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A SHORT-STEP CONVENIENT SYNTHESIS OF 2-PHENYLBENZOFURAN FROM 3-PHENYLCOUMARIN

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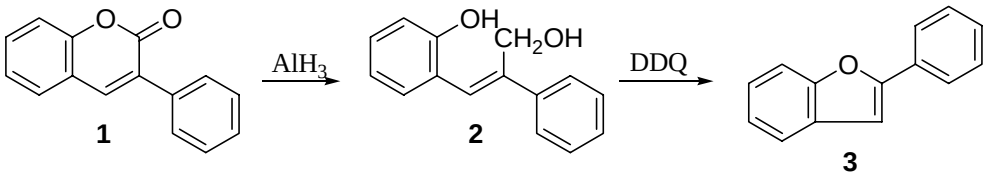
Abstract – The reaction mechanism of chemical conversion of (*E*)-β-[2-hydroxylphenylethylene]benzeneethanol into 2-phenylbenzofuran by DDQ, which involves loss of one carbon unit, was characterized and described. Five naturally occurring 2-phenylbenzofurans of not only the isoflavonoid but also stilbenoid origin were synthesized by use of this chemical scheme, which proved that this new scheme is a useful tool for quick synthesis of 2-phenylbenzofurans.

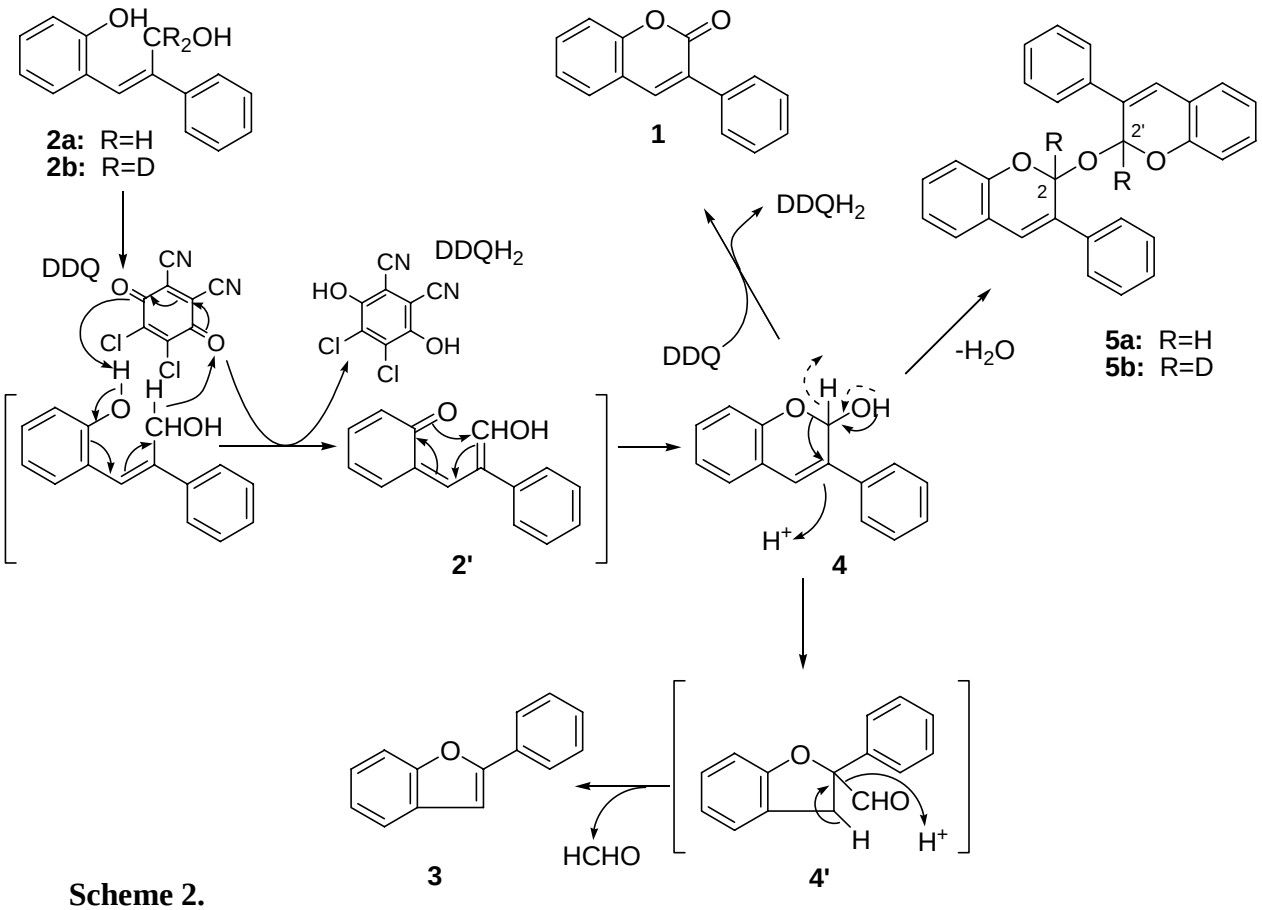
Naturally occurring 2-phenylbenzofurans[1] have been known mainly from either legumes or mulberries.[2, 3] These compounds have drawn increasing attention since many of them occur in nature as phytoalexins, a group of secondary metabolites produced *de novo* as defensive substances by plants against fungal infection.[2, 3] However, those known from mulberries are distinguished from those of leguminous origin from biogenetic viewpoints. The former are regarded as arising biogenetically from the oxidative cyclization of the corresponding stilbenes, whereas the latter are considered to be members of the isoflavonoid family. These two types of 2-phenylbenzofurans are also distinguished each other by the following structural features; those of mulberry origin possess the oxygen functionality at the 3'- and 5'-positions of 2-phenyl group while those of the isoflavonoid origin possess the oxygen functionality at the 2'- and 4'-position. Though 2-phenylbenzofurans are of interest from viewpoint of biological



Scheme 1.

activities other than anti-fungus activity, their biological activities have not been adequately characterized since they occur only in small quantity naturally. In particular, those of the isoflavonoid origin are drawing considerable attention as possible bioactive principles of herbal medicines of leguminous origin in which a growing number of reports indicated their occurrence.[4] Therefore, there is a demand from the field of health science dealing with health food and dietary suppliments for facile and efficient chemical tool to rapidly identify and prepare minor metabolites from natural source, such as 2-phenylbenzofurans, in order to evaluate their safety and pharmacological efficacy. The first author reported earlier chemical conversion of naturally occurring 3-phenylcoumarin (3-phenyl-2*H*-1-benzopyran-2-one) derivative "*glycyrin*", a constituent isolated from a worldwide reputed crude drug licorice, to the corresponding 2-phenylbenzofuran derivative during the course of structure elucidation of this natural product.[5] The scheme outlined in Scheme 1 will be of particular interest since it employs the starting materials common to the synthesis of most isoflavonoids unlike the previous methods that have been accomplished by the routes incompatible with those of other isoflavonoids.[6] The advantage of this scheme for the synthesis of naturally occurring 2-arylbenzofurans will be further substantiated by the fact that most isoflavonoidal 2-phenylbenzofurans co-occur in nature with biogenetically related isoflavonoids. However, reaction mechanisms of the above chemical scheme has been neither characterized nor applied to the synthesis of 2-phenylbenzofurans yet. These circumstances induced us to investigate this reaction more deeply with the aim of obtaining mechanistic information and optimizing the reaction procedure for the synthesis of naturally occurring 2-phenylbenzofurans as an alternative to the previous methods.[6] In this paper we describe the elucidation of mechanisms of the above reaction, and its application to the synthesis of naturally occurring 2-phenylbenzofurans of not only the isoflavonoid but also stilbenoid origin.

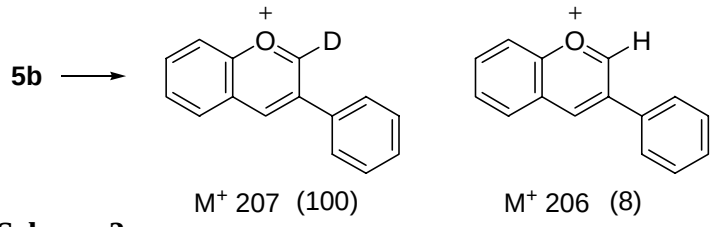
In order to elucidate the reaction mechanism shown in Scheme 1 that converts 3-phenylcoumarin derivatives into 2-phenylbenzofuran derivatives, the simplest (*E*)-β-[2-hydroxylphenylethylene]-benzeneethanol (referred to as the diol (**2**), hereafter) was prepared and treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) under reflux in dry benzene as described in the



Scheme 2.

literature,[5] and all reaction products were subjected to structure elucidation. During the reaction, a deposit of paraformaldehyde on the reflux condenser and precipitation of 2,3-dichloro-5,6-dicyano-1,4-hydroquinone ($DDQH_2$) in the reaction medium was observed. Prior to the work-up of the reaction mixture, the formation of three products was observed on TLC. The reaction mixture obtained after the usual workups was subjected to the chromatographic separation to furnish three products, 3-phenylcoumarin (**1**), 2-phenylbenzofuran (**3**), and 2,2'-oxybis[3-phenyl-2*H*-1-benzopyran] (**5a**) (referred to as the dimer (**5a**), hereafter), at the yields of 6%, 34% and 30%, respectively (all yields based on isolation in pure crystallized forms). It is apparent that the formation of paraformaldehyde in this reaction resulted from loss of one carbon unit occurred during conversion of the diol (**2a**) to 2-phenylbenzofuran (**3**). It is of particular interest to note that the formation of the dimer (**5a**) suggested isoflav-3-ene-2-ol (**4**) (3-phenyl-2*H*-1-benzopyran-2-ol) to be involved in the formation of 2-phenylbenzofuran (**3**) as an intermediate, since we have already established acid-catalyzed conversion of isoflav-3-ene-2-ol (**4**) to 2-phenylbenzofuran (**3**).[7] As the possible mechanism of the formation of isoflav-3-ene-2-ol (**4**) from the diol (**2a**) on treatment with DDQ, the first step of the reaction would be

initiated by the abstraction of a hydride at the allylic position of the diol (**2a**) followed by the deprotonation of the phenol hydroxyl to form the corresponding *o*-quinonemethide (**2'**).[8] The *o*-quinonemethide (**2'**) will readily undergo cyclization to give rise to isoflav-3-ene-2-ol (**4**). Since DDQ, a strong electron accepter, forms a charge-transfer complex with the donor phenol, the above mechanism will be quite reasonable (Scheme 2). The mechanism depicted in an earlier paper[5] for this reaction scheme was thus found to be erroneous. When (*E*)-β-[2-hydroxylphenylethylene]benzeneethanol-D_2 (**2b**) was subjected to the same reaction condition as the diol-H_2 (**2a**), retention of more than 93% of deuterium at the 2- and 2'-positions of the dimer-D_2 (**5b**) was observed according to the corresponding MS spectral analysis (Scheme 3), supporting this mechanism as shown in Scheme 2. Conversion of isoflav-3-ene-2-ol (**4**) to 2-phenylbenzofuran would be catalized by $DDQH_2$. Though the reaction was undertaken in dry aprotic condition while isoflav-3-ene-2-ol (**4**) was treated with strong acid in an earlier paper,[7] it was proved that $DDQH_2$ acted as an acid to catalyze conversion of isoflav-3-ene-2-ol (**4**) to 2-phenylbenzofuran (**3**) involving loss of one carbon unit (Scheme 2). When isoflav-3-ene-2-ol (**4**) prepared as described in the literature[7] was refluxed with $DDQH_2$ in dry benzene for 12 h, the formation of 2-phenylbenzofuran (**3**) along with the dimer (**5a**) was confirmed at the yields of 49% and 30%, respectively. The weak acidity and low solubility of $DDQH_2$ in the solvent will be one of the reasons that this reaction requires a long time heating for completion.



Scheme 3.

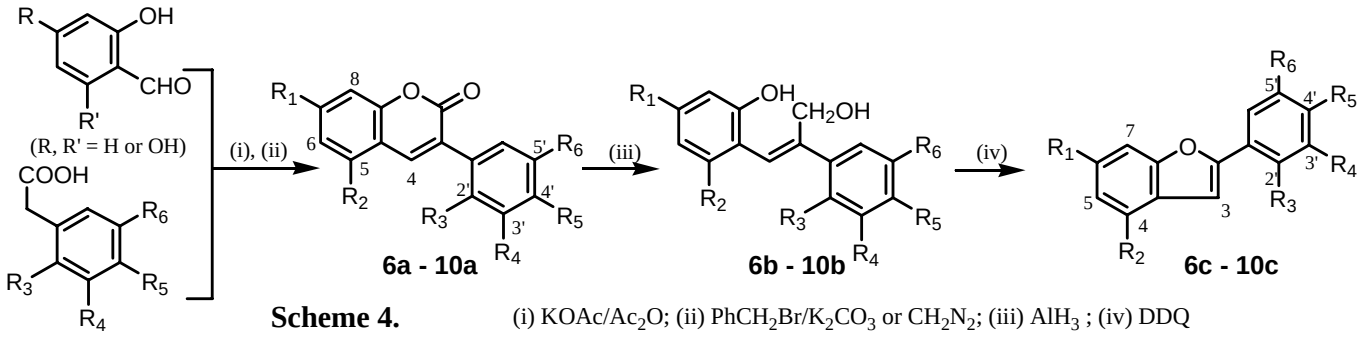
In order to apply the scheme described above to the practical synthesis of naturally occurring 2-phenylbenzofurans, an attempt to optimize the reaction condition was undertaken. First, the reaction was performed in various solvents in order to select the optimum solvent to give the highest yield. The results were summarized in Table 1. All solvents were prepared dry prior to the reaction. Benzene and dioxane are primary solvents used for reactions in which DDQ is employed as a dehydrogenation reagent.

Table 1. Effect of Solvents on Synthesis of 2-Arylbenzofuran (3)

Solvents	Yields	Solvents	Yields
Benzene	34	MeOH	9
Dioxane	15	CH_2Cl_2	25
THF	14	$CHCl_3$	39

However, results obtained from dioxane and other solvents except for benzene and chloroform were disappointing. In the actual application of the corresponding reaction to the synthesis of 2-phenylbenzofurans, dry benzene was employed on the ground that it is easy to dry and also the boiling point is higher than other solvents. With the aim of shortening the reaction time, a small amount of *p*-toluenesulfonic acid was added to the reaction medium. Though the starting material (**2a**) disappeared in less than half time of the standard condition, the dimer (**5a**) was obtained as a main product (41%) and the yield of 2-phenylbenzofuran (**3**) decreased dramatically (16%). However, it should be noted that the dimer (**5a**) can be converted to 2-phenylbenzofuran (**3**) on hydrolysis with acid in moderate yield (34%).

3-Phenylcoumarins (**6a**-**10a**) were synthesized in moderate yields (36-58%) by aldol condensation of corresponding benzaldehydes and phenylacetic acids that were readily prepared in a few steps from commercially available materials. One of the merits utilizing 3-phenylcoumarins as starting materials for the synthesis of the corresponding minor isoflavonoids is that they are stable, prone to crystallization, and thus suitable for constructing a chemical library as parts of synthesizing minor isoflavonoids. Conversion of 3-phenylcoumarins to the corresponding 2-phenylbenzofurans consists of two steps; catalytic reduction



Scheme 4. (i) $KOAc/Ac_2O$; (ii) $PhCH_2Br/K_2CO_3$ or CH_2N_2; (iii) AlH_3 ; (iv) DDQ

Table 2. Yields of 2-phenylbenzofurans synthesized according to Scheme 4

entry	Substitution						products	Yields[a]	naturally occurring 2-phenylbenzofurans[c]
	R_1	R_2	R_3	R_4	R_5	R_6			
1	H	H	H	H	H	H	**3**	34	-
2	OCH_3	OCH_3	H	OBz	H	OBz	**6c**	36	moracin A
3	OBz	H	H	OBz	H	OBz	**7c**	30[b]	moracin M
4	OBz	H	OBz	H	OBz	H	**8c**	60	unnamed
5	OCH_3	H	OCH_3	H	OBz	H	**9c**	65	vignafuran
6	OBz	H	OCH_3	OBz	OCH_3	H	**10c**	52	pterofuran

[a] all over yields of reactions (iii) and (iv).
[b] including yield of the 2-phenylbenzofuran prepared from hydrolysis of the dimer.
[c] names of natural products after hydrogenation.

of 3-phenylcoumarins by use of AlH_3, and treatment of the resulting diols with DDQ (Scheme 4). This conversion can be performed eventually in one batch by following the Micovic's method[9] during the workup of a catalytic reduction. Though yields of this conversion are moderate as shown in Table 2, it will be compensated by the following features: the products are prepared in short steps by use of conventional reactions and reagents, and are easily purified. In case of an unsubstituted 3-phenylcoumarin (**1**), this conversion gave rise to the dimer (**5a**) along with 2-phenylbenzofuran (**3**) as mentioned above. The formation of the corresponding dimer was not observed except for entry 3, which ended up with the poorest yield (11%) of the corresponding 2-phenylbenzofuran. The entry 3 gave rise to the dimer as a by-product at the yield of 38%. Since this dimer could be converted to the corresponding 2-phenylbenzofuran derivative on hydrolysis with acid (53% yield), the substantial yield (30%) was comparable to those of other entries. It is presumed that the occurrence of functional group at either the 2'- or 5-position of 3-phenylcoumarin skeleton will be ascribed to the restrained formation of the dimer. As already mentioned above, 2-phenylbenzofurans of isoflavonoid origin are characterized as possessing oxygen functionality at the 2'-position. On the other hand, those of the mulberry family origin, which are biogenetically derived from stilbenes, do not possess oxygen functionality at the 2'-position. Therefore, this method is less attractive for the synthesis of the latter type of 2-arylbenzofurans that have no oxygen functionality at the 2'- and 4-position.

As mentioned above, we have succeeded in preparing 2-phenylbenzofurans of both the isoflavonoid and stilbenoid origin starting from the corresponding 3-phenylcoumarins that are readily available from aldol condensation between oxygenated phenylacetic acids and benzaldehydes. Synthetic routes to either pterocarpan or isoflavan employing oxygenated phenylacetic acids and benzaldehydes as the starting materials have also been reported by several other groups.[10] Although yields of our method are moderate as compared to those reported by other groups,[6] one of the advantages of our method is that our method can utilize starting material library commonly used for the synthesis of other minor isoflavonoids. Our method will be more suitable for the synthesis of isotope-labeled compounds that are essential for metabolic studies dealing with bioavailability of isoflavonoids in food and suppliments. This method will be useful in the preparation of samples for quick identification and biological assay as mentioned in the introduction.

EXPERIMENTAL

General

All melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. Spectral data were obtained using the following apparatus: ^{1}H- and ^{13}C-NMR spectra with a JEOL JNM GSX-400 (^{1}H, 400 MHz) spectrometer with $SiMe_4$ as an internal standard; LRMS spectra with a JEOL SX-102A mass spectrometer, IR spectra with a JASCO FT/IR-8000 infrared spectrophotometer and UV spectra with a Shimadzu UV-240 spectrophotometer. Column chromatography was carried out with Wakogel C-200 or Merck Kieselgel 60. TLC was conducted on a 0.25 mm precoated silica gel plate ($60GF_{254}$, Merck), and spots were detected by inspection under short (254 nm) or long (365 nm) wavelength UV lights, or by the colors developed with 10% H_2SO_4 spraying followed by heating on a hot plate. All of the solvents used were dried over appropriate agents and distilled prior to use.

Starting materials

Lithium aluminum deuteride ($LiAlD_4$; 96 atom % D) was purchased from Aldrich Co. Ltd. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 97%) was purchased from Tokyo Kasei Organic Chemicals, Co. Ltd. The following materials were prepared according to the procedures described in the corresponding literatures: 3-phenyl-2*H*-1-benzopyran-2-one (3-phenylcoumarin) ;[11] 2-phenylbenzo-furan;[12] 3,5-dibenzyloxyphenylacetic acid;[13] 3-benzyloxy-2,4-dimethoxyacetophenone;[14] 4-benzyloxy-2-methoxyacetophenone.[15] 3-Benzyloxy-2,4-dimethoxyphenylacetic acid and 4-benzyloxy-2-methoxyphenylacetic acid were prepared from 3-benzyloxy-2,4-dimethoxyacetophenone and 4-benzyloxy-2-methoxyacetophenone, respectively, according to the procedure as described bellow. Each acetophenone (10 mmol) was dissolved in methanol (100 mL), and 4.89 g (11 mmol) of $Tl(NO_3)_3 \cdot 3H_2O$ added to the solution and stirred overnight at rt. The reaction mixture was poured into cold water, and the organic materials were extracted with Et_2O. The extract was successively washed with water, brine, dried over anhydrous Na_2SO_4 and then evaporated to dryness. The residue was subjected to a column chromatography over silica gel on elution with benzene-acetone to furnish the corresponding methyl phenylacetate in pure form (oil). Each of methyl phenylacetates was dissolved in 15% NaOH, which was then washed with Et_2O. The alkaline layer was neutralized by the addition of 10% HCl, and resulting precipitates were collected. The precipitates were recrystallized from EtOH-H_2O to give amorphous solids.

3-Benzyloxy-2,4-dimethoxyphenylacetic acid Yield: 67% from 3-benzyloxy-2,4-methoxyacetophenone; amorphous; IR ν_{max}^{KBr} cm^{-1}: 2935, 1724, 1606 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.46 (2H, s), 3.72, 3.74 (3H each, s), 4.98 (2H each, s), 6.59 (1H, d, *J* = 8.4 Hz), 6.82 (1H, d, *J* = 8.4 Hz), 7.20 (10H, m). Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.70; H, 6.09.

4-Benzyloxy-2-methoxyphenylacetic acid Yield: 69% from 4-benzyloxy-2-methoxyacetophenone; amorphous; IR ν_{max}^{KBr} cm^{-1}: 2915, 1712, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.40 (2H, s), 3.77 (3H, s), 5.01 (2H, s), 6.36 (1H, d, *J* = 2.5 Hz), 6.44 (1H, d, *J* = 8.3, 2.5 Hz), 6.88 (1H, d, *J* = 8.3 Hz), 7.20 (5H, m). MS *m*/*z* 272 (M^+, 60), 181 (100). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.28; H, 5.96.

3-Phenyl-2*H*-1-Benzopyran-2-ol (**4**) To a stirred solution of 3-phenylcoumarin (0.62 g, 2.79 mmol) at -78℃ in dry toluene (50 mL) was added DIBAH (0.60 g, 4.19 mmol). After stirring for 1.5 h at this temperature, the reaction mixture was quenched by the addition of acetic acid (5 mL) and then poured into cold water. The organic materials were extracted with Et_2O, and the extract was washed successively by saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was recrystallized from benzene-hexane to give colorless solids (0.42 g; 67%). mp 94-96℃; UV λ_{max}^{MeOH} nm: 207, 289 nm; IR ν_{max}^{KBr} cm^{-1}: 1483, 1452, 984 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.77 (1H, s), 6.9-7.6 (10H, m); ^{13}C-NMR ($CDCl_3$): δ 91.6, 116.6, 121.6, 122.1, 125.4, 127.3, 127.5, 128.2, 128.9, 130.0, 135.7, 149.4. MS *m*/*z* 224 (M^+, 94), 207 (M^+-OH, 100). Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.01; H, 5.44.

General procedure for the preparation of 3-phenylcoumarins (6a-10a)

A mixture of the corresponding benzaldehyde (4 mmol), phenylacetic acid (3.5 mmol), anhydrous KOAc (0.49 g, 5 mmol) and Ac_2O (1.5 mL) was heated at 150℃ under argon atmosphere for 10 h. The reaction mixture was acidified with 10% HCl and extracted with $CHCl_3$. The organic layer was evaporated to dryness and the residue was mixed with THF (12 mL) and 25% NH_4OH (8 mL). After heating for 40 min, the mixture was evaporated to dryness to afford the corresponding crude 3-phenylcoumarin derivative (referred to as the residue, hereafter).

3-(3,5-Dibenzyloxyphenyl)-5,7-dimethoxy-2*H*-1-benzopyran-2-one (6a) The residue was dissolved in THF (10 mL). To this solution an excess amount of etheral diazomethane was added at 0℃, and allowed to stand overnight. After the mixture was quenched by the addition of formic acid, it was evaporated to dryness, and the residue was repeatedly recrystallized from EtOH to furnish the product (**6a**) (yield: 39%).

Pale yellow needles, mp 114-115°C; IR ν_{max}^{KBr} cm^{-1}: 1707, 1597 cm^{-1}; ^{1}H-NMR (acetone-d_6): δ 3.87, 3.91 (3H each, s), 5.10 (4H, br s), 6.30 (1H, d, *J* = 2. 4 Hz), 6.46 (1H, d, *J* = 2.4 Hz), 6.64 (1H, t, *J* = 2.0 Hz), 7.00 (2H, d, *J* = 2.0 Hz), 7.3-7.7 (10H, m), 8.08 (1H, s). MS *m*/*z* 494 (M$^+$, 31), 403 (42), 312 (100). Anal. Calcd for $C_{31}H_{26}O_6$: C, 75.29; H, 5.30. Found: C, 74.97; H, 5.33.

3-(3,5-Dibenzyloxyphenyl)-7-benzyloxy-2*H*-1-benzopyran-2-one (7a) The residue was benzylated by benzyl bromide-K_2CO_3/acetone to furnish **7a** (yield: 45%). Colorless needles from acetone, mp 143-144°C; IR ν_{max}^{KBr} cm^{-1}: 1721, 1604 cm^{-1}; ^{1}H-NMR (acetone-d_6): δ 5.15 (4H, br s), 5.28 (2H, br s), 6.73 (1H, t, *J* = 2.0 Hz), 6.98-7.03 (2H, m), 7.05 (2H, d, *J* = 2.0 Hz), 7.00 (1H, d, *J* = 2.0 Hz), 7.3-7.5 (16H, m), 8.12 (1H, s). MS *m*/*z* 540 (M$^+$, 74), 449 (100). Anal. Calcd for $C_{36}H_{28}O_5$: C, 79.98; H, 5.22. Found: C, 79.65; H, 5.27.

3-(2,4-Dibenzyloxyphenyl)-7-benzyloxy-2*H*-1-benzopyran-2-one (8a) The residue was benzylated by benzyl bromide-K_2CO_3/acetone to furnish **8a** (yield: 58%). Colorless needles from acetone, mp 132-133°C; IR ν_{max}^{KBr} cm^{-1}: 1719, 1603 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 5.10, 5.12, 5.15 (2H each, br s), 6.60 (2H, m), 6.88 (2H, m), 7.3-7.5 (7H, m), 7.69 (1H, s). MS *m*/*z* 540 (M$^+$, 62), 449 (100). Anal. Calcd for $C_{36}H_{28}O_5$: C, 79.98; H, 5.22. Found: C, 79.84; H, 5.19.

3-(4-Benzyloxy-2-methoxyphenyl)-7-methoxy-2*H*-1-benzopyran-2-one (9a) The residue was benzylated by benzyl bromide-K_2CO_3/acetone to furnish **9a** (yield: 41%). Colorless needles from MeOH, mp 159-160°C; IR ν_{max}^{KBr} cm^{-1}: 1722, 1605 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.79, 3.88 (3H each, s), 5.10 (2H, br s), 6.62 (1H, dd, *J* = 8.0, 2.2 Hz), 6.64 (1H, d, *J* = 2.2 Hz), 6.84 (1H, dd, *J* = 8.8, 2.4 Hz), 6.85 (1H, d, *J* = 2.4 Hz), 7.30 (1H, d, *J* = 8.0 Hz), 7.35-7.5 (6H, m), 7.66 (1H, s). MS *m*/*z* 388 (M$^+$, 95), 297 (100). Anal. Calcd for $C_{24}H_{20}O_5$: C, 74.21; H, 5.19. Found: C, 74.47; H, 5.20.

3-(3-Benzyloxy-2,4-dimethoxyphenyl)-7-benzyloxy-2*H*-1-benzopyran-2-one (10a) The residue was benzylated by benzyl bromide-K_2CO_3/acetone to furnish **10a** (yield: 36%). Colorless needles from acetone, mp 120-121°C; IR ν_{max}^{KBr} cm^{-1}: 1705, 1613 cm^{-1}; ^{1}H-NMR (acetone-d_6): δ 3.83 (3H, s), 3.90 (3H, s), 5.04 (2H, br s), 5.23 (2H, br s), 6.8-7.7 (15H, m), 7.81 (1H, s). MS *m*/*z* 494 (M$^+$, 13), 403 (21), 312 (100). Anal. Calcd for $C_{31}H_{26}O_6$: C, 75.29; H, 5.30. Found: C, 75.50; H, 5.39.

General procedure for the preparation of (*E*)-β-[(2-hydroxylphenyl)ethylene]benzeneethanols (2a, 2b, 6b-10b)

To a well-stirred mixture of LAH (0.68 g, 18 mmol) and $AlCl_3$ (0.88 g, 6.6 mmol) in dry Et_2O (40 mL),

3-phenylcoumarin (2 mmol) dissolved in THF (5 mL) was added dropwise and the mixture stirred for 1.5 h. After the reaction mixture was quenched by the addition of AcOEt, 1 mL of water, 1 mL of 15% aq. NaOH and 3 mL of water were successively added to the reaction mixture, and the resulting precipitates were filtered off. The filtrate was evaporated to dryness to give the corresponding (*E*)-β-[2-hydroxylphenylethylene]benzeneethanol (the diol). The diols obtained as oil were purified by column chromatography over silica gel on elution with benzene-acetone.

(*E*)-β-[2-Hydroxylphenylethylene]benzeneethanol (2a) Yield: 75%. Colorless needles from benzene-hexane, mp 92-94°C; IR ν_{max}^{KBr} cm^{-1}: 3400, 1600, 1449 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 4.58 (2H, s), 6.7-7.7 (10H, m). MS *m*/*z* 226 (M^+, 9), 208 (74), 207 (100). Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.97; H, 6.15.

(*E*)-β-[2-Hydroxylphenylethylene]benzeneethanol-D_2 (2b) The diol-D_2 (**2b**) was prepared from 3-phenylcoumarin (**1**) in the same manner described above using $LiAlD_4$ (98 atom % D). Colorless needles from benzene-hexane, mp 90°C; IR ν_{max}^{KBr} cm^{-1}: 3400, 1600, 1450 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.7-7.7 (10H, m). MS *m*/*z* 228 (M^+, 3), 210 (M^+-H_2O, 64), 208 (100).

(*E*)-β-[2-Hydroxy-4,6-dimethoxyphenylethylene]-3,5-dibenzyloxybenzeneethanol (6b) Colorless viscous oil; IR ν_{max}^{neat} cm^{-1}: 3450, 1580 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.73 (3H, s), 3.76 (3H, s), 4.46 (2H, br s), 5.02 (4H, s), 6.09 (1H, d, *J* = 2.0 Hz), 6.18 (1H, d, *J* = 2.0 Hz), 6.60 (1H, t, *J* = 2.0 Hz), 6.88 (2H, d, *J* = 2.0 Hz), 7.3-7.5 (11H, m). MS *m*/*z* 474 (M^+).

(*E*)-β-[2-Hydroxy-4-benzyloxyphenylethylene]-3,5-dibenzyloxybenzeneethanol (7b) Colorless viscous oil; IR ν_{max}^{neat} cm^{-1}: 3470, 1596 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 4.51 (2H, br s), 5.04 (2H, br s), 5.05 (4H, br s), 6.60 (3H, m), 6.93 (3H, m), 6.4-7.6 (22H, m). MS *m*/*z* 544 (M^+).

(*E*)-β-[2-Hydroxy-4-benzyloxyphenylethylene]-2,4-dibenzyloxybenzeneethanol (8b) Colorless viscous oil; IR ν_{max}^{neat} cm^{-1}: 3440, 1583 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 4.32 (2H, br s), 5.01, 5.02, 5.04 (2H each, s), 6.45-6.60 (6H, m), 6.95 (1H, d, *J* = 8.3 Hz), 7.3 (15H, m). MS *m*/*z* 392 (M^+).

(*E*)-β-[2-Hydroxy-4-methoxyphenylethylene]-4-benzyloxy-2-methoxybenzeneethanol (9b) Colorless viscous oil; IR ν_{max}^{neat} cm^{-1}: 3440, 1583 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.79, 3.81 (3H, each), 4.29 (2H, br s), 5.04 (2H, s), 6.45-6.60 (6H, m), 6.92 (1H, d, *J* = 8.5 Hz), 7.2-7.3 (5H, m). MS *m*/*z* 392 (M^+).

(*E*)-β-[2-Hydroxy-4-benzyloxyphenylethylene]-3-benzyloxy-2,4-dimethoxybenzeneethanol (10b) Colorless viscous oil; IR ν_{max}^{neat} cm^{-1}: 3440, 1592 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.83 (3H,s), 3.88 (3H, s),

4.30 (2H, br s), 5.06 (2H, br s), 6.5-7.5 (16H, m). MS *m*/*z* 474 (M^+, 1).

General procedure for the preparation of 2-phenylbenzofurans (6c-10c)

A mixture of (*E*)-β-[2-hydroxylphenylethylene]benzeneethanol derivative (2 mmol; **2a, 2b, 6b-10b**) prepared from the corresponding 3-phenylcoumarin, DDQ (0.50 g, 2.2 mmol) and dry benzene (25 mL) was refluxed for 7.5 h. A white solid product was deposited on a reflux condensor, and was identified with the authentic paraformaldehyde (Wako Pure Chemical Ind. Co., Ltd.). After removing the precipitates ($DDQH_2$) by filtration, the filtrate was concentrated and loaded directly onto a short column packed with 10 g of silica gel in benzene. The column was eluted with benzene and the evaporation of the eluent gave rise to pure products (**3**, **5a**, **5b**, **6c-10c**).

2-Phenylbenzofuran (3) Yield: 34%. Compound (**3**) was obtained from the reaction mixture along with 2,2'-oxybis[3-phenyl-2*H*-1-benzopyran] (**5a**; 30%) and 3-phenylcoumarin (**1**; 6%). **5a**: colorless powder, mp 233-235°C (lit.,[16] 210°C); IR ν_{max}^{KBr} cm^{-1}: 1483, 1452, 1204 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.78 (2 H, s), 7.0-7.5 (20H, m); ^{13}C NMR ($CDCl_3$) δ 91.9, 116.8, 121.8, 122.1, 125.6, 127.4, 127.5, 128.2, 128.9, 130.3, 136.0, 149.7. MS *m*/*z* 430 (M^+, 0.2), 207 (100). Anal. Calcd for $C_{30}H_{22}O_3$: C, 83.67; H, 5.39. Found: C, 83.42; H, 5.17. Reaction of (*E*)-β-[2-hydroxylphenylethylene]benzeneethanol-D_2 (**2b**) with DDQ under the identical condition stated above furnished 2,2'-oxybis[3-phenyl-2*H*-1-benzopyran]-D_2 (**5b**). IR ν_{max}^{KBr} cm^{-1}: 1483, 1452, 1204 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.0-7.5 (20H, m). MS *m*/*z* 432 (M^++D_2, 0.6), 207 (100), 206 (8).

2-(3,5-Dibenzyloxyphenyl)-4,6-dimethoxybenzofuran (6c) Yield: 36%. Amorphous; IR ν_{max}^{KBr} cm^{-1}: 1590, 1503 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.78 (3H, s), 3.81 (3H, s), 5.10 (4H, br s), 6.32 (1H, d, *J* = 2.0 Hz), 6.58 (1H, t, *J* = 2.0 Hz), 6.68 (1H, br d, *J* = 2.0 Hz), 7.05 (1H, d, *J* = 2.0 Hz), 7.06 (2H, d, *J* = 2.0 Hz), 7.3-7.5 (11H, m). MS *m*/*z* 466 (M^+, 44), 375 (100). Anal. Calcd for $C_{30}H_{26}O_5$: C, 77.24; H, 5.62. Found: C, 77.59; H, 5.51. This product (62 mg) was hydrogenated over 5% Pd-C (28 mg) in EtOH (8 mL) for 2h, and the mixture was filtered off. The filtrate was evaporated to dryness and the residue was recrystalized from benzene-acetone to give Morasin A (36 mg) in pure forms. Colorless needles from benzene-acetone, mp 83-85°C.[17]

2-(3,5-Dibenzyloxyphenyl)-6-benzyloxybenzofuran (7c) Yield: 11%. Amorphous; IR ν_{max}^{KBr} cm^{-1}: 1600, 1499 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 5.10 (4H, br s), 5.13 (2H, br s), 6.60 (1H, t, *J* = 2.0 Hz), 6.92 (1H, br s), 6.95 (1H, dd, *J* = 8.5, 2.0 Hz), 7.08 (2H, d, *J* = 2.0 Hz), 7.3-7.5 (16H, m). MS *m*/*z* 512 (M^+, 36), 421

(100). Anal. Calcd for $C_{35}H_{28}O_4$: C, 82.01; H, 5.51. Found: C, 81.80; H, 5.72. The dimer 2,2'-oxybis[3-(3,5-dibenzyloxyphenyl)-6-benzyloxy-2*H*-1-benzopyran] was also obtained. Amorphous, yield: 38%. ^{1}H-NMR ($CDCl_3$): δ 5.04 (12H, s), 6.1-7.3 (46H); ^{13}C NMR ($CDCl_3$) δ 70.26, 102.61, 104.72, 105.30, 105.95, 111.69, 112.04, 117.26, 127.34, 127.75, 128.33, 131.55, 136.19, 136.36, 136.54, 146.68, 149.72, 151.77, 158.81, 159.80. A mixture of the dimer (100 mg) and aq. THF (THF : H_2O = 5 : 2; 70 mL) and H_2SO_4 (4 mL) was refluxed for 45 h. The mixture was then poured into water, and the residue was extracted with Et_2O. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was chromatographed over silica gel on elution with benzene to give 2-(3,5-dibenzyloxyphenyl)-6-benzyloxybenzofuran **(7c)**. Yield: 53%. The product (**7c**) was hydrogenated over 5% Pd-C in the same manner as described above to give Morasin M. Colorless needles from benzene-MeOH, mp 258-260°C.[18]

2-(2,4-Dibenzyloxyphenyl)-6-benzyloxybenzofuran (8c) Yield: 60%. Amorphous; IR ν_{max}^{KBr} cm^{-1}: 1603, 1506 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 5.10, 5.12, 5.15 (2H each, br s), 6.75 (1H, d, *J* = 2.0 Hz), 6.83 (1H, dd, *J* = 8.4, 2.0 Hz), 6.95 (1H, dd, *J* = 8.5, 2.2 Hz), 7.10 (1H, d, *J* = 2.2 Hz), 7.12 (1H, s), 7.3-7.5 (17H, m). MS *m*/*z* 512 (M^+, 21), 421 (100). Anal. Calcd for $C_{35}H_{28}O_4$: C, 82.01; H, 5.51. Found: C, 81.69; H, 5.66. This product was hydrogenated over 5% Pd-C in the same manner as described above to give 2-(2,4-dihydroxyphenyl)-6-hydroxybenzofuran. Colorless needles from MeOH-H_2O, mp 208-209°C.[19]

2-(4-benzyloxy-2-methoxyphenyl)-6-methoxybenzofuran (9c) Yield: 65%. Amorphous; IR ν_{max}^{KBr} cm^{-1}: 1601, 1498 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 5.10 (2H, br s), 3.83 (3H, s), 3.92 (3H, s), 6.72 (1H, d, *J* = 2.1 Hz), 6.79 (1H, dd, *J* = 8.5, 2.1 Hz), 6.92 (1H, dd, *J* = 8.2, 2.0 Hz), 7.13 (1H, d, *J* = 2.0 Hz), 7.15 (1H, s), 7.2-7.3 (6H, m), 7.39 (1H, d, *J* = 8.5 Hz). MS *m*/*z* 360 (M^+, 41), 269 (100). Anal. Calcd for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59. Found: C, 76.91; H, 5.72. This product was hydrogenated over 5% Pd-C in the same manner as described above to give vignafuran in amorphous form.[20]

2-(3-Benzyloxy-2,4-dimethoxyphenyl)-6-benzyloxybenzofuran (10c) Yield: 52%. Amorphous; IR ν_{max}^{KBr} cm^{-1}: 1597, 1504 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.86 (3H, s), 3.96 (3H, s), 5.07 (2H, br s), 5.12 (2H, br s), 6.75 (1H, d, *J* = 8.5 Hz), 6.93 (1H, dd, *J* = 2.3, 8.6 Hz), 7.12 (1H, br d, *J* = 2.3 Hz), 7.17 (1H, d, *J* = 0.8 Hz), 7.3-7.5 (11H, m), 7.65 (1H, d, *J* = 8.6 Hz). MS *m*/*z* 466 (M^+, 29), 375 (100). Anal. Calcd for $C_{30}H_{26}O_5$: C, 77.24; H, 5.62. Found: C, 77.69; H, 5.54. This product was hydrogenated over 5% Pd-C in the same manner as described above to give pterofuran. Colorless needles from benzene-EtOH, mp

210-211°C.[21]

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REFERENCES AND NOTES

1. There are several biogenetic origins for naturally occurring 2-phenylbenzofurans. Some neolignans also constitute the 2-phenylbenzofuran structure, but they are clearly distinguished from those of mulberry and leguminous origins by the presence of the propyl unit. This article does not refer to those of neoligan origin as 2-phenylbenzofurans.
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