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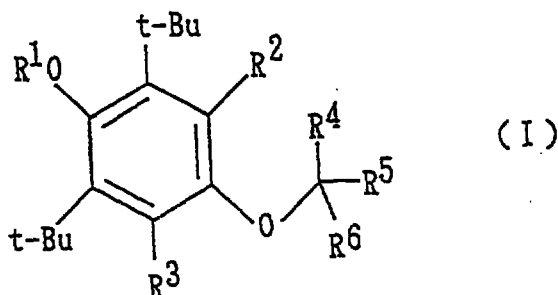
# DESCRIPTION

## 4-ALKOXY-2,6-DI-t-BUTYLPHENOL DERIVATIVES

[TECHNICAL FIELD]

This invention relates to compounds for  
5 preventing the oxidative modification of LDL, particularly,  
to compounds useful as therapeutics of arteriosclerosis,  
myocardial infarction and other ischemic diseases. More  
specifically, the invention relates to compounds represented  
by the following general formula (I), as well as compounds  
10 represented by the general formula (II) which are useful  
intermediates for the synthesis of compounds (I):

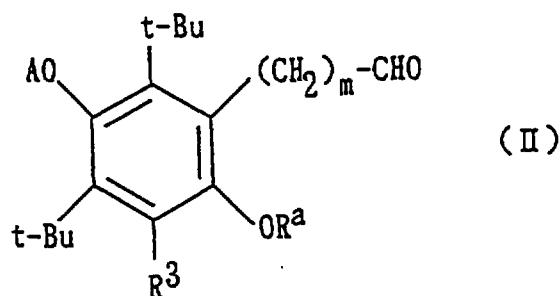
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(where R<sup>1</sup> is a hydrogen atom or an acyl group; R<sup>2</sup> is a lower  
alkyl group; R<sup>3</sup> is a hydrogen atom or a lower alkyl group;  
R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup>, which may be the same or different, are a  
15 hydrogen atom or an optionally substituted alkyl, alkenyl,  
alkynyl or aryl group; R<sup>2</sup> and R<sup>4</sup>, when taken together, may  
form a 5-membered ring; R<sup>5</sup> and R<sup>6</sup>, when taken together, may  
form a cycloalkyl group or a heterocyclic group in which  
at least one methylene on the ring of a cycloalkyl group is  
20 substituted by an oxygen atom, a sulfur atom or an alkyl-  
substituted nitrogen atom, provided that R<sup>6</sup> is not present if  
the ring formed by R<sup>2</sup> and R<sup>4</sup> taken together is a benzofuran



ring);



(where  $R^3$  has the same meaning as defined above; A is a protective group;  $R^a$  is a hydrogen atom or a lower alkyl group; and m is an integer of 0 or 1).

## 5 [BACKGROUND ART]

Atherosclerosis is one of the principal causes of ischemic diseases such as angina pectoris, myocardial infarction and cerebral apoplexy. The mechanism of initiation and progression of atherosclerosis is closely related to the oxidative modification of LDL. The modified LDLs are not recognized by the LDL receptor but by the scavenger receptor, to induce the foam cell formation which is characterized by cholesterol accumulation.

The modification of LDL is caused by endothelial cells, smooth muscle cells, macrophages, etc. and the modified LDLs are eventually taken by macrophages via the scavenger or other pathways. It is additionally known that the modification of LDL by these cells is similar to the oxidative modification of LDL by  $Cu^{2+}$ .

LDL is chiefly composed of cholesterol esters, phospholipids and apo-B-100. The oxidative modification of LDL is shown from various aspects, for example fragmentation

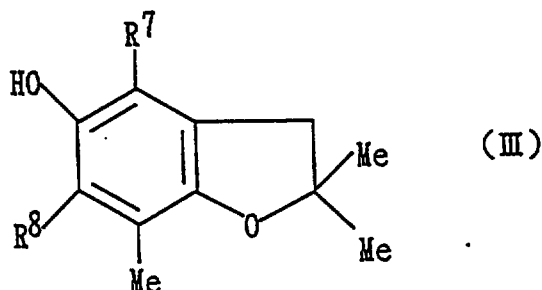
of apo-B-100 by the generated radicals, the reaction between the lipid peroxidation products and the free amino groups in apo-B-100 lysine residues, and the transformation of phosphatidyl choline to a lyso-form. One of the most  
5 established phenomena in LDL oxidation is an increase of thiobarbituric acid reactive substances (TBARS) as a result of the lipid peroxidation. Oxidized LDL, or LDL that has undergone such oxidative modification, causes the foam cell formation and the cholesterol accumulation by the scavenger  
10 and other pathways.

Under these circumstances, it is expected that compounds having the inhibitory action on lipid peroxidation can inhibit the initiation and progression of atherogenic lesions by preventing the oxidative modification of LDL  
15 and, hence, have the potential to work as therapeutics of arteriosclerosis.

In ischemic diseases such as cerebral apoplexy and myocardial infarction, various active oxygen species are generated during blood reperfusion at ischemic sites  
20 and tissue disorders can be exacerbated by the disruption of cell membranes and other effects caused by the lipid peroxidation. It is expected that compounds having the anti-oxidative activity can prevent the tissue disorders in ischemic lesions by removing the various active oxygen  
25 species and lipid peroxidation and, hence, have the potential to work as therapeutics of ischemic diseases.

Vitamin E is known as a natural antioxidant and studies have been made to develop synthetic antioxidants using vitamin E as the basic skeleton but no completely satisfactory products have yet been synthesized.

5        Some of the compounds of the present invention which are represented by the general formula (I) have been reported in the official gazette of Japanese Patent Publication (kokai) No. Hei 2-121975, in which the generic concept of those particular compounds is expressed by the  
10    general formula (III):



(where R<sup>7</sup> is a straight or branched lower alkyl group having 2 - 4 carbon atoms; R<sup>8</sup> is a straight or branched lower alkyl group having 1 - 4 carbon atoms).

Another part of the compounds of the present  
15    invention are described, by their generic concept, in Japanese Patent Publication (kokai) No. Hei 2-76869, USP No. 4,966,907, etc.

[DISCLOSURE OF INVENTION]

20    An object of the present invention is to provide antioxidants useful in the treatment of arteriosclerosis and other ischemic diseases such as myocardial infarction and cerebral apoplexy, as well as intermediates useful for

producing said compounds.

We postulated that the reason for the inadequate efficacy of existing antioxidants such as the compounds described in the official gazette of Japanese Patent Publication (kokai) No. Hei 2-121975 was that their activity was lost before they reached the target sites. Because they easily react with various free radical species besides lipid peroxidation related radicals. Based on this assumption, we conducted intensive studies with a view to developing efficient antioxidants having higher reaction specificity; as a result, we found that the compounds represented by the general formula (I) attained our intended object. The present invention has been accomplished on the basis of this finding. We also found that the compounds represented by the general formula (II) were undocumented, novel compounds, which were useful as intermediates for the synthesis of the compounds represented by the general formula (I).

It should be mentioned that the compounds of the invention which are represented by the general formula (I) have the following three characteristic features:

- (1) They are lipid-soluble antioxidants which inhibit lipid peroxidation efficiently;
- (2) While there are many species of free radicals that are involved in oxidation, the compounds react efficiently with those radical species which are responsible for the chain reaction of lipid peroxidation, therefore they inhibit lipid peroxidation intensely.

(3) / In order to develop the specific lipid peroxidation inhibiting action to be specific in lipids, the compounds have low reactivity for so-called "active oxygen" species (e.g. superoxides and singlet oxygen) in aqueous solution.

The compounds of the present invention which are represented by the general formula (I) have two t-butyl groups in both ortho-positions of the phenolic hydroxyl group and they are undocumented novel compounds. Some of the compounds of the present invention are represented by the general formula (III) in the official gazette of Japanese Patent Publication (kokai) No. Hei 2-121975 to express their generic concept; another part of the compounds of the present invention are expressed in terms of their generic concept in Japanese Patent Publication (kokai) No. Hei 2-76869 and USP No. 4,966,907; however, the compounds of the present invention are not described specifically in these patents.

The present invention is based on the fact that the compounds represented by the general formula (I) which have two t-butyl groups in both ortho-positions of the phenolic hydroxyl group exhibit by far superior effects than the compounds represented by the general formula (III) and those described in Japanese Patent Publication (kokai) No. Hei 2-76869 and USP No. 4,966,907, as will be demonstrated by test cases to be described later in this specification.

In the compounds of the invention, the acyl group as  $R^1$  may be exemplified by acetyl, formyl, propionyl, benzoyl, benzyloxycarbonyl, etc., with acetyl being preferred. The lower alkyl group as  $R^2$  and  $R^3$  or  $R^4$  refers to a straight or branched alkyl group having 1 - 6 carbon atoms, as exemplified by methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, etc. The alkyl group as  $R^4$ ,  $R^5$  and  $R^6$  refers to a straight or branched alkyl group having 1 - 20 carbon atoms, as exemplified by methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc. The alkenyl group as  $R^4$ ,  $R^5$  and  $R^6$  refers to a straight or branched alkenyl group having 2 - 20 carbon atoms, as exemplified by vinyl, allyl, butenyl, pentenyl, geranyl, farnesyl, etc. The alkynyl group as  $R^4$ ,  $R^5$  and  $R^6$  refers to a straight or branched alkynyl group having 2 - 20 carbon atoms, as exemplified by ethynyl, propynyl, butynyl, etc. The aryl group as  $R^4$ ,  $R^5$  and  $R^6$  means a monovalent substituent that is an aromatic hydrocarbon minus a hydrogen atom, as exemplified by phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl, phenanthryl, etc. Carbon atoms on the ring of the aryl group may be substituted by one or more species such as a halogen atom, a lower alkyl group, a hydroxyl group, an alkoxy group, an amino group, a nitro group, a trifluoromethyl group, etc. Exemplary substituents include a halogen atom, a hydroxyl group, an amino group, an alkoxy group, an aryloxy group, etc. The 5-membered ring which may be formed by  $R^2$  and  $R^4$  taken together is exemplified by a furan ring and a dihydro-



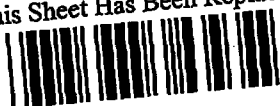
furan ring, which are taken together with the adjacent benzene ring to form a benzofuran ring and a dihydrobenzofuran ring, respectively. The cycloalkyl group which may be formed by R<sup>5</sup> and R<sup>6</sup> taken together refers to a cycloalkyl group having 3 - 8 carbon atoms, as exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc. The heterocyclic group which may be formed by R<sup>5</sup> and R<sup>6</sup> taken together and in which at least one methylene on the ring of a cycloalkyl group is substituted by an oxygen atom, a sulfur atom or an alkyl-substituted nitrogen atom may be exemplified by a tetrahydropyranyl group. The protective group as A may be exemplified by acetyl, benzoyl, methyl, methoxymethyl, methoxyethoxymethyl, benzyl, trimethylsilyl, benzyloxycarbonyl, tetrahydropyranyl, 2-trimethylsilyl)ethoxymethyl, etc., with acetyl being preferred.

[BEST MODE FOR CARRYING OUT THE INVENTION]

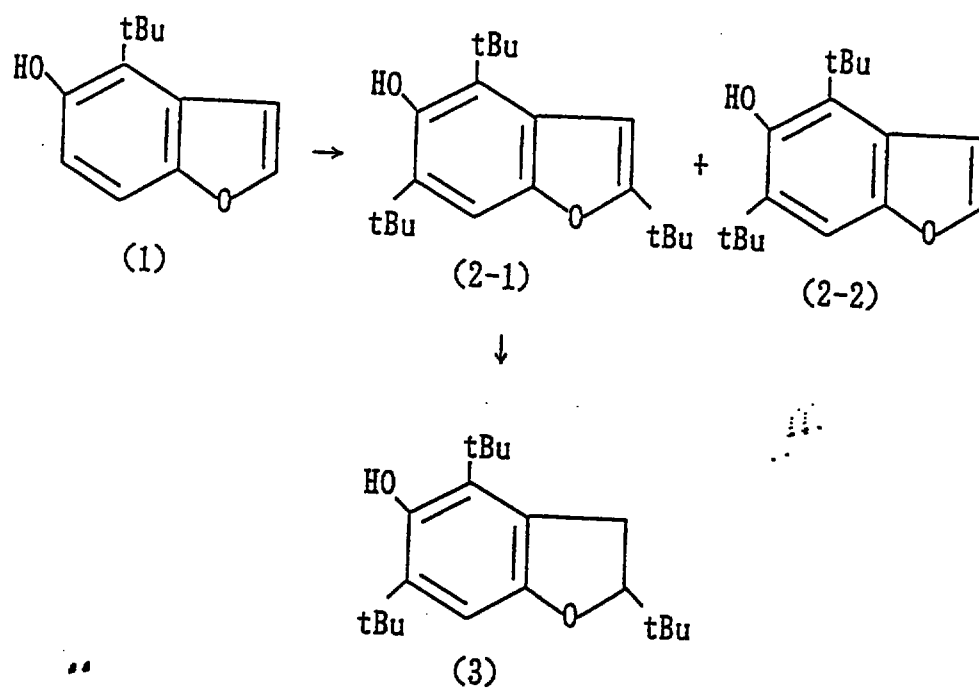
The compounds of the present invention may typically be synthesized by the following methods.

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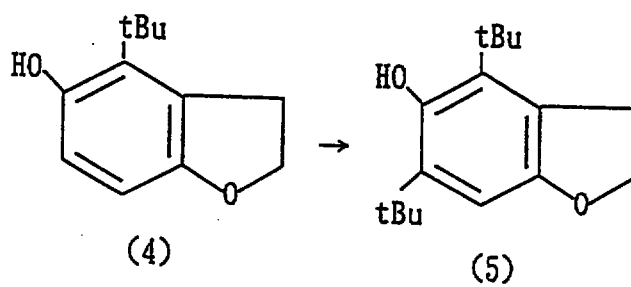
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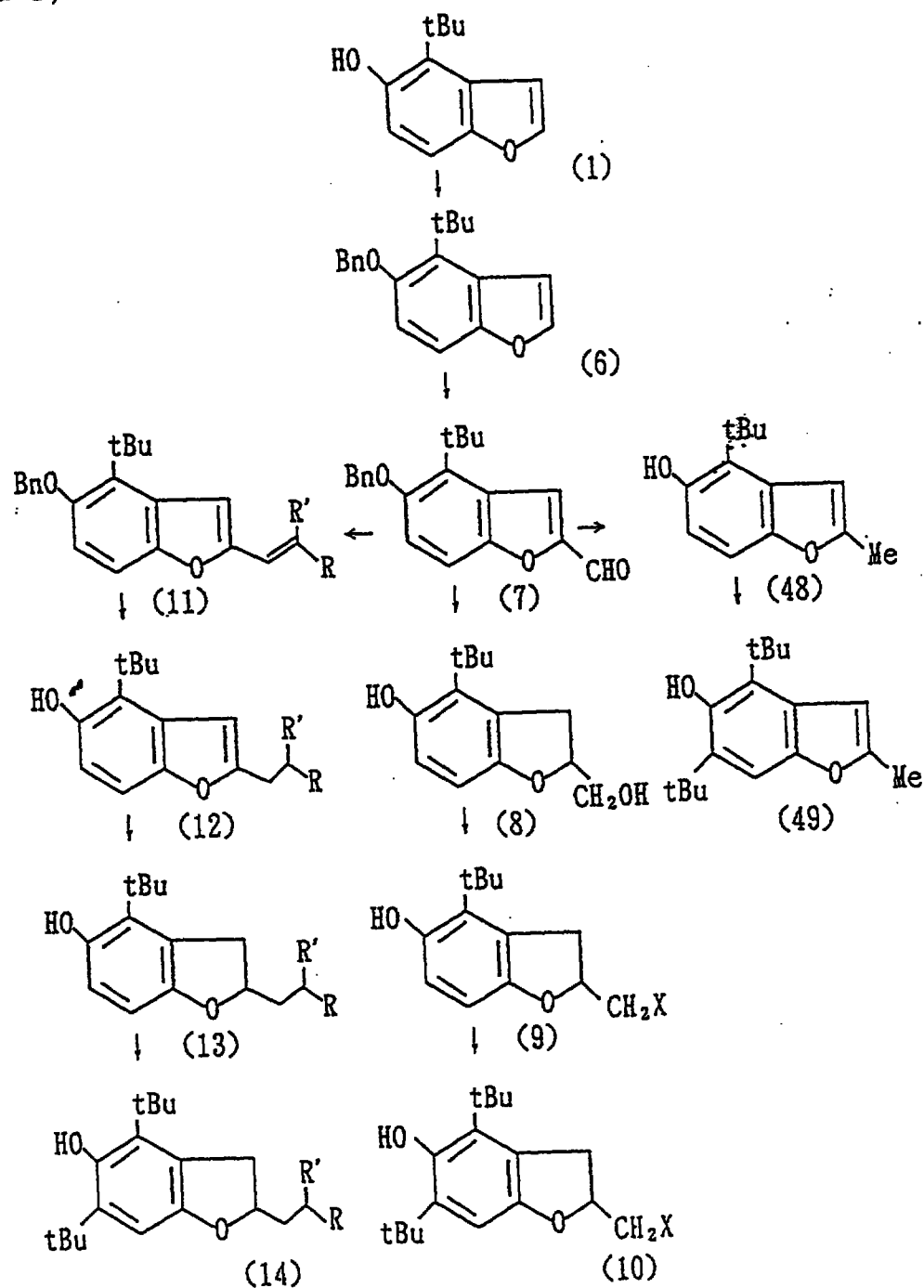
(Method A)



(Method B)

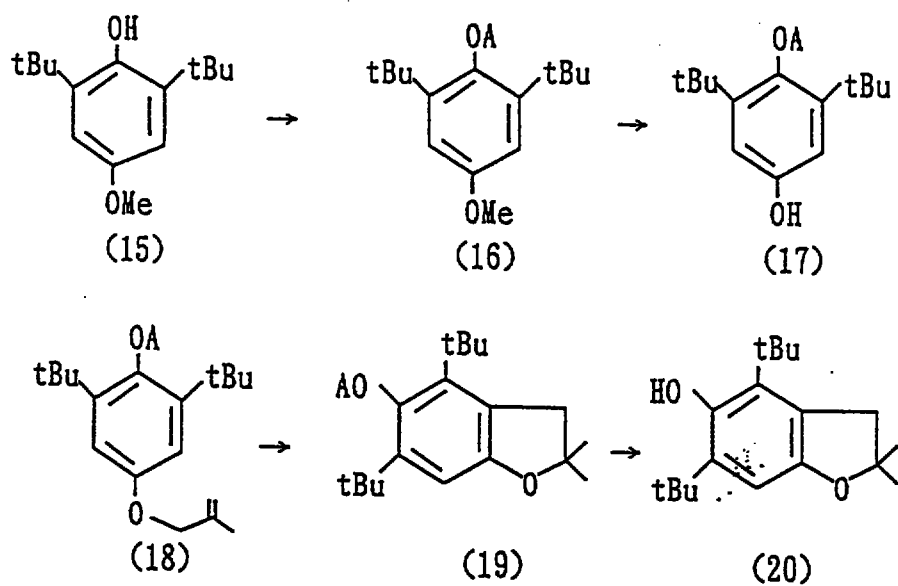


(Method C)



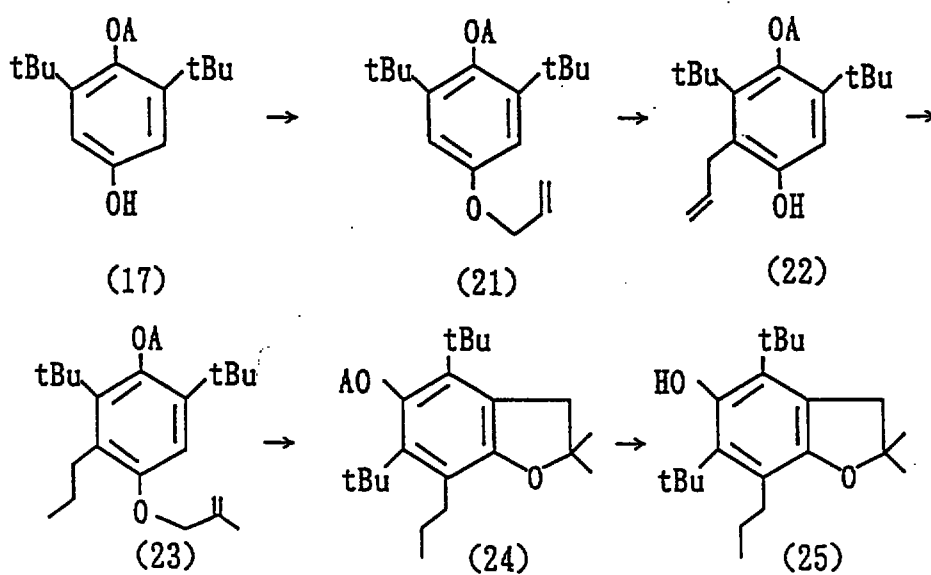
(where X is a halogen atom; R and R', which may be the same or different are an optionally substituted alkyl or aryl group).

(Method D)



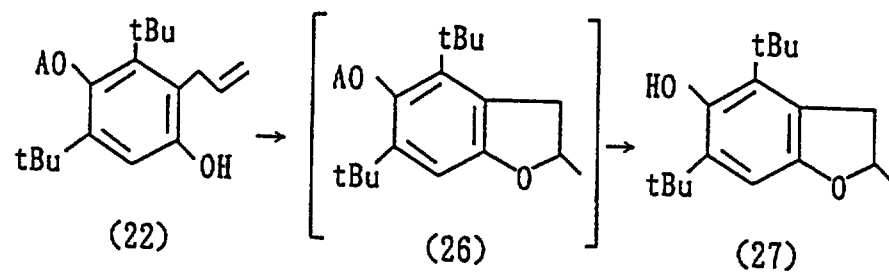
(where A is a protective group).

(Method E)



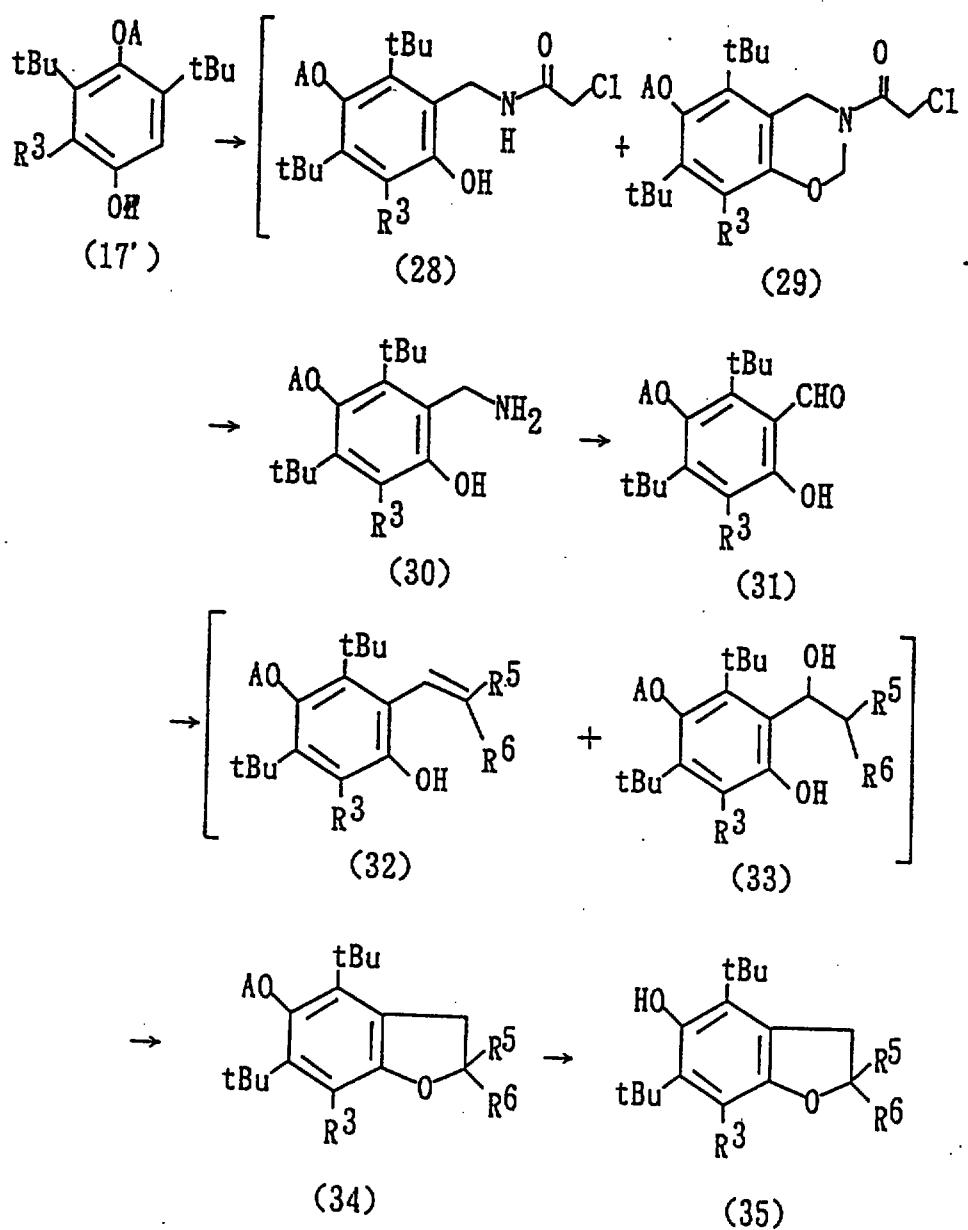
(where A is a protective group).

(Method F)<sup>iv</sup>



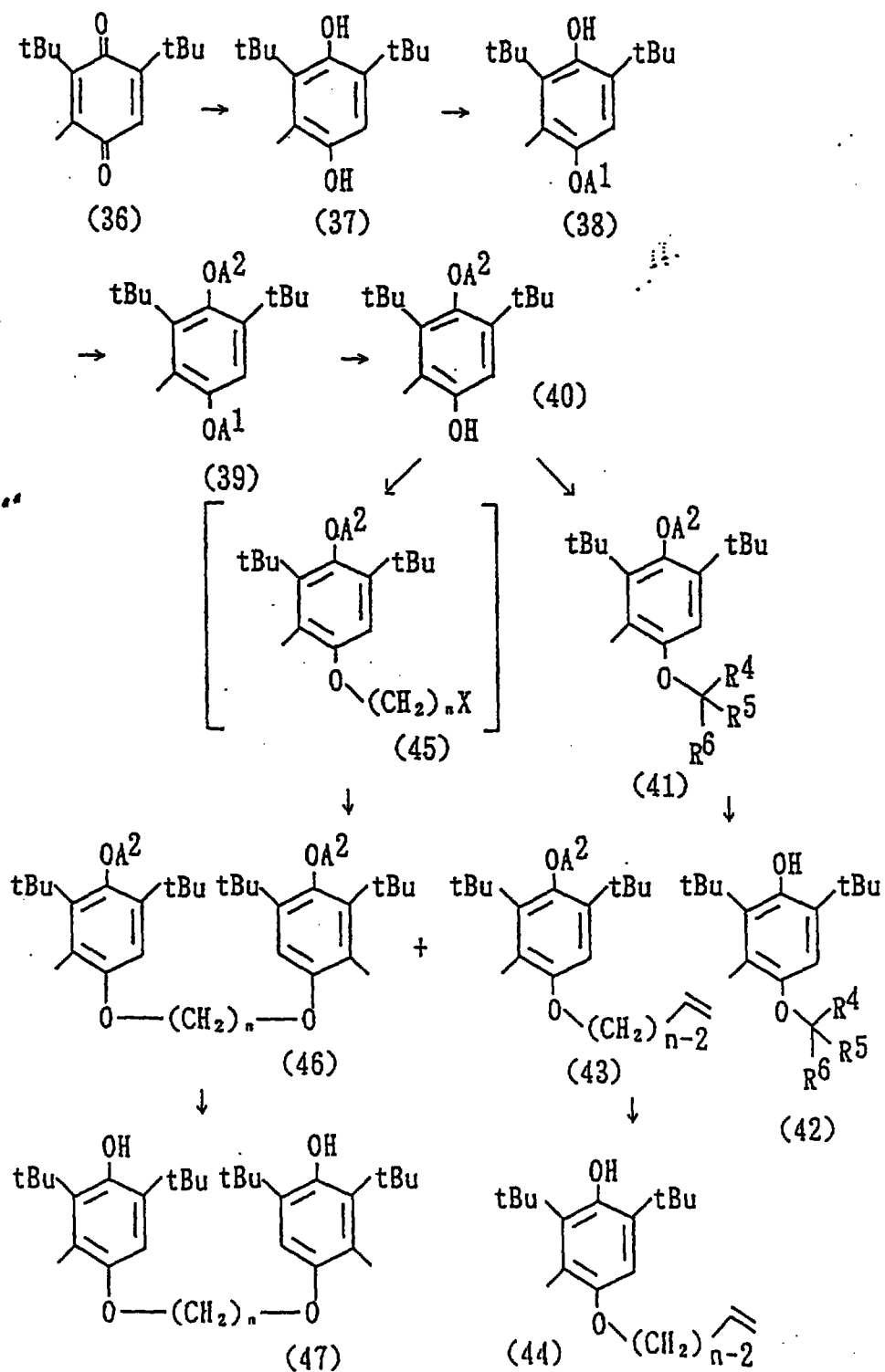
(where A is a protective group).

(Method G)



(where A is a protective group; R<sup>3</sup>, R<sup>5</sup> and R<sup>6</sup> have the same meanings as defined above).

(Method H)



(where A<sup>1</sup> and A<sup>2</sup> are each a protective group; n is an integer of 3 - 10).

In method A, the reaction for producing the compounds of formulae (2-1) and (2-2) from the compound of formula (1) is carried out by adding methanesulfonic acid to the compound of formula (1) (see J. Org. Chem., 53, 4135, 1988) and t-butanol in a solvent such as chloroform or dichloromethane at a temperature ranging from -20°C to room temperature and then stirring the mixture. Conversion from formula (2-1) to formula (3) may typically be accomplished by reduction that involves adding triethylsilane and trifluoroacetic acid to the compound of formula (2-1).

In method B, the reaction for producing the compound of formula (5) from the compound of formula (4) is carried out by adding methanesulfonic acid to the compound of formula (4) (see J. Org. Chem., 53, 4135, 1988) and t-butanol in a solvent such as chloroform or dichloromethane at a temperature ranging from -20°C to room temperature and then stirring the mixture.

In method C, the reaction for producing the compound of formula (6) from the compound of formula (1) is carried out by adding benzyl bromide to the compound of formula (1) in a solvent such as ether, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide or acetone in the presence of a base such as potassium carbonate, sodium carbonate, sodium hydroxide or potassium hydroxide at a temperature of 0 - 50°C and then stirring the mixture. To obtain the compound of formula (7) from the compound of formula (6),

formylation is performed with a suitable reagent such as a Vilsmeier reagent. The compound of formula (7) is reduced catalytically to yield the compound of formula (8), which is then treated with a halogenating agent such as thionyl chloride or thionyl bromide for conversion to the compound of formula (9) which, in turn, is processed as in method B to yield the compound of formula (10).

To obtain the compound of formula (14) from the compound of formula (7), the latter compound is first subjected to the Wittig reaction or the like for transformation to the compound of formula (11), which is then reduced catalytically to give the compound of formula (12). The compound of formula (12) is reduced typically by a reaction using triethylsilane and trifluoroacetic acid to afford the compound of formula (13) which, in turn, is processed as in method B to yield the compound of formula (14).

To obtain the compound of formula (49) from the compound of formula (7), the latter is first reduced catalytically to afford the compound of formula (48) which, in turn, is processed as in method B to yield the compound of formula (49).

In method D, the compound of formula (15) is protected at the phenolic hydroxyl group to afford the compound of formula (16), which is demethylated typically with trimethylsilyl iodide to afford the compound of formula (17). The compound of formula (17) is treated with an alkenyl halide such as 3-chloro-2-methyl-1-propene in a solvent such as tetrahydrofuran, N,N-dimethylformamide,

N,N-dimethylacetamide or acetone in the presence of a base such as sodium hydride, potassium carbonate, sodium carbonate, sodium hydroxide or potassium hydroxide to afford the compound of formula (18) which, in turn, is subjected  
5 to rearrangement by heating in a solvent such as N,N-dimethylaniline to afford the compound of formula (19), which may be deprotected as required to yield the compound of formula (20).

In method E, the reaction for producing the  
10 compound of formula (25) from the compound of formula (17) starts with adding an alkenyl halide such as 3-bromo-1-propene to the compound of formula (17) in a solvent such as tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide or acetone in the presence of a base such as  
15 sodium hydride, potassium carbonate, sodium carbonate, sodium hydroxide or potassium hydroxide to afford the compound of formula (21), which is then subjected to rearrangement by heating in a solvent such as N,N-dimethylaniline so that it is transformed to the compound of formula  
20 (22). After catalytic reduction, the compound of formula (22) is processed as in the steps of method D for affording the compounds of formulae (18), (19) and (20) from the compound of formula (17), thereby yielding the compounds of formulae (23), (24) and (25).

25 In method F, the reaction for producing the compound of formula (27) from the compound of formula (22) comprises dissolving the latter compound in a solvent such as chloroform or dichloromethane, allowing a Lewis acid such as boron

trifluoride etherate to act on the solution, thereby affording the compound of formula (26), and optionally deprotecting it to yield the compound of formula (27).

In method G, the reaction for producing the compound of formula (30) from the compound of formula (17') comprises dissolving the latter compound in hydrochloric acid, sulfuric acid, acetic acid or a mixture thereof, adding N-hydroxymethyl-2-chloroacetamide to the resulting solution at 0 - 50°C, preferably at room temperature, stirring the mixture to afford the compounds of formulae (28) and (29), dissolving these compounds in a mixed solvent system consisting of an organic solvent such as methanol or ethanol and an acidic aqueous solution such as conc. HCl, heating the solution to effect hydrolysis. The reaction for converting the compounds of formula (30) into the compound of formula (31) is carried out by dissolving the former compound in an acidic aqueous solution, adding hexamethylenetetramine, and heating the mixture, preferably dissolving said compound in an aqueous solution of acetic acid, heating the resulting solution under reflux, then adding an aqueous solution of hydrochloric acid, and heating the mixture under reflux. The compound of formula (31) is treated with a Grignard reagent, an organolithium compound and the like to afford the compound of formula (32) or (33) which, in turn, is dissolved in a solvent such as chloroform or dichloromethane; a Lewis acid such as boron trifluoride etherate is allowed to act on the solution to afford the compound of formula (34), which is optionally deprotected

to yield the compound of formula (35).

In method H, the reaction for producing the compound of formula (37) from the compound of formula (36) [see Chem. Ber., 109, 1530-1548 (1976)] is performed by  
5 allowing a reducing agent such as sodium borohydride to act on the compound of formula (36). By selective protection and deprotection of either one of the two phenolic hydroxyl groups in the compound of formula (37), the compounds of formulae (38) and (39) and then the compound of formula (40)  
10 are produced. The compound of formula (40) is treated with an alkyl halide, an alkenyl halide or an alkynyl halide in a solvent such as tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide or acetone in the presence of a base such as sodium hydride, potassium carbonate, sodium carbonate,  
15 sodium hydroxide or potassium hydroxide to afford the compound of formula (41), which is optionally deprotected to yield the compound of formula (42).

To produce the compounds of formulae (44) and (47), a halide such as 1,3-dibromopropane or 1-bromo-3-chloropropane  
20 is first allowed to act on the compound of formula (40) in a solvent such as tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide or acetone in the presence of a base such as sodium hydride, potassium carbonate, sodium carbonate, sodium hydroxide or potassium hydroxide and, thereafter,  
25 a treatment is performed in the same way as employed to obtain the compound of formula (41) from the compound of formula (40), whereby the compounds of formulae (43) and (46) are obtained. These compounds are optionally

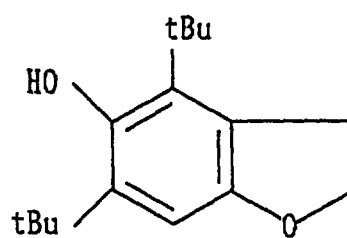
deprotected to yield the compounds of formulae (44) and (47), respectively.

The following test cases (Nos. 1 - 6) are provided for the purpose of demonstrating that the compounds of the invention are superb as highly selective antioxidants.

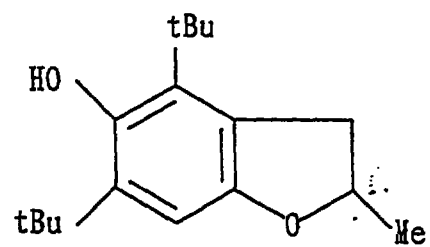
The compounds under test were as follows:

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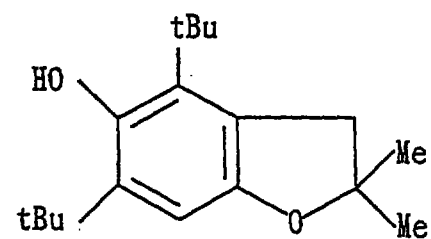
Compound a



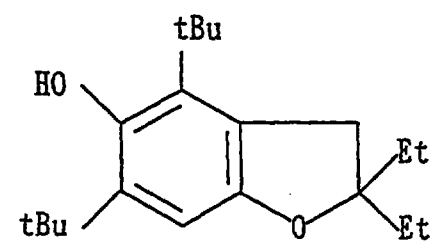
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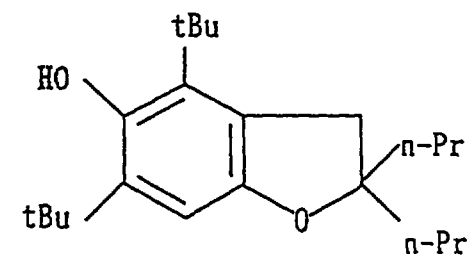
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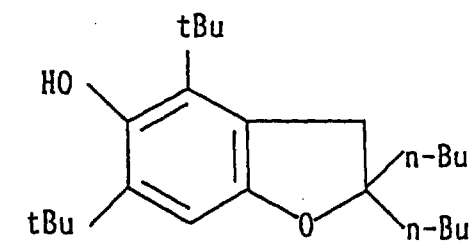
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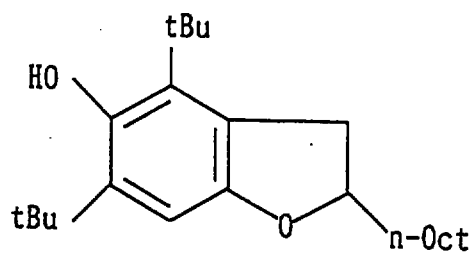
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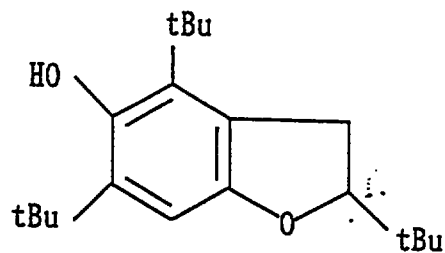
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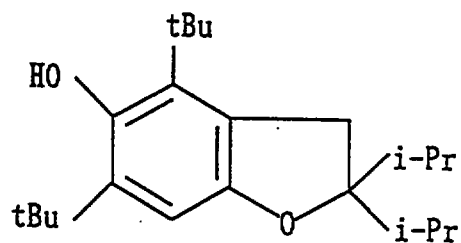
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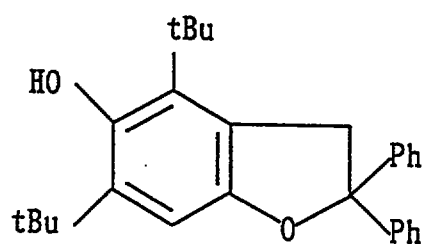
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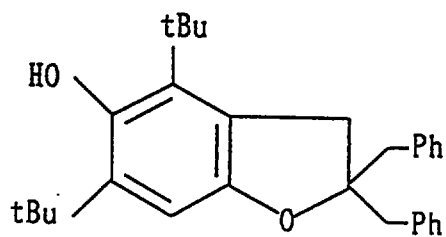
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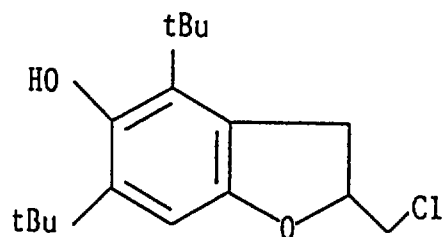
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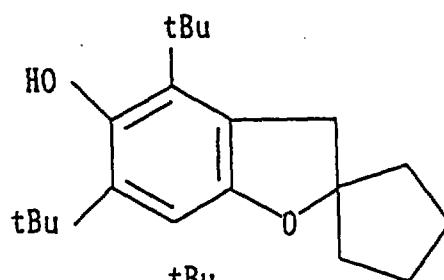
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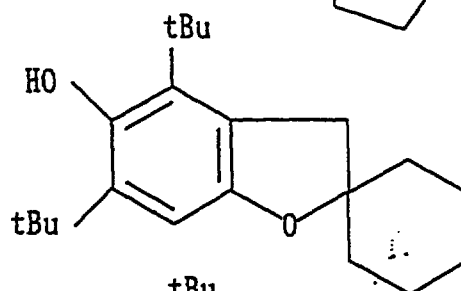
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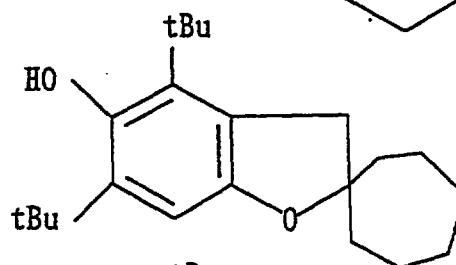
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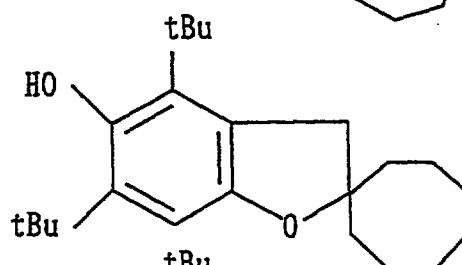
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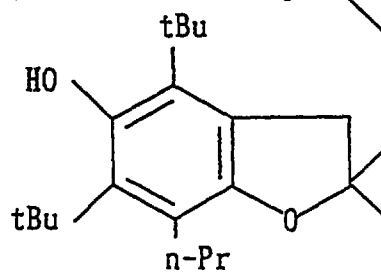
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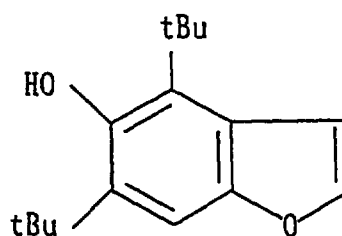
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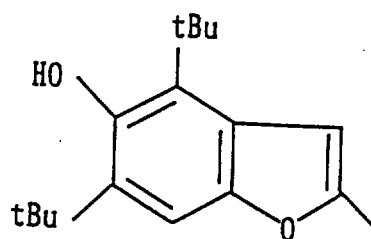
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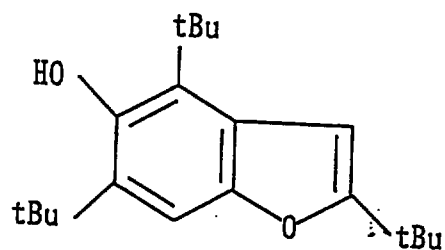
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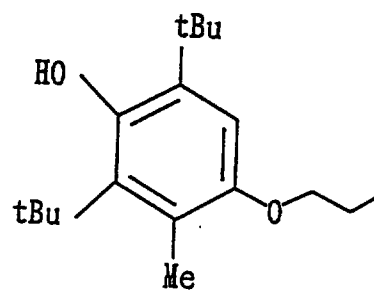
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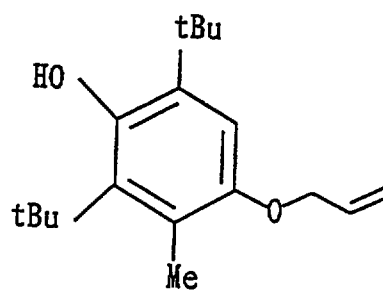
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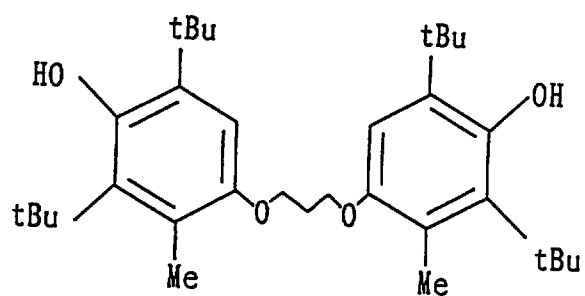
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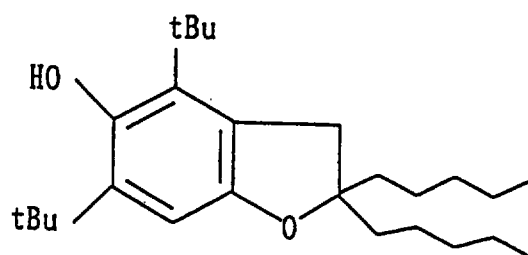
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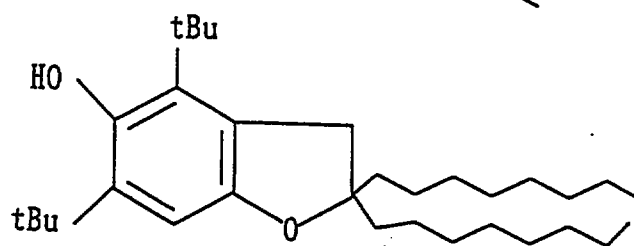
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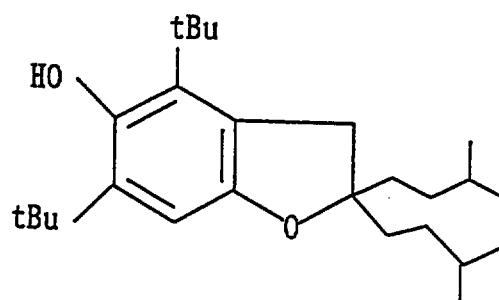
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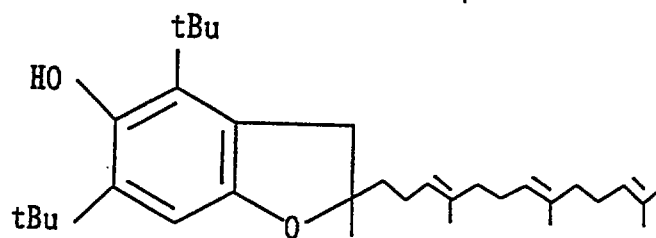
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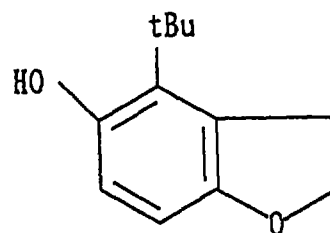
Compound z



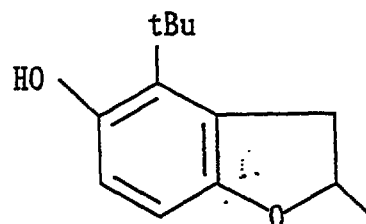
Compound  $\alpha$



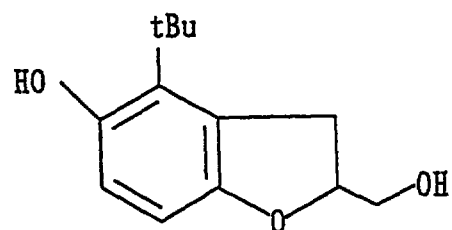
Comparative Compound 1



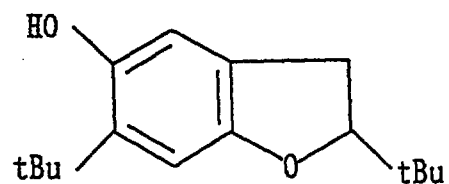
Comparative Compound 2



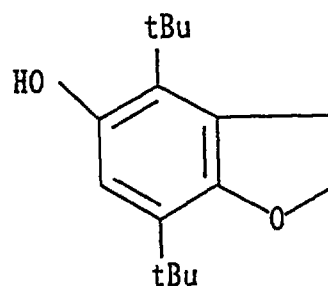
Comparative Compound 3



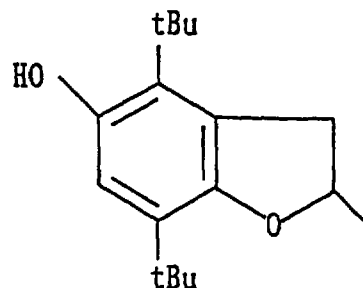
Comparative Compound 4



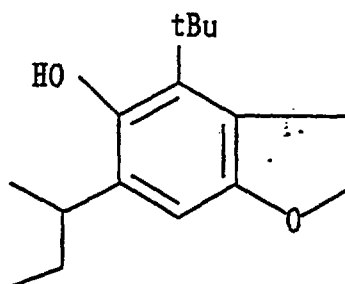
Comparative Compound 5



Comparative Compound 6



Comparative Compound 7



[Test Case '1] Amount of TBARS

Rabbit LDL was prepared in accordance with the method of Havel et al. [Havel, R.J. et al., J. Clin. Invest., 34, 1345 (1955)]. After adding 5  $\mu\text{M}$  of  $\text{Cu}^{2+}$ , the mixture was  
5 warmed until a thiobarbituric acid reactive substance (TBARS) was produced. The test compounds were evaluated for their anti-oxidative action with the amount of TBARS being used as an index.

TBARS produced =

10 
$$\frac{\text{TBARS produced when sample was added}}{\text{TBARS produced in solvent}} \times 100 (\%)$$

The results are shown in Table 1.

Table 1

| Compound | TBARS produced (%)         |                            |
|----------|----------------------------|----------------------------|
|          | at $10^{-6}$ M of compound | at $10^{-5}$ M of compound |
| a        | 52.2                       | 10.3                       |
| b        | 53.8                       | 8.9                        |
| c        | 55.3                       | 9.2                        |
| d        | 76.9                       | 9.4                        |
| e        | 86.3                       | 13.5                       |
| f        | 81.6                       | 12.2                       |
| g        | 82.6                       | 8.8                        |
| h        | 74.0                       | 10.6                       |
| i        | 90.8                       | 10.3                       |
| j        | 93.1                       | 11.6                       |
| k        | 93.0                       | 11.1                       |
| l        | 11.5                       | 8.1                        |
| m        | 85.3                       | 11.8                       |
| n        | 76.2                       | 15.6                       |
| o        | 91.2                       | 9.0                        |
| p        | 91.8                       | 22.0                       |
| q        | 97.4                       | 56.8                       |
| r        | 74.2                       | 30.1                       |
| s        | 75.7                       | 39.2                       |
| t        | 81.7                       | 68.0                       |
| u        | 87.7                       | 47.3                       |
| v        | 99.3                       | 80.3                       |
| w        | 71.3                       | 17.2                       |
| x        | 96.3                       | 42.1                       |
| y        | 85.4                       | 72.3                       |
| z        | 77.5                       | 22.9                       |

[Test Case 2] Effect Against Lipid Peroxidation by  
Autoxidation of Linoleic Acid

Using a cypridina luciferin analog (2-methyl-6-(p-methoxyphenyl)-3,7-dihydroimidazo[1,2-a]pyrazin-3-one: MCLA) as a sensitizer for lipid peroxy radicals, the test compounds were evaluated for their inhibitory effect against the generation of lipid peroxy radicals by autoxidation of linoleic acid. A n-butanol solution (0.5 ml) containing MCLA (0.2  $\mu$ M) and linoleic acid (10 mM) was used in a chemiluminescence measuring vial and the intensity of chemiluminescence due to the autoxidation of linoleic acid was measured in a thermostatic bath at 37°C.

MCLA =

$$\frac{\text{Change in chemiluminescence intensity when sample was added}}{\text{Change in chemiluminescence intensity when solvent was added}} \times 100(\%)$$

The results are shown in Table 2.

Table 2

| Compound | MCLA (%)                              |                                       |
|----------|---------------------------------------|---------------------------------------|
|          | at $2 \times 10^{-5}M$<br>of compound | at $2 \times 10^{-4}M$<br>of compound |
| a        | 21                                    | 2                                     |
| b        | 24                                    | 2                                     |
| c        | 18                                    | 1                                     |
| d        | 36                                    | 2                                     |
| e        | 23                                    | 1                                     |
| f        | 39                                    | 3                                     |
| g        | 31                                    | 2                                     |
| h        | 33                                    | 3                                     |
| i        | 72                                    | 5                                     |
| j        | 66                                    | 10                                    |
| k        | 55                                    | 4                                     |
| l        | 24                                    | 3                                     |
| m        | 24                                    | 1                                     |
| n        | 23                                    | 1                                     |
| o        | 26                                    | 1                                     |
| p        | 44                                    | 3                                     |
| q        | 11                                    | 1                                     |
| r        | 97                                    | 68                                    |
| s        | 78                                    | 36                                    |
| t        | 93                                    | 41                                    |
| u        | 83                                    | 30                                    |
| v        | 101                                   | 15                                    |
| w        | 35                                    | 2                                     |
| x        | 13                                    | 2                                     |
| y        | 16                                    | 1                                     |
| z        | 10                                    | 2                                     |
| $\alpha$ | 13                                    | 4                                     |

[Test Case 3] Effect Against Fluorescence Generation of  
Rabbit LDL by AAPH

Using 2,2'-azobis(2-aminodipropyl)hydrochloride (AAPH) which was a radical initiator for a lipid peroxidation that was not mediated by active oxygen [see Sato, K. et al., Arch. Biochem. Biophys., 279, 402 (1990)], the test compounds were evaluated for their inhibitory effect against fluorescence generation in rabbit LDL. Rabbit LDL was prepared in accordance with the method of Havel [Havel, R.J. et al., J. Clin. Invest., 34, 1345 (1955)]; after addition of AAPH (2 mM), the mixture was warmed at 37°C for 24 h and LDL fraction was separated by gel-permeation chromatography. The fluorescence intensity of LDL fraction was measured by fluorometry at an excitation wavelength of 360 nm and at an emission wavelength of 430 nm.

AAPH =

$$15 \quad \frac{\text{Fluorescence intensity of LDL fraction} \\ \text{when sample was added}}{\text{Fluorescence intensity of LDL fraction} \\ \text{when solvent was added}} \times 100 (\%)$$

The results are shown in Table 3.

Table 3

| Compound | AAPH (%) at $10^{-4}$ M<br>of compound |
|----------|----------------------------------------|
| a        | 8                                      |
| b        | 17                                     |
| c        | 16                                     |
| d        | 49                                     |
| e        | 42                                     |
| f        | 63                                     |
| g        | 66                                     |
| h        | 42                                     |
| i        | 27                                     |
| j        | 2                                      |
| k        | 65                                     |
| m        | 45                                     |
| n        | 46                                     |
| o        | 31                                     |
| p        | 70                                     |
| t        | 85                                     |
| u        | 78                                     |
| v        | 72                                     |
| w        | 39                                     |
| x        | 31                                     |
| y        | 84                                     |

The results of Test Cases 1 - 3 obviously show that the tested compounds of the invention had an excellent anti-oxidative activity. The active oxygen induced by  $\text{Cu}^{2+}$  in the TBARS experimental model in Test Case 1 is believed to be a direct radical initiator, so even a water-soluble active oxygen scavenger will be effective in that model. It should, however, be stressed that the tested compounds

of the invention also proved to be effective in the AAPH using experimental model in Test Case 3 and, hence, it became clear that those compounds also suppressed the chain reaction for lipid peroxidation due to carbon-centered radicals which could not be inhibited by water-soluble active oxygen scavengers. This fact suggests that the compounds of the invention show effective anti-oxidative actions in LDL oxidation or lipid peroxidation.

[Test Case 4] Effect Against Linoleic Acid-MCLA System

The test compounds were evaluated for their inhibitory effect against lipid peroxidation due to the autoxidation of linoleic acid.

|                    |           |
|--------------------|-----------|
| Linoleic acid      | 10 mM     |
| MCLA               | 2 $\mu$ M |
| 1-Butanol solution |           |

A reaction solution was prepared by mixing linoleic acid and MCLA (2-methyl-6-(p-methoxyphenyl)-3,7-dihydro-imidazo[1,2-a]pyrazin-3-one) in 1-butanol and stored in ice until use. An amount of this reaction solution was sampled in a chemiluminescence measuring cell and, immediately thereafter, the intensity of chemiluminescence due to the autoxidation of linoleic acid was measured at 37°C in a thermostatic bath. A normal chemiluminescence intensity measurement was conducted about 2 - 4 min later when the chemiluminescence substantially peaked. The results are shown in Table 4.

Table 4

| Compound     | 50% inhibition<br>concentration ( $\mu\text{M}$ ) |
|--------------|---------------------------------------------------|
| Comparison 1 | 62                                                |
| 2            | 54                                                |
| 3            | 54                                                |
| 4            | 42                                                |
| 5            | 41                                                |
| 6            | 19                                                |
| 7            | 7                                                 |
| h            | 9                                                 |
| c            | 7                                                 |
| a            | 7                                                 |
| q            | 5                                                 |
| f            | 8                                                 |
| m            | 7                                                 |
| n            | 9                                                 |
| x            | 5                                                 |
| z            | 6                                                 |

The data in Table 4 show that the compounds having higher hydrophobicity in both ortho-positions of the phenolic hydroxyl group had a particularly high anti-oxidative activity.

5 [Test Case 5] Effect Against Xanthine Oxidase System  
(Superoxide Generating System)

The test compounds were evaluated under the following conditions for their effect in a reaction due to a xanthine oxidase (XOD)-hypoxanthine (HX) system in aqueous solution.

|                                |             |
|--------------------------------|-------------|
| Xanthine oxidase               | 0.1 U/ml    |
| Hypoxanthine                   | 400 $\mu$ M |
| Luminol                        | 400 $\mu$ M |
| Hepes buffer solution (pH 7.4) | 100 $\mu$ M |

5           A reaction solution was prepared by mixing  
hypoxanthine and luminol in the Hepes buffer solution  
and stored in ice until use. After warming the reaction  
solution at 37°C for about 10 min, the reaction was started  
by addition of the xanthine oxidase solution. A measurement  
10 was started right after the addition of xanthine oxidase  
and subsequent stirring; chemiluminescence intensity was  
normally measured right after the start of the reaction. In  
the experimental model, luminol-dependent chemiluminescence  
induced by superoxide generated by enzymatic reaction of  
15 xanthine oxidase was detected, thus enabling the measurement  
of the reactivity with superoxide. The results are shown in  
Table 5.

Table 5

| Compound     | Chemiluminescence intensity (% of control) |                            |
|--------------|--------------------------------------------|----------------------------|
|              | at 20 $\mu$ M of compound                  | at 200 $\mu$ M of compound |
| Comparison 1 | 23.9                                       | 6.3                        |
| 2            | 32.7                                       | 3.2                        |
| 5            | 21.9                                       | 8.2                        |
| 6            | 31.9                                       | 24.0                       |
| 7            | 55.8                                       | 17.5                       |
| g            | 88.6                                       | 104.8                      |
| a            | 41.8                                       | 26.1                       |
| f            | 91.0                                       | 102.4                      |
| m            | 83.1                                       | 89.8                       |
| n            | 100.3                                      | 104.9                      |
| x            | 84.5                                       | 85.6                       |
| y            | 94.2                                       | 110.2                      |
| z            | 99.2                                       | 107.5                      |

[Test Case 6] Effect Against Lactoperoxidase System (Singlet Oxygen System)

The test compounds were evaluated under the following conditions for their effect against a lactoperoxidase

5 reaction system.

|                                  |               |
|----------------------------------|---------------|
| Lactoperoxidase                  | 10 $\mu$ g/ml |
| H <sub>2</sub> O <sub>2</sub>    | 0.1%          |
| NaBr                             | 20 mM         |
| Luminol                          | 400 $\mu$ M   |
| Acetate buffer solution (pH 4.5) | 100 $\mu$ M   |

10

A reaction solution was prepared by mixing hydrogen peroxide, sodium bromide and luminol in the acetate buffer solution and stored in ice until use. After warming the reaction solution at 37°C for about 10 min, the reaction was started by addition of the lactoperoxidase solution. A measurement was started right after the addition of lactoperoxidase and subsequent stirring; chemiluminescence intensity was measured right after the start of the reaction. In the experimental model, luminol-dependent chemiluminescence induced by singlet oxygen generated by enzymatic reaction of lactoperoxidase was detected, thus enabling the measurement of the reactivity with singlet oxygen.

Table 6

| Compound     | Chemiluminescence intensity (% of control) |                            |
|--------------|--------------------------------------------|----------------------------|
|              | at 20 $\mu$ M of compound                  | at 200 $\mu$ M of compound |
| Comparison 1 | 77.6                                       | 6.0                        |
| 2            | 82.1                                       | 15.1                       |
| 5            | 95.3                                       | 4.5                        |
| 6            | 105.8                                      | 8.1                        |
| 7            | 86.2                                       | 0.8                        |
| g            | 97.0                                       | 76.0                       |
| a            | 94.5                                       | 56.6                       |
| q            | 104.0                                      | 73.4                       |

The results of Test Cases 5 and 6 obviously show that the compounds having high hydrophobicity in both ortho-positions of the phenolic hydroxyl group had low reactivity

with so-called active oxygen species such as superoxides and singlet oxygen. It should particularly be mentioned that in the system for reaction with singlet oxygen, the test compounds of the invention which had two t-butyl groups in both ortho-positions of the phenolic hydroxyl group had a particularly low reactivity even compared with the compound (Comparative Compound 7) having a sec-butyl group in one of the two ortho-positions. This shows that compared to the conventional antioxidants described in Japanese Patent Public Disclosure (kokai) No. Hei 2-121975 and other prior patents, the compounds of the invention have a markedly high selectivity in the inhibitory action of lipid peroxidation, as evidenced by the fact that the compounds of the invention react in a particularly efficient manner with those radical species which are responsible for the lipid peroxidation while there are many free radical species in oxidation.

[Examples]

The following examples are provided for the purpose of further illustrating the invention but are in no way to be taken as limiting.

[Example 1]

Synthesis of 2,4,6-Tri-tert-Butyl-5-Hydroxybenzofuran (Compound t) and 4,6-Di-tert-Butyl-5-Hydroxybenzofuran (Compound r)

Methanesulfonic acid (140 ml) was added dropwise, under ice cooling, to a solution consisting of 4-tert-butyl-5-hydroxybenzofuran [J. Org. Chem., 53, 4135 (1988); 35 g, 0.18 mol], tert-butyl alcohol (70 g, 0.84 mol) and

chloroform (50 ml). After stirring at 0°C for 20 min, the mixture was poured into ice water. Subsequently, the mixture was neutralized with an aqueous solution of 1N sodium hydroxide and subjected to extraction with ethyl acetate. The extracted layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried over anhydrous magnesium sulfate, and concentrated. The concentrate was purified by silica gel chromatography (n-hexane) to afford 2,4,6-tri-tert-butyl-5-hydroxybenzofuran [10.87 g (yield, 20%)]. Also obtained, though in low yield, was 4,6-di-tert-butyl-5-hydroxybenzofuran.

2,4,6-Tri-tert-butyl-5-hydroxybenzofuran

m.p. 115.5°C (fine-grained, pale yellow crystal)  
Mass 302(M<sup>+</sup>), 287, 57  
15 <sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)  
δ ppm 1.33(s,9H), 1.47(s,9H), 1.62(s,9H), 5.06(s,1H),  
6.58(s,1H), 7.29(s,1H)  
IR (cm<sup>-1</sup>) 3641, 2969

4,6-Di-tert-butyl-5-hydroxybenzofuran

20 m.p. 60.3°C (fine-grained, pale yellow crystal)  
Mass 246(M<sup>+</sup>), 231, 57  
<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)  
δ ppm 1.49(s,9H), 1.62(s,9H), 5.11(s,1H),  
7.02(d,1H,J=2.4Hz), 7.35(s,1H),  
25 7.43(d,1H,J=2.4Hz)  
IR (cm<sup>-1</sup>) 3648, 2960

[Example 2]

Synthesis of 2,4,6-Tri-tert-Butyl-5-Hydroxy-2,3-Dihydrobenzofuran (Compound h)

Triethylsilane (76 ml) was added to 2,4,6-tri-tert-butyl-5-hydroxybenzofuran (24.7 g, 82 mmol) and trifluoroacetic acid (38 ml) was added dropwise to the mixture under ice cooling. The mixture was stirred first at 0°C for 15 min, then at room temperature for 15 min before it was poured into ice water. The mixture was neutralized with an aqueous solution of 1N sodium hydroxide and subjected to extraction with ethyl acetate. The extracted layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (chloroform) to afford 2,4,6-tri-tert-butyl-5-hydroxy-2,3-dihydrobenzofuran [19.0 g (yield, 76%)].

m.p            91.4°C

(white needle; recrystallized from n-hexane)

Mass           304(M<sup>+</sup>), 289, 57

20    <sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm        0.97(s,9H), 1.40(s,9H), 1.50(s,9H),  
              3.22(dd,2H,J=8.0Hz,J=11.0Hz),  
              4.24(dd,1H,J=8.0Hz,J=11.0Hz), 4.66(s,1H),  
              6.67(s,1H)

25    IR (cm<sup>-1</sup>) 3669, 2973

[Example 3]

Synthesis of 4,6-Di-tert-Butyl-5-Hydroxy-2,3-Dihydrobenzofuran (Compound a)

Methanesulfonic acid (10 ml) was added dropwise,  
5 under ice cooling, to a solution consisting of 4-tert-butyl-5-hydroxy-2,3-dihydrobenzofuran [J. Org. Chem., 53, 4135 (1988); 2.84 g, 15 mmol], tert-butyl alcohol (10 g, 120 mmol) and chloroform (20 ml). After stirring at 0°C for 15 min, the mixture was poured into ice water. The mixture  
10 was neutralized with an aqueous solution of 1N sodium hydroxide and subjected to extraction with ethyl acetate. The extracted layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried over anhydrous magnesium sulfate and concentrated. The concentrate was  
15 purified by silica gel chromatography (n-hexane) to afford 4,6-di-tert-butyl-5-hydroxy-2,3-dihydrobenzofuran [210 mg (yield, 6%)].

m.p. 113.4°C (colorless, fine-grained crystal;  
recrystallized from n-hexane)

20 Mass 248(M<sup>+</sup>), 233, 191, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.42(s,9H), 1.50(s,9H), 3.40(t,2H,J=8.0Hz),  
4.37(t,2H,J=8.0Hz), 4.72(s,1H), 6.68(s,1H)

IR (cm<sup>-1</sup>) 3623, 2969

25 [Reference Example 1]

Synthesis of 5-Benzyloxy-4-tert-Butylbenzofuran

4-tert-butyl-5-hydroxybenzofuran [J. Org. Chem., 53, 4135 (1988); 40 g, 0.21 mol], benzyl bromide (43 g,

0.25 mol) and potassium carbonate (28.8 g, 0.21 mol) were dissolved in N,N-dimethylformamide (200 ml) and the solution was stirred at room temperature for 24 h. After distilling off the N,N-dimethylformamide under vacuum, water was added  
5 to the residue and the mixture was subjected to extraction with ethyl acetate. The extracted layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography  
10 (10% ethyl acetate in n-hexane) to afford 5-benzyloxy-4-tert-butylbenzofuran [49.1 g (yield, 83%)].

Mass 280(M<sup>+</sup>), 224, 189, 161, 91

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.57(s,9H), 5.06(s,2H), 6.86-7.43(m,9H)

15 [Reference Example 2]

Synthesis of 5-Benzyloxy-4-tert-Butyl-2-Formylbenzofuran

Phosphorus oxychloride (26.2 ml, 0.29 mol) was added dropwise to N,N-dimethylformamide (17 ml, 0.22 mol) under ice cooling; subsequently, a solution of 5-benzyloxy-4-tert-  
20 butylbenzofuran (40 g, 0.14 mol) in N,N-dimethylformamide (10 ml) was added dropwise. The mixture was stirred first at room temperature for 20 min, then under heating at 80°C for 2 h. After cooling, the reaction mixture was poured into water and extracted with ethyl acetate. The extracted  
25 layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and water, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (10% ethyl acetate in n-hexane) to

afford 5-benzyloxy-4-tert-butyl-2-formylbenzofuran [16.2 g (yield, 36%)].

m.p. 135.7°C

Mass 308(M<sup>+</sup>), 91

5 <sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.58(s,9H), 5.10(s,2H), 7.20-7.48(m,7H),  
7.92(s,1H), 9.76(s,1H)

[Reference Example 3]

10 Synthesis of 4-tert-Butyl-5-Hydroxy-2-Hydroxymethyl-2,3-Dihydrobenzofuran

5-Benzyloxy-4-tert-butyl-2-formylbenzofuran (5.0 g, 16 mmol) was dissolved in a 25:1 mixed solution (260 ml) of ethyl acetate and acetic acid. After adding 10% Pd on carbon (5.0 g), the solution was stirred under a hydrogen atmosphere for 48 h. After filtering off the Pd on carbon, the filtrate was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried over anhydrous magnesium sulfate and concentrated. The concentrate was subjected to silica gel chromatography and eluted with a solvent system consisting of a 4:1 mixture of hexane and ethyl acetate to afford 4-tert-butyl-5-hydroxy-2-hydroxymethyl-2,3-dihydrobenzofuran [3.1 g (yield, 87%)] as a colorless oil.

Mass 222(M<sup>+</sup>), 207, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

25 δ ppm 1.44(s,9H), 2.95(bs,1H), 3.09-3.91(m,4H),  
4.51-4.93(m,1H), 6.04(bs,1H), 6.46(s,2H)

[Reference Example 4]

Synthesis of 4-tert-Butyl-2-Chloromethyl-5-Hydroxy-2,3-Dihydrobenzofuran

Pyridine (180 mg, 2.2 mmol) was added to a  
5 solution of 4-tert-butyl-5-hydroxy-2-hydroxymethyl-2,3-dihydrobenzofuran (430 mg, 1.9 mmol) in benzene (15 ml) and, subsequently, thionyl chloride (310 mg, 2.6 mmol) was added dropwise under ice cooling. After being allowed to warm to room temperature, the mixture was heated under reflux for  
10 24 h. After cooling, water was added and the solution was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and water, then dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by  
15 silica gel chromatography (chloroform) to afford 4-tert-butyl-2-chloromethyl-5-hydroxy-2,3-dihydrobenzofuran [280 mg (yield, 61%)] as a colorless oil.

Mass 242(M+2), 240(M<sup>+</sup>), 227, 225, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

20 δ ppm 1.45(s,9H), 3.07-3.83(m,4H), 4.56-5.02(m,1H),  
5.39(s,1H), 6.47(s,2H)

[Example 4]

Synthesis of 4,6-tert-Butyl-2-Chloromethyl-5-Hydroxy-2,3-Dihydrobenzofuran (Compound 1)

25 Methanesulfonic acid (1.2 ml) was added dropwise to a solution of 4-tert-butyl-2-chloromethyl-5-hydroxy-2,3-dihydrobenzofuran (280 mg, 1.2 mmol) and tert-butyl alcohol (500 mg, 6.0 mmol) in chloroform (2 ml) under ice cooling.

After stirring at 0°C for 15 min, the mixture was poured into ice water. The mixture was then neutralized with an aqueous solution of 1N sodium hydroxide and subjected to extraction with ethyl acetate. The extracted layer  
5 was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (n-hexane) to afford 4,6-tert-butyl-2-chloromethyl-5-hydroxy-2,3-dihydrobenzofuran (10 mg) as  
10 a pale yellow oil.

Mass 298(M+2), 296(M<sup>+</sup>), 283, 281, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.41(s,9H), 1.50(s,9H), 3.19-3.91(m,4H),  
4.58-5.03(m,1H), 4.76(s,1H), 6.69(s,1H)

15 IR (cm<sup>-1</sup>) 3460, 2960

[Reference Example 5]

Synthesis of 5-Benzyloxy-4-tert-Butyl-2-(1-octenyl)benzofuran

A pentane solution (2.6 ml, 4.2 mmol) of 1.6 M  
20 n-butyllithium was added dropwise to a solution of n-heptyl-triphenylphosphonium bromide (1.84 g, 4.2 mmol) in tetrahydrofuran (10 ml) under a nitrogen atmosphere. After stirring the mixture at room temperature for 30 min, a solution of 5-benzyloxy-4-tert-butyl-2-formylbenzofuran  
25 (1.0 g, 3.2 mmol) in tetrahydrofuran (10 ml) was added dropwise. Subsequently, the mixture was stirred at room temperature for 30 min, poured into ice water and subjected to extraction with ethyl acetate. The organic layer was

washed with a saturated aqueous solution of sodium hydrogen carbonate and water, then dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (chloroform) to afford 5-benzyloxy-4-tert-butyl-2-(1-octenyl)benzofuran [1.14 g (yield, 91%)].

Mass 392(M<sup>+</sup>), 301, 277, 167, 91, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 0.89(t,3H), 1.13-1.72(m,8H), 1.56(s,9H),  
10 1.93-2.62(m,2H), 5.03(s,2H), 6.02-6.40(m,2H),  
6.78-7.46(m,8H)

[Reference Example 6]

Synthesis of 4-tert-Butyl-5-Hydroxy-2-Octylbenzofuran

10% Palladium on carbon (1.1 g) was added to a solution of 5-benzyloxy-4-tert-butyl-2-(1-octenyl)benzofuran (1.1 g, 2.9 mmol) in acetic acid (50 ml), and the mixture was stirred for 36 h under a hydrogen atmosphere. After filtering off the Pd on carbon, the solvent was distilled off with an evaporator. The concentrate was purified by silica gel chromatography (chloroform) to afford 4-tert-butyl-5-hydroxy-2-octylbenzofuran [600 mg (yield, 69%)] as a pale yellow oil.

Mass 302(M<sup>+</sup>), 287, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

25 δ ppm 0.87(t,3H), 1.06-1.83(m,12H), 1.57(s,9H),  
2.70(t,2H), 4.67(s,1H), 6.50(d,1H,J=8.4Hz),  
6.68(s,1H), 7.07(d,1H,J=8.4Hz)

[Reference Example 7]

Synthesis of 4-tert-Butyl-5-Hydroxy-2-Octyl-2,3-Dihydrobenzofuran

Triethylsilane (2.8 ml) was added to 4-tert-butyl-  
5 5-hydroxy-2-octylbenzofuran (300 mg, 1.0 mmol) and, then,  
trifluoroacetic acid (1.4 ml) was added dropwise under ice  
cooling. The mixture was stirred first at 0°C for 15 min,  
then at room temperature for 1 h. Thereafter, the mixture  
was poured into ice water and subjected to extraction  
10 with ethyl acetate. The organic layer was washed with a  
saturated aqueous solution of sodium hydrogen carbonate,  
dried over anhydrous magnesium sulfate and concentrated.  
The concentrate was purified by silica gel chromatography  
(chloroform) to afford 4-tert-butyl-5-hydroxy-2-octyl-2,3-  
15 dihydrobenzofuran [252 mg (yield, 83%)] as a colorless oil.

Mass 304(M<sup>+</sup>), 289, 137, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 0.87(t,3H), 1.12-1.75(m,14H), 1.44(s,9H),  
2.75-3.70(m,2H), 4.09-4.68(m,1H), 4.45(s,1H),  
20 6.42(s,2H)

[Example 5]

Synthesis of 4,6-Di-tert-Butyl-5-Hydroxy-2-Octyl-2,3-Dihydrobenzofuran (Compound g)

Methanesulfonic acid (1.5 ml) was added dropwise,  
25 under ice cooling, to a solution consisting of 4-di-tert-  
butyl-5-hydroxy-2-octyl-2,3-dihydrobenzofuran (510 mg,  
1.7 mmol), tert-butyl alcohol (850 mg, 10.0 mmol) and  
chloroform (2 ml). After stirring at 0°C for 15 min, the

mixture was poured into ice water. The mixture was then neutralized with an aqueous solution of 1N sodium hydroxide and subjected to extraction with ethyl acetate. The extracted layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (n-hexane) to afford 4,6-di-tert-butyl-5-hydroxy-2-octyl-2,3-dihydrobenzofuran (83 mg) as a pale yellow oil.

10 Mass 360(M<sup>+</sup>), 345, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 0.90(t,3H), 1.12-1.95(m,14H), 1.42(s,9H),  
1.50(s,9H), 2.80-3.70(m,2H), 4.35-4.80(m,1H),  
4.67(s,1H), 6.63(s,1H)

15 IR (cm<sup>-1</sup>) 3624, 2935

[Reference Example 8]

#### Synthesis of 4-Acetoxy-3,5-Di-tert-Butylanisole

4-Hydroxy-3,5-di-tert-butylanisole (23.6 g) was dissolved in acetic anhydride (150 ml). Following the addition of conc. sulfuric acid (0.5 ml), the mixture was stirred at 70°C for 2 h. The reaction mixture was concentrated under reduced pressure and a saturated aqueous solution of sodium hydrogen carbonate was added to the concentrate, followed by extraction with ethyl acetate. The extracted layer was dried over anhydrous magnesium acetate and concentrated. The precipitating solid was recrystallized from methanol-water (2:1) to afford 4-acetoxy-3,5-di-tert-butylanisole [24.5 g (yield, 88%)]

as a white solid.

m.p. 96.6°C

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.06(s,18H), 2.02(s,3H), 3.47(s,3H), 6.53(s,2H)

5 Mass 278(M<sup>+</sup>)

[Reference Example 9]

Synthesis of 4-Acetoxy-3,5-Di-tert-Butylphenol

4-Acetoxy-3,5-di-tert-butylanisole (0.50 g) was dissolved in dichloromethane (2 ml). After cooling with  
10 ice, trimethylsilyl iodide (0.31 ml) was added dropwise. The mixture was allowed to warm slowly to room temperature and stirred for 2 days; thereafter, a saturated aqueous solution of sodium hydrogen carbonate was added to the reaction mixture. The mixture was subjected to extraction  
15 with diethyl ether and the organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel chromatography (15% ethyl acetate in n-hexane) to afford 4-acetoxy-3,5-di-tert-butylphenol [0.38 g (yield, 80%)] as  
20 a white solid.

m.p. 156.9°C

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.27(s,18H), 2.27(s,3H), 5.22(brs,1H), 6.67(s,2H)

Mass 222(M<sup>+</sup>)

25 [Reference Example 9]

Synthesis of 4-Acetoxy-3,5-Di-tert-Butyl-1-(2-Methyl-2-Propenyloxy)benzene

60% oily sodium hydride (0.18 g) was suspended in N,N-dimethylformamide (10 ml). A solution of 4-acetoxy-3,5-di-*tert*-butylphenol (1 g) in N,N-dimethylformamide (5 ml) was added dropwise to the suspension under ice cooling and the mixture was stirred for 30 min. Subsequently, the reaction mixture was allowed to warm to room temperature and 3-chloro-2-methyl-1-propene (0.45 ml) was added dropwise. After stirring at room temperature for 2 h, a saturated aqueous solution of ammonium chloride (15 ml) was added to the reaction mixture. The mixture was subjected to extraction with diethyl ether and the organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (10% ethyl acetate in n-hexane) to afford 4-acetoxy-3,5-di-*tert*-butyl-1-(2-methyl-2-propenyloxy)benzene [1.08 g (yield, 90%)] as a colorless liquid.

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      1.30(s,18H), 1.83(s,3H), 2.30(s,3H),  
4.37(brd,J=6.6Hz,2H), 6.83(s,2H)

Mass      318(M<sup>+</sup>)

[Example 6]

Synthesis of 5-Acetoxy-4,6-Di-*tert*-Butyl-2,2-Dimethyl-2,3-Dihydrobenzofuran

4-Acetoxy-3,5-di-*tert*-butyl-1-(2-methyl-2-propenyloxy)benzene (2.22 g) was dissolved in N,N-dimethylaniline (8 ml) and the solution was refluxed under a nitrogen atmosphere for 36 h. After cooling to room temperature,

the reaction solution was concentrated under reduced pressure and, after addition of 1N HCl (5 ml) and diethyl ether (10 ml), stirring was continued for 15 min. The organic layer was separated and the aqueous layer was subjected to extraction with diethyl ether. The combined extracts were washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (5% ethyl acetate in n-hexane) to afford 5-acetoxy-4,6-di-tert-butyl-2,2-dimethyl-2,3-dihydrobenzofuran [1.19 g (yield, 54%)] as a white solid.

m.p. 97.7°C

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.16-1.60(m,24H), 2.25(s,3H), 3.18(s,2H),  
6.63(s,1H)

Mass 318(M<sup>+</sup>)

[Example 7]

Synthesis of 5-Hydroxy-4,6-Di-tert-Butyl-2,2-Dimethyl-2,3-Dihydrobenzofuran (Compound c)

Lithium aluminum hydride (0.10 g) was suspended in tetrahydrofuran (5 ml) under a nitrogen atmosphere. A solution of 5-acetoxy-4,6-di-tert-butyl-2,2-dimethyl-2,3-dihydrobenzofuran (0.86 g) in tetrahydrofuran (6 ml) was added dropwise to the suspension and the mixture was refluxed for 4 h. After cooling the mixture to room temperature, water was added dropwise to quench the excess lithium aluminum hydride. After adding 1N aqueous sodium hydroxide (5 ml), the mixture was subjected to extraction

with diethyl ether. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (5% ethyl acetate in n-hexane) to afford  
5 5-acetoxy-4,6-di-*tert*-butyl-2,2-dimethyl-2,3-dihydrobenzo-furan [0.62 g (yield, 83%)] as a white solid.

m.p. 139.6°C

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.42(s,18H), 1.50(s,6H), 3.25(s,2H), 4.70(s,1H),  
10 6.66(s,1H)

Mass 276(M<sup>+</sup>)

IR (cm<sup>-1</sup>) 3632, 2964, 1404, 1386, 1134

[Reference Example 10]

15 Synthesis of 4-Acetoxy-3,5-Di-*tert*-Butyl-1-(2-Propenyloxy)benzene

4-Acetoxy-3,5-di-*tert*-butylphenol (10 g) and potassium carbonate (15.6 g) were dissolved in acetone (300 ml). After addition of 3-bromo-1-propene (6.55 ml), the mixture was refluxed for 24 h. The reaction mixture  
20 was concentrated under reduced pressure and water was added to the concentrate. The mixture was subjected to extraction with diethyl ether and the organic layer was washed with water and saturated brine, then dried over anhydrous magnesium sulfate and concentrated. The concentrate was  
25 purified by silica gel chromatography (10% ethyl acetate in n-hexane) to afford 4-acetoxy-3,5-di-*tert*-butyl-1-(2-propenyloxy)benzene (11 g) as a colorless liquid in a quantitative yield.

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.30(s,18H), 2.27(s,3H), 4.47(d,J=5.0Hz,2H),  
5.05-5.57(brm,2H), 5.68-6.37(brm,1H), 6.81(s,2H)

Mass 304(M<sup>+</sup>)

5 [Reference Example 11]

Synthesis of 4-Acetoxy-3,5-Di-tert-Butyl-2-(2-Propenyloxy)phenol

4-Acetoxy-3,5-di-tert-butyl-1-(2-propenyloxy)benzene (11.0 g) was dissolved in N,N-dimethylaniline (50 ml) and the solution was refluxed for 18 h under a nitrogen atmosphere. After cooling to room temperature, the reaction solution was concentrated under reduced pressure and purified by silica gel chromatography (15% ethyl acetate in n-hexane) to afford 4-acetoxy-3,5-di-tert-butyl-2-(2-propenyl)phenol [8.84 g (yield, 77%)] as a white solid.

m.p. 103.6°C

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.30(s,9H), 1.42(s,9H), 2.28(s,3H), 3.52-  
3.84(m,2H), 4.88-5.42(m,3H), 5.68-6.45(m,1H),  
6.79(s,1H)

Mass 304(M<sup>+</sup>)

[Reference Example 12]

4-Acetoxy-3,5-Di-tert-Butyl-1-(2-Methyl-2-Propenyloxy)-2-Propylbenzene

4-Acetoxy-3,5-tert-butyl-2-(2-propenyl)phenol (0.90 g) was dissolved in ethyl acetate (15 ml). After adding 10% Pd on carbon (0.005 g), the solution was stirred vigorously under a hydrogen atmosphere for 18 h. The Pd on

carbon was filtered off and the filtrate was concentrate.  
The concentrate was dissolved in N,N-dimethylformamide  
(5 ml) and the solution was added dropwise to a suspension  
of 60% oily sodium hydride (0.14 g) in N,N-dimethylformamide  
5 (7 ml) under ice cooling and the mixture was stirred for  
30 min. Subsequently, the reaction mixture was allowed to  
warm to room temperature and 3-chloro-2-methyl-1-propene  
(0.35 ml) was added dropwise. After stirring at room  
temperature for 2 h, water (15 ml) was added to the reaction  
10 mixture. The mixture was subjected to extraction with  
diethyl ether and the organic layer was washed with water  
and saturated brine, then dried over anhydrous magnesium  
sulfate and concentrated. The concentrate was purified by  
silica gel chromatography (5% ethyl acetate in n-hexane) to  
15 afford 4-acetoxy-3,5-di-tert-butyl-1-(2-methyl-2-propenyloxy)-2-propylbenzene [0.82 g (yield, 77%)] as a colorless  
liquid.

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      0.70-1.72(m,23H), 1.86(s,3H), 2.28(s,3H), 2.65-  
20      3.12(m,2H), 4.39(s,2H), 5.06(d,J=9.0Hz,2H),  
            6.82(s,1H)

Mass      360(M<sup>+</sup>)

[Example 8]

25      Synthesis of 5-Acetoxy-4,6-Di-tert-Butyl-2,2-Dimethyl-7-Propyl-2,3-Dihydrobenzofuran

4-Acetoxy-3,5-di-tert-butyl-1-(2-methyl-2-propenyl-  
oxy)-2-propylbenzene (0.82 g) was dissolved in N,N-dimethyl-  
aniline (8 ml) and the solution was refluxed for 18 h under

a nitrogen atmosphere. After cooling to room temperature, the reaction solution was concentrated under reduced pressure and 1N HCl (5 ml) and diethyl ether (10 ml) were added to the concentrate, followed by stirring for 15 min.

5 The organic layer was separated and the aqueous layer was subjected to extraction with diethyl ether. The combined extracts were washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (5% ethyl acetate in n-hexane) to afford 5-acetoxy-4,6-di-tert-butyl-2,2-dimethyl-7-propyl-2,3-dihydrobenzofuran [0.60 g (yield, 73%)] as a pale yellow solid.

m.p. 106.0°C

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

15 δ ppm 0.55-2.08(m,29H), 2.23(s,3H), 2.72(t,J=7.0Hz,2H), 3.17(s,2H)

Mass 360(M<sup>+</sup>)

[Example 9]

20 Synthesis of 5-Hydroxy-4,6-Di-tert-Butyl-2,2-Dimethyl-7-Propyl-2,3-Dihydrobenzofuran (Compound g)

Lithium aluminum hydride (0.08 g) was suspended in tetrahydrofuran (5 ml) under a nitrogen atmosphere. A solution of 5-acetoxy-4,6-di-tert-butyl-2,2-dimethyl-7-propyl-2,3-dihydrobenzofuran (0.60 g) in tetrahydrofuran (5 ml) was added dropwise to the suspension and the mixture was refluxed for 4 h. After cooling the reaction mixture to room temperature, water was added dropwise to quench the excess lithium aluminum hydride. Thereafter 1N aqueous

sodium hydroxide (5 ml) was added and the mixture was subjected to extraction with diethyl ether, washed with saturated brine, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (5% ethyl acetate in n-hexane) to afford 5-hydroxy-4,6-di-*tert*-butyl-2,2-dimethyl-7-propyl-2,3-dihydrobenzofuran [0.17 g (yield, 32%)] as a pale yellow solid.

m.p. 90.3°C (dec.)

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 0.70-2.10(m,29H), 2.57-3.10(m,4H), 3.23(s,2H), 4.83(s,1H)

Mass 318(M<sup>+</sup>)

IR (cm<sup>-1</sup>) 3648, 2952, 2868, 1368, 1366, 1290, 1260, 1152, 924

[Example 10]

Synthesis of 4,6-Di-*tert*-Butyl-5-Hydroxy-2-Methyl-2,3-Dihydrobenzofuran (Compound b)

4-Acetoxy-3,5-di-*tert*-butyl-2-(2-propenyl)phenol

(1.0 g, 3.3 mmol) was dissolved in dichloromethane (10 ml) and BF<sub>3</sub> etherate (0.7 ml) was added dropwise to the solution under a nitrogen atmosphere. The mixture was stirred for 24 h at room temperature and, thereafter, water was added and the mixture was extracted with ethyl acetate. The extracted layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried over anhydrous magnesium sulfate and concentrated. The concentrate was dissolved in tetrahydrofuran (5 ml) and the solution was added

dropwise to a suspension of lithium aluminum hydride (76 mg) in tetrahydrofuran (5 ml) that had been prepared under a nitrogen atmosphere. After refluxing for 3 h, the reaction mixture was cooled to room temperature and water was added dropwise. Following the addition of 1N aqueous sodium hydroxide, the mixture was subjected to extraction with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (10% ethyl acetate in n-hexane) to afford 4,6-di-*tert*-butyl-5-hydroxy-2-methyl-2,3-dihydrobenzofuran [450 mg (yield, 52%)].

m.p. 86.8°C

Mass <sup>+</sup>262(M<sup>+</sup>), 247, 205, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.40(d,3H), 1.42(s,9H), 1.50(s,9H), 2.80-3.80(m,2H), 4.42-4.92(m,1H), 4.71(s,1H), 6.70(s,1H)

IR (cm<sup>-1</sup>) 3616, 2960

[Reference Example 13]

Synthesis of 4-Acetoxy-3,5-Di-*tert*-Butyl-2-(Chloroacetylaminomethyl)phenol and 6-Acetoxy-5,7-Di-*tert*-Butyl-3-(2-Chloroacetyl)-2,3-Dihydro-1,3,4H-Benzoxazine

4-Acetoxy-3,5-di-*tert*-butylphenol (29 g, 0.11 mol) was dissolved in a 9:1 mixed solution (200 ml) of acetic acid and sulfuric acid. Following addition of N-hydroxymethyl-2-chloroacetamide (34 g, 0.28 mol), the mixture was stirred at room temperature for 48 h. Subsequently, the

reaction mixture was poured into water, neutralized with 1N aqueous sodium hydroxide and subjected to extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The concentrate was  
5 used in the subsequent reaction without further purification. When part of the concentrate was subjected to silica gel chromatography and eluted with a solvent system consisting of a 4:1 mixture of hexane and ethyl acetate, the following two products were obtained: 4-acetoxy-3,5-di-  
10 tert-butyl-2-(chloroacetylaminomethyl)phenol and 6-acetoxy-5,7-di-tert-butyl-3-(2-chloroacetyl)-2,3-dihydro-1,3,4H-benzoxazine.

4-Acetoxy-3,5-Di-tert-Butyl-2-

(Chloroacetylaminomethyl)phenol (colorless oil)

15 Mass 369(M<sup>+</sup>), 327, 234, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.30(s,9H), 1.43(s,9H), 2.28(s,3H), 4.00(s,2H),  
4.73(d,2H,J=6.0Hz), 6.88(s,1H),  
7.54(t,1H,J=6.0Hz)

20 6-Acetoxy-5,7-Di-tert-Butyl-3-(2-Chloroacetyl)-2,3-Dihydro-1,3,4H-Benzoxazine (colorless oil)

Mass 381(M<sup>+</sup>), 339, 304, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.30(s,9H), 1.47(s,9H), 2.30(s,3H), 4.17(s,2H),  
25 5.00(s,2H), 5.33(s,2H), 6.83(s,1H)

[Reference Example 14]

Synthesis of 4-Acetoxy-2-Aminomethyl-3,5-Di-tert-Butylphenol

The concentrate obtained in Reference Example 13 was dissolved in a 10:3 mixed solution (550 ml) of ethanol and conc. HCl and the solution was heated under reflux for 2 h. After cooling, the reaction solution was poured into water  
5 and the mixture was neutralized with 1N aqueous sodium hydroxide, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The concentrate was used in the subsequent reaction without further purification. When part of the  
10 concentrate was subjected to silica gel chromatography and eluted solvent system consisting of a 4:1 mixture of chloroform and methanol, 4-acetoxy-2-aminomethyl-3,5-di-tert-butylphenol was obtained as a main product.

4-Acetoxy-2-Aminomethyl-3,5-Di-tert-Butylphenol  
15 (colorless oil)

Mass 293(M<sup>+</sup>), 234, 191, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.27(s,9H), 1.37(s,9H), 2.25(s,3H), 4.22(s,2H),  
5.18(bs,3H), 6.85(s,1H)

20 [Example 11]

Synthesis of 5-Acetoxy-4,6-Di-tert-Butyl-2-Hydroxybenzaldehyde

The concentrate obtained in Reference Example 14 was dissolved in a 11:3 mixed solution (636 ml) of acetic  
25 acid and water and, after addition of hexamethylenetetramine (19.3 g, 0.11 mol), the mixture was heated under reflux for 4 h. Subsequently, 4.5N HCl (85 ml) was added and the mixture was heated under reflux for 20 min. After cooling,



the reaction mixture was poured into water, neutralized with 1N aqueous sodium hydroxide and subjected to extraction with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (chloroform) to afford 5-acetoxy-4,6-di-*tert*-butyl-2-hydroxybenzaldehyde (19.0 g).

m.p. 79.0°C

Mass 292(M<sup>+</sup>), 250, 235, 217, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

10 δ ppm 1.35(s,9H), 1.54(s,9H), 2.35(s,3H), 6.92(s,1H),  
10.67(s,1H), 12.32(s,1H)

IR (cm<sup>-1</sup>) 2976, 1758

[Reference Example 15]

Synthesis of 4-Acetoxy-3,5-Di-*tert*-Butyl-2-(2-Ethyl-1-Butenyl)phenol

15 A solution of 3-bromopentane (1.3 g, 8.6 mmol) in tetrahydrofuran (10 ml) was added to magnesium (0.21 g, 8.6 mg atom) under a nitrogen atmosphere to prepare a Grignard reagent. A solution of 5-acetoxy-4,6-di-*tert*-butyl-2-hydroxydibenzaldehyde (1.0 g, 3.4 mmol) in 20 tetrahydrofuran (5 ml) was added dropwise to the reagent. After stirring the mixture at room temperature for 30 min, a 5:2 mixed solution (7 ml) of water and conc. HCl was added to the reaction mixture, followed by stirring at 25 room temperature for 30 min and subsequent extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (10% ethyl acetate in

n-hexane) to afford 4-acetoxy-3,5-di-tert-butyl-2-(2-ethyl-1-butenyl)phenol [0.85 g (yield, 72%)] as a yellow oil.

Mass 346(M<sup>+</sup>), 304, 289, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

5    δ ppm    0.78-1.57(m,6H), 1.33(s,9H), 1.37(s,9H), 1.73-  
2.48(m,4H), 2.27(s,3H), 5.38(d,1H), 6.17(s,1H),  
6.87(s,1H)

[Example 12]

Synthesis of 5-Acetoxy-4,6-Di-tert-Butyl-2,2-Diethyl-2,3-

10    Dihydrobenzofuran

4-Acetoxy-3,5-di-tert-butyl-2-(2-ethyl-1-butenyl)phenol (0.85 g, 2.5 mmol) was dissolved in dichloromethane (10 ml) and BF<sub>3</sub> etherate (0.4 ml) was added dropwise to the solution under a nitrogen atmosphere. After stirring  
15 at room temperature for 3 h, water was added to the reaction mixture and extracted with ethyl acetate. The extracted layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica  
20 gel chromatography (10% ethyl acetate in n-hexane) to afford 5-acetoxy-4,6-di-tert-butyl-2,2-diethyl-2,3-dihydrobenzofuran [0.45 g (yield, 53%)] as a pale yellow oil.

Mass 346(M<sup>+</sup>), 304, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

25    δ ppm    0.80-1.79(m,10H), 1.29(s,9H), 1.37(s,9H),  
2.26(s,3H), 3.10(s,2H), 6.71(s,1H)

[Example 13]

Synthesis of 4,6-Di-tert-Butyl-2,2-Diethyl-5-Hydroxy-2,3-Dihydrobenzofuran (Compound d)

Lithium aluminum hydride (76 mg) was suspended  
5 in tetrahydrofuran (5 ml) under a nitrogen atmosphere.  
A solution of 5-acetoxy-4,6-di-tert-butyl-2,2-diethyl-2,3-dihydrobenzofuran (0.17 g, 0.5 mmol) in tetrahydrofuran (5 ml) was added dropwise to the suspension. After heating under reflux for 3 h, the reaction mixture was cooled to  
10 room temperature and water was added dropwise. After addition of 1N aqueous sodium hydroxide (5 ml), the mixture was subjected to extraction with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel  
15 chromatography (10% ethyl acetate in n-hexane) to afford 4,6-di-tert-butyl-2,2-diethyl-5-hydroxy-2,3-dihydrobenzofuran [130 mg (yield, 87%)] as a pale yellow oil.

Mass 304(M<sup>+</sup>), 289, 163, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

20 δ ppm 0.92(t,3H), 1.20-1.87(m,8H), 1.43(s,9H),  
1.51(s,9H), 3.17(s,2H), 4.62(s,1H), 6.62(s,1H)

IR (cm<sup>-1</sup>) 3663, 2975

Similar procedures were taken to prepare the following compounds.

25 4,6-Di-tert-Butyl-2,2-Di-n-Propyl-5-Hydroxy-2,3-Dihydrobenzofuran (Compound e)

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      0.92(t,6H), 1.17-1.82(m,8H), 1.40(s,9H),  
                  1.49(s,9H), 3.17(s,2H), 4.59(s,1H), 6.60(s,1H)

IR (cm<sup>-1</sup>)   3662, 2971

5      Mass      332(M<sup>+</sup>)

4,6-Di-tert-Butyl-2,2-Di-n-Butyl-5-Hydroxy-2,3-  
          Dihydrobenzofuran (Compound f)

Mass      360(M<sup>+</sup>)

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

10      δ ppm      0.90(t,6H), 1.11-1.75(m,12H), 1.41(s,9H),  
                  1.48(s,9H), 3.17(s,2H), 4.63(s,1H), 6.61(s,1H)

IR (cm<sup>-1</sup>)   3663, 2964

4,6-Di-tert-Butyl-5-Hydroxy-2,3-Dihydrobenzofuran-2-  
          Spiro-1'-Cyclopentane (Compound m)

15      m.p.      101.5°C

         Mass      302(M<sup>+</sup>)

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      1.40(s,9H), 1.49(s,9H), 1.67-2.02(m,8H),  
                  3.43(s,2H), 4.68(s,1H), 6.63(s,1H)

20      IR (cm<sup>-1</sup>)   3644, 2979

4,6-Di-tert-Butyl-5-Hydroxy-2,3-Dihydrobenzofuran-2-  
          Spiro-1'-cyclohexane (Compound n)

m.p.      124.5°C

Mass      316(M<sup>+</sup>)

25      <sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      1.20-1.90(m,10H), 1.39(s,9H), 1.47(s,9H),  
                  3.15(s,2H), 4.61(s,1H), 6.61(s,1H)

IR (cm<sup>-1</sup>)   3650, 2934

4,6-Di-tert-Butyl-2,2-Diphenyl-5-Hydroxy-2,3-Dihydrobenzofuran (Compound j)

m.p. 115.3°C

Mass 400(M<sup>+</sup>)

5 <sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.27(s,9H), 1.48(s,9H), 4.72(s,1H),  
4.91(d,1H,J=2.0Hz), 5.26(d,1H, J=2,0Hz),  
6.88-7.41(m,11H)

IR (cm<sup>-1</sup>) 3642, 2961

10 4,6-Di-tert-Butyl-5-Hydroxy-2,3-Dihydrobenzofuran-2-Spiro-1'-Cycloheptane (Compound o)

m.p. 91.6°C

Mass 344(M<sup>+</sup>)

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

15 δ ppm 1.30-2.03(m,12H), 1.38(s,9H), 1.47(s,9H),  
3.20(s,2H), 4.62(s,1H), 6.61(s,1H)

IR (cm<sup>-1</sup>) 3646, 2927

4,6-Di-tert-Butyl-2,2-Dibenzyl-5-Hydroxy-2,3-Dihydrobenzofuran (Compound k)

20 m.p. 128.5°C

Mass 328(M<sup>+</sup>)

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.39(s,18H), 2.96(s,4H), 3.23(s,2H), 4.56(s,1H),  
6.63(s,1H), 7.20(s,10H)

25 IR (cm<sup>-1</sup>) 3661, 2970

4,6-Di-tert-Butyl-2,2-Di-i-Propyl-5-Hydroxy-2,3-Dihydrobenzofuran (Compound i)

Mass 332(M<sup>+</sup>)

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)  
 δ ppm 0.92(dd,12H,J=6.0Hz), 1.39(s,9H), 1.50(s,9H),  
 2.01(m,2H), 3.10(s,2H), 5.52(s,1H), 6.52(s,1H)  
 IR (cm<sup>-1</sup>) 3658, 2972

5     4,6-Di-tert-Butyl-5-Hydroxy-2,3-Dihydrobenzofuran-2-Spiro-1'-Cyclooctane (Compound p)

Mass       344(M<sup>+</sup>)  
<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)  
 δ ppm 1.40(s,9H), 1.47-1.94(m,14H), 1.50(s,9H),  
 10       3.18(s,2H), 4.67(s,1H), 6.63(s,1H)  
 IR (cm<sup>-1</sup>) 3660, 2933

4,6-Di-tert-Butyl-5-Hydroxy-2,3-Dihydrobenzofuran-2-Spiro-4"-Tetrahydropyran

m.p.       181.4°C

15     Mass       318(M<sup>+</sup>)  
<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)  
 δ ppm 1.41(s,9H), 1.50(s,9H), 1.72-1.92(m,4H),  
 3.23(s,2H), 3.74-3.96(m,4H), 4.72(s,1H),  
 6.73(s,1H)

20     IR (cm<sup>-1</sup>) 3365, 2972

4,6-Di-tert-Butyl-2,2-Di-n-Pentyl-5-Hydroxy-2,3-Dihydrobenzofuran (Compound x)

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)  
 δ ppm 0.88(t,6H), 1.30(br,12H), 1.40(s,9H), 1.49(s,9H),  
 25       1.62(m,4H), 3.18(s,2H), 4.66(s,1H), 6.62(s,1H)  
 IR (cm<sup>-1</sup>) 3652, 2956  
 Mass       388(M<sup>+</sup>)

4,6-Di-tert-Butyl-2,2-Di-n-Octyl-5-Hydroxy-2,3-Dihydrobenzofuran (Compound y)

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

5      δ ppm      0.88(m,6H), 1.26(bs,24H), 1.40(s,9H), 1.49(s,9H),  
1.59-1.65(m,4H), 3.18(s,2H), 4.66(s,1H),  
6.62(s,1H)

Mass      472(M<sup>+</sup>)

4,6-Di-tert-Butyl-2,2-Di-n-Heptyl-5-Hydroxy-2,3-Dihydrobenzofuran

10      <sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm      0.87(t,6H), 1.27(br,20H), 1.40(s,9H), 1.49(s,9H),  
1.62(m,4H), 3.18(s,2H), 4.66(s,1H), 6.62(s,1H)

IR (cm<sup>-1</sup>)      3656, 2928

Mass      444(M<sup>+</sup>)

15      4,6-Di-tert-Butyl-2,2-Di-n-Hexyl-5-Hydroxy-2,3-Dihydrobenzofuran

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm      0.87(t,6H), 1.28(br,16H), 1.40(s,9H), 1.49(s,9H),  
1.63(m,4H), 3.19(s,2H), 4.65(s,1H), 6.62(s,1H)

20      IR (cm<sup>-1</sup>)      3650, 2920

Mass      416(M<sup>+</sup>)

[Reference Example 16]

Synthesis of 2,6-Di-tert-Butyl-3-Methyl-4-Tetrahydropyranyloxyphenol

25      2,6-di-tert-butyl-3-methyl-1,4-benzoquinone (49 g)  
was dissolved in methylene chloride (300 ml) and sodium  
borohydride (15 g) was added to the solution under a  
nitrogen atmosphere. After adding methanol (30 ml)

dropwise, the mixture was stirred for 3 h, poured into 5% HCl under ice cooling, and subjected to extraction with methylene chloride. The extract was washed with water, dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was dissolved in methylene chloride (200 ml) and, after adding 3,4-dihydropyran (26 ml) and a catalytic amount of paratoluenesulfonic acid, the mixture was stirred overnight at room temperature. The reaction mixture was washed with water, dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was purified by silica gel chromatography (10% ethyl acetate in n-hexane) to afford 2,6-di-tert-butyl-3-methyl-4-tetrahydropyranyloxyphenol [54.4 g (yield, 81%)] as a colorless oil.

Mass 320(M<sup>+</sup>)

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 0.8-1.9(br,6H), 1.39(s,9H), 1.56(s,9H), 3.6-4.0(m,2H), 2.37(s,3H), 4.95(s,1H), 5.15(br,1H), 6.98(s,1H)

[Reference Example 17]

Synthesis of 1-Acetoxy-2,6-Di-tert-Butyl-3-Methyl-4-Tetrahydropyranyloxybenzene

2,6-Di-tert-butyl-3-methyl-4-tetrahydropyranyloxyphenol (4.4 g) was dissolved in anhydrous tetrahydrofuran (50 ml) and a n-hexane solution (1.1 eq.) of n-butyllithium was added dropwise at 0°C under a nitrogen atmosphere. After stirring the mixture for 30 min, acetyl chloride (1.08 ml, 1.1 eq.) was added and the mixture was allowed

to warm to room temperature. After stirring for 3 h,  
the reaction mixture was poured into a saturated aqueous  
solution of ammonium chloride and the mixture was subjected  
to extraction with diethyl ether. The extract was washed  
5 with water and saturated brine, then dried over anhydrous  
sodium sulfate and the solvent was distilled off. The  
residue was purified by silica gel chromatography (10% ethyl  
acetate in n-hexane) to afford 1-acetoxy-2,6-di-tert-butyl-  
3-methyl-4-tetrahydropyranyloxybenzene [4.09 g (yield,  
10 82.2%)] as a colorless crystal.

Mass 362(M<sup>+</sup>)

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 0.8-1.8(br, 6H), 1.30(s, 9H), 1.42(s, 9H),  
2.26(s, 3H), 2.35(s, 3H), 3.4-4.1(m, 2H),  
15 5.28(m, 1H), 7.07(s, 1H)

[Reference Example 18]

Synthesis of 4-Acetoxy-3,5-Di-tert-Butyl-2-Methylphenol

1-Acetoxy-2,6-di-tert-butyl-3-methyl-4-tetrahydro-  
pyranyloxybenzene (4.09 g) was dissolved in tetrahydrofuran  
20 (20 ml). After adding 10% HCl (3 ml), the mixture was  
stirred at room temperature for 3 h. The reaction mixture  
was poured into water and subjected to extraction with  
diethyl ether. The extract was washed with 5% aqueous  
sodium hydrogen carbonate and saturated brine, then dried  
25 over anhydrous sodium sulfate and the solvent was distilled  
off. The residue was recrystallized from n-hexane to  
afford 4-acetoxy-3,5-di-tert-butyl-2-methylphenol (3.1 g)  
as a colorless needle.

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      1.31(s,9H), 1.44(s,9H), 2.30(s,3H), 2.35(s,3H),  
            4.73(s,1H), 6.72(s,1H)

[Example 14]

5      Synthesis of 1-Acetoxy-2,6-Di-tert-butyl-3-Methyl-4-propyloxybenzene

Sodium hydride (100 mg) was suspended in N,N-dimethylformamide (5 ml) and a solution of 4-acetoxy-3,5-di-tert-butyl-2-methylphenol (0.5 g) in N,N-dimethylformamide  
10 (5 ml) was added dropwise to the suspension at 0°C. After stirring for 20 min, propyl bromide (0.2 ml) was added and the mixture was stirred for an additional 2 h. The reaction mixture was then poured into a saturated aqueous solution of ammonium chloride and extracted with diethyl ether.  
15 The extract was washed with water and saturated brine, then dried over anhydrous sodium sulfate. The solvent was distilled off to afford 1-acetoxy-2,6-di-tert-butyl-3-methyl-4-propyloxybenzene which was substantially pure on TLC. It was used in the subsequent reaction without further  
20 purification.

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      1.33(s,9H), 1.45(s,9H), 1.84(m,2H), 2.27(s,3H),  
            2.34(s,3H), 3.87(m,2H), 6.74(s,1H)

[Example 15]

25      Synthesis of 2,6-Di-tert-Butyl-3-Methyl-4-Propyloxyphenol  
            (Compound u)

Lithium aluminum hydride (100 mg) was suspended in tetrahydrofuran (5 ml) under a nitrogen atmosphere.



A solution of the 1-acetoxy-2,6-di-*tert*-butyl-3-methyl-4-propyloxybenzen in tetrahydrofuran (5 ml) was added to the suspension and the mixture was refluxed for 3 h. A saturated aqueous solution of ammonium chloride was added to the reaction mixture under ice cooling and the precipitate was filtered off together with the anhydrous sodium sulfate. The filtrate was concentrated and purified by silica gel chromatography (10% ethyl acetate in n-hexane) to afford 2,6-di-*tert*-butyl-3-methyl-4-propyloxyphenol (150 mg) as a colorless oil.

Mass 278(M<sup>+</sup>)

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.06(t,3H,J=6Hz), 1.45(s,9H), 1.61(s,9H),  
1.80(m,2H), 2.38(s,3H), 3.85(t,2H,J=6Hz),  
4.90(s,1H), 6.75(s,1H)

[Example 16]

Synthesis of 1-Acetoxy-4-Allyloxy-2,6-Di-*tert*-Butyl-3-Methylbenzene and 1,3-Bis(4-Acetoxy-3,5-Di-*tert*-Butyl-2-Methylphenoxy)propane

Sodium hydride (110 mg) was suspended in N,N-dimethylformamide (5 ml) and a solution of 4-acetoxy-3,5-di-*tert*-butyl-2-methylphenol (0.6 g) in N,N-dimethylformamide (5 ml) was added dropwise to the suspension at 0°C. After stirring for 30 min, 1,3-dibromopropane (0.36 ml) was added in one portion and the mixture was stirred for an additional 2 h. The reaction mixture was poured into a saturated aqueous solution of ammonium chloride and subjected to extraction with diethyl ether. The extract was washed with

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water and saturated brine, then dried over anhydrous sodium sulfate and the solvent was distilled off. The residue was dissolved in N,N-dimethylformamide (5 ml) and added to a solution prepared in the same manner as described above  
5 (4-acetoxy-3,5-di-*tert*-butyl-2-methylphenol, 0.4 g; sodium hydride, 86 mg; N,N-dimethylformamide, 5 ml). The mixture was allowed to warm from 0°C to room temperature and stirred for 2 h. Subsequently, it was poured into a saturated aqueous solution of ammonium chloride and treated as  
10 described above. The residue was purified by silica gel chromatography (10% ethyl acetate in n-hexane). The first fraction gave 1-acetoxy-4-allyloxy-2,6-di-*tert*-butyl-3-methylbenzene (370 mg). The next fraction gave 1,3-bis(4-acetoxy-3,5-di-*tert*-butyl-2-methylphenoxy)propane (200 mg).

15 1-Acetoxy-4-Allyloxy-2,6-Di-*tert*-Butyl-3-Methylbenzene

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      1.30(s,9H), 14.2(s,9H), 2.25(s,3H), 2.35(s,3H),  
             4.44(m,2H), 5.0-5.5(m,2H), 5.83-6.43(m,1H),  
             6.72(s,1H)

20 1,3-Bis(4-Acetoxy-3,5-Di-*tert*-Butyl-2-Methylphenoxy)propane

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      1.32(s,18H), 1.37(s,18H), 1.85(m,2H), 2.25(s,6H),  
             2.33(s,6H), 4.12(m,4H), 6.76(s,2H)

25 [Example 17]

Synthesis of 4-Allyloxy-2,6-Di-*tert*-Butyl-3-Methylphenol  
(Compound v)

1-Acetoxy-4-allyloxy-2,6-di-tert-butyl-3-methylbenzene was treated as in Example 15 to afford 4-allyloxy-2,6-di-tert-butyl-3-methylphenol quantitatively as a pale yellow oil.

5      Mass          276(M<sup>+</sup>)

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      1.39(s,9H), 1.58(s,9H), 2.33(s,3H), 4.84(s,1H),  
             4.35(m,2H), 5.0-5.5(m,2H), 5.7-6.3(m,1H),  
             6.64(s,1H)

10      [Example 18]

Synthesis of 1,3-Bis(3,5-Di-tert-Butyl-4-Hydroxy-2-Methylphenoxy)propane (Compound w)

1,3-Bis(4-acetoxy-3,5-di-tert-butyl-2-methylphenoxy)propane was treated as in Example 15 to afford 1,3-bis(3,5-di-tert-butyl-4-hydroxy-2-methylphenoxy)propane as a colorless crystal in 76% yield.

Mass          512(M<sup>+</sup>)

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      1.42(s,18H), 1.60(s,18H), 2.15-2.4(m,2H),  
20           2.35(s,6H), 4.06(t,4H,J=6Hz), 4.90(s,2H),  
             6.72(s,2H)

m.p.          120.4°C

[Example 19]

Synthesis of 3-Acetoxy-2,4-Di-tert-Butyl-6-Hydroxy-5-Methylbenzaldehyde

4-Acetoxy-3,5-di-tert-butyl-2-methylphenol was treated as in Reference Example 13 or 14 or in Example 11 to afford 3-acetoxy-2,4-di-tert-butyl-6-hydroxy-5-methyl-

benzaldehyde as a pale yellow crystal in 7% overall yield.

Mass 292(M<sup>+</sup>)

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.44(s,9H), 1.50(s,9H), 2.27(s,3H), 2.35(s,3H),  
5 10.54(s,1H), 12.66(s,1H)

[Reference Example 19]

Synthesis of 4-tert-Butyl-5-Hydroxy-2-Methylbenzofuran

5-Benzyloxy-4-tert-butyl-2-formylbenzofuran (700 mg,  
2.3 mmol) was dissolved in acetic acid (30 ml) and, after  
10 addition of 10% Pd on carbon (700 mg), the solution was  
stirred under a hydrogen atmosphere (5 atm.) for 8 h. After  
filtering off the Pd on carbon, the filtrate was washed with  
a saturated aqueous solution of sodium hydrogen carbonate,  
dried over anhydrous magnesium sulfate and concentrated.  
15 The concentrate was subjected to silica gel chromatography  
and eluted with a solvent system consisting of a 4:1 mixture  
of hexane and ethyl acetate to afford 4-tert-butyl-5-  
hydroxy-2-methylbenzofuran [320 mg (yield, 68%)] as a pale  
yellow, fine-grained crystal.

20 m.p. 49.9°C

Mass 204(M<sup>+</sup>), 189

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.48(s,9H), 2.29(s,3H), 4.87(s,1H),  
6.43(d,1H,J=8.8Hz), 6.60(s,1H),  
25 6.98(d,1H,J=8.8Hz)

[Example 20]

Synthesis of 4,6-Di-tert-Butyl-5-Hydroxy-2-Methylbenzofuran (Compound s)

Methanesulfonic acid (1.2 ml) was added dropwise to a chloroform solution of 4-*tert*-butyl-5-hydroxy-2-methylbenzofuran (250 mg, 1.2 mmol) and *tert*-butyl alcohol (500 mg, 6.0 mmol) under cooling with ice. After stirring at 5 0°C for 15 min, the mixture was poured into ice water. The mixture was then neutralized with 1N aqueous sodium hydroxide and subjected to extraction with ethyl acetate. The extracted layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried over anhydrous 10 magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (*n*-hexane) to afford 4,6-di-*tert*-butyl-5-hydroxy-2-methylbenzofuran (35 mg) as a pale yellow oil.

Mass 260(M<sup>+</sup>), 245, 57

15 <sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.46(s,9H), 1.61(s,9H), 2.37(s,3H), 5.07(s,1H),  
6.63(s,1H), 7.27(s,1H)

IR (cm<sup>-1</sup>) 3651, 2964

[Reference Example 20]

20 Synthesis of 4-Acetoxy-3,5-Di-*tert*-Butyl-2-(1'-Hydroxy-2',6',10',14'-Tetramethylpentadecyl)phenol

A solution of 2-bromo-6,10,14-trimethylpentadecane (3.4 g, 10.2 mmol) in tetrahydrofuran (15 ml) was added to magnesium (0.25 g, 10.2 mg atom) under a nitrogen atmosphere to prepare a Grignard reagent. A solution of 5-acetoxy-4,6-di-*tert*-butyl-2-hydroxybenzaldehyde (1.0 g, 3.4 mmol) in 25 tetrahydrofuran (5 ml) was added dropwise to the reagent. After stirring the reaction mixture at room temperature for

30 min, a saturated aqueous solution of ammonia chloride was added and the mixture was subjected to extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (10% ethyl acetate in n-hexane) to afford 4-acetoxy-3,5-di-tert-butyl-2-(1'-hydroxy-2',6',10',14'-tetramethylpentadecyl)phenol [0.11 g (yield, 6%)] as a colorless oil.

Mass 486(M<sup>+</sup>), 57

10 <sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 0.85(d,15H), 1.02-1.95(m,22H), 1.27(s,9H),  
1.37(s,9H), 2.23(s,3H), 2.95(d,1H,J=3.4Hz),  
5.08(dd,1H,J=3.4Hz,J=9.6Hz), 6.73(s,1H),  
7.88(s,1H)

15 [Example 21]

Synthesis of 4,6-Di-tert-Butyl-5-Hydroxy-2-Methyl-2-(4',8',12'-Trimethyltridecyl)-2,3-Dihydrobenzofuran

4-Acetoxy-3,5-di-tert-butyl-2-(1'-hydroxy-2',6',10',14'-tetramethylpentadecyl)phenol (0.11 g, 0.2 mmol) was dissolved in dichloromethane (5 ml) and BF<sub>3</sub> etherate (0.2 ml) was added dropwise to the solution under a nitrogen atmosphere. After stirring the mixture at room temperature for 24 h, water was added and the mixture was subjected to extraction with ethyl acetate. The extracted layer was washed with a saturated aqueous solution of sodium hydrogen carbonate, dried over anhydrous magnesium sulfate and concentrated. The concentrate was dissolved in tetrahydrofuran (3 ml) and added dropwise to a suspension of



lithium aluminum hydride (10 mg) in tetrahydrofuran (2 ml) under a nitrogen atmosphere. After refluxing for 2 h, the mixture was cooled to room temperature and water was added dropwise. After adding 1N aqueous sodium hydroxide (5 ml),  
 5 the mixture was subjected to extraction with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (n-hexane) to afford 4,6-di-*tert*-butyl-5-hydroxy-2-methyl-2-(4',8',12'-trimethyldecyl)-2,3-dihydro-  
 10 benzofuran [54 mg (yield, 56%)] as a colorless oil.

Mass 486(M<sup>+</sup>), 471, 149, 57

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm 0.83-0.88(m,12H), 1.08-1.64(m,18H), 1.36(s,3H),  
 1.41(s,9H), 1.49(s,9H), 3.14(d,1H,J=15.7Hz),  
 15 3.27(d,1H,J=15.7Hz), 4.68(s,1H), 6.63(s,1H)

IR (cm<sup>-1</sup>) 3656, 2956

[Reference Example 21]

Synthesis of 4-Acetoxy-3,5-Di-*tert*-Butyl-2-(2,2-Diisoamyl-1-Hydroxyethyl)phenol

20 Lithium (2.8 g) was added to a solution of 5-acetoxy-4,6-di-*tert*-butyl-2-hydroxybenzaldehyde (24.3 g) and 5-bromo-2,8-dimethylnonane (47.0 g) in tetrahydrofuran (200 ml) under ice cooling under a nitrogen atmosphere and the mixture was stirred overnight. The reaction mixture was  
 25 poured into ice water, neutralized with a saturated aqueous solution of ammonium chloride and subjected to extraction with diethyl ether. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and the

solvent was distilled off. The residue was purified by silica gel chromatography (10% ethyl acetate in n-hexane) to afford 4-acetoxy-3,5-di-*tert*-butyl-2-(2,2-diisoamyl-1-hydroxyethyl)phenol [17.0 g (yield, 46%)] as a colorless oil.

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      0.80-1.81(m,11H), 0.87(d,12H), 1.25(s,9H),  
1.37(s,9H), 2.24(s,3H), 3.51(br,1H), 5.19(d,1H),  
6.72(s,1H), 7.92(s,1H)

Mass      448(M<sup>+</sup>)

[Example 22]

Synthesis of 5-Acetoxy-2,2-Diisoamyl-4,6-Di-*tert*-Butyl-2,3-Dihydrobenzofuran

BF<sub>3</sub> etherate (4.7 ml) was added dropwise to a solution of 4-acetoxy-3,5-di-*tert*-butyl-2-(2,2-diisoamyl-1-hydroxyethyl)-phenol (17.0 g) in dichloromethane (200 ml) under cooling with ice under a nitrogen atmosphere. After stirring the mixture overnight at room temperature, a saturated aqueous solution of sodium hydrogen carbonate was added. After separating the organic layer, the aqueous layer was subjected to extraction with dichloromethane. The extract was combined with the organic layer, washed with saturated brine, dried over anhydrous magnesium sulfate and the solvent was distilled off to afford 5-acetoxy-2,2-diisoamyl-4,6-di-*tert*-butyl-2,3-dihydrobenzofuran [15.5 g (yield, 95%)] as a colorless oil.

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      0.87(d,12H), 1.04-1.93(m,10H), 1.28(s,9H),  
             1.35(s,9H), 2.25(s,3H), 3.14(s,2H), 6.67(s,1H)

IR (cm<sup>-1</sup>) 2956, 1764

5      Mass      430(M<sup>+</sup>)

[Example 23]

Synthesis of 2,2-Diisoamyl-4,6-Di-tert-Butyl-5-Hydroxy-  
2,3-Dihydrobenzofuran (Compound z)

Lithium aluminum hydride (1.90 g) was suspended  
10 in tetrahydrofuran (200 ml) under a nitrogen atmosphere.  
A solution of 5-acetoxy-2,2-diisoamyl-4,6-di-tert-butyl-  
2,3-dihydrobenzofuran (17.4 g) in tetrahydrofuran (60 ml)  
was added dropwise to the suspension under cooling with  
ice. After heating under reflux overnight, the mixture  
15 was cooled to room temperature and water and a saturated  
aqueous solution of ammonium chloride were added in that  
order. The resulting insolubles were filtered off on  
Celite. The filtrate was subjected to extraction with  
diethyl ether, washed with saturated brine, dried over  
20 anhydrous magnesium sulfate and the solvent was distilled  
off. The residue was purified by silica gel chromatography  
(n-hexane) to afford 2,2-diisoamyl-4,6-di-tert-butyl-5-  
hydroxy-2,3-dihydrobenzofuran [9.0 g (yield, 57%)] as  
a colorless oil.

25      <sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm      0.89(d,12H), 1.19-1.69(m,10H), 1.41(s,9H),  
             1.49(s,9H), 3.17(s,2H), 4.66(s,1H), 6.62(s,1H)

IR (cm<sup>-1</sup>) 3652, 2956

Mass 388(M<sup>+</sup>)

[Example 24]

Synthesis of 4,6-Di-tert-Butyl-5-Hydroxy-2,3-Dihydrobenzofuran

5 1) Synthesis of 4-Acetoxy-3,5-Di-tert-Butyl-2-(2-Propenyl)anisole

4-Acetoxy-3,5-di-tert-butyl-2-(2-propenyl)phenol (30 g) and potassium carbonate (13.8 g) were dissolved in acetone (300 ml) and, after addition of methyl iodide (28 g), the solution was stirred for 24 h. After cooling, the reaction mixture was concentrated under reduced pressure and water was added. The mixture was then subjected to extraction with ethyl acetate and the organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (10% ethyl acetate in n-hexane) to afford 4-acetoxy-3,5-di-tert-butyl-2-(2-propenyl)anisole (31 g) quantitatively.

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

20 δ ppm 1.34(s,9H), 1.43(s,9H), 2.30(s,3H),  
3.63-3.68(m,2H), 3.78(s,3H), 4.88-5.02(m,2H),  
5.89-6.02(m,1H), 6.83(s,1H)

Mass 318(M<sup>+</sup>)

25 2) Synthesis of 4-Acetoxy-3,5-Di-tert-Butyl-2-Formylmethylanisole

4-Acetoxy-3,5-di-tert-butyl-2-(2-propenyl)anisole (19 g) was dissolved in a 1:1 mixture (200 ml) of tetrahydrofuran and water. After adding osmium tetroxide

(0.12 g) and sodium periodate (26.9 g), the mixture was stirred at room temperature for 48 h. After the end of the reaction, a saturated aqueous solution of sodium thiosulfate was added and the mixture was subjected to extraction with ethyl acetate and the organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (25% ethyl acetate in n-hexane) to afford 4-acetoxy-3,5-di-tert-butyl-2-formylmethylanisole [16 g (yield, 83%)].

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      1.36(s,9H), 1.40(s,9H), 2.30(s,3H), 3.77(s,3H),  
            '3.87(bs,2H), 6.89(s,1H), 9.63(bs,1H)

Mass        320(M<sup>+</sup>)

### 3) Synthesis of 5-Acetoxy-4,6-Di-tert-Butylbenzofuran

4-Acetoxy-3,5-di-tert-butyl-2-formylmethylanisole (16 g) was dissolved in dichloromethane (100 ml) and trimethylsilyl iodide (7.1 ml) was added dropwise to the solution under cooling with ice. After stirring the mixture at room temperature for 1 h, a saturated aqueous solution of sodium thiosulfate was added and the mixture was subjected to extraction with chloroform. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (10% ethyl acetate in n-hexane) to afford 5-acetoxy-4,6-di-tert-butylbenzofuran quantitatively (14.3 g) as a white solid.

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm      1.39(s,9H), 1.51(s,9H), 2.35(s,3H),  
6.98(d,1H,J=2.3Hz), 7.46(s,1H),  
7.55(d,1H,J=2.3Hz)

5      Mass      288(M<sup>+</sup>)

m.p.      87.7°C

4) Synthesis of 4,6-Di-tert-Butyl-5-Hydroxybenzofuran  
(Compound r)

Lithium aluminum hydride (1.31 g) was suspended  
10 in tetrahydrofuran (150 ml) under a nitrogen atmosphere.  
A solution of 5-acetoxy-4,6-di-tert-butylbenzofuran (10 g)  
in tetrahydrofuran (100 ml) was added dropwise to the  
suspension under cooling with ice. After heating under  
reflux for 3 h, the mixture was cooled to room temperature  
15 and, after addition of water and 10% aqueous HCl (100 ml),  
the mixture was subjected to extraction with ethyl acetate.  
The organic layer was dried over anhydrous magnesium sulfate  
and concentrated. The concentrate was purified by silica  
gel chromatography (10% ethyl acetate in n-hexane) to afford  
20 4,6-di-tert-butyl-5-hydroxybenzofuran [8.3 g (yield, 98%)].

5) Synthesis of 4,6-Di-tert-Butyl-5-Hydroxy-2,3-  
Dihydrobenzofuran (Compound a)

4,6-Di-tert-butyl-5-hydroxybenzofuran (6.0 g) was  
dissolved in acetic acid (50 ml). After addition of 10% Pd  
25 on carbon (5.0 g), the solution was stirred under a hydrogen  
atmosphere (4 atm.) for 15 min. After filtering off the  
Pd on carbon, the filtrate was concentrated under vacuum.  
The concentrate was purified by silica gel chromatography

(10% ethyl acetate in n-hexane) to afford 4,6-di-*tert*-butyl-5-hydroxy-2,3-dihydrobenzofuran [4.4 g (yield, 73%)] as a colorless, fine-grained crystal.

[Example 25]

5        Synthesis of 4,6-Di-*tert*-Butyl-5-Hydroxy-2-Octyl-2,3-Dihydrobenzofuran

1) Synthesis of 5-Acetoxy-4,6-Di-*tert*-Butyl-2-Formylbenzofuran

Phosphorus oxychloride (1.1 g) was added dropwise  
10 to N,N-dimethylformamide (0.4 g) under cooling with ice and, subsequently, a solution of 5-acetoxy-4,6-di-*tert*-butylbenzofuran (1.0 g) in N,N-dimethylformamide (2 ml) was added dropwise. The mixture was stirred first at room temperature for 20 min, then under heating at 80°C for  
15 75 min. After cooling, the reaction mixture was poured into water and subjected to extraction ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography  
20 (10% ethyl acetate in n-hexane) to afford 5-acetoxy-4,6-di-*tert*-butyl-2-formylbenzofuran [0.95 g (yield, 86%)] as a colorless, fine-grained crystal.

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm        1.40(s,9H), 1.54(s,9H), 2.37(s,3H), 7.57(s,1H),  
25                7.83(s,1H), 9.88(s,1H)

Mass        316(M<sup>+</sup>)

m.p.        159.9°C

2) Synthesis of 5-Acetoxy-4,6-Di-tert-Butyl-2-(1-Octenyl)benzofuran

A pentane solution (6.0 ml) of 1.6 M n-butyllithium was added dropwise to a solution of n-heptyltriphenylphosphonium bromide (4.2 g) in tetrahydrofuran (30 ml) under a nitrogen atmosphere. After stirring the mixture at room temperature for 90 min, a solution of 5-acetoxy-4,6-di-tert-butyl-2-formylbenzofuran (2.54 g) in tetrahydrofuran (20 ml) was added dropwise. Subsequently, the mixture was heated under reflux for 1 h and, after cooling, a saturated aqueous solution of ammonium chloride was added and the mixture was subjected to extraction with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (10% ethyl acetate in n-hexane) to afford 5-acetoxy-4,6-di-tert-butyl-2-(1-octenyl)benzofuran [3.1 g (yield, 97%)] as a colorless oil.

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      0.88(t,3H), 1.15-1.54(m,8H), 1.37(s,9H),  
1.48(s,9H), 2.31(s,3H), 2.51(m,2H), 6.10(m,1H),  
6.27(m,1H), 6.67(s,1H), 7.33(s,1H)

Mass      398(M<sup>+</sup>)

3) Synthesis of 5-Acetoxy-4,6-Di-tert-Butyl-2-Octylbenzofuran

5-Acetoxy-4,6-di-tert-butyl-2-(1-octenyl)benzofuran (3.1 g) was dissolved in ethyl acetate containing 10% acetic acid (50 ml) and, after addition of 10% Pd on carbon

(0.3 g), the solution was stirred under a hydrogen atmosphere for 3 h. After filtering off the Pd on carbon, the filtrate was concentrated under vacuum. The concentrate was purified by silica gel chromatography (10% ethyl acetate in n-hexane) to afford 5-acetoxy-4,6-di-*tert*-butyl-2-octylbenzofuran [2.95 g (yield, 96%)] as a colorless oil.

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      0.88(t,3H), 1.17-1.57(m,12H), 1.35(s,9H),  
             1.47(s,9H), 2.29(s,3H), 2.70(t,2H,J=7.0Hz),  
10            6.56(s,1H), 7.35(s,1H)

Mass        400(M<sup>+</sup>)

#### 4) Synthesis of 4,6-Di-*tert*-Butyl-5-Hydroxy-2-Octylbenzofuran

Lithium aluminum hydride (0.26 g) was suspended in tetrahydrofuran (50 ml) under a nitrogen atmosphere and a solution of 5-acetoxy-4,6-di-*tert*-butyl-2-octylbenzofuran (2.7 g) in tetrahydrofuran (20 ml) was added to the suspension under cooling with ice. After heating under reflux for 3 h, the mixture was cooled to room temperature and water was added dropwise. After adding 10% aqueous HCl (50 ml), the mixture was subjected to extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (10% ethyl acetate in n-hexane) to afford 4,6-di-*tert*-butyl-5-hydroxybenzofuran [2.2 g (yield, 92%)] as a colorless oil.

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm      0.88(t,3H), 1.20-1.53(m,12H), 1.45(s,9H),  
             1.61(s,9H), 2.67(t,2H,J=7.0Hz), 5.03(s,1H),  
             6.58(s,1H), 7.21(s,1H)

5    Mass      358(M<sup>+</sup>)

IR (cm<sup>-1</sup>) 3384, 2928

5) Synthesis of 4,6-Di-tert-Butyl-5-Hydroxy-2-Octyl-2,3-Dihydrobenzofuran (Compound g)

Triethylsilane (17.4 ml) was added to 4,6-di-tert-  
10 butyl-5-hydroxy-2-octylbenzofuran (2.2 g) and trifluoro-  
acetic acid (8.7 ml) was added dropwise to the mixture  
under cooling with ice. After stirring at 0°C for 1 h,  
the mixture was poured into ice water and subjected to  
extraction with ethyl acetate. The organic layer was  
15 washed with a saturated aqueous solution of sodium hydrogen  
carbonate, dried over anhydrous magnesium sulfate and  
concentrated. The concentrate was purified by silica gel  
chromatography (n-hexane) to afford 4,6-di-tert-butyl-5-  
hydroxy-2-octyl-2,3-dihydrobenzofuran [0.6 g (yield, 27%)].  
20 [Reference Example 22]

Synthesis of 4-Acetoxy-2-Acetonyl-3,5-Di-tert-  
Butylanisole

Palladium chloride (2.96 g) and copper chloride  
(16.5 g) were added to a solvent system (88 ml) consisting  
25 of a 7:1 mixture of N,N-dimethylformamide and water under  
an oxygen atmosphere and the resulting mixture was stirred  
at room temperature for 1 h. Subsequently, a solution of  
4-acetoxy-3,5-di-tert-butyl-2-(2-propenyl)phenol (53.2 g)

in a solvent system (48 ml) consisting of a 7:1 mixture of N,N-dimethylformamide and water was added and the resulting mixture was stirred at room temperature for 48 h. After the end of the reaction, water was added to the reaction mixture, which was then subjected to extraction with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (25% ethyl acetate in n-hexane) to afford 4-acetoxy-2-acetonyl-3,5-di-tert-butylanisole [33 g (yield, 59%)] as a colorless, fine-grained crystal.

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm     '1.34(s,9H), 1.40(s,9H), 2.20(s,3H), 2.31(s,3H),  
3.74(s,3H), 3.90(d,1H,J=7.8Hz),  
4.02(d,1H,J=17.8Hz), 6.83(s,1H)

Mass       334(M<sup>+</sup>)

m.p.       133.2°C

[Reference Example 23]

Synthesis of 4-Acetoxy-2-[4-(1,3-Dioxo-2-Cyclopentyl)-2-Hydroxy-2-Methylbutyl]-3,5-Di-tert-Butylanisole

A solution of 2-(2-bromoethyl)-1,3-dioxane (50 g) in tetrahydrofuran (200 ml) was added to magnesium (6.6 g) under a nitrogen atmosphere to prepare a Grignard reagent. A solution of 4-acetoxy-2-acetonyl-3,5-di-tert-butylanisole in tetrahydrofuran (200 ml) was added dropwise to the reagent. After stirring the mixture at room temperature for 3 h, a saturated aqueous solution of ammonium chloride was added and the resulting mixture was subjected to extraction

with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (33% ethyl acetate in n-hexane) to afford  
5 4-acetoxy-2-[4-(1,3-dioxo-2-cyclopentyl)-2-hydroxy-2-methyl-butyl]-3,5-di-*tert*-butylanisole [27.9 g (yield, 69%)] as a colorless oil.

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm      1.33(s,9H), 1.36(s,9H), 1.38(s,3H),  
10            1.52-1.89(m,4H), 2.28(s,3H), 3.26(s,2H),  
              3.73-3.88(m,2H), 3.82(s,3H), 4.06-4.15(m,3H),  
              4.56(t,1H), 6.82(s,1H)

Mass      • 436(M<sup>+</sup>)

[Example 26]

15      Synthesis of 5-Acetoxy-2-[2-(1,3-Dioxo-2-Cyclopentyl)ethyl]-4,6-Di-*tert*-Butyl-2-Methyl-2,3-Dihydrobenzofuran

4-Acetoxy-2-[4-(1,3-dioxo-2-cyclopentyl)-2-hydroxy-2-methylbutyl]-3,5-di-*tert*-butylanisole (27.9 g) was dissolved  
20 in dichloromethane (200 ml) and trimethylsilyl iodide (12.8 ml) was added dropwise to the solution under cooling with ice. After stirring the mixture at room temperature for 5 min, a saturated aqueous solution of sodium thiosulfate was added and the mixture was subjected to extraction with  
25 chloroform. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (25% ethyl acetate in n-hexane) to afford 5-

acetoxy-2-[2-(1,3-dioxa-2-cyclopentyl)ethyl]-4,6-di-tert-butyl-2-methyl-2,3-dihydrobenzofuran [17.3 g (yield, 67%)] as a colorless oil.

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

5     δ ppm     1.29(s,9H), 1.36(s,9H), 1.37(s,3H),  
                 1.69-1.83(m,4H), 2.29(s,3H), 3.06-3.33(m,2H),  
                 3.75(t,2H), 4.07-4.13(m,2H), 4.51-4.56(m,1H),  
                 6.70(s,1H)

Mass        404(M<sup>+</sup>)

10    [Example 27]

Synthesis of 5-Acetoxy-4,6-Di-tert-Butyl-2-(2-Formylethyl)-2-Methyl-2,3-Dihydrobenzofuran

5-Acetoxy-2-[2-(1,3-dioxa-2-cyclopentyl)ethyl]-4,6-di-tert-butyl-2-methyl-2,3-dihydrobenzofuran (17.3 g) was  
15 dissolved in 80% acetic acid (150 ml) and the solution was heated under reflux for 1 h. After cooling the solution, the acetic acid was distilled off under vacuum and, after addition of water, the resulting mixture was extracted with ethyl acetate. The organic layer was washed with water and  
20 saturated brine, then dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (25% ethyl acetate in n-hexane) to afford 5-acetoxy-4,6-di-tert-butyl-2-(2-formylethyl)-2-methyl-2,3-dihydrobenzofuran quantitatively (15.53 g) as a colorless  
25 oil.

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm     1.30(s,9H), 1.37(s,9H), 1.39(s,3H),  
           1.91-2.12(m,2H), 2.30(s,3H), 2.59(q,2H),  
           3.13-3.32(m,2H), 6.71(s,1H), 9.78(s,1H)

5     Mass     360(M<sup>+</sup>)

[Example 28]

Synthesis of 5-Acetoxy-4,6-Di-tert-Butyl-2-(4-Ethoxycarbonyl-4-Methyl-3(E)-Butenyl)-2-Methyl-2,3-Dihydrobenzofuran

10            5-Acetoxy-4,6-di-tert-butyl-2-(2-formylethyl)-2-methyl-2,3-dihydrobenzofuran (15.5 g) and ethyl 2-(tri-phenylphosphoranylidene)propionate (32.4 g) were dissolved in benzene (250 ml) and the solution was heated under reflux for 1 h. After cooling, the solution was subjected  
15 to extraction with ethyl acetate and the organic layer was washed with water and saturated brine, then dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (10% diethyl ether in n-hexane) to afford a mixture (2.4 g)  
20 containing 27% Z-form and 5-acetoxy-4,6-di-tert-butyl-2-(4-ethoxycarbonyl-4-methyl-3(E)-butenyl)-2-methyl-2,3-dihydrobenzofuran (13.2 g) as a colorless oil.

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm     1.28(t,3H,J=7.3Hz), 1.30(s,9H), 1.37(s,9H),  
25           1.41(s,3H), 1.74-1.88(m,2H), 1.81(d,3H),  
           2.21-2.36(m,2H), 2.30(s,3H), 3.11-3.34(m,2H),  
           4.18(q,2H,J=7.3Hz), 6.73(s,1H), 6.72-6.78(m,1H)

Mass     444(M<sup>+</sup>)

[Example 29]

Synthesis of 5-Acetoxy-4,6-Di-tert-Butyl-2-(5-Hydroxy-4-Methyl-3(E)-Pentenyl)-2-Methyl-2,3-Dihydrobenzofuran

5-Acetoxy-4,6-di-tert-butyl-2-(4-ethoxycarbonyl-4-methyl-3(E)-butenyl)-2-methyl-2,3-dihydrobenzofuran (13.2 g) was dissolved in benzene (250 ml) and a tetrahydrofuran solution (60 ml) of 1 M diisobutylaluminum hydride was added dropwise to the solution under cooling with ice. After stirring the mixture for 1 h, a saturated aqueous solution of ammonium chloride was added and the mixture was subjected to extraction with ethyl acetate. The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (33% ethyl acetate in n-hexane) to afford 5-acetoxy-4,6-di-tert-butyl-2-(5-hydroxy-4-methyl-3(E)-pentenyl)-2-methyl-2,3-dihydrobenzofuran [3.9 g (yield, 33%)] as a colorless oil. In addition, 4,6-di-tert-butyl-5-hydroxy-2-(5-hydroxy-4-methyl-3(E)-pentenyl)-2-methyl-2,3-dihydrobenzofuran [4.2 g (yield, 39%)] was obtained as a colorless oil.

5-Acetoxy-4,6-Di-tert-Butyl-2-(5-Hydroxy-4-Methyl-3(E)-Pentenyl)-2-Methyl-2,3-Dihydrobenzofuran

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm      1.30(s,9H), 1.37(s,9H), 1.44(s,3H), 1.64(d,3H),  
1.68-1.80(m,2H), 2.05-2.22(m,2H), 2.29(s,3H),  
3.08-3.34(m,2H), 3.97(bs,2H), 5.41(m,1H),  
6.73(s,1H)

Mass      402(M<sup>+</sup>)

4,6-Di-tert-Butyl-5-Hydroxy-2-(5-Hydroxy-4-Methyl-3(E)-  
Pentenyl)-2-Methyl-2,3-Dihydrobenzofuran

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm      1.39(s,3H), 1.41(s,9H), 1.49(s,9H),  
5            1.65(s,3H), 1.69-1.76(m,2H), 2.12-2.20(m,2H),  
             3.17(d,1H,J=15.5Hz), 3.30(d,1H,J=15.5Hz),  
             3.98(bs,2H), 4.70(s,1H), 5.42(m,1H), 6.63(s,1H) .

Mass        360(M<sup>+</sup>)

IR (cm<sup>-1</sup>)   3648, 3440, 2964

10 [Example 30]

Synthesis of 5-Acetoxy-2-(5-Chloro-4-Methyl-3(E)-  
Pentenyl)-4,6-Di-tert-Butyl-2-Methyl-2,3-  
Dihydrobenzofuran

N-Chlorosuccinimide (150 mg) was suspended in  
15 dichloromethane (4 ml). After adding dimethyl sulfide  
(0.1 ml) dropwise at -5°C, the suspension was stirred for  
15 min. Subsequently, a solution of 5-acetoxy-4,6-di-tert-  
butyl-2-(5-hydroxy-4-methyl-3(E)-pentenyl)-2-methyl-2,3-  
dihydrobenzofuran (0.4 g) in dichloromethane (1 ml) was  
20 added dropwise and the resulting mixture was stirred at -5°C  
for 90 min. After the end of the reaction, dichloromethane  
was distilled off under reduced pressure and the concentrate  
was purified by silica gel chromatography (25% ethyl acetate  
in n-hexane) to afford 5-acetoxy-2-(5-chloro-4-methyl-3(E)-  
25 pentenyl)-4,6-di-tert-butyl-2-methyl-2,3-dihydrobenzofuran  
[0.3 g (yield, 70%)] as a colorless oil.

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm      1.30(s,9H), 1.37(s,9H), 1.43(s,3H), 1.72(d,3H),  
1.78(m,2H), 2.17(m,2H), 2.29(s,3H), 3.15-  
3.34(m,2H), 3.98(s,2H), 5.53(m,1H), 6.73(s,1H)

5      Mass      422(M+2), 420(M<sup>+</sup>)

[Example 31]

Synthesis of 5-Acetoxy-4,6-Di-tert-Butyl-2-Methyl-  
2-(6-p-Toluenesulfonyl-4,8,12-Trimethyltrideca-  
3(E),7(E),11-Trienyl)-2,3-Dihydrobenzofuran

10            3,7-Dimethyl-1-(p-toluenesulfonyl)-2(E),6-octadiene  
(0.26 g) synthesized in the usual manner was dissolved in  
a solvent system (2 ml) consisting of a 4:1 mixture of  
tetrahydrofuran and hexamethylphosphoric triamide. After  
adding a pentane solution (0.55 ml) of 1.6 M n-butyllithium  
15 at -78°C, the mixture was stirred for 2 h. Subsequently,  
a solution of 5-acetoxy-2-(5-chloro-4-methyl-3(E)-pentenyl)-  
4,6-di-tert-butyl-2-methyl-2,3-dihydrobenzofuran (0.3 g) in  
tetrahydrofuran (1 ml) was added dropwise at -78°C and the  
mixture was stirred for 4 h. After the end of the reaction,  
20 a saturated aqueous solution of ammonium chloride was added  
and the resulting mixture was extracted with ethyl acetate.  
The organic layer was washed with water and saturated  
brine, then dried over anhydrous magnesium sulfate, and  
concentrated. The concentrate was purified by silica gel  
25 chromatography (25% ethyl acetate in n-hexane) to afford 5-  
acetoxy-4,6-di-tert-butyl-2-methyl-2-(6-p-toluenesulfonyl-  
4,8,12-trimethyltrideca-3(E),7(E),11-trienyl)-2,3-dihydro-  
benzofuran [0.26 g (yield, 55%)] as a colorless oil.

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm      1.21(s,3H), 1.29(s,9H), 1.36(s,9H), 1.39(s,3H),  
1.47(m,4H), 1.52(s,3H), 1.58(s,3H), 1.67(s,3H),  
1.93-2.12(m,4H), 2.22(d,1H), 2.29(s,3H),  
5      2.42(s,3H), 2.85(d,1H), 3.17(m,2H), 3.87(m,1H),  
4.88(d,1H), 5.02(m,1H), 5.15(m,1H), 6.71(s,1H),  
7.29(d,2H,J=7.26Hz), 7.71(d,2H,J=7.26Hz)

Mass      676(M<sup>+</sup>)

[Example 32]

10      Synthesis of 5-Acetoxy-4,6-Di-tert-Butyl-2-Methyl-2-  
(4,8,12-Trimethyltrideca-3(E),7(E),11-Trienyl)-2,3-  
Dihydrobenzofuran

5-Acetoxy-4,6-di-tert-butyl-2-(6-p-toluenesulfonyl-  
4,8,12-trimethyltrideca-3(E),7(E),11-trienyl)-2,3-dihydro-  
15 benzofuran (0.26 g) was dissolved in tetrahydrofuran (2 ml)  
under a nitrogen atmosphere. Palladium chloride [1,4-  
bis(diphenylphosphono)butane] complex (23 mg) prepared in  
the usual manner was added to the solution at 0°C; there-  
after, a tetrahydrofuran solution (0.76 ml) of 1 M lithium  
20 triethylborohydride was added dropwise and the mixture was  
stirred for 24 h at -20°C. After the end of the reaction,  
a saturated aqueous solution of ammonium chloride was added  
the resulting mixture was extracted with ethyl acetate. The  
organic layer was washed with water and saturated brine,  
25 dried over anhydrous magnesium and concentrated. The  
concentrate was purified by silica gel chromatography (10%  
ethyl acetate in n-hexane) to afford 5-acetoxy-4,6-di-tert-  
butyl-2-methyl-2-(4,8,12-trimethyltrideca-3(E),7(E),11-

trienyl)-2,3-dihydrobenzofuran [0.11 g (yield, 55%)] as a colorless oil.

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

5      δ ppm      1.30(s,9H), 1.37(s,12H), 1.43(s,3H), 1.59(s,6H),  
1.67(s,3H), 1.98-2.11(m,12H), 2.29(s,3H),  
3.07-3.35(m,2H), 5.10(m,3H), 6.73(s,1H)

Mass      522(M<sup>+</sup>)

[Example 33]

10      Synthesis of 4,6-Di-tert-Butyl-5-Hydroxy-2-Methyl-2-  
(4,8,12-Trimethyltrideca-3(E),7(E),11-Trienyl)-2,3-  
Dihydrobenzofuran (Compound α)

15      Lithium aluminum hydride (8 mg) was suspended in tetrahydrofuran (3 ml) under a nitrogen atmosphere. A solution of 5-acetoxy-4,6-di-tert-butyl-2-methyl-2-(4,8,12-trimethyltrideca-3(E),7(E),11-trienyl)-2,3-dihydrobenzofuran (0.11 g) in tetrahydrofuran (2 ml) was added dropwise to the suspension under cooling with ice. After heating under reflux for 3 h, the mixture was cooled to room temperature and water was added dropwise. Following addition of 10%  
20      aqueous HCl, the mixture was subjected to extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (n-hexane) to afford  
25      4,6-di-tert-butyl-5-hydroxy-2-methyl-2-(4,8,12-trimethyltrideca-3(E),7(E),11-trienyl)-2,3-dihydrobenzofuran [70 mg (yield, 69%)] as a colorless oil.

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm      1.38(s,3H), 1.41(s,9H), 1.43(s,3H), 1.49(s,9H),  
            1.59(s,6H), 1.67(s,3H), 1.90-2.14(m,12H),  
            3.15(d,1H,J=15.7Hz), 3.31(d,1H,J=15.7Hz),  
            4.68(s,1H), 5.10(m,3H), 6.63(s,1H)

Mass        480(M<sup>+</sup>)

5      IR (cm<sup>-1</sup>) 3648, 2964

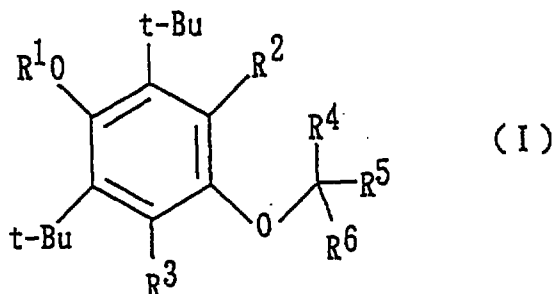
[INDUSTRIAL APPLICABILITY]

10      The compounds of the invention that are represented  
by the general formula (I) have a highly selective anti-  
oxidative activity and are useful as therapeutics of  
ischemic diseases such as myocardial infarction, cerebral  
apoplexy and arteriosclerosis. The compounds of the  
invention that are represented by the general formula (II)  
are intermediates suitable for producing the compounds of  
the general formula (I).



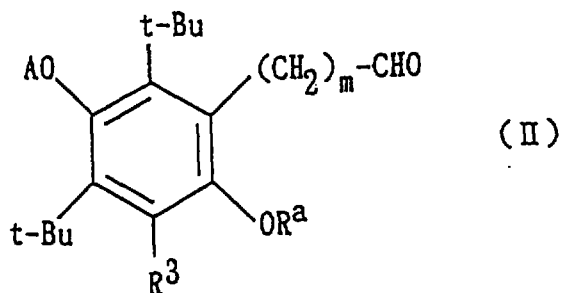
# CLAIMS

1. A compound represented by the general formula (I):



where  $R^1$  is a hydrogen atom or an acyl group;  $R^2$  is a lower alkyl group;  $R^3$  is a hydrogen atom or a lower alkyl group;  $R^4$ ,  $R^5$  and  $R^6$ , which may be the same or different, are  
5 a hydrogen atom or an optionally substituted alkyl, alkenyl, alkynyl or aryl group;  $R^2$  and  $R^4$ , when taken together, may form a 5-membered ring;  $R^5$  and  $R^6$ , when taken together, may form a cycloalkyl group or a heterocyclic group in which  
10 at least one methylene on the ring of a cycloalkyl group is substituted by an oxygen atom, a sulfur atom or an alkyl-substituted nitrogen atom, provided that  $R^6$  is not present if the ring formed by  $R^2$  and  $R^4$  taken together is a benzofuran ring.

2. A compound represented by the general formula (II):



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15 where  $R^3$  has the same meaning as defined above; A is

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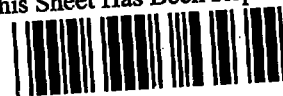
a protective group;  $R^a$  is a hydrogen atom or a lower alkyl group; and  $m$  is an integer of 0 or 1.



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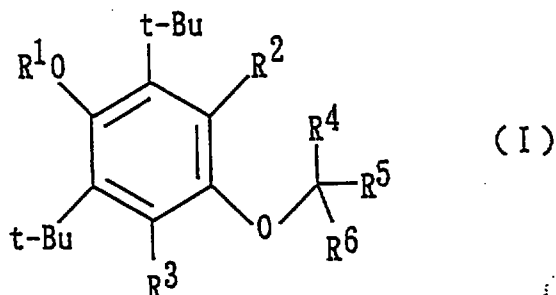


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## ABSTRACT

Compounds represented by the general formula (I),  
as well as intermediates for the synthesis of thereof:



where  $R^1$  is a hydrogen atom or an acyl group;  $R^2$  is a lower alkyl group;  $R^3$  is a hydrogen atom or a lower alkyl group;  
 5  $R^4$ ,  $R^5$  and  $R^6$ , which may be the same or different, are  
 a hydrogen atom or an optionally substituted alkyl, alkenyl,  
 alkynyl or aryl group;  $R^2$  and  $R^4$ , when taken together, may  
 form a 5-membered ring;  $R^5$  and  $R^6$ , when taken together, may  
 form a cycloalkyl group or a heterocyclic group in which  
 10 at least one methylene on the ring of a cycloalkyl group  
 is substituted by an oxygen atom, a sulfur atom or an alkyl-  
 substituted nitrogen atom, provided that  $R^6$  is not present if  
 the ring formed by  $R^2$  and  $R^4$  taken together is a benzofuran  
 ring. The compounds represented by the general formula (I)  
 15 have a highly selective anti-oxidative activity and are  
 useful as therapeutics of ischemic diseases such as  
 arteriosclerosis and myocardial infarction.

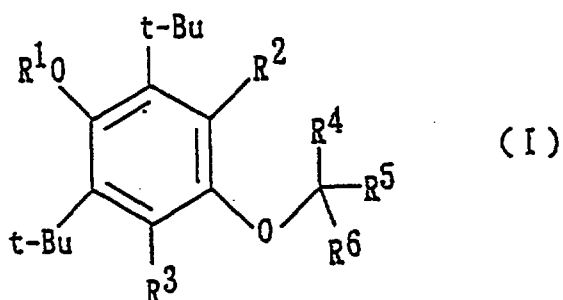
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-97-

## ABSTRACT

4-ALKOXY-2, 6-DI-T-BUTYLPHENOL DERIVATIVES

Compounds represented by the general formula (I),  
as well as intermediates for the synthesis of thereof:



where  $R^1$  is a hydrogen atom or an acyl group;  $R^2$  is a lower alkyl group;  $R^3$  is a hydrogen atom or a lower alkyl group;  $R^4$ ,  $R^5$  and  $R^6$ , which may be the same or different, are a hydrogen atom or an optionally substituted alkyl, alkenyl, alkynyl or aryl group;  $R^2$  and  $R^4$ , when taken together, may form a 5-membered ring;  $R^5$  and  $R^6$ , when taken together, may form a cycloalkyl group or a heterocyclic group in which at least one methylene on the ring of a cycloalkyl group is substituted by an oxygen atom, a sulfur atom or an alkyl-substituted nitrogen atom, provided that  $R^6$  is not present if the ring formed by  $R^2$  and  $R^4$  taken together is a benzofuran ring. The compounds represented by the general formula (I) have a highly selective anti-oxidative activity and are useful as therapeutics of ischemic diseases such as arteriosclerosis and myocardial infarction.

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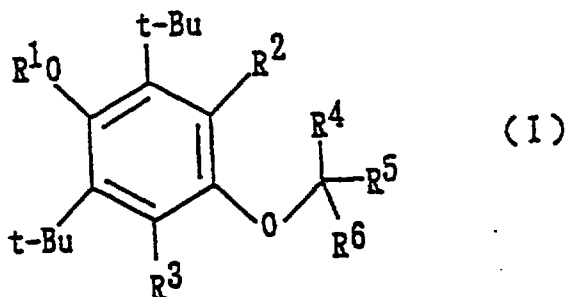
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# DESCRIPTION

## 4-ALKOXY-2,6-DI-T-BUTYLPHENOL DERIVATIVES

### [TECHNICAL FIELD]

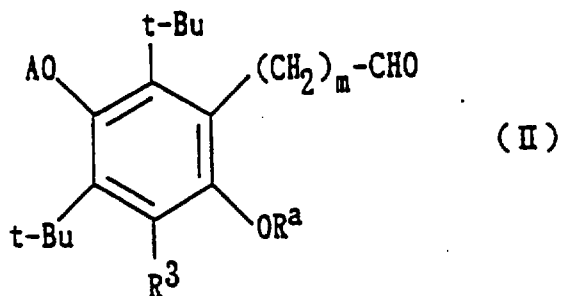
This invention relates to compounds for preventing the oxidative modification of low density lipoprotein (LDL), particularly, to compounds useful as therapeutics of arteriosclerosis myocardial infarction and other ischemic diseases. More specifically, the invention relates to compounds represented by the following general formula (I), as well as compounds represented by the general formula (II) which are useful intermediates for the synthesis of compounds (I):



(where R<sup>1</sup> is a hydrogen atom or an acyl group; R<sup>2</sup> is a straight or branched alkyl group having 1-6 carbon atoms; R<sup>3</sup> is a hydrogen atom or a straight or branched alkyl group having 1-6 carbon atoms; R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup>, which may be the same or different, are a hydrogen atom or an optionally substituted alkyl, alkenyl, alkynyl or aryl group; R<sup>2</sup> and R<sup>4</sup>, when taken together, may form a furan or a dihydrofuran ring; R<sup>5</sup> and R<sup>6</sup>, when taken together, may form a cycloalkyl group or a heterocyclic group in which at least one methylene on the ring of a cycloalkyl group is substituted by an oxygen atom, a sulfur atom or an alkyl-substituted nitrogen atom, provided that R<sup>6</sup> is not present if the ring formed by R<sup>2</sup> and R<sup>4</sup> taken together is a benzofuran

- 2 -

ring);



(where  $R^3$  has the same meaning as defined above; A is a protective group;  $R^a$  is a hydrogen atom or a straight or branched alkyl group having 1-6 carbon atoms; and m is an integer of 0 or 1).

[BACKGROUND ART]

Atherosclerosis is one of the principal causes of ischemic diseases such as angina pectoris, myocardial infarction and cerebral apoplexy. The mechanism of initiation and progression of atherosclerosis is closely related to the oxidative modification of LDL. The modified LDLs are not recognized by the LDL receptor but by the scavenger receptor, to induce the foam cell formation which is characterized by cholesterol accumulation.

The modification of LDL is caused by endothelial cells, smooth muscle cells, macrophages, etc. and the modified LDLs are eventually taken by macrophages via the scavenger or other pathways. It is additionally known that the modification of LDL by these cells is similar to the oxidative modification of LDL by  $Cu^{2+}$ .

LDL is chiefly composed of cholesterol esters, phospholipids and apo-B-100. The oxidative modification of LDL is shown from various aspects, for example fragmentation

- 7 -

In the compounds of the invention, the acyl group as  $R^1$  may be exemplified by acetyl, formyl, propionyl, benzoyl, benzyloxycarbonyl, with acetyl being preferred. The alkyl group as  $R^2$  and  $R^3$  or  $R^4$  refers to a straight or branched alkyl group having 1 - 6 carbon atoms, as exemplified by methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl. The alkyl group as  $R^4$ ,  $R^5$  and  $R^6$  refers to a straight or branched alkyl group having 1 - 20 carbon atoms, as exemplified by methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl. The alkenyl group as  $R^4$ ,  $R^5$  and  $R^6$  refers to a straight or branched alkenyl group having 2 - 20 carbon atoms, as exemplified by vinyl, allyl, butenyl, pentenyl, geranyl, farnesyl. The alkynyl group as  $R^4$ ,  $R^5$  and  $R^6$  refers to a straight or branched alkynyl group having 2 - 20 carbon atoms, as exemplified by ethynyl, propynyl, butynyl. The aryl group as  $R^4$ ,  $R^5$  and  $R^6$  means a monovalent substituent that is an aromatic hydrocarbon minus a hydrogen atom, as exemplified by phenyl, tolyl, xylyl, biphenyl, naphthyl, anthryl, phenanthryl.

Carbon atoms on the ring of the aryl group may be substituted by one or more species such as a halogen atom, an alkyl group, a hydroxyl group, an alkoxy group, an amino group, a nitro group, a trifluoromethyl group. Exemplary substituents include a halogen atom, a hydroxyl group, an amino group, an alkoxy group, an aryloxy group.

The 5-membered ring which may be formed by  $R^2$  and  $R^4$  taken together is exemplified by a furan ring and a dihydro-

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- 8 -

furane ring, which are taken together with the adjacent benzene ring to form a benzofuran ring and a dihydrobenzofuran ring, respectively. The cycloalkyl group which may be formed by  $R^5$  and  $R^6$  taken together refers to a cycloalkyl group having 3 - 8 carbon atoms, as exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl. The heterocyclic group which may be formed by  $R^5$  and  $R^6$  taken together and in which at least one methylene on the ring of a cycloalkyl group is substituted by an oxygen atom, a sulfur atom or an alkyl-substituted nitrogen atom may be exemplified by a tetrahydropyranyl group. The protective group as A may be exemplified by acetyl, benzoyl, methyl, methoxymethyl, methoxyethoxymethyl, benzyl, trimethylsilyl, benzyloxycarbonyl, tetrahydropyranyl, 2-trimethylsilyl)ethoxymethyl, with acetyl being preferred.

[BEST MODE FOR CARRYING OUT THE INVENTION]

The compounds of the present invention may typically be synthesized by the following methods.

- 59 -

the reaction mixture was poured into water, neutralized with 1N aqueous sodium hydroxide and subjected to extraction with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (chloroform) to afford 5-acetoxy-4,6-di-tert-butyl-2-hydroxybenzaldehyde (19.0 g).

m.p. 79.0°C

Mass 292(M<sup>+</sup>), 250, 235, 217, 57

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.35(s,9H), 1.54(s,9H), 2.35(s,3H), 6.92(s,1H),  
10.67(s,1H), 12.32(s,1H)

IR (cm<sup>-1</sup>) 2976, 1758

[Reference Example 15]

Synthesis of 4-Acetoxy-3,5-Di-tert-Butyl-2-(2-Ethyl-1-Butenyl)phenol

A solution of 3-bromopentane (1.3 g, 8.6 mmol) in tetrahydrofuran (10 ml) was added to magnesium (0.21 g, 8.6 mg atom) under a nitrogen atmosphere to prepare a Grignard reagent. A solution of 5-acetoxy-4,6-di-tert-butyl-2-hydroxybenzaldehyde (1.0 g, 3.4 mmol) in tetrahydrofuran (5 ml) was added dropwise to the reagent. After stirring the mixture at room temperature for 30 min, a 5:2 mixed solution (7 ml) of water and conc. HCl was added to the reaction mixture, followed by stirring at room temperature for 30 min and subsequent extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (10% ethyl acetate in

- 69 -

A solution of the 1-acetoxy-2,6-di-tert-butyl-3-methyl-4-propyloxybenzene in tetrahydrofuran (5 ml) was added to the suspension and the mixture was refluxed for 3 h. A saturated aqueous solution of ammonium chloride was added to the reaction mixture under ice cooling and the precipitate was filtered off together with the anhydrous sodium sulfate. The filtrate was concentrated and purified by silica gel chromatography (10% ethyl acetate in n-hexane) to afford 2,6-di-tert-butyl-3-methyl-4-propyloxyphenol (150 mg) as a colorless oil.

Mass 278(M<sup>+</sup>)

<sup>1</sup>H NMR (60MHz, CDCl<sub>3</sub>)

δ ppm 1.06(t,3H,J=6Hz), 1.45(s,9H), 1.61(s,9H),  
1.80(m,2H), 2.38(s,3H), 3.85(t,2H,J=6Hz),  
4.90(s,1H), 6.75(s,1H)

[Example 16]

Synthesis of 1-Acetoxy-4-Allyloxy-2,6-Di-tert-Butyl-3-Methylbenzene and 1,3-Bis(4-Acetoxy-3,5-Di-tert-Butyl-2-Methylphenoxy)propane

Sodium hydride (110 mg) was suspended in N,N-dimethylformamide (5 ml) and a solution of 4-acetoxy-3,5-di-tert-butyl-2-methylphenol (0.6 g) in N,N-dimethylformamide (5 ml) was added dropwise to the suspension at 0°C. After stirring for 30 min, 1,3-dibromopropane (0.36 ml) was added in one portion and the mixture was stirred for an additional 2 h. The reaction mixture was poured into a saturated aqueous solution of ammonium chloride and subjected to extraction with diethyl ether. The extract was washed with

- 75 -

lithium aluminum hydride (10 mg) in tetrahydrofuran (2 ml) under a nitrogen atmosphere. After refluxing for 2 h, the mixture was cooled to room temperature and water was added dropwise. After adding 1N aqueous sodium hydroxide (5 ml), the mixture was subjected to extraction with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The concentrate was purified by silica gel chromatography (n-hexane) to afford 4,6-di-tert-butyl-5-hydroxy-2-methyl-2-(4',8',12'-trimethyltridecyl)-2,3-dihydro-benzofuran [54 mg (yield, 56%)] as a colorless oil.

Mass 486(M<sup>+</sup>), 471, 149, 57

<sup>1</sup>H NMR (270MHz, CDCl<sub>3</sub>)

δ ppm 0.83-0.88(m,12H), 1.08-1.64(m,18H), 1.36(s,3H),  
1.41(s,9H), 1.49(s,9H), 3.14(d,1H,J=15.7Hz),  
3.27(d,1H,J=15.7Hz), 4.68(s,1H), 6.63(s,1H)

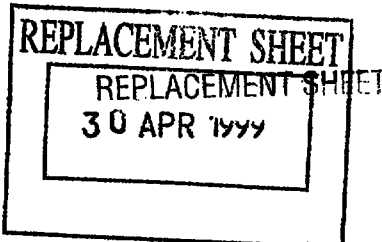
IR (cm<sup>-1</sup>) 3656, 2956

[Reference Example 21]

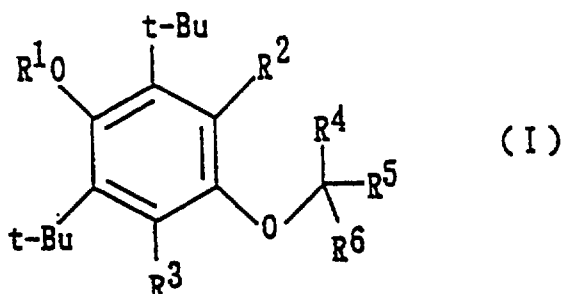
Synthesis of 4-Acetoxy-3,5-Di-tert-Butyl-2-(2,2-Diisoamyl-1-Hydroxyethyl)phenol

Lithium (2.8 g) was added to a solution of 5-acetoxy-4,6-di-tert-butyl-2-hydroxybenzaldehyde (24.3 g) and 5-bromo-2,8-dimethylnonane (47.0 g) in tetrahydrofuran (200 ml) under ice cooling under a nitrogen atmosphere and the mixture was stirred overnight. The reaction mixture was poured into ice water, neutralized with a saturated aqueous solution of ammonium chloride and subjected to extraction with diethyl ether. The extract was washed with saturated brine, dried over anhydrous magnesium sulfate and the

CLAIMS

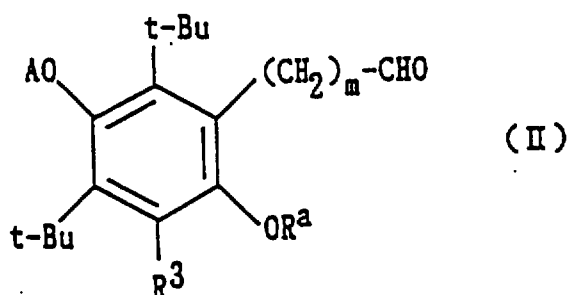


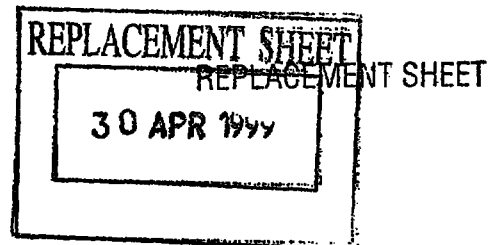
1. A compound represented by the general formula (I):



where  $R^1$  is a hydrogen atom or an acyl group;  $R^2$  is a straight or branched alkyl group having 1-6 carbon atoms;  $R^3$  is a hydrogen atom or a straight or branched alkyl group having 1-6 carbon atoms;  $R^4$ ,  $R^5$  and  $R^6$ , which may be the same or different, are a hydrogen atom or an optionally substituted alkyl, alkenyl, alkynyl or aryl group;  $R^2$  and  $R^4$ , when taken together, may form a furan or a dihydrofuran ring;  $R^5$  and  $R^6$ , when taken together, may form a cycloalkyl group or a heterocyclic group in which at least one methylene on the ring of a cycloalkyl group is substituted by an oxygen atom, a sulfur atom or an alkyl-substituted nitrogen atom, provided that  $R^6$  is not present if the ring formed by  $R^2$  and  $R^4$  taken together is a benzofuran ring.

2. A compound represented by the general formula (II):





- 96 -

where  $R^3$  has the same meaning as defined in claim 1; A is a protective group;  $R^4$  is a hydrogen atom or a straight or branched alkyl group having 1-6 carbon atoms; and m is an integer of 0 or 1.

