FUROFURAN LIGNANS FROM THE BARK OF *Magnolia kobus*

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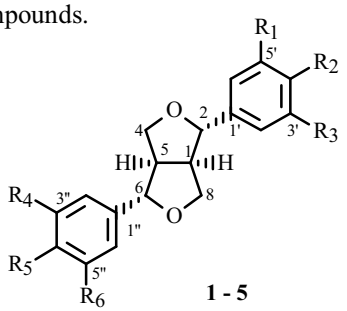
*A new furofuran lignan (**1**) along with four knownones (**2–5**) were isolated from the bark of* Magnolia kobus. *Their structures were elucidated as (+)-2α-(3′,4′-dimethoxyphenyl)-6α-(3″-hydroxy-4″,5″-dimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (**1**), (+)-sesamin (**2**), (+)-yangambin (**3**), (+)-kobusin (**4**), and (+)-eudesmin (**5**) on the basis of their comprehensive spectroscopic analysis, including 2D NMR, and by comparison of their spectral data with those of related compounds.*

Key words: *Magnolia kobus*, Magnoliaceae, furofuran lignan, (+)-2α-(3′,4′-dimethoxyphenyl)-6α-(3″-hydroxy-4″,5″-dimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane.

Magnolia kobus DC belongs to the Magnoliaceae family. It is a medium sized deciduous tree native to Japan, also found in China and Korea [1]. It is a valuable decorative plant in Japan and is famous, with the local name Kobusi. Young buds of *M. kobus* are important ingredients in the Chinese medicine 'Shin-I', which is used as a sedative or analgesic. In Japan 'Shin-I' is taken internally for the treatment of headaches or colds [2]. Earlier chemical studies on *M. kobus* revealed it to be a source of bioactive terpenes and lignans [3–7]. Lignans have evoked a great deal of interest due to their widespread occurrence in nature [8, 9] and use in traditional medicines [10, 11]. Furofurans, one of the major subclasses of the lignan family, exhibit a wide variety of biological activities, including antitumor, antimitotic, antiviral [12], antioxidant, antihypertensive [13, 14], and antidiabetic [15], and is an inhibitor of platelet-activating factor (PAF) [16].

Literature survey of *M. kobus* revealed that this plant has not been studied much so far except for a few short reports [3–7]. As part of our ongoing research on *M. kobus,* we isolated a new furofuran lignan **1** along with four knownones **2–5** from the bark of *M. kobus*. This paper deals with the isolation and structure elucidation of these compounds using their detailed NMR (^{1}H, ^{13}C, DEPT, COSY, NOESY, HMQC and HMBC), HREIMS, EIMS, IR, and UV spectroscopic analysis and comparison of their spectral data with those of related compounds.



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1: R_1 = H, R_2 = R_3 = R_5 = R_6 = OCH_3, R_4 = OH
2: R_1 = R_6 = H, R_2R_3 = R_4R_5 = OCH_2O
3: R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = OCH_3
4: R_1 = R_6 = H, R_2 = R_3 = OCH_3, R_4R_5 = OCH_2O
5: R_1 = R_6 = H, R_2 = R_3 = R_4 = R_5 = OCH_3

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TABLE 1. 1D[a] and 2D NMR Data in $CDCl_3$ for Compound **1**

C atom	DEPT	δ_C	δ_H (J/Hz)	COSY	HMBC
1	CH	54.17	3.10 m	H-2, H-8a, H-8b	C-2, C-5, C-6, C-1′
2	CH	85.75	4.72 d (J = 4.5)	H-1	C-1, C-4, C-5, C-8, C-1′, C-2′, C-6′
4	CH_2	71.78	4.26 m, 3.92 m	H-5	C-2, C-6, C-5
5	CH	54.24	3.10 m	H-4a, H-4b, H-6	C-1, C-2, C-6, C-1″
6	CH	85.81	4.73 d (J = 3.5)	H-5	C-1, C-4, C-5, C-8, C-1″, C-2″, C-6″
8	CH_2	72.01	4.26 m, 3.92 m	H-1	C-2, C-6, C-1
1′	C	133.59	-	-	-
2′	CH	109.37	6.90 d (J = 1.5)	-	C-6′, C-1′, C-4′, C-2
3′	C	149.30	-	-	-
4′	C	148.74	-	-	-
5′	CH	111.18	6.84 d (J = 8.0)	H-6′	C-6′, C-1′, C-4′, C-3′
6′	CH	118.32	6.87 dd (J = 2.0, 8.0)	H-5′	C-2′, C-4′, C-1′, C-2
1″	C	137.50	-	-	-
2″	CH	105.53	6.57 d (J = 2.0)	-	C-6″, C-4″, C-1″, C-3″, C-6
3″	C	149.37	-	-	-
4″	C	134.93	-	-	-
5″	C	152.56	-	-	-
6″	CH	101.80	6.51 d (J = 1.5)	-	C-2″, C-4″, C-1″, C-6
3′-OMe	CH_3	60.95	3.91 s	-	C-3′
4′-OMe	CH_3	55.96	3.87 s	-	C-4′
3″-OH	-		5.81 br.s	-	C-4″, C-3″, C-2″
4″-OMe	CH_3	56.00	3.89 s	-	C-4″
5″-OMe	CH_3	55.97	3.87 s	-	C-5″

[a]: ^1H and ^{13}C NMR recorded at 500 and 125 MHz respectively.

The diethyl ether soluble fraction from the ethanol extract of *M. kobus* bark was processed as described in the experimental section to afford a new furofuran lignan, which was established to be (+)-2α-(3′,4′-dimethoxyphenyl)-6α-(3″-hydroxy-4″,5″-dimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]-octane (**1**), along with four known furofuran lignans, (+)-sesamin (**2**), (+)-yangambin (**3**), (+)-kobusin (**4**), and (+)-eudesmin (**5**), which were identified by comparison of their physical and spectral data with previously reported values [7, 17–20].

Compound **1** was obtained as a white solid and exhibited UV maxima in $CHCl_3$ at 246 and 278 nm. A molecular ion peak was observed at *m/z* 402 ($[M]^+$); in the EIMS spectrum of compound **1**, its molecular formula could be determined as $C_{22}H_{26}O_7$ by HREIMS. ^1H and ^{13}C NMR signals of compound **1** were assigned by the interpretation of the DEPT, COSY, NOESY, HMQC, and HMBC spectra (Table 1). The ^{13}C NMR spectrum of compound **1** showed the signals for 22 carbons, which were distinguished into four methyls, two methylenes, nine methines, and seven quaternary carbons with the help of DEPT experiments. The ^1H NMR spectrum of compound **1** showed signals for two methine protons at δ 3.10 (2H, m), two benzylic oxymethine protons at δ 4.72 (1H, d, J = 3.5 Hz) and 4.73 (1H, d, J = 4.5 Hz), two oxygenated methylene protons at 4.26 (2H, m) and 3.92 (2H, m), a 1,3,4-trisubstituted benzene ring at 6.90 (1H, d, J = 1.5 Hz), 6.87 (1H, dd, J = 2.0, 8.0 Hz), and 6.84 (1H, d, J = 8.0 Hz), and a 1,3,4,5-tetrasubstituted benzene ring at 6.57 (1H, d, J = 2.0 Hz) and 6.51 (1H, d, J = 1.5 Hz) (Table 1), which were assigned to a lignan of the 3,7-dioxobicyclo[3.3.0]octane type, compared with those previously reported [21, 22]. This observation was further confirmed from their corresponding carbon signals at δ_C 54.17 and 54.24 (two methine carbons), 85.75 and 85.81 (two benzylic oxymethine carbons), 71.78 and 72.01 (two oxygenated methylene carbons), a 1,3,4-trisubstituted benzene carbons at 133.59, 149.30, and 148.74 (three aromatic quaternary carbons), 109.37, 111.18, and 118.32 (three aromatic methine carbons), and a 1,3,4,5-tetrasubstituted benzene carbon at 137.50, 149.37, 134.93, and 152.56 (four aromatic quaternary carbons), and 105.53 and 101.80 (two aromatic methine carbons) in the ^{13}C NMR spectrum. ^1H–^{13}C one bond (HMQC) experiment also supported this observation. In addition, the ^1H NMR spectrum showed the signals for a hydroxyl group at δ 5.81 (1H, bs) and four methoxy groups at 3.87 (6H, s), 3.89 (3H, s), and 3.91(3H, s) substituted at benzene rings. The presence of these groups and their positions were confirmed by ^{13}C, DEPT, and 2D NMR data.

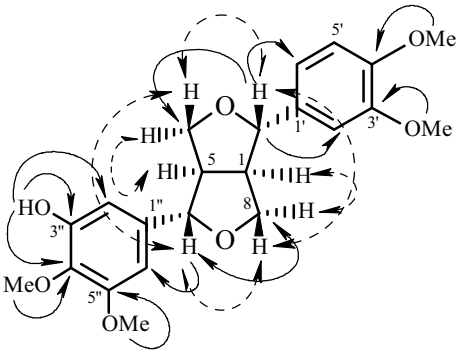

Fig. 1. Key NOE (↔) in the NOESY spectrum and HMBC (→) correlations of compound **1**.

In HMBC (Fig. 1) the hydroxyl proton at δ 5.81 (1H, bs) showed the $^{2}J_{C-H}$ correlation with quaternary carbon at δ_C 149.37 (C-3″), and $^{3}J_{C-H}$ correlations with a quaternary carbon at 134.93 (C-4″) and a methine carbon at 105.53 (C-2″) confirmed the position of the OH group at C-3″, while correlations between proton/carbon signals at δ 3.87(6H, s)/δ 148.7 (C-4′) and δ_C 152.56 (C-5″), δ 3.89 (3H, s)/δ_C 134.93 (C-4″) and at δ 3.91(3H, s)/δ_C 149.30 (C-3′) confirmed the position of methoxy groups at C-4′, C-5″, C-4″, and at C-3′ respectively in compound **1**. The resonances for the protons of the fused difuran system showed equivalence for H-1/H-5, H-2/H-6, and H_2-4/H_2-8, thus requiring a symmetrical substitution stereochemistry for the aryl substituents [17, 21]. Furthermore, the small coupling constants of H-2 (J = 4.5Hz) and H-6 (J = 3.5Hz) and the chemical shifts for the benzylic protons (H-2/H-6; 4.72, δ/4.73, d) and for bridge carbons (C-1/C-5; 54.17/54.24) confirmed that two aryl substituents are equatorial in compound **1** [17, 21, 23, 24]. This observation was further confirmed by the NOE effects of the NOESY spectrum of compound **1** (Fig. 1), which showed the proton correlations (H/H) at δ 4.73 (H_{ax}-2)/3.92 (H_{ax}-4 and H_{ax}-8) and at 4.72 (H_{ax}-6)/3.92 (H_{ax}-4 and H_{ax}-8). The specific rotation of compound **1** is +34.7°; following Freudenberg and Sidhu [25], all (+)-sesamin type lignans belong to the same series with the absolute configuration R at the bridge carbons **1** and **5**. Hence, the absolute configuration for compound **1** must be R at carbons **1** and **5**. Since the aryl substituents of compound **1** are diequatorial and showed dextrorotatory specific rotation, thus confirming the S configuration at carbons **2** and **6**, all (+)-sesamin type lignans with absolute configuration R at bridge carbons **1** and **5** having diequatorial aryl substitution belong to the same series with the absolute configuration S at the benzylic carbon **2** and **6** [18]. On the basis of these spectroscopic data, compound **1** is characterized as 1*R*,2*S*,5*R*,6*S*-(+)-2α-(3′,4′-dimethoxyphenyl)-6α-(3″-hydroxy-4″, 5″-dimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane.

The known compounds **2–5** were identified by comparison of their spectral data with literature values as follows: (+)-sesamin (**2**) [7, 19], (+)-yangambin (**3**) [19, 20], (+)-kobusin (**4**) [7, 17], and (+)-eudesmin (**5**) [7, 17].

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 with a NEXUS FT-IR spectrophotometer. The EIMS and HREIMS were obtained with a JEOL JMS-SX102A spectrophotometer. The ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), DEPT, COSY, NOESY, HMQC, and HMBC spectra were obtained with a Varian Unity-Inova 500 spectrophotometer. The NMR samples were prepared in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. The chemical shifts and coupling constants (J) were expressed in δ and Hz, respectively. The 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 5:4:1 and 7:2:1 v/v/v) and B (chloroform–methanol 40:1 and 30:1 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 CHF161RA (Toyo Seisakusho Kaisha Ltd., Japan) automated fraction collector was used in the column chromatography.

Plant Material. The bark of *M. kobus* was collected from the experimental forest of Southern Forest Research Center, Kyungnam, Korea in June, 2001 and identified by Dr. Y. H. Kwon (Korea National Arboretum, Pocheon, Korea). A voucher specimen was deposited at the Korea Forest Research Institute, Seoul, Korea.

Extraction and Isolation. 12.0 kg shade air-dried and powdered barks of *M. kobus* were extracted three times with 95% ethanol at room temperature for 72 hrs each. The combined EtOH extracts were concentrated under vacuum at 40°C until the EtOH was completely removed. The concentrated EtOH extract was dissolved in distilled water and successively partitioned with petroleum ether, diethyl ether (Et_2O), and ethyl acetate (EtOAc).

The diethyl ether soluble fraction (85.0 g) on a sephadex LH-20 column gave two major fractions MKBE-1 and MKBE-2 in MeOH:EtOH (3:7, v/v). Fraction MKBE-2 was chromatographed on silica gel column using (benzene–ethylacetate 8:1, v/v) as an eluent to collect eight fractions MKBE-2-1 to MKBE-2-8. Among these fractions MKBE-2-2 gave pure compound **2** as a white crystal (500 mg), while fraction MKBE-2-4 (7.0 g) on the silica gel column in (hexane–ethyl acetate 2:1, v/v) and fraction MKBE-2-5 (3.3 g) on the sephadex column in MeOH (100%) gave pure compounds **4** (1.25 g) and **5** (120 mg) respectively. On the other hand, fraction MKBE-2-6 (20.1 g) on the silica gel column yielded three fractions MKBE-2-6-1 to MKBE-2-6-3 using (hexane–ethyl acetate 2:1, v/v) as an eluent. Fraction MKBE-2-6-3 (15.3 g) was again chromatographed on the sephadex LH-20 column in ethanol to yield three fractions. Fraction 1 (1.0 g) was further chromatographed on silica gel in ($CHCl_3$–MeOH 100:1, v/v) to yield six fractions. Finally, fraction 5 (250 mg) on the silica gel column in ($CHCl_3$–MeOH 80:1, v/v) yielded two pure compounds **1** (30 mg) and **3** (25 mg).

(+)-2α-(3′,4′-Dimethoxyphenyl)-6α-(3″-hydroxy-4″,5″-dimethoxyphenyl)-3,7-dioxabicyclo[3.3.0]octane (1). White solid, mp 122–124°C, $[\alpha]_D^{20.4}$ +34.7° (*c* 0.19, $CHCl_3$), UV (λ_{max}, nm, log ε): 246 (3.5), 278 (3.4). IR (KBr, ν_{max}): 3417, 2927, 2359, 1599, 1515, 1264, 1235, 1141, 1058 and 1026 cm^{-1}, EIMS *m/z*: 402 ($[M]^+$ base ion), HREIMS *m/z*: 402.1679 ($[M]^+$, calcd. for $C_{22}H_{26}O_7$, 402.1679), ^1H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz), COSY and HMBC see Table 1.

(+)-Sesamin (2). White crystal, mp 122°C, $[\alpha]_D^{20.4}$ +61.5° (*c* 0.58, CH_2Cl_2), lit. [14] +63.2°, EIMS *m/z*: 354 ($[M]^+$), UV, IR, ^1H and ^{13}C NMR data are in agreement with literature [7, 19], COSY: H-1↔H-8α/H-8β/H-2, H-5↔H-4α/H-4β/H-6, H-5′↔H-6′, H-5″↔H-6″, NOESY: H-2↔H-4β/H-8β, H-6↔H-4β/H-8β, HMBC: H-1→C-2/C-5/C-6/C-1′, H-2→C-1/C-4/C-5/ C-8/C-1′/ C-2′/C-6′, H-4→C-2/C-6/C-5, H-5→C-1/C-2/C-6/C-1″, H-6→C-1/C-4/C-5/C-8/C-1″/C-2″/C-6″, H-8→C-2/C-6/C-1, H-2′→C-6′/C-1′/C-4′/C-2, H-5′→C-6′/C-4′/C-3′/C-1′, H-6′→C-2′/C-4′/C-1′/C-2, H-2″→C-6″/C-4″/C-1″/C-3″/C-6, H-5″→ C-3″/C-1″/C-4″, H-6″→ C-1″/C-C-6/C-4″/C-2″, OCH_2O→C-3′/C-4′, OCH_2O→C-3″/C-4″.

(+)-Yangambin (3). White solid, mp 118–119°C, $[\alpha]_D^{20.4}$ +43.2° (*c* 0.42, CH_2Cl_2), lit. [15] +45.1°, EIMS *m/z*: 446 ($[M]^+$), UV, IR, ^1H and ^{13}C NMR data are in agreement with literature [18, 20], COSY: H-1↔H-8α/H-8β/H-2, H-5↔H-4α/ H-4β/H-6, HMBC: H-1→C-2/C-5/C-6/C-1′, H-2→C-1/C-4/C-5/ C-8/C-1′/C-2′/C-6′, H-4→C-2/C-6/C-5, H-5→C-1/C-2/C-6/ C-1″, H-6→C-1/C-4/C-5/C-8/C-1″/C-2″/C-6″, H-8→C-2/C-6/C-1, H-2′→C-6′/C-1′/C-4′/C-2, H-6′→C-2′/C-4′/C-1′/C-2, H-2″→C-6″/C-4″/C-1″/C-3″/C-6, H-6″→C-2″/C-4″/C-1″/C-6, 3′-OMe→C-3′, 4′-OMe → C-4′, 5′-OMe→C-5′, 3″-OMe→C-3″, 4″-OMe→C-4″, 5″-OMe→C-5″.

(+)-Kobusin (4). Colorless oil, $[\alpha]_D^{20.4}$ +56.8° (*c* 0.54, CH_2Cl_2), lit. [17] +58.0°, EIMS *m/z*: 370 ($[M]^+$), UV, IR, ^1H and ^{13}C NMR data are in agreement with literature [7, 17], COSY: H-1↔H-8α/H-8β/H-2, H-5↔H-4α/H-4β/H-6, H-5′↔ H-6′, H-5″↔H-6″, HMBC: H-1→C-2/C-5/C-6/C-1′, H-2→C-1/C-4/C-5/ C-8/C-1′/C-2′/C-6′, H-4→C-2/C-6/C-5, H-5→C-1/ C-2/C-6/C-1″, H-6→C-1/C-4/C-5/C-8/C-1″/C-2″/C-6″, H-8→C-2/C-6/ C-1, H-2′→C-6′/C-1′/C-4′/C-2, H-5′→C-6′/C-4′/C-3′/ C-1′, H-6′→C-2′/C-4′/C-1′/C-2, H-2″→C-6″/C-4″/C-1″/C-3″/C-6, H-5″→C-3″/C-1″/C-4″, H-6″→C-1″/C-C-6/C-4″/C-2″, OCH_2O→ C-3″/C-4″, 3′-OMe→C-3′, 4′-OMe→C-4′.

(+)-Eudesmin (5). Powder, mp 105–107°C, $[\alpha]_D^{20.4}$ +59.9° (*c* 0.59, acetone), lit. [17] +61.0°, EIMS *m/z*: 386 ($[M]^+$), UV, IR, ^1H and ^{13}C NMR data are in agreement with literature [7, 17], COSY: H-1↔H-8α/H-8β/H-2, H-5↔H-4α/H-4β/H-6, H-5′↔ H-6′, H-5″↔H-6″, HMBC: H-1→C-2/C-5/C-6/C-1′, H-2→C-1/C-4/C-5/ C-8/C-1′/C-2′/C-6′, H-4→C-2/C-6/C-5, H-5→C-1/C-2/C-6/C-1″, H-6→C-1/C-4/C-5/C-8/C-1″/C-2″/C-6″, H-8→C-2/ C-6/C-1, H-2′→C-6′/C-1′/C-4′/C-2, H-5′→ C-6′/C-4′/C-3′/C-1′, H-6′→C-2′/C-4′/C-1′/C-2, H-2″→C-6″/C-4″/C-1″/C-3″/C-6, H-5″→C-3″/C-1″/C-4″, H-6″→C-1″/C-C-6/ C-4″/C-2″, 3′-OMe→C-3′, 4′-OMe→C-4′, 3″-OMe→C-3″, 4″-OMe→C-4″.

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