BENZOFURANS AND STEROL FROM THE SEEDS OF *Styrax obassia*

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*Two benzofurans (**1**, **2**) along with five known compounds (**3**–**7**) were isolated from the seeds of* S. obassia. *Their structures were elucidated as methyl 3-[7-methoxy-2-(3′,4′-methylenedioxyphenyl)-5-benzofuranyl]-propionate (**1**), methyl 3-[2-(3′,4′-methylenedioxyphenyl)-5-benzofuranyl]-propionate (**2**), egonol (**3**), egonolacetate (**4**), egonol-2-methylbutanoate (**5**), 7-demethoxyegonol-2-methylbutanoate (**6**), and stigmasterol (**7**) on the basis of their comprehensive spectroscopic analysis including 2D NMR data. Compounds **1**, **2** are obtained for the first time from nature, while this is the first record of compound **7** from the* Styrax *species.*

Key words: *Styrax obassia*, Styracaceae, benzofuran, sterol.

Styrax obassia, also known as 'fragrant snowbell', is a member of the Styracaceae family. It is a shrub or tree native to tropical and subtropical regions, with the majority in eastern and southern Asia [1, 2]. The genus *Styrax* is different from other genera of this family due to the production of resinous material, usually secreted when the barks and trunks are injured by sharp objects [1]. This resin, in the past considered a miraculous remedy in several parts of Asia and America, has been used in traditional medicine to treat inflammatory diseases [3]. Its resin was used by Romans, Egyptians, Phoenicians, and Ionians as incense and in therapeutics [4]. The pericarps are used as washing soap (skin elastic material), cough medicine, and as a piscicidal agent [5]. *Styrax* species contain egonol, a natural benzofuran, which is known to be an effective pyrethrum synergist [6, 7]. Earlier chemical studies on several *Styrax* species have revealed them to be a rich source of arylpropanoids, triterpenoids, and their glycosides [6–12] with various biological activities such as antisweat [5], antimicrobial [7], antiproliferative [11], cytotoxic [12], and matrix metalloproteinase-1inhibitor [13]. However, careful literature survey of *Styrax* species revealed that *S. obassia* has not been studied much so far except for a few short reports [6, 8]. Phytochemical investigation of *S. obassia* seeds led us to isolate two benzofurans which we established to be methyl 3-[7-methoxy-2-(3′,4′-methylenedioxyphenyl)-5-benzofuranyl]-propionate (**1**) and methyl 3-[2-(3′,4′-methylenedioxyphenyl)-5-benzofuranyl]-propionate (**2**), along with five known compounds egonol (**3**), egonolacetate (**4**), egonol-2-methylbutanoate (**5**), 7-demethoxyegonol-2-methylbutanoate (**6**), and stigmasterol (**7**). Compounds **1**, **2** have been previously obtained as intermediate products for the synthesis of 2-phenylbenzofurans [14–16]; however, this is the first report of compounds **1**, **2** from any natural source, while compound **7** is being reported for the first time from the *Styrax* species. This paper deals with the isolation and structure elucidation of compounds **1**–**7** by their comprehensive spectroscopic analysis, including 2D NMR, and comparison of their spectral data with those of related compounds.

Compound **1** was obtained as a white powder and exhibited UV absorbance in MeOH at 238 and 316 nm. The IR spectrum of compound **1** showed bands at 2935, 1736, 1603, 1481, 1232, and 941 cm^{-1} for the presence of aliphatic CH_2, an ester, unsaturated ring, substituted furan ring, cyclic ether, and methylenedioxy groups respectively in the molecule. Compound **1** showed a molecular ion peak at *m/z* 354 ($[M]^+$, base ion) in the EIMS spectrum; its molecular formula could be determined as $C_{20}H_{18}O_6$ by its HREIMS spectrum. The ^1H and ^{13}C NMR signals of compound **1** were assigned by interpretation of the DEPT, COSY, HMQC, and HMBC, spectra (Table 1).

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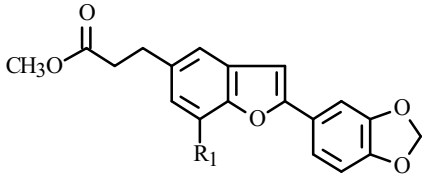
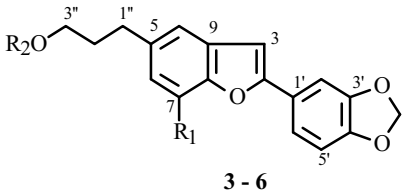
TABLE 1. ^{1}H and ^{13}C NMR Data in $CDCl_3$ for Compounds **1-2**

C atom	Compound **1**		Compound **2**		**1**, **2**
	δ_C	δ_H (J/Hz)	δ_C	δ_H (J/Hz)	COSY
2	155.1 s	-	155.2 s	-	-
3	101.1 d	6.98 s	100.8 d	7.13 s	-
4	111.9 d	7.18 s	120.0 d	7.41 m	-
5	138.1 s	-	136.9 s	-	-
6	107.7 d	6.79 s	124.1 d	7.12 dd (J = 2.0, 8.5)	-
7	144.2 s	-	110.5 d	7.43 m	-
8	141.6 s	-	152.6 s	-	-
9	130.4 s	-	129.0 s	-	-
1′	124.0 s	-	124.8 s	-	-
2′	104.9 d	7.38 d (J = 1.5)	105.0 d	7.45 s	-
3′	147.9 s	-	148.0 s	-	-
4′	147.8 s	-	147.8 s	-	-
5′	108.8 d	7.02 d (J = 8.5)	108.9 d	7.02 d (J = 8.0)	H-6′
6′	118.7 d	7.41 dd (J = 1.5, 8.0)	118.8 d	7.39 m	H-5′
OCH_2O	101.4 t	6.15 s	101.5 t	6.07 s	-
1″	31.8 t	3.01 t (J = 8.0)	31.9 t	2.88 t (J = 7.5)	H-2″
2″	37.9 t	2.57 t (J = 8.0)	38.7 t	2.44 t (J = 7.5)	H-1″
3″	175.0 s	-	175.0 s	-	-
OMe	55.7 q	4.08 s	-	-	-
3″-CO_2Me	48.6 q	3.02 s	48.7 q	3.15 s	-



1, 2



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1: R_1 = OMe; **2:** R_1 = H

3: R_1 = OMe; R_2 = H

4: R_1 = OMe, R_2 = $\overset{2a\ \ 1a}{CH_3CO}$

5: R_1 = OMe, R_2 = $\overset{4a\ \ 3a\ \ 5a\ \ 2a\ 1a}{CH_3CH_2(CH_3)CHCO}$

6: R_1 = H, R_2 = $\overset{4a\ \ 3a\ \ 5a\ \ 2a\ 1a}{CH_3CH_2(CH_3)CHCO}$

The ^{13}C NMR spectrum of compound **1** showed the signals for 20 carbons which were distinguished into two methyl (δ_C 48.6, 55.7), three methylene (δ_C 31.8, 37.9, 101.4), six methine (δ_C 101.1, 104.9, 107.7, 108.8, 111.9, 118.7), and nine quaternary (δ_C 124.0, 130.4, 138.1, 141.6, 144.2, 147.8, 147.9, 155.1, 175.0) carbons with the help of DEPT experiments. Upon integration, the ^{1}H NMR spectrum of compound **1** showed the presence of 18 protons. Two doublets at δ 7.38 (1H, d, J = 1.5 Hz, H-2′) and δ 7.02 (1H, d, J = 8.5 Hz, H-5′), two singlets at δ 7.18 (1H, s, H-4) and δ 6.79 (1H, s, H-6), and a double of doublets at δ 7.41 (1H, dd, J = 1.5, 8.0 Hz, H-6′) are attributable to aromatic protons. In addition, singlets at δ 6.98 (1H), δ 4.08 (3H), and δ 6.15 (2H) correspond to H-3 (methine proton), a methoxy proton, and a methylene dioxy proton, respectively, in the molecule. The presence of these groups was further confirmed by their respective carbon signals at δ_C 101.1 (C-3), δ_C 55.7 (OCH_3), and δ_C 101.4 (-O-CH_2-O-) corresponding to a methine carbon, a methoxy carbon, and a methylene carbon, respectively, in the ^{13}C NMR spectrum. This observation was supported by ^{1}H-^{13}C one-bond (HMQC) experiments. This spectroscopic pattern is characteristics for the 7-methoxy-2-(3′,4′-methylenedioxyphenyl)-benzofuran moiety [6]. ^{1}H NMR spectral data also revealed a three-proton singlet at δ 3.02 assignable to methyl ester carbon and two vicinal methylene proton

triplets (J = 8.0 Hz) at δ 3.01 and 2.57. Considering the chemical shifts, the relatively downfield signal at δ 3.01 was attributed to benzylic methylene (H_2-1″), while that at δ 2.57 could be assigned to H_2-2″. This observation was well supported by their corresponding carbon signals at δ_C 48.6 (3″-CO_2Me), 31.8 (C-1″) and 37.9 (C-2″) from ^1H–^{13}C one-bond (HMQC) experiments. Further evidence for the presence of these groups and their positions came from the 2D NMR data in which ^1H–^1H COSY showed the correlation between methylene proton H_2-1″ at δ 3.01 (2H, t, J = 8.0 Hz) and methylene proton H_2-2″ at δ 2.57 (2H, t, J = 8.0 Hz). In HMBC (see experimental), long-range $^3J_{C-H}$ correlations between methylene protons H_2-1″ to carbons (C-4/C-6/C-3″) and H_2-2″ to carbon C-5 and $^2J_{C-H}$ correlations between H_2-1″ to carbons (C-5/C-2″) and H_2-2″ to carbons (C-1″/C-3″) confirmed their substitution unambiguously at C-5 carbon. Thus, compound **1** was elucidated as methyl 3-[7-methoxy-2-(3′,4′-methylenedioxyphenyl)-5-benzofuranyl]-propionate.

Compound **2** was obtained as a white powder and exhibited UV absorbance in MeOH at 238 and 318 nm. Compound **2** showed a molecular ion peak at *m/z* 324 ($[M]^+$) in the EIMS spectrum; its molecular formula $C_{20}H_{18}O_6$ was deduced from its HREIMS spectrum. All the spectral data of compound **2** were similar to those of compound **1** except for the absence of a methoxy signal at δ 4.08 (3H, s) in the ^1H NMR spectrum and at δ_C 55.7 (OCH_3) in the ^{13}C NMR spectrum. The absence of a methoxy group in compound **2** was also confirmed from the observed downfield-shifted carbon signals at δ_C 124.1 (C-6), δ_C 152.6 (C-8) and δ_C 120.0(C-4) of compound **2** in comparison to carbon signals at δ_C 107.7 (C-6), δ_C 141.6 (C-8), and δ_C 111.9 (C-4) of compound **1** and upfield-shifted carbon signals at δ_C 110.5 (C-7), δ_C 136.9 (C-5), and δ_C 129.0 (C-9) of compound **2** in comparison to carbon signals at δ_C 144.2 (C-7), δ_C 138.1 (C-5), and δ_C 130.4 (C-9) of compound **1** and the presence of an extra methine proton at δ 7.43 (1H, m, H-7) in compound **2**. Thus, compound **2** was deduced to be methyl 3-[2-(3′,4′-methylenedioxyphenyl)-5-benzofuranyl]-propionate.

The known compounds (**3–7**) were identified by comparison of their spectral data with literature values as follows: egonol [6, 8, 9] (**3**), egonolacetate [6, 8, 9] (**4**), egonol-2-methylbutanoate [6, 8, 9] (**5**) 7-demethoxyegonol-2-methylbutanoate [6, 8] (**6**), and stigmasterol [17] (**7**).

EXPERIMENTAL

General Methods. Melting points were determined on an Electrothermal IA-9200 melting point apparatus (Electrothermal Engg. Ltd. U.K.) and are uncorrected. Optical rotations were taken on a Jasco P1020 polarimeter. The UV spectra were recorded on a Hewlett Packard 8452A Diode Array spectrophotometer. The IR spectra were recorded in KBr with a NEXUS FT-IR spectrophotometer. The EIMS and HREIMS were obtained with a JEOL JMS-SX102A spectrophotometer. The ^1H NMR (500 MHz), ^{13}C NMR (125 MHz), DEPT, COSY, HMQC, and HMBC spectra were obtained with a Varian Unity-Inova 500 spectrophotometer. The NMR samples were prepared in $CDCl_3$/DMSO with tetramethylsilane (TMS) as an internal standard. The chemical shifts and coupling constants (J) were expressed in δ and Hz, respectively. Thin layer chromatography (TLC) was carried out on pre-coated Silica gel 60 F_{254} (0.2 mm, Merck) plates. The TLC plates were developed with solvent system A (toluene–ethyl formate–formic acid 20:2:1, v/v/v) and B (*n*-hexane–ethyl acetate–toluene 8:1:1, v/v/v). The developed TLC plates were visualized under UV light at 254 and 365 nm. Silica gel 60 (40~100 μm, Kanto Chemical Co.) was used for the column chromatography. An ADVENTEC SF-1600 was used as the automated fraction collector in the column chromatography.

Plant Material. The fruits of *S. obassia* were collected from Jiri mountain (Hadong-kun) in Kyungnam, Korea in September, 2004 and identified by Dr. Y. H. Kwon (Korea National Arboretum, Pocheon, Korea). A voucher specimen has been deposited at the Korea Forest Research Institute, Seoul, Korea.

Extraction and Isolation. 8.0 kg air-dried and powdered seeds of *S. obassia* were extracted three times with MeOH at room temperature for 72 hrs each. The combined MeOH extracts were concentrated under vacuum at 40°C until the MeOH was completely removed. The concentrated MeOH extract was dissolved in distilled water and successively partitioned with *n*-hexane, dichloromethane, and ethyl acetate.

Column chromatography of the oily mass from the *n*-hexane soluble fraction on a silica column gave 93 fractions (250 mL each) in benzene–ethyl acetate (20:1, v/v). On the basis of TLC profiles, these fractions are divided into four groups. Group one (46.6 g) was chromatographed on the silica gel column using *n*-hexane–ethyl acetate (17:1, v/v) as an eluent to collect nine fractions (100 ml each) and then the column was washed with MeOH to give an oily mass (43.7 g). Fraction 2 formed some precipitate, which was washed with MeOH to give a pure compound **4** (3.7 g). Similarly, fraction 4 also formed

some precipitate, which was first washed with MeOH and then the insoluble precipitate was purified with a silica gel column using *n*-hexane–toluene–ethyl acetate–$CHCl_3$ (9.5:4:2:1, v/v/v) to yield a pure compound **7**. At the same time, fraction 7 was purified by preperative TLC in *n*-hexane–ethyl acetate (5:1, v/v) to give a pure compound **5** (40 mg). The oily mass (43.7 g) upon silica gel column chromatography in *n*-hexane–ethyl acetate (15:1, v/v) gave 85 fractions (250 mL each). The TLC profiles of these fractions led them to be divided into four groups. Group 1 (10.0 g) was chromatographed on a silica column in *n*-hexane–chloroform:ethyl acetate (23:1:1, v/v/v) to give three fractions. Rechromatography of fraction 2 (3.5 g) on a silica column in chloroform:toluene–ethyl acetate (17:1:1, v/v/v) gave pure compound **6** (88.8 mg).

The ethyl acetate soluble fraction (122.7 g) from the MeOH extract was chromatographed on a silica column with increasing polarity of *n*-hexane–ethyl acetate–acetone (9:2:1→5:2:1→3:2:1→1:2:2, v/v/v) to collect five fractions. Fraction 3 was concentrated to produce a powdery mass, which was washed with toluene, benzene, and finally with ethyl acetate. The ethyl acetate soluble part produced pure compound **3** (1.08 g). On the other hand, fraction 2 was chromatographed on a silica gel column in *n*-hexane–ethyl acetate (3:1, v/v) to give 180 fractions, which on the basis of the TLC chromatogram was divided into three groups. Group 1 (30 mg) and group 3 (125 mg) were purified separately by preparative TLC in toluene–ethyl formate (1:1, v/v) to give pure compounds **2** (10 mg) and **1** (6.3 mg) respectively.

Methyl 3-[7-methoxy-2-(3′,4′-methylenedioxyphenyl)-5-benzofuranyl]-propionate (1). White powder, mp 154-155°C. $[\alpha]_D^{20.4}$ +2.6° (*c* 0.10, $CHCl_3$). UV ($CHCl_3$, λ_{max}, nm, log ε): 238 (3.4), 316 (3.9). IR (KBr, ν_{max}, cm^{-1}): 2935, 1736, 1603, 1481, 1365, 1232, 1039, 941 and 825. EIMS *m/z*: 354 ($[M]^+$, base ion), 293, 281, 252, 167, 149, 127, 97, 85, 71 and 57. HREIMS *m/z*: 354.1105 ($[M]^+$, calcd. for $C_{20}H_{18}O_6$, 354.3593). ^{1}H NMR ($CDCl_3$, 500 MHz), ^{13}C NMR ($CDCl_3$, 125 MHz) and COSY (see Table 1). HMBC: H-1″→C-3″/C-5/C-6/C-4, H-2″→C-3″/C-5, CO_2CH_3→C-3″, H-4→C-5/C-9/C-8/C-3, H-6→C-5/C-1″/C-4/C-7, OCH_3→C-7, H-3→C-2/C-9/C-4/C-1′/C-8, H-2′→C-1′/C-3′/C-6′, H-6′→C-1′/C-5′/C-2/C-2′/C-4′, H-5′→C-4′/C-6′/C-3′/C-1′.

Methyl 3-[2-(3′,4′-methylenedioxyphenyl)-5-benzofuranyl]-propionate (2). White powder, mp 126–128°C. $[\alpha]_D^{20.4}$ +4.0° (*c* 0.10, $CHCl_3$). UV ($CHCl_3$, λ_{max}, nm, log ε): 238 (3.6), 318 (4.0). IR (KBr, ν_{max}, cm^{-1}): 2938, 1736, 1570, 1490, 1364, 1255, 1044 and 804. EIMS *m/z*: 324 ($[M]^+$), 293, 267, 251, 167, 149, 127, 97, 85, 71 and 57. HREIMS *m/z*: 324.1106 ($[M]^+$, calcd. for $C_{19}H_{16}O_5$, 324.3330). ^{1}H NMR ($CDCl_3$, 500 MHz), ^{13}C NMR ($CDCl_3$, 125 MHz) and COSY (see Table 1). HMBC: H-1″→C-3″/C-5/C-6/C-4, H-2″→C-3″/C-5, CO_2CH_3→C-3″, H-4→C-5/C-9/C-8/C-3, H-6→C-5/C-1″/C-4/C-7, H-3→ C-2/C-9/C-4/C-1′/C-8, H-2′→C-1′/C-3′/C-6′, H-6′→C-1′/C-5′/C-2/ C-2′/C-4′, H-5′→C-4′/C-6′/C-3′/C-1′.

Egonol (3). White powder, mp 112–113°C. EIMS *m/z*: 326 ($[M]^+$). UV, IR, ^{1}H, and ^{13}C NMR data are in agreement with the literature [6, 8, 9]. COSY: H-3″↔H-2″, H-2″↔H-1″, H-5′↔H-6′. HMBC: H-1″→C-3″/C-5/C-6/C-4, H-4→C-5/C-9/C-8/C-3, H-6→C-5/C-1″/C-4/C-7, OCH_3→C-7, H-3→C-2/C-9/C-4/C-1′/C-8, H-2′→C-1′/C-3′/C-6′, H-6′→C-1′/C-5′/C-2/C-2′/C-4′, H-5′→C-4′/C-6′/C-3′/C-1′.

Egonolacetate (4). Yellowish powder, mp 104–105°C. EIMS *m/z*: 368 ($[M]^+$). UV, IR, ^{1}H, and ^{13}C NMR data are in agreement with the literature [6, 8, 9]. COSY: H-3″↔H-2″, H-2″↔H-1″, H-5′↔H-6′. HMBC: H-1″→C-3″/C-5/C-6/C-4/C-2″, H-4→C-5/C-9/C-8/C-3, H-6→C-5/C-1″/C-4/C-7, OCH_3→C-7, H-2a→ C-1a, H-3→C-2/C-9/C-4/C-1′/C-8, H-2′ →C-1′/C-3′/C-6′, H-6′ →C-1′/C-5′/C-2/C-2′/C-4′, H-5′→C-4′/C-6′/C-3′/C-1′.

Egonol-2-methylbutanoate (5). Pale yellow oil, EIMS *m/z*: 410 ($[M]^+$). UV, IR, ^{1}H, and ^{13}C NMR data are in agreement with the literature [6, 8, 9]. COSY: H-3″↔H-2″, H-2″↔H-1″, H-5′↔H-6′, H-4a↔H-3a, H-3a↔H-2a, H-2a↔H-5a. HMBC: H-1″→C-3″/C-5/C-6/C-4/C-2″, H-4→C-5/C-9/C-8/C-3, H-6→C-5/C-1″/C-4/C-7, OCH_3→C-7, H-2a→C-1a, H-3→ C-2/C-9/C-4/C-1′/C-8, H-2′→C-1′/C-3′/C-6′, H-6′→C-1′/C-5′/C-2/C-2′/C-4′, H-5′→C-4′/C-6′/C-3′/C-1′, H-5a→C-3a/C-1a, H-3a→C-1a/C-5a, H-2a→C-1a/C-5a/C-4a/3a.

7-Demethoxyegonol-2-methylbutanoate (6). Colourless needles, mp 54–55°C. EIMS *m/z*: 380 ($[M]^+$). UV, IR, and ^{1}H NMR data are in agreement with the literature [6, 8]. ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.6 q (C-4a), 16.6 q (C-5a), 26.8 t (C-3a), 30.9 t (C-2″), 32.1 t (C-1″), 41.1 d (C-2a), 63.4 t (C-3″), 100.0 d (C-3), 101.3 t (-O-CH_2-O-), 105.4 d (C-2′), 108.6 d (C-5′), 110.7 d (C-7), 119.1 d (C-6′), 120.0 d (C-4), 124.5 d (C-6), 124.8 s (C-1′), 129.5 s (C-9), 135.9 s (C-5), 148.0 s (C-4′), 148.1 s (C-3′), 153.4 s (C-8), 156.0 s (C-2), 176.8 s (C-1a), COSY: H-3″↔H-2″, H-2″↔H-1″, H-5′↔H-6′, H-6↔H-7, H-4a↔H-3a, H-3a↔H-2a, H-2a↔H-5a. HMBC: H-1″→C-3″/C-5/C-6/C-4/C-2″, H-4→C-5/C-9/C-8/C-3, H-6→C-5/C-1″/C-4/C-7, H-7→C-5/ C-8/C-9, OCH_3→C-7, H-2a→C-1a, H-3→C-2/C-9/C-4/C-1′/C-8, H-2′→C-1′/C-3′/C-6′, H-6′→C-1′/C-5′/C-2/C-2′/C-4′, H-5′→C-4′/C-6′/C-3′/C-1′, H-5a→C-3a/C-2a/C-1a, H-3a→C-4a/C-2a/C-1a/C-5a, H-2a→C-1a/C-5a/C-4a/3a.

Stigmasterol (7). White solid, mp 165–167°C. EIMS *m/z*: 412 ($[M]^+$). Spectroscopic data are in good agreement with the literature [17]. COSY: H-3↔H-2, H-3↔H-4, H-20↔H-22, H-22↔H-23, H-6↔H-7.

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