A SHORT SYNTHETIC ROUTE TO BENZOFURANS. SYNTHESES OF NATURALLY OCCURRING EUPARIN AND RELATED COMPOUNDS

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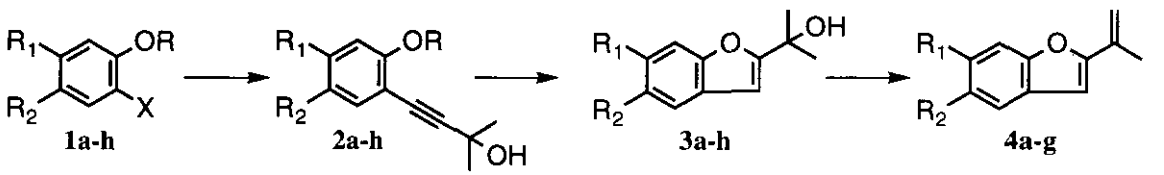
Abstract —— Euparin (**4a**) and related benzofurans (**4b-e, g**) were synthesized by conversion of the corresponding *o*-(3-hydroxy-3-methylbutynyl)phenyl tosylates (**2**) in the presence of base into the 2-(1-hydroxy-1-methylethyl)benzofurans (**3**), followed by dehydration in high yields. 2-(1-Bromo-1-methylethyl)benzofurans (**5g, h**) were converted into 2,2-dimethylchromenes (**6g, h**) in good yields.

Benzofurans and their modifications are widely distributed in nature,[1] some of which have biological activity.[2] Benzofuran derivatives have been synthesized by a variety of methods,[1] and R. Stevenson[3] has synthesized 5-acetyl-2-isopropenylbenzofurans in 42% yield by a short procedure involving the reaction of an *o*-halophenol with copper (I) isopropenylacetylide. In the course of our work on the syntheses of naturally occurring prenylphenols,[4] *o*-alkynylphenyl tosylates were easily synthesized by the coupling reaction of halophenyl tosylates (**1**) with 2-methyl-3-butyn-2-ol,[5] and it was considered that they would be easily converted into the



1a-h, 2a-h

a : R = Ts, R_1 = OTs, R_2 = Ac, X = I
b : R = Ts, R_1 = H, R_2 = Ac, X = I
c : R = Ts, R_1 = R_2 = H, X = Br
d : R = Ts, R_1 = Me, R_2 = H, X = I
e : R = Ts, R_1 = H, R_2 = Me, X = Br
f : R = Ts, R_1 = OTs, R_2 = H, X = Br
g : R = Bn, R_1 = OBn, R_2 = Ac, X = I
h : R = Me, R_1 = R_2 = H, X = I

3a, 4a : R_1 = OH, R_2 = Ac
3b, 4b : R_1 = H, R_2 = Ac
3c, 4c : R_1 = R_2 = H
3d, 4d : R_1 = Me, R_2 = H
3e, 4e : R_1 = H, R_2 = Me
3g, 4g : R_1 = OEt, R_2 = H
3f : R_1 = OH, R_2 = H
3h : R_1 = OPr, R_2 = H

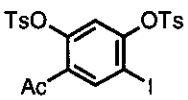
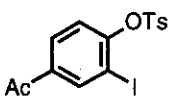
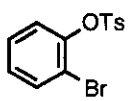
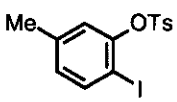
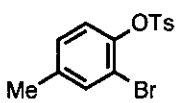
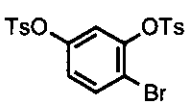
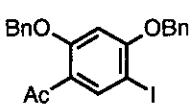
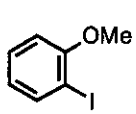
Scheme 1

corresponding benzofurans. We report here on the short step syntheses of euparin[6] (**4a**) and related benzofurans (**4b-e** and **4g**) from *o*-alkynylphenyl tosylates (**2**) through 2-(1-hydroxy-1-methylethyl)benzofurans (**3**), which are of great importance as precursors of 2,3-dihydrobenzofuran derivatives, and the conversion of 2-(1-bromo-1-methylethyl)benzofurans (**5g** and **5h**) into 2,2-dimethylchromenes (**6g** and **6h**).

Iodophenols were synthesized from the corresponding phenols with iodine in the presence of silver trifluoroacetate in chloroform.[7] 4'-Hydroxy-3'-iodoacetophenone was synthesized by sodium iodide-sodium hypochlorite method.[8] *o*-Halophenols were converted into *o*-halophenyl tosylates (**1**) with tosyl chloride in the presence of K_2CO_3 in acetone.

The coupling reaction of *o*-halophenyl tosylates (**1**) with 2-methyl-3-butyn-2-ol in the presence of Pd(0) in

Table 1. Synthesis of *o*-Alkynylphenyl Tosylates (**2**)

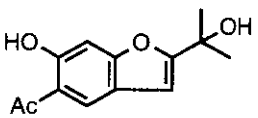
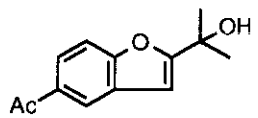
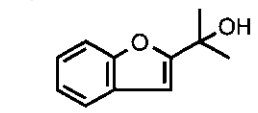
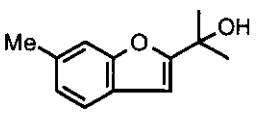
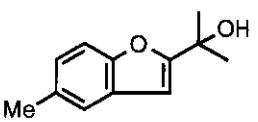
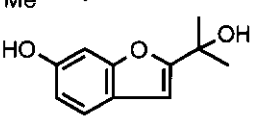
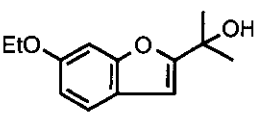
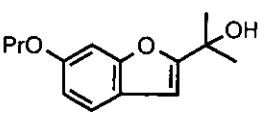
Entry	Phenol		React. cond.		Product (Yield %)	
1	**1a**		80°C	0.8 h	**2a**	97
2	**1b**		85°C	0.8 h	**2b**	90
3	**1c**		85°C	9 h	**2c**	78
4	**1d**		85°C	0.5 h	**2d**	95
5	**1e**		85°C	23 h	**2e**	94
6	**1f**		85°C	5 h	**2f**	95
7	**1g**		85°C	0.8 h	**2g**	90
8	**1h**		50°C	1.5 h	**2h**	98

NEt3-DMF under N_2 under appropriate conditions afforded the desired *o*-alkynylphenyl tosylates (**2**) in high yields (Scheme 1 and Table 1). However, the coupling reaction of *o*-bromophenyl tosylates (Entries 3, 5, and 6) took up much more time than that of *o*-iodophenyl tosylates (Table 1).

o-Alkynylphenyl tosylates (**2**), when were refluxed with bases in alcohols under N_2 in the oil bath, underwent cyclization to give the corresponding 2-(1-hydroxy-1-methylethyl)benzofurans (**3**) in high yields (Scheme 1 and Table 2). 2-(1-Hydroxy-1-methylethyl)benzofurans (**3**) are greatly useful as synthetic intermediates of 2-(1-hydroxy-1-methylethyl)-2,3-dihydrobenzofurans,[9,10] racemic dihydrotremetone,[10,11] 2-isopropenyl-2,3-dihydrobenzofurans,[9,12] and 2-isopropylbenzofurans.[9,11,12]

The reaction of **2f** with K_2CO_3 in methanol at 75 °C gave 6-hydroxybenzofuran (**3f**) in 34% yield, but 2-(1-hydroxy-1-methylethyl)-6-methoxybenzofuran was not obtained. On the other hand, cyclization of **2f** with

Table 2. Synthesis of 2-(1-Hydroxyalkyl)benzofurans (**3**)

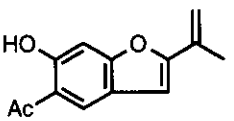
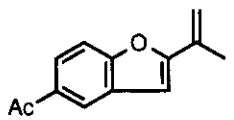
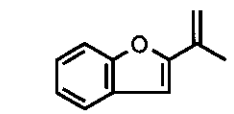
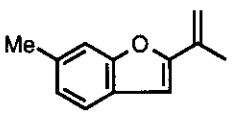
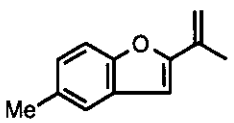
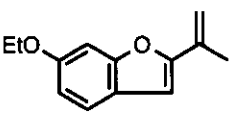
Entry	Substrate	Base (equiv.)	Solvent (reflux)	Time (h)	Product (Yield %)		
1	**2a**	K_2CO_3 (50)	MeOH	0.8	**3a**	88	
2	**2b**	K_2CO_3 (30)	EtOH	1.5	**3b**	91	
3	**2c**	KOH (10)	MeOH	4	**3c**	84	
4	**2d**	KOH (10)	EtOH	4.5	**3d**	79	
5	**2e**	KOH (10)	EtOH	3.5	**3e**	88	
6	**2f**	K_2CO_3 (20)	MeOH	23	**3f**	34	
7	**2f**	K_2CO_3 (20)	EtOH	28	**3g**	66	
8	**2f**	K_2CO_3 (30)	PrOH	23	**3h**	72	

K_2CO_3 in ethanol or propanol at temperatures of more than 90 °C gave 6-ethoxy- or 6-propoxybenzofuran (**3g** or **3h**) in good yield, and 6-hydroxybenzofuran (**3f**) was not obtained. These facts suggest that **3g** or **3h** would be produced by the reaction of TsOEt or TsOPr with the phenoxy anion of **3f** at higher temperatures than 90 °C. Therefore, a 3:1 mixture of **3g** and 2-(1-hydroxy-1-methylethyl)-6-methoxybenzofuran, which was identified by its ^{1}H nmr (60 MHz) spectrum [peaks due to $OC\underline{H}_2CH_3$ at δ 4.05 (2H, q, J=7 Hz) and OCH_3 at δ 3.82 (3H, s)], was obtained upon treatment of **2f** with K_2CO_3 in the presence of TsOMe (2 equiv. to **2f**) in ethanol at 90 °C for 13 h. These results show that the displacement reaction of the formed TsOEt or TsOPr with the phenoxy anion of **3f** proceeds by a type of S_N2 reaction.

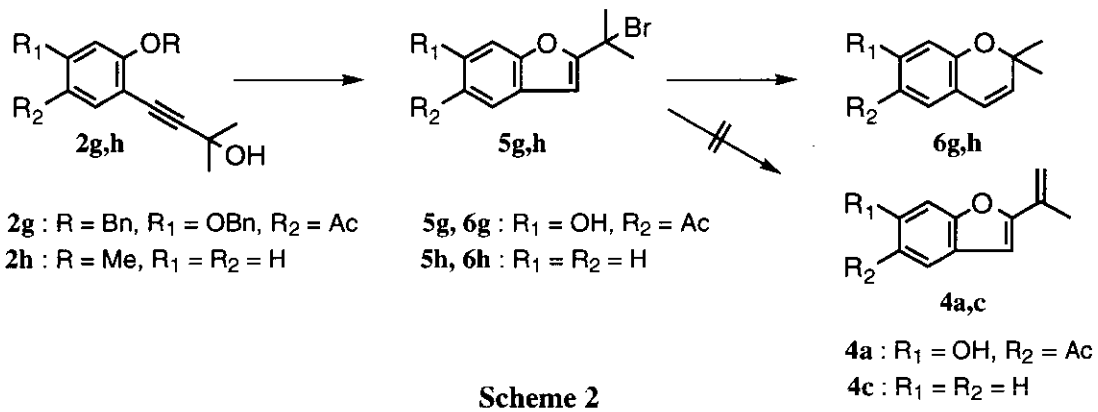
Dehydration of 2-(1-hydroxy-1-methylethyl)benzofurans (**3**) with acids gave the corresponding 2-isopropenylbenzofurans (**4**) in high yields (Scheme 1 and Table 3). 6-Ethoxybenzofuran (**4g**) alone was obtained in 50% yield. In this dehydration, hydrobromic acid is more useful than other acids as a dehydrating agent.

It is considered that *o*-alkynylphenyl alkyl ethers also would be converted into the corresponding benzofurans by treatment with BBr_3, and synthetic methods of benzofuran derivatives seem to be extended further. Thus, the reaction of *o*-alkynylphenyl alkyl ethers (**2g** and **2h**) with BBr_3 in CH_2Cl_2 for 5 min at 0°C underwent cyclization and simultaneous bromination to give 2-(1-bromo-1-methylethyl)benzofurans (**5g** and **5h**) in

Table 3. Synthesis of 2-Isopropenylbenzofurans (**4**)

Entry	Substrate	Acid (equiv.)	React. cond.		Product (Yield %)		
1	**3a**	BBr_3 (1.3)	-70°C	5 min	**4a**	82	
2	**3b**	HBr (5)	room temp.	30 min	**4b**	90	
3	**3c**	*p*-TsOH (0.1)	120°C	15 min	**4c**	81	
4	**3d**	HBr (0.3)	room temp.	25 min	**4d**	93	
5	**3e**	HBr (0.3)	room temp.	30 min	**4e**	85	
6	**3g**	HBr (0.3)	0°C	25 min	**4g**	50	

moderate yields, respectively (Scheme 2 and Table 4), but 2-(1-hydroxy-1-methylethyl)benzofurans (**3a** and **3c**) were not obtained. The crude benzofurans (**5g** and **5h**), when were refluxed in the presence of KOH in methanol and ethanol, were converted into the unexpected 2,2-dimethylchromenes (**6g** and **6h**) in good yields (Scheme 2 and Table 4). In this reaction, 2-isopropenylbenzofurans (**4a** and **4c**) were not obtained. The ring-expansion reaction of 2-(1-bromo-1-methylethyl)benzofurans (**5g** and **5h**) with KOH in ethanol is a new synthesis of benzopyrans from halobenzofurans. Studies on the reaction mechanism are in progress and will be reported in due course.



2g : R = Bn, R_1 = OBn, R_2 = Ac
2h : R = Me, R_1 = R_2 = H

5g, 6g : R_1 = OH, R_2 = Ac
5h, 6h : R_1 = R_2 = H

4a : R_1 = OH, R_2 = Ac
4c : R_1 = R_2 = H

Scheme 2

Table 4. Synthesis of 2-(1-Bromoalkyl)benzofurans (**5g,h**) and Chromenes (**6g,h**)

Entry	Substrate	Benzofuran	(Yield %)	Base (equiv.)	Time (h)	Chromene	(Yield %)
1	**2g**	**5g**	64	KOH (50)	1	**6g**	95
2	**2h**	**5h**	54	KOH (30)	4	**6h**	63

EXPERIMENTAL

All the melting points are uncorrected. The ^{1}H nmr spectra were measured with a Hitachi R-24B spectrometer (60 MHz), using tetramethylsilane as an internal standard (δ, ppm). Column chromatography and thin-layer chromatography were carried out on Kieselgel 60 (70-230 mesh) and with Kieselgel 60 F-254 (Merck).

General Procedure for Iodination. (A) **Iodine-Silver Trifluoroacetate Method**: The phenol (0.1 mol) was added to a stirred suspension of silver trifluoroacetate (22 g, 0.1 mol) in dry chloroform (200 ml). To the suspension, was added a solution of iodine (25 g, 0.1 mol) in dry chloroform (800 ml) dropwise with stirring over a period of 1 h at 20-25 °C. The mixture was filtered and the separated silver iodide was washed with

chloroform. The filtrate was washed with 5% aqueous $Na_2S_2O_3$, 5% aqueous $NaHCO_3$, and water, and dried (Na_2SO_4). The resulting compound was purified by silica gel column chromatography.

2',4'-Bis(benzyloxy)-5'-iodoacetophenone (1g). Compound (**1g**) was prepared from 2',4'-bis(benzyloxy)acetophenone (9.97 g, 30 mmol) as described above and recrystallized from acetone as colorless needles (12.2 g, 89% yield), mp 152-153 °C. ^{1}H Nmr ($CDCl_3$): δ 2.49 (3H, s, CH_3CO), 5.03 and 5.06 (each 2H, s, PhC$\underline{H}_2$), 6.40 (1H, s, C_3-H), 7.32 (10H, s, C_6H_5 x 2), 8.20 (1H, s, C_6-H). Anal. Calcd for $C_{22}H_{19}O_3I$: C, 57.66; H, 4.18. Found: C, 57.89; H, 4.21.

2',4'-Dihydroxy-5'-iodoacetophenone. To a solution of **1g** (4.60 g, 10 mmol) in CH_2Cl_2 (200 ml), was added a solution of BBr_3-CH_2Cl_2 (20 ml, 2.6 equiv.) [BBr_3 (25 ml) had been dissolved in CH_2Cl_2 (175 ml)] with stirring at -70 °C and the reaction mixture was stirred at that temperature for 5 min, and then water was added. After the aqueous mixture was stirred for 1 h, the solvent was removed at below 40 °C under reduced pressure. The residue was extracted with AcOEt, and the extract was washed with 5% aqueous $NaHCO_3$ and water, and dried (Na_2SO_4). The resulting compound was crystallized from hexane as pale yellow needles (2.70 g, 97%), mp 180-181 °C. ^{1}H Nmr (DMSO): δ 2.50 (3H, s, CH_3CO), 6.32 (1H, s, C_3-H), 8.02 (1H, s, C_6-H), 12.24 (1H, s, OH). Anal. Calcd for $C_8H_7O_3I$: C, 34.56; H, 2.54. Found; C, 34.80; H, 2.61.

2-Iodo-5-methylphenol. 2-Iodo-5-methylphenol was prepared from *m*-cresol (11 g, 0.1 mol) as described above and purified by column chromatography (CCl_4-AcOEt=10:1) to give a pale brown oil (11 g, 47%). ^{1}H Nmr ($CDCl_3$): δ 2.29 (3H, s, CH_3), 5.22 (1H, s, OH), 6.48 (1H, dd, J=2, 8 Hz, C_4-H), 6.81 (1H, d, J=2 Hz, C_6-H), 7.48 (1H, d, J=8 Hz, C_3-H).

(B) **Sodium Iodide-Sodium Hypochlorite Method: 3'-Iodo-4'-hydroxyacetophenone.** To a solution of 4'-hydroxyacetophenone (4.0 g, 29.4 mmol) and sodium iodide (5.28 g, 35.2 mmol) in MeOH (80 ml), was added 5% aqueous NaOCl (44 ml, 29.4 mmol) gradually with stirring over a period of 20 min at 15 °C and then stirred for further 1 h. To the reaction mixture was added 10% aqueous $Na_2S_2O_3$ (25 ml), and the mixture was neutralized with 2% aqueous HCl to give precipitates. MeOH in the mixture was evaporated under reduced pressure, and the residue was allowed to stand at room temperature for a while. The resulting precipitates were separated by filtration and washed with water, and dried. The crude precipitates (6.07 g) were a 4:1 mixture of 3'-iodo- and 3',5'-diiodo-4'-hydroxyacetophenones by ^{1}H nmr (400 MHz) analysis. To a solution of the precipitates (6.07 g) in THF (5 ml), was added CCl_4 (60 ml) to give precipitates. The collected precipitates by filtration were 3'-iodoacetophenone (3.85 g), and after removal of the solvent from the filtration, the residue was chromatographed over a silica gel column ($CHCl_3$-Me_2CO=20:1) to give 3'-iodoacetophenone (0.78 g). The total yield of 3'-iodo-4'-hydroxyacetophenone (4.63 g) was 60%, mp 155-156 °C, colorless needles. ^{1}H Nmr (DMSO): δ 2.49 (3H, s, CH_3CO), 6.91 (1H, d, J=8 Hz, C_5-H), 7.80 (1H, dd, J=2, 8 Hz, C_6-H), 8.20 (1H, d, J=2 Hz, C_2-H), 11.40 (1H, s, OH). Anal. Calcd for $C_8H_7O_2I$: C, 36.67; H, 2.69. Found: C, 36.59; H, 2.71.

5'-Iodo-2',4'-bis(tosyloxy)acetophenone (1a). A mixture of 2',4'-dihydroxy-5'-iodoacetophenone (3.5 g, 12.5 mmol), TsCl (7.5 g, 39 mmol), and K_2CO_3 (15 g, 108 mmol) in acetone (150 ml) was refluxed with stirring under N_2 for 45 min. The resulting compound was recrystallized from MeOH to give **1a** (6.25 g, 85%) as colorless needles, mp 108-109 °C. ^{1}H Nmr ($CDCl_3$): δ 2.45 (6H, s, PhC$\underline{H}_3$ x 2), 2.50 (3H, s,

CH_3CO), 7.07 (1H, s, C_3-H), 7.32-7.71 (8H, m, $C_6\underline{H}_4SO_2$ x 2), 7.96 (1H, s, C_6-H). Anal. Calcd for $C_{22}H_{19}O_7IS_2$: C, 45.06; H, 3.27. Found: C, 45.06; H, 3.16.

3'-Iodo-4'-tosyloxyacetophenone (1b). A mixture of 3'-iodo-4'-hydroxyacetophenone (5.3 g, 20 mmol), TsCl (5.72 g, 30 mmol), and K_2CO_3 (11.3 g, 81 mmol) in acetone (80 ml) was refluxed for 40 min as described above to give **1b** (7.34 g, 87%) as colorless needles (from MeOH), mp 86.5-88 °C. ^{1}H Nmr ($CDCl_3$): δ 2.44 (3H, s, CH_3CO), 2.44 (3H, s, $PhC\underline{H}_3$), 7.16-7.38, 7.62-7.75 (each 2H, m, Ar-H x 2), 7.33 (1H, d, J=8 Hz, C_5-H), 7.83 (1H, dd, J=2, 8 Hz, C_6-H), 8.23 (1H, d, J=2 Hz, C_2-H). Anal. Calcd for $C_{15}H_{13}O_4IS$: C, 43.28; H, 3.15. Found: C, 43.01; H, 3.14.

2-Tosyloxybromobenzene (1c). A mixture of *o*-bromophenol (13 g, 75 mmol), TsCl (17.2 g, 90 mmol), and K_2CO_3 (20 g, 150 mmol) in acetone (200 ml) was refluxed for 20 min as described above to give **1c** (22.2 g, 91%) as colorless prisms (from MeOH), mp 70-73 °C. Anal. Calcd for $C_{13}H_{11}O_3BrS$: C, 47.72; H, 3.39. Found: C, 47.82; H, 3.39.

4-Methyl-2-tosyloxyiodobenzene (1d). A mixture of 2-iodo-5-methylphenol (7 g, 30 mmol), TsCl (6.3 g, 33 mmol), and K_2CO_3 (5 g, 36 mmol) in acetone (150 ml) was refluxed for 45 min to give **1d** (7.6 g, 66%) as colorless needles (from MeOH), mp 94-96 °C. Anal. Calcd for $C_{14}H_{13}O_3IS$: C, 43.31; H, 3.38. Found: C, 43.08; H, 3.32.

5-Methyl-2-tosyloxybromobenzene (1e). A mixture of 2-bromo-4-methylphenol (9.36 g, 50 mmol), TsCl (9.63 g, 51 mmol), and K_2CO_3 (8.3 g, 60 mmol) in acetone (200 ml) was refluxed for 20 min to give **1e** (13.7 g, 80%) as colorless plates (from MeOH), mp 115-116 °C. ^{1}H Nmr ($CDCl_3$): δ 2.30 and 2.47 (each 3H, s, $PhC\underline{H}_3$), 6.93-7.48 (5H, m, Ar-H x 5), 7.58-7.92 (2H, m, Ar-H x 2). Anal. Calcd for $C_{14}H_{13}O_3BrS$: C, 49.28; H, 3.84. Found: C, 49.07; H, 3.71.

2,4-Bis(tosyloxy)bromobenzene (1f). A mixture of 4-bromoresorcinol (6 g, 31.7 mmol), TsCl (12.7 g, 67 mmol), and K_2CO_3 (13.1 g, 95 mmol) in acetone (80 ml) was refluxed for 1 h to give **1f** (14.1 g, 89%) as colorless needles (from Et_2O), mp 80.5-81.5 °C. ^{1}H Nmr ($CDCl_3$): δ 2.41 (6H, s, $PhC\underline{H}_3$ x 2), 6.71 (1H, dd, J=2, 8 Hz, C_5-H), 6.90 (1H, d, J=2 Hz, C_3-H), 7.08-7.77 (9H, m, Ar-H x 9). Anal. Calcd for $C_{20}H_{17}O_6BrS_2$: C, 48.30; H, 3.45. Found: C, 48.50; H, 3.70.

General Procedure for Coupling Reaction of *o*-Halogenophenols (1) with 2-Methyl-3-butyn-2-ol. To a solution of *o*-halophenol (**1**) (40 mmol) and 2-methyl-3-butyn-2-ol (10.1 g, 120 mmol) in a mixture of NEt_3 (150 ml)-DMF (50 ml) was added $PdCl_2$ (3 mol%, 1.2 mmol), PPh_3 (6 mol%, 2.4 mmol), and CuI (3 mol%, 1.2 mmol). The mixture solution was stirred under N_2 for 0.5-23 h at 50-85 °C until completion of reaction by tlc. The reaction mixture was filtered through charcoal to remove the catalyst. The filtrate was concentrated under reduced pressure and then extracted with AcOEt, and the extract was washed with 2% aqueous HCl and water, and dried (Na_2SO_4). The resulting compound was purified by silica gel column chromatography.

5'-(3-Hydroxy-3-methylbutynyl)-2',4'-bis(tosyloxy)acetophenone (2a). Mp 75-77°C, pale yellow needles (from hexane), ($CHCl_3$-Me_2CO=5:1 as a solvent for chromatography). ^{1}H Nmr ($CDCl_3$): δ 1.54 (6H, s, CH_3 x 2), 2.49 (9H, s, CH_3CO and $PhC\underline{H}_3$ x 2), 7.06 (1H, s, C_3-H), 7.35-7.73 (8H, m, $C_6\underline{H}_4SO_2$ x 2), 7.87 (1H, s, C_6-H). Anal. Calcd for $C_{27}H_{26}O_8S_2$: C, 59.77; H, 4.83. Found: C, 59.95; H, 4.86.

3'-(3-Hydroxy-3-methylbutynyl)-4'-tosyloxyacetophenone (2b). Mp 100-101 °C, colorless needles (from CCl_4), ($CHCl_3$-Me_2CO=10:1 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 1.54 (6H, s, CH_3 x 2), 2.43 (3H, s, PhC<u>H</u>3), 2.54 (3H, s, CH_3CO), 7.11-7.42 (3H, m, Ar-H x 3), 7.57-8.03 (4H, m, Ar-H x 4). Anal. Calcd for $C_{20}H_{20}O_5S$: C, 64.50; H, 5.41. Found: C, 64.37; H, 5.17.

1-(3-Hydroxy-3-methylbutynyl)-2-tosyloxybenzene (2c). A pale brown oil ($CHCl_3$-Me_2CO=30:1 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 1.54 (6H, s, CH_3 x 2), 2.41 (3H, s, PhC<u>H</u>3), 2.51 (1H, s, OH), 7.01-7.43 (6H, m, Ar-H x 6), 7.56-7.84 (2H, m, Ar-H x 2). Anal. Calcd for $C_{18}H_{18}O_4S$: C, 65.44; H, 5.49. Found: C, 65.17; H, 5.43.

1-(3-Hydroxy-3-methylbutynyl)-4-methyl-2-tosyloxybenzene (2d). A pale brown paste (hexane-AcOEt=2:1 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 1.55 (6H, s, CH_3 x 2), 2.33 and 2.45 (each 3H, s, PhC<u>H</u>3), 6.80-7.41 (5H, m, Ar-H x 5), 7.57-7.89 (m, 2H, Ar-H x 2). Anal. Calcd for $C_{19}H_{20}O_4S$: C, 66.26; H, 5.85. Found: C, 66.08; H, 6.06.

1-(3-Hydroxy-3-methylbutynyl)-5-methyl-2-tosyloxybenzene (2e). A pale brown paste (hexane-AcOEt=2:1 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 1.54 (6H, s, CH_3 x 2), 2.24 (1H, br s, OH), 2.30 and 2.45 (each 3H, s, PhC<u>H</u>3), 7.02-7.45 (5H, m, Ar-H x 5), 7.69-7.92 (2H, m, Ar-H x 2). Anal. Calcd for $C_{19}H_{20}O_4S$: C, 66.26; H, 5.85. Found: C, 66.21; H, 5.96.

1-(3-Hydroxy-3-methylbutynyl)-2,4-bis(tosyloxy)benzene (2f). A brown paste (CCl_4-AcOEt=3:1 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 1.46 (6H, s, CH_3 x 2), 2.36 (6H, s, PhC<u>H</u>3 x 2), 2.43 (1H, s, OH), 6.70-6.97 (2H, m, C_3- and C_5-H), 7.16-7.50 (5H, m, Ar-H, x 5), 7.57-7.85 (4H, m, Ar-H x 4). Anal. Calcd for $C_{25}H_{24}O_7S_2$: C, 59.99; H, 4.83. Found: C, 59.74; H, 5.10.

2',4'-Bis(benzyloxy)-5'-(3-hydroxy-3-methylbutynyl)acetophenone (2g). Mp 123-124 °C, colorless needles (from MeOH). ^1H Nmr ($CDCl_3$): δ 1.50 (1H, s, OH), 1.57 (6H, s, CH_3 x 2), 2.50 (3H, s, CH_3CO), 5.09 (4H, s, PhC<u>H</u>2 x 2), 6.45 (1H, s, C_3-H), 7.34 (10H, s, C_6<u>H</u>$_5CH_2$ x 2), 7.88 (1H, s, C_6-H). Anal. Calcd for $C_{27}H_{26}O_4$: C, 78.24; H, 6.32. Found: C, 78.43; H, 6.42.

1-(3-Hydroxy-3-methylbutynyl)-2-methoxybenzene (2h). A brown oil (hexane-AcOEt=3:1 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 1.60 (6H, s, CH_3 x 2), 2.82 (1H, s, OH), 3.82 (3H, s, OCH_3), 6.63-7.42 (4H, m, Ar-H x 4). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.49; H, 7.55.

General Synthesis of Benzofurans (3) from *o*-Alkynylphenyl Tosylates (2). A mixture of *o*-alkynylphenyl tosylates (**2**) (20 mmol) and KOH or K_2CO_3 (10-50 equiv) in MeOH, EtOH or PrOH (150 ml) was refluxed with stirring under N_2 for 0.8-28 h at 75-105 °C in the oil bath. After removal of K_2CO_3, the reaction mixture was diluted with water, extracted with ether, and the extract was washed with 2% aqueous HCl and water, and dried (Na_2SO_4). The resulting compound was purified by silica gel column chromatography to give benzofurans (**3**).

5-Acetyl-6-hydroxy-2-(1-hydroxy-1-methylethyl)benzofuran (3a). Mp 107-108°C, pale yellow needles (from CCl_4), (hexane-AcOEt=1:1 as a solvent for chromatography). ^1H Nmr($CDCl_3$): δ 1.50 (1H, s, OH), 1.65 (6H, s, CH_3 x 2), 2.63 (3H, s, CH_3CO), 6.45 (1H, s, C_3-H), 6.92 (1H, s, C_7-H), 7.82 (1H, s, C_4-H), 12.37 (1H, s, C_6-OH). Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.45; H, 5.97.

5-Acetyl-2-(1-hydroxy-1-methylethyl)benzofuran (3b). Mp 72-73°C, colorless needles (from petroleum ether), ($CHCl_3$-Me_2CO=10:1 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 1.67 (6H, s, CH_3 x 2), 2.59 (3H, s, CH_3CO), 2.71 (1H, s, OH), 6.60 (1H, s, C_3-H), 7.37(1H, d, J=8 Hz, C_7-H), 7.81 (1H, dd, J=2, 8 Hz, C_6-H), 8.05 (1H, J=2 Hz, C_4-H). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.26; H, 6.41.

2-(1-Hydroxy-1-methylethyl)benzofuran (3c). A pale brown oil (CH_2Cl_2 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 1.62 (6H, s, CH_3 x 2), 2.99 (1H, s, OH), 6.45 (1H, s, C_3-H), 7.00-7.55 (4H, m, Ar-H x 4). Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Calcd for C, 74.72; H, 6.74.

2-(1-Hydroxy-1-methylethyl)-6-methylbenzofuran (3d). A pale brown oil (hexane-AcOEt=3:1 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 1.65 (6H, s, CH_3 x 2), 2.29 (1H, s, OH), 2.45 (3H, s, PhC<u>H</u>3), 6.48 (1H, s, C_3-H), 6.99 (1H, dd, J=2, 8 Hz, C_5-H), 7.23 (1H, d, J=2 Hz, C_7-H), 7.37 (1H, d, J=8 Hz, C_4-H). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.56; H, 7.24.

2-(1-Hydroxy-1-methylethyl)-5-methylbenzofuran (3e). A pale brown paste (hexane-AcOEt=2:1 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 1.63 (6H, s, CH_3 x 2), 2.25 (1H, s, OH), 2.41 (3H, s, PhC<u>H</u>3), 6.47 (1H, s, C_3-H), 7.02 (1H, dd, J=2, 8 Hz, C_6-H), 7.29 (1H, d, J=2 Hz, C_4-H), 7.32 (1H, d, J=8 Hz, C_7-H). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.57; H, 7.50.

6-Hydroxy-2-(1-hydroxy-1-methylethyl)benzofuran (3f). Mp 123-124 °C, pale brown needles (from $CHCl_3$), ($CHCl_3$-Me_2CO=5:1 as a solvent for chromatography). ^1H Nmr[$(CD_3)_2CO$]: δ 1.57 (6H, s, CH_3 x 2), 4.25 (1H, s, C_6-OH), 6.42 (1H, s, C_3-H), 6.67 (1H, dd, J=2, 8 Hz, C_5-H), 6.83 (1H, d, J=2 Hz, C_7-H), 7.22 (1H, d, J=8 Hz, C4-H). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.73; H, 6.27.

6-Ethoxy-2-(1-hydroxy-1-methylethyl)benzofuran (3g). A pale brown paste ($CHCl_3$-Me_2CO=20:1 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 1.37 (3H, t, J=7 Hz, CH_3), 1.60 (6H, s, CH_3 x 2), 2.56 (1H, s, OH), 3.95 (2H, q, J=7 Hz, OCH_2), 6.45 (1H, s, C_3-H), 6.70 (1H, dd, J=2, 8 Hz, C_5-H), 6.88 (1H, d, J=2 Hz, C_7-H), 7.23 (1H, d, J=8 Hz, C_4-H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.69; H, 7.14.

2-(1-Hydroxy-1-methylethyl)-6-propoxybenzofuran (3h). Mp 41-42°C, brown needles (*$CHCl_3$:Me_2CO=20:1 as a solvent for chromatography*). ^1H Nmr ($CDCl_3$): δ 0.99 (3H, t, J=7 Hz, CH_2C<u>H</u>3), 1.57 (6H, s, CH_3 x 2), 1.87 (2H, q, J=7 Hz, OCH_2), 2.80 (1H, s, OH), 3.83 (2H, t, J=7 Hz, C<u>H</u>2CH3), 6.34 (1H, s, C_3-H), 6.72 (1H, dd, J=2, 8 Hz, C_5-H), 6.87 (1H, d, J=8 Hz, C_4-H), 7.37 (1H, d, J=2 Hz, C_7-H). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77: H, 7.74. Found: C, 71.55; H, 7.84.

Reation of 2f with K_2CO_3 in the presence of TsOMe. A *mixture of* **2f** (260 mg, 0.52 mmol), TsOMe (210 mg, 1.15 mmol), and K_2CO_3 (2.16 g, 15.6 mmol) in EtOH (25 ml) was refluxed with stirring under N_2 for 13 h at 90 °C in the oil bath. The resulting compound was chromatographed over a silica gel column with CCl_4-AcOEt (3:1) to give a pale brown paste (50 mg), which was identified to be a 3:1 mixture of **3g** and 2-(1-hydroxy-1-methylethyl)-6-methoxybenzofuran by its ^1H nmr analysis.

General Procedure for Dehydration of Benzofurans (3). (A) **Dehydration of 3a with BBr_3: 5-Acetyl-6-hydroxy-2-isopropenylbenzofuran (Euparin)**[3,6] **(4a):** To a solution of **3a** (120 mg, 0.51 mmol) in dry CH_2Cl_2 (10 ml) was added BBr_3 (1.3 mol in CH_2Cl_2) (0.5 ml, 0.66 mmol) with stirring at -70°C. After the reaction mixture was stirred for 5 min at -70 °C, water was added to it. The mixture was extracted with

CH_2Cl_2, and the extract was washed with 5% aqueous $NaHCO_3$ and water, and dried (Na_2SO_4). The resulting compound was purified by silica gel chromatography with $CHCl_3$ to give **4a** as pale yellow needles, mp 119-120 °C (lit.,[3] 118-120 °C).

2-Isopropenylbenzofuran (4c). A mixture of **3c** (360 mg, 2 mmol) and $TsOH \cdot H_2O$ (40 mg, 0.2 mmol) in toluene (20 ml) was refluxed for 15 min at 120 °C. The reaction mixture was extracted with ether, and the extract was washed with 5% aqueous $NaHCO_3$ and water, and dried (Na_2SO_4). The resulting compound was purified by silica gel column chromatography (CCl_4-hexane=1:1) to give **4c** as a colorless oil (260 mg). ^1H Nmr ($CDCl_3$): δ 2.10 (3H, s, CH_3), 5.12 and 5.74 (each 1H, s, $=CH_2$), 6.54 (1H, s, C3-H), 7.01-7.60 (4H, m, Ar-H x 4). Anal. Calcd for $C_{11}H_{10}O$: C, 83.52; H, 6.37. Found: C, 83.27; H, 6.60.

(B) **Dehydration of 3b-g with HBr**: A mixture of **3b-g** (1 mmol) and 47% HBr (0.58 ml, 5 mmol) in CH_2Cl_2 (30 ml) was stirred for 30 min at 0 °C–room temperature. The reaction mixture was extracted with CH_2Cl_2, and the extract was washed with 5% aqueous $NaHCO_3$ and water, and dried (Na_2SO_4). The resulting compound was purified by silica gel column chromatography.

5-Acetyl-2-isopropenylbenzofuran[2,3] **(4b).** Mp 83-84 °C (lit.,[3] 82.5-83.5 °C), colorless needles (from petroleum ether), (hexane-AcOEt=3:1 as a solvent for chromatography).

6-Methyl-2-isopropenylbenzofuran (4d). An unstable colorless oil (hexane-$CHCl_3$=5:1 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 2.11 (3H, s, CH_3), 2.46 (3H, s, Ar-C<u>H</u>3), 5.12 and 5.76 (each 1H, s, $=CH_2$), 6.56 (1H, s, C3-H), 6.98 (1H, dd, J=2, 8 Hz, C5-H), 7.21 (1H, d, J=2 Hz, C7-H), 7.38 (1H, d, J=8 Hz, C4-H).

5-Methyl-2-isopropenylbenzofuran (4e). Mp 46-48°C, colorless needles (hexane-$CHCl_3$=5:1 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 2.10 (3H, s, CH_3), 2.40 (3H, s, Ar-C<u>H</u>3), 5.13 and 5.77 (each 1H, s, $=CH_2$), 6.54 (1H, s, C3-H), 7.02 (1H, dd, J=2, 8 Hz, C6-H), 7.30 (1H, d, J=2 Hz, C4-H), 7.32 (1H, d, J=8 Hz, C7-H). Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.54; H, 7.03.

6-Ethoxy-2-isopropenylbenzofuran (4g). An unstable colorless oil ($CHCl_3$-hexane=1:1 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 1.38 (3H, t, J=7 Hz, OCH_2C<u>H</u>3), 2.06 (3H, s, CH_3), 3.97 (2H, q, J=7 Hz, O<u>C</u>H2CH3), 5.03 and5.67 (each 1H, s, $=CH_2$), 6.47 (1H, s, C3-H), 6.74 (1H, dd, J=2, 8 Hz, C5-H), 6.90 (1H, d, J=2 Hz, C7-H), 7.29 (1H, d, J=8 Hz, C4-H).

5-Acetyl-6-hydroxy-2-(1-bromo-1-methylethyl)benzofuran (5g). To a solution of **2g** (2.9 g, 7 mmol) in CH_2Cl_2 (150 ml), was added BBr_3-CH_2Cl_2 (21 ml, 27.3 mmol) at 0 °C and stirred for 10 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with 5% aqueous $NaHCO_3$ and water, and dried (Na_2SO_4). The resulting compound was chromatographed over a silica gel column with $CHCl_3$ to give **5g** (1.33 g, 64%) as pale yellow needles, mp 143-144 °C. ^1H Nmr ($CDCl_3$): δ 1.45 (6H, s, CH_3 x 2), 2.56 (3H, s, CH_3CO), 5.90 (1H, s, C3-H), 6.27 (1H, s, C7-H), 7.67(1H, s, C4-H), 12.67 (1H, s, C6-OH). Anal. Calcd for $C_{13}H_{13}O_3Br$: C, 52.55; H, 4.41. Found: C, 52.36; H, 4.32.

2-(1-Bromo-1-methylethyl)benzofuran (5h). Compound (**5h**) was prepared from **2h** (1.9 g, 10 mmol) in the similar manner as described above as a pale yellow oil (1.3 g, 54% yield), (hexane-$CHCl_3$=5:1 as a solvent for chromatography). ^1H Nmr ($CDCl_3$): δ 1.42 (6H, s, CH_3 x 2), 5.90 (1H, s, C3-H), 6.55-7.42 (4H, m, Ar-H x 4). Anal. Calcd for $C_{11}H_{11}OBr$: C, 55.25; H, 4.64. Found: C, 55.20; H, 4.62.

Ring Expansion of 2-(1-Bromo-1-methylethyl)benzofurans (5g and 5h) to 2,2-Dimethylchromenes (6g and 6h). 6-Acetyl-7-hydroxy-2,2-dimethylchromene (6g). To a solution of crude **5g** (60 mg, 0.2 mmol) in MeOH (20 ml), was added 30% aqueous KOH (1.9 ml, 10 mmol) under N_2 and the mixture was refluxed with stirring for 1 h at 75 °C. After addition of water and 6% aqueous HCl to the reaction mixture, MeOH was evaporated under reduced pressure. The residue was extracted with AcOEt, and the extract was washed with water, and dried (Na_2SO_4). The resulting compound was chromatographed over a silica gel column with $CHCl_3$ to give **6g** (42 mg, 95%) as pale yellow needles, mp 73-75 °C. ^1H Nmr ($CDCl_3$): δ 1.40 (6H, s, CH_3 x 2), 2.48 (3H, s, $COCH_3$), 5.50 and 6.21 (each 1H, d, J=10 Hz, C_3- and C_4-H), 6.25 (1H, s, C_8-H), 7.22 (1H, s, C_5-H), 12.62 (1H, s, OH). Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.28; H, 6.35.

2,2-Dimethylchromene (6h). To a solution of crude **5h** (0.4 g, 1.7 mmol) in EtOH (20 ml), was added 30% aqueous KOH (9.4 ml, 50 mmol) under N_2 and the mixture was refluxed with stirring for 4 h at 90 °C. The resulting compound was chromatographed over a silica gel column with hexane-$CHCl_3$ (1:1) to give **6h** (0.17 g, 63%) as a colorless oil. ^1H Nmr ($CDCl_3$): δ 1.40 (6H, s, CH_3 x 2), 5.53 and 6.23 (each 1H, d, J=10 Hz, C_3- and C_4-H), 6.53-7.21 (4H, m, Ar-H x 4). Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.33; H, 7.60.

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