Total Synthesis of a Natural Antioxidant and Structure–Activity Relationships of Related Compounds

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Received April 23, 1999; accepted June 25, 1999

A total synthesis of benzodioxole derivative 1 was achieved *via* a palladium(0)-catalyzed cross-coupling reaction in a 68% overall yield (4 steps). A novel series of benzodioxoles bearing a variety of aromatic and heterocyclic rings was also prepared and the antioxidative activity evaluated using *in vitro* model systems. Structure-activity studies revealed that i) intramolecular hydrogen-bonding in the phenol moiety reduced activity, ii) introduction of disubstituents at the *ortho* location relative to the phenol increased activity, and iii) the methylenedioxy function contributed to stabilization of the phenoxy radical. Among of these compounds, 5,7-di-(4-methoxyphenyl)-4-methoxy-6-hydroxy-1,3-benzodioxole (7p) was the most favorable agent and more potent than *n*-propyl gallate.

Key words benzodioxole derivative; antioxidative activity; structure–activity relationship; palladium(0)-catalyzed cross-coupling reaction; intramolecular hydrogen-bonding

Active oxygen species and free radicals react with biomolecular constituents like lipid, protein, and DNA.[1] This damage causes chemical spoilage in foods and the pathogenesis of certain clinical diseases, such as cerebral ischemia,[2] atherosclerosis,[3] Parkinson's disease,[3a] inflammation,[4] diabetes,[5] and cancer.[6] Therefore, antioxidants have been proposed as promising therapeutic drugs for these diseases and various kinds of natural and synthetic antioxidants have been explored.

A crystalline antioxidant extracted from various yeasts was shown to protect *in vitro* the erythrocytes of vitamin E deficient rats from hemolysis.[7] The structure of this substance was determined as benzodioxole (**1**) by degradation studies (Fig. 1).[8] The first total synthesis of **1** was accomplished by Wagner *et al.* using the Hoesch reaction (the last 2 steps in 10% yield).[9] Later, McKittrick and Stevenson prepared **1** as an application for their elegant arylbenzofuran formation by the intramolecular Wittig reaction.[10] In both syntheses, the crucial steps were construction of a benzofuran skeleton. In addition to low yields, application of their methods was limited to benzofuran derivatives. In our preceding communication,[11] we reported a practical total synthesis of **1**. Herein we wish to describe details of the preparation of the natural antioxidant (**1**).

On the other hand, Ingold and co-workers studied the effects of chemical structure on the stability of phenoxy radicals *via* tocopherol analogs. It was shown that better overlap between the 2*p*-type lone-pair orbital of *para* nonphenolic oxygen and the aromatic π electron system resulted in resonance stabilization of the phenoxy radical.[12] In particular, the activity of compound (II) having a 2,3-dihydrobenzofuran skeleton was more potent than the parent chromanol (I) (Fig. 2). There are many reports describing the design, synthesis, and evaluation of various antioxidants possessing 5- or 6-membered heterocyclic rings.[13] Some of these compounds have been developed as therapeutic drugs for diabetes[13a] and hyperlipemia.[13b] The difference in the basic skeleton between II and III is only the carbon and oxygen at the 3-position. Therefore, the two natural compounds (I, III) are quite similar in terms of the stereoelectronic effect of the attached heterocycles, despite superficial structural differences. This concept prompted us to explore comprehensive derivatization of the benzodioxoles (III) and their structure–activity relationships (SAR).

In this paper, we describe the synthesis of various kinds of benzodioxoles and their antioxidative activity and discuss the SAR. We also examined the effect of the methylenedioxy moiety on stabilizing the phenoxy radical.

Chemistry In the synthesis of benzodioxoles, we utilized palladium(0)-catalyzed cross-coupling reactions between organometallic reagents (organoboranes,[14] organostannanes[15]) and organic electrophiles. This reaction is a powerful synthetic tool for carbon–carbon bond formation. Chart 1 outlines our synthetic route. The key intermediate 5-bromobenzodioxole **4** was prepared by regioselective bromination of **3** with *N*-bromosuccinimide (NBS) (77% yield from **2**). This procedure for **4** was superior to our previous method which involved bromination of **2** followed by protection with a benzyl group to give **4** in 66% yield.[11] Reaction of **4** with benzo[*b*]furan-2-boronic acid in the presence of tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) and tri-*o*-

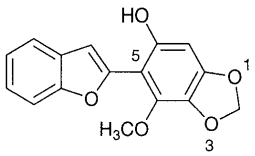

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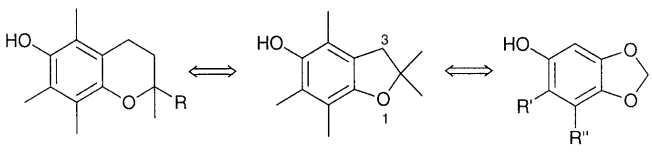
Fig. 1



I (Tocopherol) II III

Fig. 2

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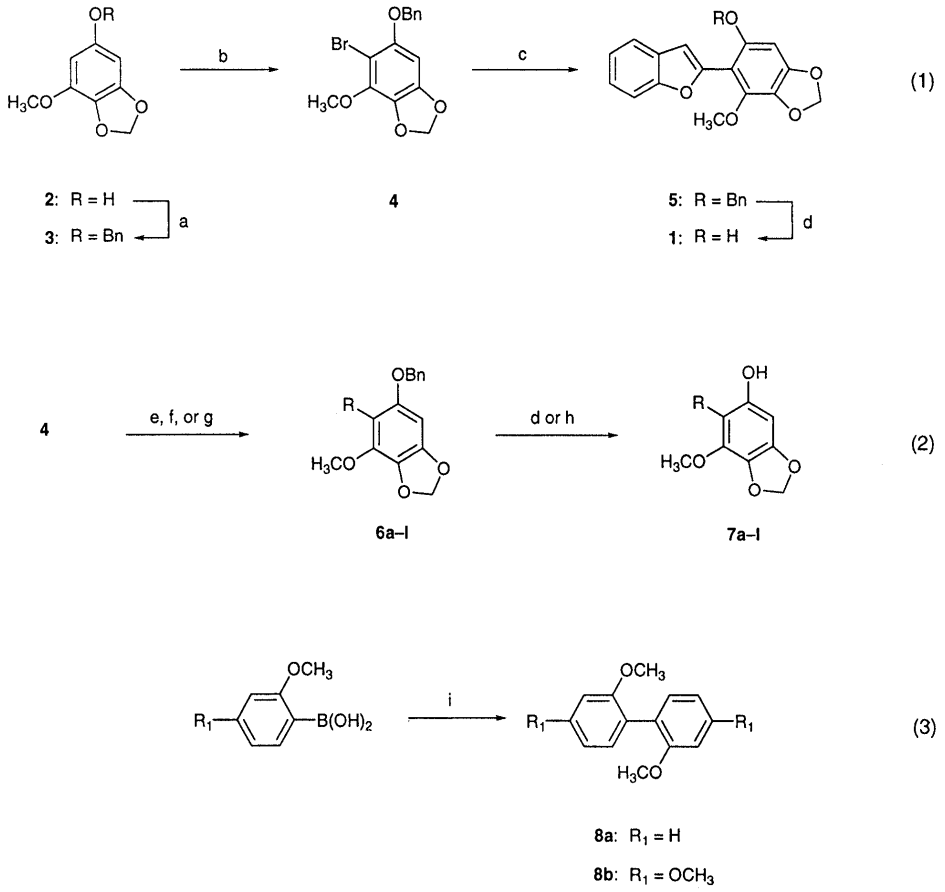


a) BnBr, NaH, DMF; b) NBS, THF; c) Benzo[*b*]furan-2-boronic acid, iso-Pr_2NEt, $Pd_2(dba)_3$, $P(o\text{-tol})_3$, DMF (method A); d) H_2, Pd-C, EtOAc; e) $ArB(OH)_2$, $n\text{-}Bu_4NBr$, K_2CO_3, $Pd(OAc)_2$, H_2O (method B); f) $HetSn(n\text{-}Bu)_3$, $Pd(PPh_3)_4$, HMPA (method C); g) $ArB(OH)_2$, 2 M K_2CO_3, $Pd(PPh_3)_4$, Toluene (method D); h) H_2, Pd-$BaCO_3$, EtOAc; i) **4**, $n\text{-}Bu_4NBr$, K_2CO_3, $Pd(OAc)_2$, H_2O (method B)

Chart 1

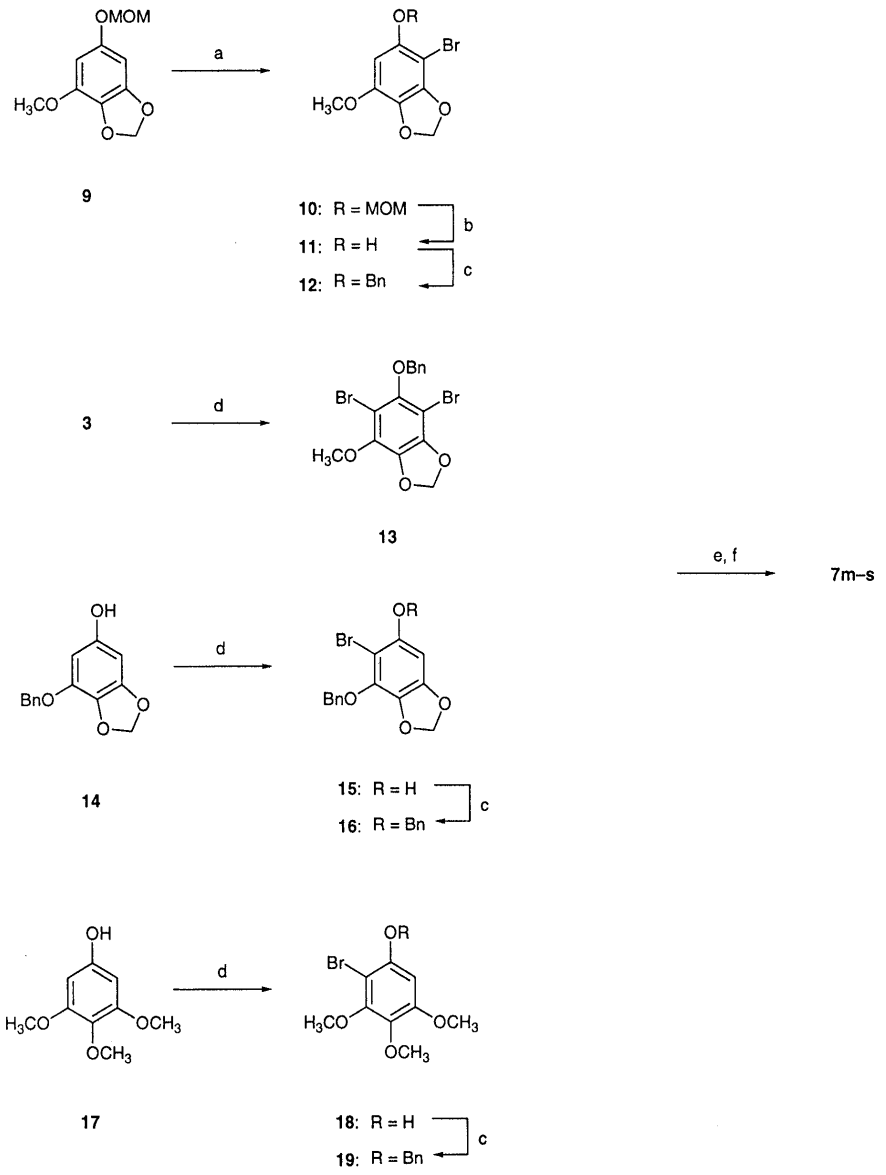
tolylphosphine ($P(o\text{-tol})_3$) (method A) gave arylbenzofuran (**5**) in excellent yield, which upon deprotection by hydrogenation over Pd–C afforded **1** (Eq. 1). The physicochemical data of synthetic product (**1**) showed good agreement with the reported data.[7—10]

This efficient methodology was applied to the synthesis of novel benzodioxole analogs. At first, we synthesized 5-substituted benzodioxole derivatives (Eq. 2). In the synthesis of the various aromatic derivatives (**6a—e**, **h**, **j**, **l**), method A was low yielding and considerable amounts of starting materials remained. Among many trials of different reaction conditions (base, ligand, solvent, temperature), coupling reaction in aqueous media in the presence of $n\text{-}Bu_4NBr$, K_2CO_3, and $Pd(OAc)_2$ (method B)[16] gave the desired products in good yields (71—100%). In the case of heterocyclic derivatives, Suzuki reaction provided no desired product. Fortunately, tributylstannyl heterocyclic analogs reacted smoothly with **4** using $Pd(PPh_3)_4$ (method C) to give the compounds (**6f**, **g**) almost quantitatively.

Generally, in the Suzuki palladium(0)-catalyzed cross-coupling reaction, steric hindrance in the arylboronic acids is not a major inhibitory factor for the formation of substituted biaryls.[14] However, using the phase-transfer catalyst (method B) for the synthesis of the 2′-methoxy analogs gave only homo-coupling products (**8a**, **b**)[17] (Eq. 3). However, coupling in the presence of K_2CO_3 and $Pd(PPh_3)_4$ in toluene (method D) furnished the targets (**6i**, **k**) in moderate yields.

Subsequent hydrogenation of the resulting coupled products on Pd–C catalyst yielded aromatic derivatives (**7a—e**, **7h—l**). Cleavage of the benzyl ether in thienyl derivative **6g** by catalytic hydrogenation over Pd–C gave only a small amount of the target product **7g** (10% yield). Attempted deprotection under acidic conditions led to complete recovery of unreacted **6g**. Under these deblocking conditions the furanyl derivative **6f** was predominantly over-reduced or polymerized to give no desired compound, however the target furanyl derivative **7f** was obtained by hydrogenation over Pd on barium bicarbonate.

Other benzodioxoles and trimethoxy analogs were prepared as shown in Chart 2. Regioselective bromination of methoxymethoxybenzodioxole **9**[10] with *n*-BuLi and bromine afforded 7-bromobenzodioxole **10**. Attempted on coupling between **10** and arylboronic acid yielded no coupled product. Conversion of the methoxymethyl group into a benzyl moiety gave a good result. Arylation of 7-bromobenzyloxybenzodioxole **12** using method B followed by catalytic hydrogenation afforded the desired 7-substituted benzodioxoles (**7m**, **n**) in good yields. Treatment of **3** with NBS gave 5,7-dibromobenzodioxole **13**. Dibenzyl analog **16** and trimethoxy analog **19** were prepared from 4-benzyloxy-6-hydroxy-1,3-benzodioxole **14**[18a] and trimethoxyphenol **17** by bromination and benzylation in the usual way, respectively. Reaction of



a)*n*-BuLi, Br_2; b) AcOH, cat H_2SO_4; c) BnBr, NaH, DMF; d) NBS, THF;
e) $ArB(OH)_2$, *n*-Bu_4NBr, K_2CO_3, $Pd(OAc)_2$, H_2O (method B); f) H_2, Pd-C, EtOAc

Chart 2

bromobenzenes (**13**, **16**, **19**) with arylboronic acid using method B followed by catalytic hydrogenation provided the corresponding phenols (**7o—s**).

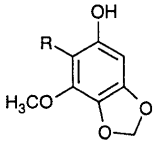
Results and Discussion

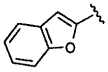
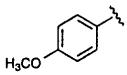
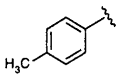
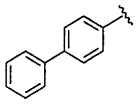
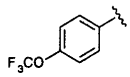
The compounds synthesized in this study were evaluated for antioxidant activity using lipid peroxidation of guinea pig liver microsomes enzymatically induced with CCl_4.[19] Tables 1—4 summarizes the 50% inhibitory concentration (IC_{50}) for each compound. α-Tocopherol and *n*-propyl gallate were also tested as reference compounds and their IC_{50} values were 280 and 50 μM, respectively.

Initially, we examined the effect of introduction of the substituents at the 5-position (Table 1). The numbering system indicated in Fig. 1 is used throughout the discussion in order to simplify discussion; proper nomenclature is assigned to each compound in the Experimental Section. Incorporation of aromatics into benzodioxole **2** at the 5-position enhanced antioxidative activity (except **7f**) and modification of the aromatics affected activity. Interestingly, most compounds tested were more active than α-tocopherol and some of them exhibited higher activity than the natural product (**1**). Comparison of *para*-substituents on the phenyl moiety revealed that the relative activity profile was methoxy (**7b**)≥methyl (**7c**)≫hydrogen atom (**7a**)≫phenyl (**7d**)≫trifluoromethoxy (**7e**). This result shows that electron-donating substituents at the 4′-position increase activity.

Replacement of benzofuran by thiophene resulted in a significant increase in activity (**1** *vs.* **7g**), whereas conversion to furan decreased activity (**1** *vs.* **7f**). The influence of intramolecular hydrogen-bond formation on antioxidative activity has been documented.[18] In our previous paper,[18a] we demonstrated that intramolecular hydrogen-bonding of a phenolic hydroxy group impaired activity. ^{1}H-NMR signals of the hydroxy group at δ 7.84 ppm for **1** and 7.46 ppm for **7f** were shifted about 2—3 ppm downfield compared with those of

Table 1. Antioxidative Activity of 5-Substituted Benzodioxole Derivatives



No.	R	Method	Yield (%)[a]	IC_{50} (μM)[b]
2	H			265
1		A	100	98
7a		B	81	83
7b		B	84	56
7c		B	100	65
7d		B	100	107
7e		B	84	226
7f		C	96	282
7g		C	93	44

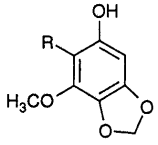
a) Yields obtained in the palladium-catalyzed cross-coupling reaction. *b*) IC_{50} values of α-tocopherol and *n*-propyl gallate were 280 and 50 μM, respectively.

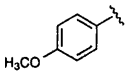
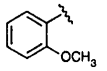
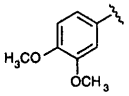
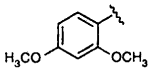
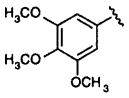
other benzodioxoles. This means compounds **1** and **7f**, bearing benzofuranyl and furanyl groups, have intramolecular hydrogen-bonding between the phenolic hydroxy group and the oxygen of the furan moiety. This intramolecular hydrogen-bond formation might cause their low activity.

Among the novel synthetic derivatives, highly active compounds (**7b**, **7g**) showed equal potency to *n*-propyl gallate and we thus selected **7b** as a lead because of its easy preparation. We then optimized the positions and numbers of methoxy groups on the phenyl ring at the 5-position (Table 2). As the number of methoxy groups became greater, the activity tended to decrease. Changing the position from the *para* position to the *ortho* or *meta* positions resulted in a significant loss of activity. The 4-methoxyphenyl group was found to be the optimal substituent among the methoxy substituted phenyl derivatives studied.

Next, attention was focused on substituent effects on the phenol ring (Table 3). The activity of 7-substituted benzodioxoles (**7m**, **n**) was slightly better than that of 5-substituted ones (**7a**, **b**). This led us to consider that the regioisomer of

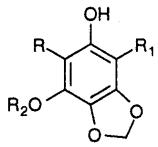
Table 2. Antioxidative Activity of **7b** Analogs

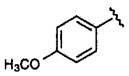
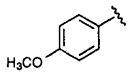
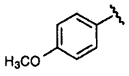


No.	R	Method	Yield (%)[a]	IC_{50} (μM)[b]
7b		B	84	56
7h		B	80	151
7i		D	56	133
7j		B	75	248
7k		D	45	188
7l		B	71	269

a) Yields obtained in the palladium-catalyzed cross-coupling reactions. *b*) IC_{50} values of α-tocopherol and *n*-propyl gallate were 280 and 50 μM, respectively.

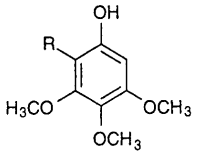
Table 3. Antioxidative Activity of Other Benzodioxole Derivatives

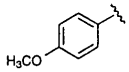


No.	R	R_1	R_2	Yield (%)[a]	IC_{50} (μM)[b]
7m	H		CH_3	81	70
7n	H		CH_3	81	40
7o			CH_3	83	48
7p			CH_3	73	30
7q		H	H	99	16

a) Yields obtained in the palladium-catalyzed cross-coupling reaction (method B). *b*) IC_{50} values of α-tocopherol and *n*-propyl gallate were 280 and 50 μM, respectively.

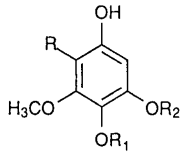
Table 4. Antioxidative Activity of Trimethoxyphenol Derivatives

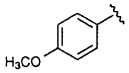
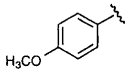


No.	R	Yield (%)[a]	IC_{50} (μM)[b]
7r		100	278
7s		100	254

a) Yields obtained in the palladium-catalyzed cross-coupling reaction (method B). *b*) IC_{50} values of α-tocopherol and *n*-propyl gallate were 280 and 50 μM, respectively.

Table 5. Antioxidative Activity of Substituted Phenols against Autoxidation of EPA on TLC Plates



No.	R	R_1	R_2	Threshold value (nmol)[a]
7a		$-CH_2-$		0.19
7r		CH_3	CH_3	0.24
7b		$-CH_2-$		0.17
7s		CH_3	CH_3	0.30

a) Threshold value of α-tocopherol is 0.28 nmol.

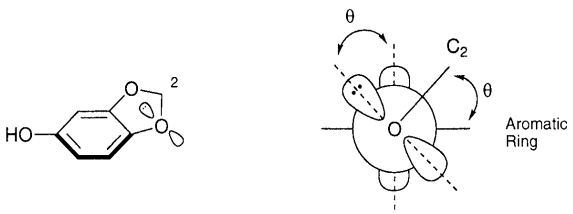


Fig. 3

the natural product **1** at the 7-side chain may exhibit more potent activity than the natural product. Among the 7-substituted compounds, 4′-methoxyphenyl derivative **7n** was also more active than phenyl derivative **7m**.

Steric hindrance by neighboring groups to the phenoxy radical serves to enhance its stability[20] and this stability relates to antioxidative activity. Accordingly, we envisioned that more sterically hindered 5,7-disubstituted compounds would show improved activity. As expected, 5,7-disubstituted derivatives (**7o**, **p**) were more effective than 5- or 7-monosubstituted derivatives (**7a**, **b**, **m**, **n**) and the active profile of 5,7-disubstituted compounds displayed the same pattern as the monosubstituted compounds. This result indicates that instead of a *tert*-butyl function, an aryl moiety can be also used as a neighboring group to generate a stable and persistent phenoxy radical *via* steric and electronic effects.

In studies of various kinds of antioxidants, the number of hydroxy groups plays an important role in the activity.[21] Although dihydroxy derivative **7q** showed the highest activity among all compounds synthesized, it was less stable than the other compounds. These findings suggest that compound **7q** showed high activity at the expense of its chemical stability. A more electron-rich *para* methoxyphenyl derivative was too unstable to be isolated.

Finally, we investigated the effect of the methylenedioxy function on antioxidative activity. Conversion of methylenedioxy to dimethoxy substituents resulted in a pronounced loss of activity (**7a**, **b** *vs.* **7r**, **s**). In CCl_4-stimulated lipid peroxidation, the reactive trichloromethyl free radical ($CCl_3\cdot$) was produced by metabolic activation involving the NADPH–cytochrome P450 system.[22] Additionally, the methylenedioxymethamphetamine was demethylenated by P450[23] and in the test using hepatocytes, the antioxidative activity of some methylenedioxybenzene analogs was attributed to the corresponding catecholic metabolite generated by P450.[24] This metabolism of benzodioxoles should be also taken into consideration. To examine the intact activity of benzodioxoles, we employed an alternative evaluation system for antioxidative activity in the absence of P450. Table 5 summarizes the threshold value inhibiting the autoxidation of ethyl icosapentaenoate (EPA) on a TLC plate[25] for each compound. The threshold value of α-tocopherol, a reference compound, was 0.28 nmol. In this antioxidation assay, it was observed that benzodioxoles (**7a**, **b**) blocked lipid peroxidation more significantly than trimethoxybenzenes (**7r**, **s**). These results led us to conclude that these benzodioxoles directly inhibit lipid peroxidation and that the presence of the methylenedioxy function appears to be related to the stability of the resulting phenoxy radical.[26]

Ingold and co-workers[12] reported that the stability of the phenoxy radical depends on overlap of the lone pair on the *para* heteroatom. For benzodioxoles, the extent of such overlap will correlate with dihedral angle (θ) of the oxygen at the 3-position of the benzodioxole ring and the aromatic moiety (Fig. 3). Molecular orbital calculations (MOPAC Ver. 6, PM3) indicated that the phenoxy radical from **7b** (θ=1°) was more stable than that from **7s** (θ=68°).[27] This result also supported the experimental result.

In conclusion, we have achieved a facile and versatile total synthesis of benzodioxole natural product (**1**) by using a palladium-catalyzed reaction. As an application of this methodology, a series of benzodioxoles has been synthesized. We also evaluated antioxidative activity using two different systems. We obtained a more active compound (**7p**) than *n*-propyl gallate. Our SAR investigations suggest that i) intramolecular hydrogen-bonding in the phenolic hydroxy group decreased activity, ii) introduction of disubstituents at the *ortho* location relative to the hydroxy group increased activity, and iii) the methylenedioxy function contributed to sta-

bilization of the phenoxy radical (benzodioxoles exhibited higher activity than dimethoxybenzenes in the assay system that did not contain P450).

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. All reactions were carried out under an inert atmosphere with dry solvents under anhydrous conditions unless stated otherwise. Infrared (IR) spectra were recorded on a JASCO FT/IR spectrometer VALOR III. ^{1}H-NMR spectra were obtained at 400 MHz using a Brucker DPX400. Chemical shifts are given on the δ (ppm) scale downfield from tetramethylsilane as an internal standard. The electron impact mass (EI-MS) spectra were taken on a JEOL JMS-AX500. Microanalyses were carried out with a Perkin-Elmer CHN Analyzer 2400 Series II. Melting points (mp) were measured with a Yanaco micro melting point apparatus MP-500D and are uncorrected. Column chromatography was carried out using Micro Sphere Gel D75-60A (Asahi Glass Co.) or Silica Gel 60, spherical neutral (Kanto Chemical Co., Inc.). TLC experiments were performed on silica gel plates 60 F_{254} 0.25 mm (E. Merck).

5-Bromo-6-benzyloxy-4-methoxy-1,3-benzodioxole (4) To a cold solution of NaH (283 mg, 0.46 mmol) in *N*,*N*-dimethylformamide (DMF) (1 ml) was added compound **2**[10] (1.20 g, 0.30 mol) in DMF (3 ml) at 0 °C and the mixture was stirred at room temperature for 30 min. Benzyl bromide (915 μl, 0.46 mmol) was added dropwise at 0 °C. After stirring for 30 min at room temperature, the reaction mixture was poured into aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to give **3** (1.46 g, 80%). **3**: mp 50.6—62.2 °C. EI-MS *m/z*: 180 (M^+), 88. IR (KBr) cm^{-1}: 1634, 1496, 1443. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (3H, s), 5.17 (2H, s), 5.90 (2H, s), 6.12 (1H, d, J=2.3 Hz), 6.18 (1H, d, J=2.3 Hz), 7.30—7.46 (5H, m).

To a cold solution of **3** (1.12 g, 4.32 mmol) in tetrahydrofuran (THF) (10 ml) was added NBS (770 mg, 4.33 mmol) at 0 °C and the mixture was stirred at the same temperature for 1 h. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with water, neutralized with aqueous $NaHCO_3$, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified chromatographically (*n*-hexane : EtOAc=85 : 15) to afford **4** (1.40 g, 96%). **4**: mp 57.6—59.7 °C. EI-MS *m/z*: 338, 336 (M^+), 257, 245. IR (KBr) cm^{-1}: 2902, 1631, 1605, 1482. ^{1}H-NMR ($CDCl_3$) δ: 4.07 (3H, s), 5.06 (2H, s), 5.90 (2H, s), 6.34 (1H, s), 7.3—7.5 (5H, m). *Anal.* Calcd for $C_{15}H_{13}BrO_4$: C, 53.43; H, 3.89. Found: C, 53.72; H, 3.88.

7-Bromo-6-benzyloxy-4-methoxy-1,3-benzodioxole (12) To a cold solution of **9**[10] (1.13 g, 5.30 mmol) in Et_2O (10 ml) was added 1.63 M *n*-BuLi (3.51 ml, 5.72 mmol) at 0 °C and the mixture was stirred for 100 min at the same temperature. Bromine (272 μl, 5.30 mmol) was added slowly to the yellow suspension at −78 °C. The mixture was stirred at room temperature for 30 min. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with water, neutralized with aqueous $NaHCO_3$, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified chromatographically to afford **10** (998 mg, 65%). **10**: mp 209.1—212.3 °C. EI-MS *m/z*: 261, 259 (M^+), 248, 246. IR (KBr) cm^{-1}: 3312, 1624, 1488, 1446, 1360. ^{1}H-NMR ($CDCl_3$) δ: 3.53 (3H, s), 3.89 (3H, s), 5.15 (2H, s), 6.00 (2H, s), 6.42 (1H, s).

Table 6. Physicochemical Data for Substituted Phenols

No.	mp (°C)	Appearance (Recryst. solvent)	Formula	Analysis (%) Calcd (Found)		EI-MS *m/z*
				C	H	
7a	88.1—89.4	Colorless plates (Petroleum ether)	$C_{14}H_{12}O_4$	68.85 (69.14	4.95 4.80)	244 (M^+), 199, 171, 115
7b	83.0—83.8	Colorless plates (Petroleum ether)	$C_{15}H_{14}O_5$	65.69 (65.80	5.14 4.95)	274 (M^+), 259, 229, 201, 145
7c	124.8—126.6	Yellow plates (Petroleum ether)	$C_{15}H_{14}O_4$	69.76 (70.12	5.46 5.38)	258 (M^+), 213, 185, 129
7d	141.8—143.5	Yellow plates (Petroleum ether)	$C_{20}H_{16}O_4$	74.99 (75.06	5.03 4.98)	320 (M^+), 275, 247, 191
7e	68.7—69.3	Colorless plates (Petroleum ether)	$C_{15}H_{11}F_3O_5$	54.89 (55.13	3.38 3.23)	328 (M^+), 283, 255, 199
7f	66.5—68.3	Amorphous	$C_{12}H_{10}O_5$	61.54 (61.49	4.30 4.13)	234 (M^+), 205, 190
7g	75.6—77.0	Colorless needles (Petroleum ether)	$C_{12}H_{10}O_4S$	57.59 (57.44	4.03 3.94)	250 (M^+), 235, 219, 205, 121
7h	112.9—114.6	Pale yellow plates (Petroleum ether)	$C_{15}H_{14}O_5$	65.69 (65.45	5.14 5.01)	274 (M^+), 259, 229, 201, 145
7i	134.4—134.9	Colorless plates (EtOAc–hexane)	$C_{15}H_{14}O_5$	65.69 (65.85	5.14 5.00)	274 (M^+), 229, 213
7j	143.5—144.4	Colorless plates (EtOAc–hexane)	$C_{16}H_{16}O_6$	63.15 (62.97	5.30 5.02)	304 (M^+), 289, 152
7k	110.6—111.5	Colorless plates (EtOAc–hexane)	$C_{16}H_{16}O_6$	63.15 (63.10	5.30 5.11)	304 (M^+), 289, 259, 243, 152
7l	199.7—201.5	Colorless needles (EtOAc–hexane)	$C_{17}H_{18}O_7$	61.07 (60.96	5.43 5.19)	334 (M^+), 319, 303, 167
7m	131.7—133.4	Colorless needles (Petroleum ether)	$C_{14}H_{12}O_4$	68.85 (68.61	4.95 4.95)	244 (M^+), 201, 129
7n	123.9—125.7	Colorless plates (Petroleum ether)	$C_{15}H_{14}O_5$	65.69 (65.67	5.14 5.12)	274 (M^+), 259, 145
7o	152.6—154.2	Colorless plates (EtOAc–hexane)	$C_{20}H_{16}O_4$	74.99 (74.86	5.03 4.83)	320 (M^+), 275, 191, 145
7p	162.8—163.9	Colorless plates (EtOAc–hexane)	$C_{22}H_{20}O_6$	69.46 (69.66	5.30 5.12)	380 (M^+), 365, 335, 190
7q	107.9—108.4	Amorphous	$C_{13}H_{10}O_4$	67.82 (67.73	4.38 4.24)	230 (M^+), 144, 115
7r	98.2—99.0	Amorphous	$C_{15}H_{16}O_4$	69.22 (69.30	6.20 6.01)	260 (M^+), 245, 213, 185
7s	110.2—111.2	Colorless plates (EtOAc–hexane)	$C_{16}H_{18}O_5$	66.20 (66.23	6.25 6.07)	290 (M^+), 275, 243, 215, 145

Compound **10** (995 mg, 3.42 mmol) was dissolved in AcOH (5 ml) in the presence of catalytic H_2SO_4 (50 μl). After being stirred for 10 min, the mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with water, neutralized with aqueous $NaHCO_3$, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The crude product was recrystallized from benzene to give **11** (852 mg, 100%).

Compound **12** was prepared from **11** in 53% yield as described for **4** *via* **3**. **12**: mp 86.9—89.7 °C. IR (KBr) cm^{-1}: 1634, 1495, 1444, 1404, 1386. ^{1}H-NMR ($CDCl_3$) δ: 3.86 (3H, s), 5.06 (2H, s), 5.99 (2H, s), 6.17 (1H, s), 7.30—7.46 (5H, m). *Anal.* Calcd for $C_{15}H_{13}BrO_4$: C, 53.43; H, 3.89. Found: C, 53.57; H, 3.83.

Compound **13** was prepared from **3** in 65% yield as described for **4** *via* **3** (except 2 eq of NBS was used). **13**: mp 76.8—78.8 °C. EI-MS *m/z*: 418, 416, 414 (M^+), 337, 335. IR (KBr) cm^{-1}: 1598, 1498, 1436. ^{1}H-NMR ($CDCl_3$) δ: 4.05 (3H, s), 4.96 (2H, s), 6.05 (2H, s), 7.40 (3H, m), 7.46 (2H, m). *Anal.* Calcd for $C_{15}H_{12}Br_2O_4$: C, 43.30; H, 2.91. Found: C, 43.14; H, 2.91.

Compound **16** was prepared from **14**[18a] in 55% yield (2 steps) as described for **4** *via* **3**. **16**: EI-MS *m/z*: 414, 412 (M^+), 242. IR (KBr) cm^{-1}: 2889, 1630, 1499, 1479, 1371. ^{1}H-NMR ($CDCl_3$): 5.02 (2H, s), 5.30 (2H, s), 5.90 (2H, s), 7.31—7.51 (10H, m). *Anal.* Calcd for $C_{21}H_{17}BrO_4$: C, 61.03; H, 4.15. Found: C, 61.17; H, 4.12.

Compound **19** was prepared from **17** in 45% yield (2 steps) as described for **4** *via* **3**. **19**: mp 57.8—58.4 °C. EI-MS *m/z*: 354, 352 (M^+), 273, 263, 261, 167. IR (KBr) cm^{-1}: 3370, 1648, 1506, 1445, 942, 831, 797. ^{1}H-NMR ($CDCl_3$) δ: 3.80 (3H, s), 3.82 (3H, s), 3.92 (3H, s), 5.11 (2H, s), 6.38 (1H, s), 7.33—7.34 (1H, m), 7.37—7.41 (2H, m), 7.47—7.49 (2H, m). *Anal.* Calcd for $C_{16}H_{17}BrO_4$: C, 54.41; H, 4.85. Found: C, 54.64; H, 4.75.

5-(2-Benzofuranyl)-6-hydroxy-4-methoxy-1,3-benzodioxole (1) (Method A) Compound **4** (960 mg, 2.82 mmol), benzo[*b*]furan-2-boronic acid (684 mg, 4.22 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (109 mg, 0.105 mmol), P(*o*-tol)$_3$ (128 mg, 0.421 mmol), and iso-Pr_2NEt (0.982 g, 5.64 mmol) were added to DMF (10 ml). The mixture was stirred at 90 °C for 1 h. The reaction mixture was poured into ice water and extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (*n*-hexane : benzene = 1 : 1) to afford the protected benzodioxole **5** (1.14 g, 100%).

A mixture of **5** and EtOAc (70 ml) in the presence of 10% Pd–C (56 mg) was stirred overnight under a hydrogen atmosphere. The catalyst was removed by filtration and washed with EtOAc. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (*n*-hexane : EtOAc = 85 : 15) to give **1** (715 mg, 88%) as colorless needles (from petroleum ether), mp 118 °C (lit.[9]) mp 118 °C, lit.[10]) 117.5 °C). EI-MS *m/z*: 284 (M^+), 269, 142. IR (KBr) cm^{-1}: 3370, 1648, 1506, 1445, 942, 831, 797. ^{1}H-NMR ($CDCl_3$) δ: 4.06 (3H, s), 5.93 (2H, s), 6.33 (1H, s), 7.12 (1H, s), 7.26—7.28 (2H, m), 7.48—7.51 (1H, m), 7.58—7.60 (1H, m), 7.85 (1H, br s). *Anal.* Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 67.86; H, 4.08.

5-Phenyl-6-hydroxy-4-methoxy-1,3-benzodioxole (7a) (Method B) Compound **4** (300 mg, 0.89 mmol), phenylboronic acid (119 mg, 0.98 mmol), $Pd(OAc)_2$ (4 mg, 0.018 mmol), *n*-Bu_4NBr (287 mg, 0.89 mmol), and K_2CO_3 (307 mg, 2.22 mmol) were added to H_2O (2 ml). The mixture was stirred at 70 °C for 1 h. The reaction mixture was poured into ice water and extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (*n*-hexane : EtOAc = 20 : 1) to afford the protected benzodioxole **6a** (333 mg, 100%).

A mixture of **6a** (200 mg, 0.60 mmol) and EtOAc (20 ml) in the presence

Table 7. IR and ^{1}H-NMR Data for Substituted Phenols

No.	IR (KBr) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ
7a	3502, 3435, 2890, 1636, 1620, 1458, 940, 854, 776, 705	3.83 (3H, s), 4.78 (1H, br s), 5.91 (2H, s), 6.31 (1H, s), 7.32—7.34 (2H, m), 7.37—7.41 (1H, m), 7.46—7.50 (2H, m)
7b	3470, 2885, 1629, 1609, 1460, 926, 861, 826	3.83 (3H, s), 3.85 (3H, s), 4.79 (1H, br s), 5.90 (2H, s), 6.30 (1H, s), 7.00—7.02 (2H, m), 7.23—7.25 (2H, m)
7c	3506, 2893, 1632, 1483, 1462, 934, 860, 820	2.40 (3H, s), 3.83 (3H, s), 4.80 (1H, br s), 5.90 (2H, s), 6.30 (1H, s), 7.20—-7.22 (2H, m), 7.28—7.30 (2H, m)
7d	3531, 3478, 2891, 1627, 1463, 938, 865, 823, 773, 694	3.87 (3H, s), 4.86 (1H, br s), 5.91 (2H, s), 6.33 (1H, s), 7.35—7.41 (3H, m), 7.44—7.48 (2H, m), 7.63—7.65 (2H, m), 7.68—7.71 (2H, m)
7e	3513, 2899, 1634, 1485, 1469, 1319, 936, 867, 838	3.85 (3H, s), 4.62 (1H, br s), 5.91 (2H, s), 6.30 (1H, s), 7. 30—7.32 (2H, m), 7.35—7.37 (2H, m)
7f	3497, 3149, 2948, 1628, 1459, 938, 885, 830	4.00 (3H, s), 5.90 (2H, s), 6.29 (1H, s), 6.54 (1H, dd, J=1.7, 3.2 Hz), 6.74 (1H, d, J=3.2 Hz), 7.46 (1H, br s), 7.49 (1H, d, J=1.7 Hz)
7g	3464, 3103, 2889, 1620, 1462, 938, 846, 719	3.91 (3H, s), 5.21 (1H, br s), 5.91 (2H, s), 6.31 (1H, s), 7.06 (1H, dd, J=0.8, 3.5 Hz), 7.15 (1H, dd, J=3.5, 5.0 Hz), 7.48 (1H, dd, J=0.8, 5.0 Hz)
7h	3466, 2948, 1625, 1595, 1463, 932, 874, 797, 702	3.83 (3H, s), 3.84 (3H, s), 4.86 (1H, br s), 5.91 (2H, s), 6.31 (1H, s), 6.86—6.95 (3H, m), 7.40 (1H, dd, J=7.9, 7.9 Hz)
7i	3502, 3411, 2893, 1622, 1464, 944, 863, 762	3.82 (3H, s), 3.83 (3H, s), 5.03 (1H, br s), 5.90—5.92 (2H, m), 6.34 (1H, s), 7.03—7.08 (2H, m), 7.22—7.25 (1H, m), 7.37—7.41 (1H, m)
7j	3437, 2942, 1629, 1617, 1463, 938, 857, 816	3.85 (3H, s), 3.88 (3H, s), 3.93 (3H, s), 4.88 (1H, br s), 5.90 (2H, s), 6.31 (1H, s), 6.83 (1H, d, J=1.9 Hz), 6.88 (1H, dd, J=1.9, 8.0 Hz), 6.98 (1H, d, J=8.0 Hz)
7k	3435, 2955, 1616, 1465, 937, 854, 830	3.80 (3H, s), 3.82 (3H, s), 3.85 (3H, s), 4.96 (1H, br s), 5.89—5.91 (2H, m), 6.32 (1H, s), 6.60—6.62 (2H, m), 7.12—7.14 (1H, m)
7l	3310, 2944, 1638, 1588, 1482, 947, 842, 811	3.86 (6H, s), 3.88 (3H, s), 3.90 (3H, s), 4.92 (1H, br s), 5.91 (2H, s), 6.31 (1H, s), 6.53 (2H, s)
7m	3414, 2894, 1655, 1602, 1427, 943, 883, 771, 695	3.90 (3H, s), 4.96 (1H, br s), 5.92 (2H, s), 6.23 (1H, s), 7.37—7.51 (5H, m)
7n	3412, 2882, 1653, 1610, 1437, 938, 885, 834	3.85 (3H, s), 3.90 (3H, s), 4.92 (1H, br s), 5.91 (2H, s), 6.22 (1H, s), 7.01—7.03 (2H, m), 7.38—7.40 (2H, m)
7o	3546, 2895, 1640, 1607, 1418, 941, 755, 723, 701	3.87 (3H, s), 4.93 (1H, br s), 5.93 (2H, s), 7.37—7.59 (10H, m)
7p	3501, 2943, 1635, 1608, 1436, 939, 831	3.83 (3H, s), 3.85 (3H, s), 3.85 (3H, s), 4.91 (1H, br s), 5.91 (2H, s), 6.97—7.00 (4H, m), 7.29—7.31 (2H, m), 7.50—7.52 (2H, m)
7q	3531, 3279, 1647, 1477, 932, 850, 774, 703	4.71 (1H, br s), 4.88 (1H, br s), 5.92 (2H, s), 6.23 (1H, s), 7.37—7.40 (2H, m), 7.45—7.47 (1H, m), 7.52—7.56 (2H, m)
7r	3294, 2940, 1612, 1459, 1407, 836, 761, 701	3.64 (3H, s), 3.84 (3H, s), 3.87 (3H, s), 4.88 (1H, br s), 6.39 (1H, s), 7.35—7.42 (3H, m), 7.47—7.51 (2H, m)
7s	3351, 2937, 1609, 1458, 856, 830	3.63 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 3.86 (3H, s), 4.88 (1H, br s), 6.38 (1H, s), 7.01—7.03 (2H, m), 7.27—7.29 (2H, m)

of 10% Pd–C (20 mg) was stirred for 1 h under a hydrogen atmosphere. The catalyst was removed by filtration and washed with EtOAc. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (*n*-hexane : EtOAc=5 : 1) to give **7a** (136 mg, 93%).

Compounds **7b**—**e**, **7h**, **7j**, and **7l**—**s** were prepared as described above. The physical data for these compounds are summarized in Tables 6 and 7.

5-(2-Furanyl)-6-hydroxy-4-methoxy-1,3-benzodioxole (7f) (Method C) Compound **4** (250 mg, 0.74 mmol), 2-(tributylstannyl)furan (467 μl, 1.48 mmol), and $Pd(PPh_3)_4$ (43 mg, 0.037 mmol) were added to hexamethylphosphoramide (HMPA) (4 ml). The mixture was stirred at 100 °C for 1.5 h. The reaction mixture was poured into ice water and extracted with Et_2O. The extract was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (*n*-hexane : EtOAc=10 : 1) to afford the protected benzodioxole **6f** (231 mg, 96%).

A mixture of **6f** (200 mg, 0.62 mmol) and EtOAc (10 ml) in the presence of 5% Pd on barium carbonate (50 mg) was stirred for 4 h under a hydrogen atmosphere. The catalyst was removed by filtration and washed with EtOAc. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (*n*-hexane : EtOAc=10 : 1) to give **7f** (131 mg, 91%).

Compound **7g** was prepared as described above. In the synthesis of **7g**, 10% Pd–C was used. The physical data for these compounds are summarized in Tables 6 and 7.

5-(2-Methoxyphenyl)-6-hydroxy-4-methoxy-1,3-benzodioxole (7i) (Method D) Compound **4** (360 mg, 1.07 mmol), 2-methoxyphenylboronic acid (240 mg, 1.61 mmol), $Pd(PPh_3)_4$ (120 mg, 0.11 mmol), and 2 M K_2CO_3 (0.6 ml) were added to toluene (6 ml). The mixture was stirred at 120 °C for 16 h. The reaction mixture was poured into ice water and extracted with EtOAc. The extract was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (*n*-hexane : EtOAc=5 : 1) to afford the protected benzodioxole **6i** (222 mg, 56%).

A mixture of **6i** (200 mg, 0.55 mmol) and EtOAc (10 ml) in the presence of 10% Pd–C (20 mg) was stirred for 1 h under a hydrogen atmosphere. The catalyst was removed by filtration and washed with EtOAc. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (*n*-hexane : EtOAc=3 : 1) to give **7i** (118 mg, 78%).

Compound **7k** was prepared as described above. The physical data for these compounds are summarized in Tables 6 and 7.

Antioxidative Activity using the Liver Microsome System[28] Antioxidative activity was examined by using the lipid peroxidation of guinea pig liver microsomes enzymatically induced with CCl_4.[19] Guinea pig liver microsomes were prepared by the described methods.[29] The synthetic compounds were dissolved in methyl sulfoxide (DMSO) and 5 μl of the sample solution was mixed with 30 μl of liver microsomes (70 mg protein/ml), 200 μl of 0.25 M potassium phosphate buffer (pH 7.4, including 0.1 mM EDTA), a NADPH-generating system (50 μl of 10 mM NADP, 50 μl of 200 mM glucose-6-phosphate, and 0.4 μl of 500 U/ml glucose-6-phosphate dehydrogenase), and 144.6 μl of water. To initiate the reaction, 20 μl of 1 M CCl_4 in ethanol was added. After incubation at 37 °C for 20 min, 500 μl of thiobarbituric acid (TBA) buffer (1 M trichloroacetic acid, 3.25 mM TBA, and 1.95% HCl) was added to quench the reaction. The reaction mixture was centrifuged (4000×***g***, 4 min, room temperature) and 900 μl of the supernant was incubated at 95 °C for 25 min. The quantity of TBA reactive substance was determined at 530 nm using a UV spectrophotometer. As a positive control, α-tocopherol and *n*-propyl gallate were used and the values without test compounds were taken as 100% lipid peroxidation. In this assay, the inhibitory value of **7b** at 100 μM was 56.3±1.3% (n=6).

Antioxidative Activity on a TLC Plate Antioxidative activity was evaluated on a TLC plate.[25] The test sample was charged on a TLC plate and developed. On this plate was sprayed a 5% EPA in 2,2,4-trimethylpentane solution. The plate was successively heated at 55 °C for 20 min to generate peroxides of EPA. *N,N*-Dimethyl-1,4-phenylenediamine–AcOH solution was then used as a coloring reagent for the peroxides. The threshold value of α-tocopherol on a TLC plate was 0.28±0.02 nmol (n=5).

Acknowledgments The authors are grateful to Dr. Shinya Yamashita and Dr. Hiroyuki Onuki (Nippon Suisan Kaisha, Ltd.) for their helpful comments.

References and Notes

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