		116.8	7.17 (1H, s)
6	121.8		117.3	
7	120.4	7.13 (1H, d, 9)	154.1	
8	112.7	6.72 (1H, d, 9)	100.4	6.53 (1H, s)
8a	145.2		144.9	
1′	127.4		122.5	
2′	150.9		154.3	
3′	135.8		106.2	6.78 (1H, s)
4′	144.2		142.8	
5′	118.5	6.96 (1H, d, 9)	135.5	
6′	124.8	7.23 (1H, d, 9)	122.1	7.07 (1H, s)
=CHCOO	117.1	6.43 (1H, d, 16)	116.6	6.39 (1H, d, 16)
ArCH=	139.3	7.92 (1H, d, 16)	139.4	7.91 (1H, d, 16)
$OCOCH_3$	20.3, 20.6	2.28, 2.35 (each, 3H, s)	20.5, 20.6	2.24, 2.28 (each, 3H, s)
5-OCH_3	61.5	3.98 (3H, s)	7-OCH_3 55.9	7-OCH_3 3.82 (3H, s)
2′-OCH_3	61.7	3.90 (3H, s)	56.1	3.84 (3H, s)
=CHCOOCH_3	51.6	3.80 (3H, s)	51.5	3.78 (3H, s)
3-COOCH_3	52.8	3.70 (3H, s)	52.6	3.70 (3H, s)
OCOCH_3	167.4, 167.9		167.9, 168.4	
=CHCOOCH_3	167.8		168.0	
3-COOCH_3	167.6		168.0	

a) Ref. 3.

16a was deduced to have a benzodioxane structure formed by the homolytic addition of the vicinal phenolic hydroxy groups of **11** to the double bond of the (*E*)-propenoate chain in another molecule of **11**. In this coupling reaction there are two possible modes through which the regioisomers **16a** and **16b** can be formed. The discrimination of the structure **16a** from **16b** was performed by the application of ^{1}H–^{13}C-NMR gated decoupling and long-range spin decoupling (LSPD) techniques; coupling was observed between the signals due to the methine proton at the 2 position and the aromatic carbon (C-8a, δ 145.2), and between the signals due to the methine proton at the 3 position and the aromatic carbon (C-4a, δ 135.6). The stereochemistry of the dioxane ring in **16a** was assigned as *cis* from the coupling constant value (J_{H2-H3} = 5 Hz) with reference to previous data.[3,6]

The second product **17** was formulated as $C_{28}H_{28}O_{13}$ (MS and elemental analysis), indicating that **17** is the triacetate of a dimer. The ^{1}H-NMR spectrum of **17** was similar to those of the acetate of the dihydrobenzofuran compound **3**[2] and **9**.[1] Thus, the signal patterns observed in the ^{1}H- and ^{13}C-NMR fully substantiated the formulation of the product as **17**. The stereochemistry of the dihydrobenzofuran ring in **17** was assigned as *trans* on the basis of the coupling constant value (J_{H2-H3} = 6 Hz), with reference to previous data.[1,7]

The third product **18** has the molecular formula $C_{30}H_{30}O_{14}$ as revealed by elemental analysis and MS measurement, thus being the tetraacetate of the dimer. In the ^{1}H-NMR spectrum of **18**, the typical AX-type signal due to the protons of the (*E*)-propenoate chain of **11** disappeared and a new methine proton signal (δ 7.85, s) appeared instead. In addition, two singlets due to acetyl groups, a singlet due to a methoxy group and a singlet due to a methyl ester group were observed. These spectral data, in conjunction with the molecular formula, suggested that the product **18** might be the symmetric dimer formed by the mutual combination of β position radicals derived from **11**. The ^{13}C-NMR spectrum was also compatible

TABLE II. ^{13}C-NMR and ^{1}H-NMR Data for Compounds **17** in $CDCl_3$

Position	**17**	
	^{13}C-NMR	^{1}H-NMR
2	84.4	6.39 (1H, d, 6)
3	54.4	4.32 (1H, dd, 1, 6)
3a	121.8	
4	120.9	7.41 (1H, d, 1)
5	121.9	
6	153.0	
7	128.2	
7a	153.5	
1′	131.3	
2′	150.1	
3′	135.8	
4′	143.8	
5′	118.4	6.95 (1H, d, 9)
6′	124.3	7.28 (1H, d, 9)
=CHCOO	117.0	6.39 (1H, d, 16)
ArCH=	139.0	7.87 (1H, d, 16)
OCOCH_3	20.3, 20.4, 20.6	2.28, 2.33, 2.36 (each 3H, s)
6-OCH_3	62.1	3.84 (3H, s)
2′-OCH_3	61.3	3.78 (3H, s)
3-COOCH_3	52.9	3.83 (3H, s)
=CHCOOCH_3	51.6	3.80 (3H, s)
OCOCH_3	167.5, 167.9, 168.0	
3-COOCH_3	170.6	
=CHCOOCH_3	167.7	

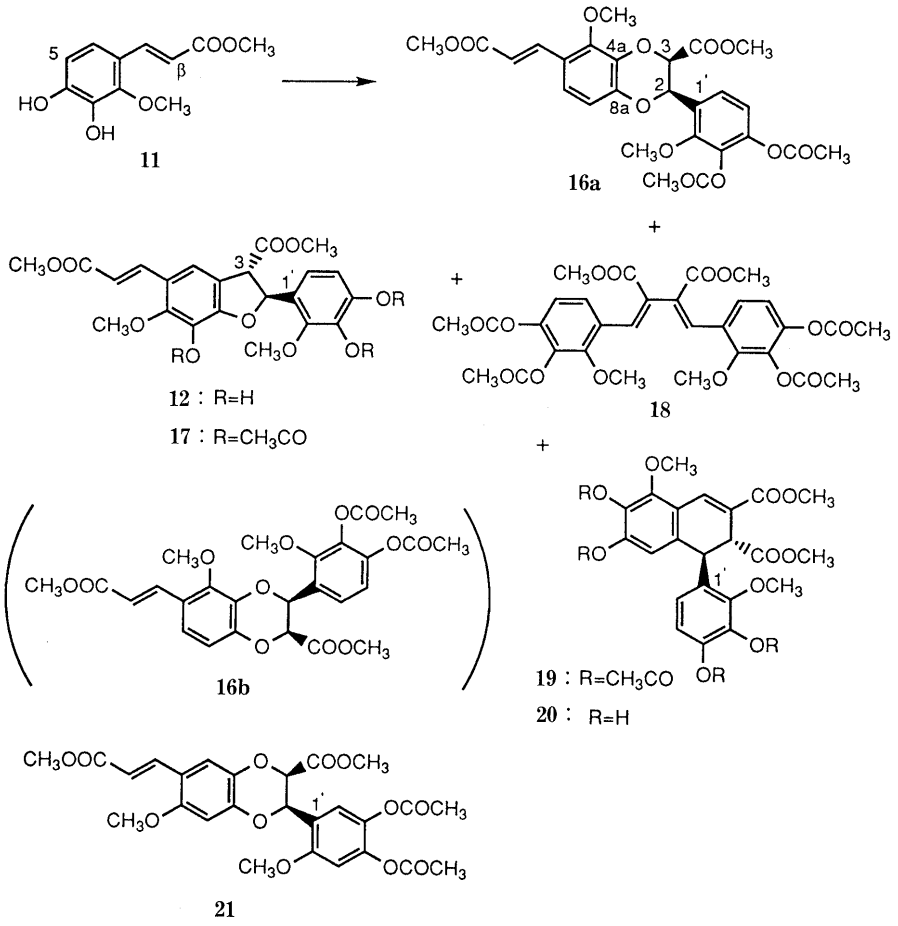


Chart 3

with this formulation. The configuration of the bis(benzylidene)succinate structure in **18** was determined based on ^{1}H–^{13}C-NMR gated decoupling and LSPD experiments, in which a coupling constant value of $^{3}J_{CH}=7$ Hz was observed between the carbonyl carbon of the methoxycarbonyl group (δ 166.8) and the vinyl proton of the double bond (δ 7.85). Since this value was comparable to the known value for a *trans* relationship ($^{3}J_{CH}=ca.$ 10 Hz), the configuration of the methoxycarbonyl group and the vinyl hydrogen atom is *trans* and thus the two double bonds in **18** were concluded to have *Z*,*Z*-configuration.

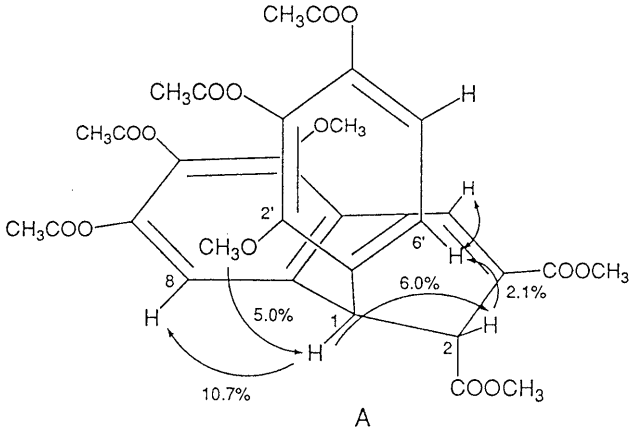
The molecular formula $C_{30}H_{30}O_{14}$ of the fourth product **19** suggested that it is the tetraacetate of a dimer. The ^{1}H-NMR spectrum of **19** was very similar to that of the acetate **6**.[3] Namely, while the AX-type vinyl proton signal of the (*E*)-propenoate chain of **11** was no longer observed, the presence of signals due to a pair of vicinal methine protons (δ 5.08, 4.03 each d, $J=3.7$ Hz, 1-H, 2-H, respectively) and a vinyl proton at a highly deshielded position (δ 7.97, s, 4-H), and an aromatic methine proton (δ 6.70, s) was indicated. One set of aromatic protons appeared as AB-type doublets with an *ortho* coupling constant ($J=9$ Hz), indicating the presence of a 1,2,3,4-tetrasubstituted benzene unit in **19**. As for the configuration of the dihydronaphthalene ring in **19**, it was noted that the value of the coupling constant between H-1 and H-2 ($J=3.7$ Hz) is considerably higher than that observed in the case of **6** ($J=1$ Hz). A survey of the literature indicates that the usual values for *trans* and *cis* compounds are 0.8—1.5 Hz[8-10] and 8 Hz[11,12] respectively. In addition, even higher values have also been reported for *trans* compounds ($J=3$ Hz[11] and $J=4$ Hz[13]). These data seem to favor the assignment of *trans* configuration for **19**.

The problem was investigated by means of nuclear Overhauser effect (NOE) spectroscopy (NOESY) and difference NOE experiments. Upon irradiation of the H-1 signal, NOE enhancements of 6.0 and 10.7% were observed at the signals of H-2 and H-8, respectively. Irradiation of H-2 caused intensification of the H-6′ signal (2.1%) as well as the H-1 signal (6.7%). Enhancement of the H-1 signal (5.0%) was observed on irradiation of the methoxy signal at the 2′ position. In addition, a weak correlation was present between the signals of H-4 and H-6′ in the NOESY spectrum. These results suggested that compound **19** should have a *trans*-configuration and take the conformation depicted in A, the plane of the *quasi*-axial 1-aryl group being disposed approximately perpendicular to the C-1, C-8a bond (Chart 4). Since appreciable allylic coupling was not observed between the signals of H-2 and H-4, the H-2 hydrogen bond was concluded to be *quasi*-equatorial. Consequently the dihedral angle of the C-1, H-1 and C-2, H-2 bonds was presumed to be around 65°, corresponding to the observed coupling constant of $J_{H1-H2}=3.7$ Hz. Thus, the fourth product was determined to have the *trans*-dihydronaphthalene structure **19**.

TABLE III. ^{13}C-NMR and ^{1}H-NMR Data for Compounds **19**, **20** and **6** in $CDCl_3$

Position	**19**		**20**		**6**[a]	
	^{13}C-NMR	^{1}H-NMR	^{13}C-NMR	^{1}H-NMR	^{13}C-NMR	^{1}H-NMR
1	39.6	5.08 (1H, d, 3.7)	39.2	4.65 (1H, d, 3.7)	33.3	5.28 (1H, d, 1)
2	45.6	4.03 (1H, d, 3.7)	45.7	3.79 (1H, d, 3.7)	43.5	4.02 (1H, d, 1)
3	135.1		128.8		130.7	
4	130.6	7.97 (1H, s)	132.2	7.78 (1H, s)	130.7	8.06 (1H, s)
4a	123.9		116.5		119.5	
5	150.7		146.2		154.5	
6	135.0		136.8		105.3	6.79 (1H, s)
7	144.9		149.4		144.8	
8	119.0	6.70 (1H, s)	111.3	6.24 (1H, s)	133.5	
8a	125.4		125.9		123.8	
1′	132.9		120.8		125.8	
2′	150.2		145.7		154.0	
3′	135.8		138.2		106.0	6.74 (1H, s)
4′	142.5		145.5		141.4	
5′	118.1	6.76 (1H, d, 9)	110.4	6.32 (1H, d, 8)	134.9	
6′	125.9	6.52 (1H, d, 9)	117.5	5.76 (1H, d, 8)	122.9	6.18 (1H, s)
$OCOCH_3$	20.3, 20.3, 20.6, 20.6	2.24, 2.25, 2.34, 2.34 (each 3H, s)			19.8, 20.5, 20.7, 20.8	2.09, 2.15, 2.23, 2.23 (each 3H, s)
OH				8.46, 8.67, 9.10, 9.77 (each 1H, s)		
5-OCH_3	62.6	3.90 (3H, s)	61.0	3.82 (3H, s)	55.9	3.88, 3.90 (each, 3H, s)
2′-OCH_3	61.7	3.94 (3H, s)	59.9	3.83 (3H, s)	56.1	
2-$COOCH_3$	52.6	3.65 (3H, s)	52.1	3.55 (3H, s)	52.5	3.63 (3H, s)
3-$COOCH_3$	52.1	3.78 (3H, s)	51.6	3.66 (3H, s)	51.9	3.75 (3H, s)
$OCOCH_3$	167.6, 167.6, 167.7, 168.1				166.0, 167.5, 167.7	
2-$COOCH_3$	172.2		175.5		171.6	
3-$COOCH_3$	166.5		166.6		166.7	

a) Ref. 3.



A

Chart 4

Next we examined the oxidative coupling reactions of **11** with potassium hexacyanoferrate(III) and iron(III) chloride. The reaction of **11** with an equimolar amount of potassium hexacyanoferrate(III) and 1.5 molar eq of aqueous 1% Na_2CO_3 solution in $CHCl_3$ at room temperature for 24 h gave **16a** and **19** as acetates in 2% and 5% yields, respectively. On the other hand, **11** was treated with 0.6 molar eq of iron(III) chloride in aqueous acetone solution at room temperature and the products was purified by chromatography on silica gel to afford **20** in 16% yield. The elemental analysis and spectral data suggested that the product **20** is the phenolic compound corresponding to the dihydronaphthalene acetate **19** obtained above and this was confirmed by the acetylation of **20** to **19**.

TABLE IV. Product Distribution in the Oxidative Coupling Reaction of **11**

	Silver oxide	Potassium hexacyanoferrate(III)/ sodium carbonate		Iron(III) chloride
16a	7%	2%		—
17	15%	—		—
18	1%	—		—
19	1%	5%	**20**	16%

The products distribution in the oxidative coupling reactions of **11** under various conditions is summarized in Table IV. The reaction of **11** with silver oxide showed preference for the combination between the 5 position and β position radicals (o–β coupling), which is in common with the reaction of **2** and **8**. In all of the substrates **2**, **8** and **11**, position **5** is unhindered. On the other hand, the reaction of **5** led to the mutual coupling of two β position radicals (β–β coupling) due to the steric influence of the 2-methoxy group in the 3 position radical, the dihydronaphthalene derivative **6** being the major product as reported previously.[3] In this respect, the reaction propensity of **11** is intermediate between those of the substrates **8** and **5**. The reaction of **11** afforded the dihydronaphthalene derivative **19** or **20** in variable amounts, depending on the oxidizing agents used. Whereas the oxidation of **11** with silver oxide afforded the dihy-

TABLE V. 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	10^{-6} M
16a	97	86	27
17	92	80	27
18	91	78	45
19	100	74	33
20	98	97	66
Idebenone	93	27	—

TABLE VI. Inhibitory Effect of the Products Obtained by Oxidative Coupling Reaction on Lipid Peroxidation in Rat Liver Microsomes

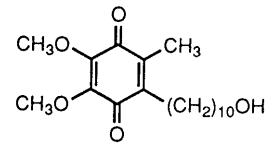
Compound	IC_{50} (10^{-6} M)[a]
17	2.26 (2.08— 2.48)
20	4.27 (4.14— 4.40)
Schizotenuin A	36.26 (33.54—39.76)
(±)-α-Tocopherol	976 (880—1149)

a) The IC_{50} values and 95% confidence limits were calculated by probit analysis by using 4 determinations of 3—5 different concentrations (geometric ratio = 1.4) for each compound.

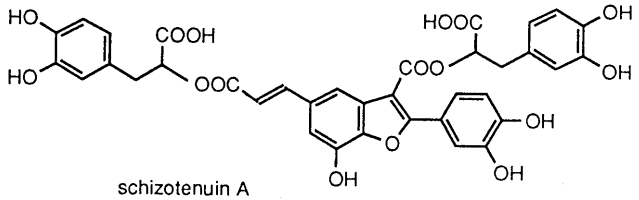
dronaphthalene derivative **19** only as a minor product, that with potassium hexacyanoferrate gave it as a major product. In contrast to **5** and **8**, which were unreactive on treatment with iron(III) chloride,[1,3] **11** reacted with this reagent to afford the dihydronaphthalene derivative **20**. As for the oxidative coupling reaction of methyl caffeate, the reaction with silver oxide has been reported to give the dihydrobenzofuran compound and that with iron(III) chloride affords the dihydronaphthalene compound.[8,13]

Inhibitory Effect on Lipid Peroxidation We examined compounds **16a**, **17**, **18**, **19** and **20** for inhibitory activity on the lipid peroxidation in rat brain homogenate and further examined **17** and **20** in rat liver microsomes, according to the method described in a previous paper.[2] The results are summarized in Tables V and VI. Since the activity of the acetate **19** did not differ significantly from that of the corresponding phenol **20**, the acetyl groups in **16a**, **17** and **18** are presumed to be hydrolyzed during incubation.

In spite of the wide structural variation among the five compounds tested in rat brain homogenate, they all showed comparable inhibitory activities, being more potent than idebenone, a nootropic drug. The results indicate that the presence of polyphenolic rings in the former compounds is important for the inhibitory activity on lipid peroxidation. Among the compounds obtained by the oxidative coupling reaction of the hydroxycinnamates derived from the coumarins, those from esculetin and daphnetin showed inhibitory activities superior to that of idebenone, while those derived from umbelliferone did not.[1-3] Therefore the presence of vicinal free phenolic hydroxy groups is concluded to be indispensable for prominent activity. Furthermore, when two compounds **17** and **20** were tested in rat liver microsomes, their activities were found to be much more potent than that of (±)-α-tocopherol. Interestingly the dihydrobenzofuran



idebenone



schizotenuin A

Chart 5

derivative **17** was more potent than schizotenuin A,[2] which is the major bioactive component of *Schizonepeta tenuifolia* BRIQ.

Conclusion

The oxidative coupling reaction of methyl (*E*)-3-(3,4-dihydroxy-2-methoxyphenyl)propenoate (**11**), obtained from daphnetin, has been investigated with the aim of obtaining bioactive lignans. In the reaction of **11** with silver oxide and potassium hexacyanoferrate(III), the major product obtained after acetylation was the dihydrobenzofuran derivative **17**, a product of *o*–*β* coupling, which is general for hydroxycinnamate substrates with an unhindered *ortho* position. In addition, the formation was observed of a benzodioxane derivative **16a**, a dihydronaphthalene derivative **19** and an open chain symmetric dimer **18**, of which the first compound was produced by O–*β* union and the latter two by *β*–*β* coupling. The reaction of **11** using iron(III) chloride afforded the dihydronaphthalene derivative **20**. Thus, the substrate **11** exhibited a rather diverse reactivity on oxidative coupling. Testing of the synthetic lignans for lipid peroxidation inhibiting activity was carried out in rat brain homogenate and, for some compounds, in rat liver microsomes. All of the compounds tested showed prominent activities. Further evaluation 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.[1,2]

Bis(methoxymethyl)daphnetin (13) A solution of daphnetin (**10**) (56.0 g, 0.31 mol) in dry THF–DMF (560 ml, 5 : 3) was added dropwise to a suspension of sodium hydride (60%, in oil) (26.4 g, 0.66 mol) in dry THF–DMF (780 ml, 5 : 1) at 0 °C under N_2. After the reaction mixture had been stirred for 3 h at room temperature, chloromethyl methyl ether (53.2 g, 0.66 mol) was added dropwise at 0 °C and the mixture was stirred for 17 h at room temperature. The mixture was concentrated, ice-water was added, and the product was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The residue was recrystallized from MeOH to give **13** (60.6 g, 73%) as colorless needles, mp 77—79 °C. IR (KBr): 1745, 1723 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.52, 3.71 (each 3H, s, $CH_2OCH_3 \times 2$), 5.25, 5.29 (each 2H, s, $CH_2OCH_3 \times 2$), 6.28 (1H, d, J=10 Hz, 3-H), 7.11, 7.19 (each 1H, d, J=9 Hz, 5-, 6-H), 7.65 (1H, d, J=10 Hz, 4-H).

Methyl (*E*)-3-[2-Hydroxy-3,4-bis(methoxymethoxy)phenyl]propenoate

(14) A sodium methoxide solution (28% in MeOH) (73 ml, 0.38 mol) was added to a solution of **13** (50.0 g, 0.19 mol) in dry MeOH (500 ml) and the mixture was refluxed for 4 h. The reaction mixture was concentrated and ice-water was added. After acidification with 6 M HCl, the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a crude product, which was recrystallized from benzene to afford **14** (43.0 g, 77%) as colorless needles, mp 94—95 °C. IR (KBr): 3356 (OH), 1706 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.49, 3.59 (each 3H, s, $CH_2OC\underline{H}_3 \times 2$), 3.79 (3H, s, $=CHCOOC\underline{H}_3$), 5.14, 5.22 (each 2H, s, $C\underline{H}_2OCH_3 \times 2$), 6.55 (1H, d, J=16 Hz, $=C\underline{H}COOCH_3$), 6.70, 7.18 (each 1H, d, J=9 Hz, 5-, 6-H), 7.21 (1H, s, OH), 7.87 (1H, d, J=16 Hz, ArCH=). *Anal.* Calcd for $C_{14}H_{18}O_7$: C, 56.36; H, 6.09. Found: C, 56.32; H, 6.08.

Methyl (*E*)-3-[2-Methoxy-3,4-bis(methoxymethoxy)phenyl]propenoate (15) A mixture of **14** (28.0 g, 0.094 mol), anhydrous K_2CO_3 (65 g, 0.47 mol) and dimethyl sulfate (22 ml, 0.23 mol) in dry acetone (450 ml) was refluxed for 4 h. The insoluble inorganic material was removed by filtration and the filtrate was concentrated. Excess dimethyl sulfate was decomposed by the addition of 5% aqueous ammonia solution, and the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to dryness. The resulting residue was recrystallized from ether, giving **15** (25.0 g, 85%) as colorless needles, mp 38—40 °C. IR (KBr): 1717 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.51, 3.62 (each 3H, s, $CH_2OC\underline{H}_3 \times 2$), 3.80, 3.89 (each 3H, s, $ArOCH_3$, $=CHCOOC\underline{H}_3$), 5.15, 5.23 (each 2H, s, $C\underline{H}_2OCH_3 \times 2$), 6.43 (1H, d, J=16 Hz, $=C\underline{H}COOCH_3$), 6.94, 7.26 (each 1H, d, J=9 Hz, 5-, 6-H), 7.89 (1H, d, J=16 Hz, ArCH=). *Anal.* Calcd for $C_{15}H_{20}O_7$: C, 57.68; H, 6.47. Found: C, 57.63; H, 6.48.

Methyl (*E*)-3-(3,4-Dihydroxy-2-methoxyphenyl)propenoate (11) To a solution of **15** (24.0 g, 0.08 mol) in dry MeOH (300 ml) was added acetyl chloride (1 g, 0.01 mol) and the mixture was stirred at room temperature for 18 h. The solution was neutralized with saturated $NaHCO_3$ solution, and concentrated. Ice-water was added, and the mixture was extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated to give a crude product. Recrystallization from ether gave **11** (17.9 g, 100%) as colorless prisms, mp 142—144 °C. IR (KBr): 3479, 3295 (OH), 1683 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.78, 3.85 (each 3H, s, $ArOCH_3$, $=CHCOOC\underline{H}_3$), 6.38 (1H, d, J=16 Hz, $=C\underline{H}COOCH_3$), 6.68, 6.97 (each 1H, d, J=9 Hz, 5-, 6-H), 7.55 (1H, s, OH), 7.86 (1H, d, J=16 Hz, ArCH=), 8.55 (1H, s, OH). *Anal.* Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.41. Found: C, 58.92; H, 5.42.

Oxidative Coupling Reaction with Silver Oxide Silver oxide (1.9 g, 8.0 mmol) was added to a solution of **11** (3.0 g, 13.4 mmol) in benzene–acetone (90 ml, 2:1) at 0 °C under N_2, and the mixture was stirred at 0 °C for 1 h and then at room temperature for 24 h. The suspension was filtered and the precipitate was sufficiently washed with acetone. The filtrate and the washing were combined, and the combined mixture was evaporated to dryness. The residue was dissolved in dry pyridine (19 ml) and acetic anhydride (15 ml, 0.16 mol), and the mixture was stirred at room temperature for 18 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 chromatographed on a silica gel column (*n*-hexane–AcOEt, 5:2 then 1:1). The first eluate was recrystallized from EtOH to give the acetate of unchanged **11** (0.85 g), and the second eluate was recrystallized from ether to give methyl (*E*)-3-[(2*R**,3*R**)-2-(3,4-diacetoxy-2-methoxyphenyl)-5-methoxy-3-methoxycarbonyl-1,4-benzodioxan-6-yl]propenoate (**16a**) (0.24 g, 7%) as colorless scales, mp 171—173 °C. The third eluate was recrystallized from ether, giving methyl (*E*)-3-[(2*R**,3*R**)-7-acetoxy-2-(3,4-diacetoxy-2-methoxyphenyl)-2,3-dihydro-6-methoxy-3-methoxycarbonylbenzofuran-5-yl]propenoate (**17**) (0.56 g, 15%) as colorless needles, mp 120—121 °C. The fourth eluate was recrystallized from EtOH, giving dimethyl (2*Z*,3*Z*)-2,3-bis(3,4-diacetoxy-2-methoxybenzylidene)succinate (**18**) (0.04 g, 1%) as colorless prisms, mp 198—199 °C, and the fifth eluate was recrystallized from EtOH, giving dimethyl (1*R**,2*S**)-6,7-diacetoxy-1-(3,4-diacetoxy-2-methoxyphenyl)-1,2-dihydro-5-methoxynaphthalene-2,3-dicarboxylate (**19**) (0.05 g, 1%) as colorless prisms, mp 178—180 °C.

16a: IR (KBr): 1779, 1764, 1697 (C=O) cm^{-1}. *Anal.* Calcd for $C_{26}H_{26}O_{12}$: C, 58.86; H, 4.95. Found: C, 58.86; H, 5.00. MS *m/z*: 530 (M^+).

17: IR (KBr): 1779, 1746, 1720 (C=O) cm^{-1}. *Anal.* Calcd for $C_{28}H_{28}O_{13}$: C, 58.73; H, 4.94. Found: C, 58.78; H, 5.00. MS *m/z*: 572 (M^+).

18: IR (KBr): 1774, 1717 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.25, 2.29 (each 6H, s, $CH_3CO \times 4$), 3.45 (6H, s, $Ar\text{-}OCH_3 \times 2$), 3.79 (6H, s, $=CCOOCH_3 \times 2$), 6.80 (2H, d, J=9 Hz, 5-H × 2), 7.06 (2H, d, J=9 Hz, 6-H × 2), 7.85 (2H, s, ArCH= × 2). ^{13}C-NMR ($CDCl_3$) δ: 20.2, 20.6 ($\underline{C}H_3CO \times 4$), 52.4 ($=CCOO\underline{C}H_3 \times 2$), 62.4 ($Ar\text{-}OCH_3 \times 2$), 118.4 (C5 × 2), 126.3 (C6 × 2), 127.3 (C1 × 2), 128.7 ($=\underline{C}COOCH_3 \times 2$), 136.1 (C3 × 2), 137.1 (Ar-1-CH= × 2), 144.0 (C4 × 2), 152.0 (C2 × 2), 166.8 ($=C\underline{C}OOCH_3 \times 2$), 167.5, 167.8 ($CH_3\underline{C}O \times 4$). *Anal.* Calcd for $C_{30}H_{30}O_{14}$: C, 58.62; H, 4.93. Found: C, 58.34; H, 5.06. MS *m/z*: 614 (M^+).

19: IR (KBr): 1779, 1734, 1712 (C=O) cm^{-1}. *Anal.* Calcd for $C_{30}H_{30}O_{14}$: C, 58.62; H, 4.93. Found: C, 58.52; H, 4.95. MS *m/z*: 614 (M^+).

Oxidative Coupling Reaction with Potassium Hexacyanoferrate(III)–Sodium Carbonate To a solution of **11** (1.0 g, 4.5 mmol) in $CHCl_3$ (400 ml) was added dropwise a solution of potassium hexacyanoferrate(III) (1.5 g, 4.6 mmol) and anhydrous Na_2CO_3 (0.7 g, 6.7 mmol) in water (70 ml) at 0 °C under N_2. After the mixture had been stirred at 0 °C for 1 h and at room temperature for 24 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 leave a residue, which was chromatographed on a silica gel column (CH_2Cl_2–AcOH–EtOH, 98:1:1 then 8:1:1), giving unchanged **11** (0.27 g) from the first eluate. The other eluates were combined and the residue was dissolved in dry pyridine (6 ml) and acetic anhydride (5 ml, 0.05 mol). This solution was stirred at room temperature for 18 h, then poured into 6 M HCl–ice water, 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, 5:2 then 1:1). The first eluate was recrystallized from ether to give **16a** (0.02 g, 2%) and the second eluate gave, after recrystallization from EtOH, **19** (0.07 g, 5%).

Oxidative Coupling Reaction with Iron(III) Chloride To a solution of **11** (1.0 g, 4.5 mmol) in acetone–water (40 ml, 3:1) was added dropwise a solution of iron(III) chloride heptahydrate (0.72 g, 2.7 mmol) in water (10 ml) at 0 °C under N_2 and the reaction mixture was stirred at room temperature for 21 h, 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 chromatographed on a silica gel column (CH_2Cl_2–EtOH, 99:1 then 98:2), giving unchanged **11** (0.41 g) from the first eluate, and the second eluate was recrystallized from EtOH to give dimethyl (1*R**,2*S**)-1-(3,4-dihydroxy-2-methoxyphenyl)-1,2-dihydro-6,7-dihydroxy-5-methoxynaphthalene-2,3-dicarboxylate (**20**) (0.16 g, 16%) as pale yellow scales, mp 221—223 °C. IR (KBr): 3480, 3385, 3278 (OH), 1722, 1676 (C=O) cm^{-1}. *Anal.* Calcd for $C_{22}H_{22}O_{10}$: C, 59.13; H, 4.98. Found: C, 59.13; H, 5.01. MS *m/z*: 446 (M^+).

References

1) Part III: S. Maeda, H. Masuda, T. Tokoroyama, *Chem. Pharm. Bull.*, **42**, 2536 (1994).
2) S. Maeda, H. Masuda, T. Tokoroyama, *Chem. Pharm. Bull.*, **42**, 2500 (1994).
3) S. Maeda, H. Masuda, T. Tokoroyama, *Chem. Pharm. Bull.*, **42**, 2506 (1994).
4) Jiangsu New Medical College (ed.), "Zhong Yao Da Ci Dian," Shanghai Science Technique Publishing Co., Shanghai, 1977.
5) R. J. Molyneux, L. Jurd, *Aust. J. Chem.*, **27**, 2697 (1974).
6) S. Antus, E. Baitz-Gacs, R. Bauer, A. Gottsegen, O. Seligmann, H. Wagner, *Justus Liebigs Ann. Chem.*, **1989**, 1147.
7) S. Antus, A. Gottsegen, P. Kolonits, H. Wagner, *Justus Liebigs Ann. Chem.*, **1989**, 593.
8) I. Agata, T. Hatano, S. Nishibe, T. Okuda, *Chem. Pharm. Bull.*, **36**, 3223 (1988).
9) T. Kikuti, S. Kadota, K. Yanada, K. Tanaka, K. Watanabe, M. Yoshizaki, T. Yokoi, T. Shingu, *Chem. Pharm. Bull.*, **31**, 1112 (1983).
10) R. Ahmed, M. Lehrer, R. Stevenson, *Tetrahedron*, **29**, 3753 (1973).
11) D. W. Jones, A. M. Thompson, *J. Chem. Soc.*, **1988**, 1095.
12) S. P. Maddaford, J. L. Charlton, *J. Org. Chem.*, **58**, 4132 (1993).
13) M. Pfau, S. Combrisson, J. E. Rowe, N. D. Heindel, *Tetrahedron*, **34**, 3459 (1978).