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(−)-MAGNOFARGESIN AND (+)-MAGNOLIADIOL, TWO LIGNANS FROM *MAGNOLIA FARGESII*

MITSUO MIYAZAWA,* HIROYUKI KASAHARA and HIROMU KAMEOKA

Department of Applied Chemistry, Faculty of Science and Engineering, Kinki University, Kowakae, Higashiosaka-shi, Osaka 577, Japan

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Key Word Index—*Magnolia fargesii*; Magnoliaceae; (−)-magnofargesin; (+)-magnoliadiol; 8′-hydro-7′-hydroxymagnofargesin; 7,9′-epoxylignan; aryl-1,2-dihydronaphthalene.

Abstract—Two new lignans, (−)-magnofargesin and (+)-magnoliadiol, were isolated from the flower buds of *Magnolia fargesii*. The absolute configuration assignment of (−)-magnofargesin was achieved by its isomerization to (+)-magnolin.

INTRODUCTION

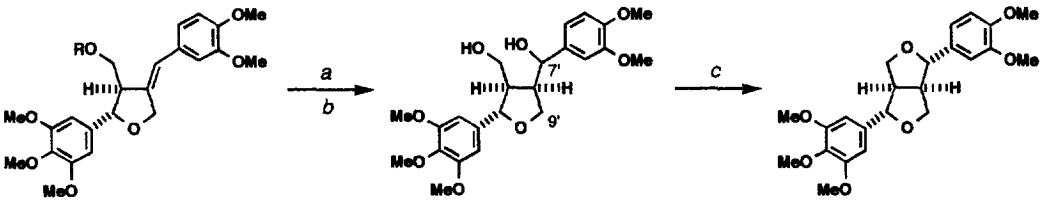
In our search for new bioactive lignans from plants which have historical safe usage as drugs in Japan and China, (+)-epimagnolin A was isolated as a growth inhibitory lignan against the larva of *Drosophila melanogaster* from the flower buds of *Magnolia fargesii* [1], along with two unidentified compounds and some known furofuran lignans. This paper deals with the structural elucidation of (−)-magnofargesin (**1**) and (+)-magnoliadiol (**2**).

RESULTS AND DISCUSSION

(−)-Magnofargesin (**1**) was assigned the molecular formula $C_{23}H_{28}O_7$ (HRMS: $[M]^+$ *m/z* 416.1815 Δ 2.0 amu) with ten degrees of unsaturation. Detailed analysis of the NMR and DEPT spectra showed signals for five methoxyl groups, two methylenes, eight methines, eight quaternary carbons and one hydroxyl group. The IR spectrum supported the presence of a hydroxyl group (3497 cm^{-1}), and the mass spectrum showed ions *m/z* 220 $[M - ArCHO]^+$, 189 $[220 - CH_2OH]^+$, 195 $[ArCO]^+$, 181 $[ArCH_2]^+$ (Ar = 3,4,5-trimethoxyphenyl), and 151 $[Ar'CH_2]^+$ (Ar′ = 3,4-dimethoxyphenyl). Therefore, eight degrees of unsaturation are accounted for by the presence of these aryl groups. Since this molecular formula requires ten degrees of unsaturation, the spectral data allowed us to deduce the planar structure of **1**. The *Z*-geometry of C-7′-8′ double bond was established by the NOE spectrum [2], and the absolute configuration (7S, 8R) by isomerization to (+)-magnolin via cyclization of 8′-hydro-7′-hydroxymagnofargesin (**3**). Hydroboration of the acetate of **1** by diborane in THF followed by oxidation with H_2O_2/NaOH gave **3** (60%). This diol was readily cyclized by refluxing in acidic EtOH to give (+)-epimagnolin A (4.9%) and (+)-magnolin (28.8%) [3]. (+)-Epimagnolin A had $[\alpha]_D$ + 110.6° (*c* 0.2, $CHCl_3$) [1] and (+)-magnolin had $[\alpha]_D$ + 49.4° (*c* 0.5, $CHCl_3$) [4].

(+)-Magnoliadiol (**2**) was assigned the molecular formula $C_{23}H_{28}O_7$ (HRMS: $[M]^+$ *m/z* 416.1835 Δ 0.0 amu) with ten degrees of unsaturation. Detailed analysis of the NMR and DEPT spectra showed that **2** contained five methoxyl groups, two methylenes, seven methines, nine quaternary carbons, and two hydroxyl groups. The IR spectrum showed a wide absorption band at 3418 cm^{-1} for hydroxyl groups, and the presence of two hydroxyl groups was determined by acetylation. The mass spectrum showed an ion *m/z* 151 $[ArCH_2]^+$ (Ar = 3,4-dimethoxyphenyl). The ^1H NMR spectrum contained a specific resonance for a methoxyl group at higher field (δ 3.53) than those of the other four. This resonance reminded us of the features of aryltetrahydronaphthalenes; interaction between the C-7′-aryl group (C ring) and the fused aromatic A ring generates a shielding effect against the C-3-methoxyl group and causes it to be shifted to higher field [5]. However, the existence of a C-7-8 double bond was revealed by interpretation of the 2D NMR and NOE spectra, furthermore, the presence of two hydroxymethyl groups attached to C-8 and C-8′ was revealed; these spectra completely satisfied the molecular formula requirement of ten degrees of unsaturation. The ^{13}C NMR and DEPT spectra supported the planar structure of **2**. The relative configuration at C-8′ and C-9′ were confirmed by the NOE spectrum.

*Author to whom correspondence should be addressed.



R = H: (-)-magnofargesin (**1**)
R = Ac : monoacetate

8'-hydro-
7'-hydroxymagnofargesin (**3**)

7'*S* : (+)-magnolin
7'*R* : (+)-epimagnolin A

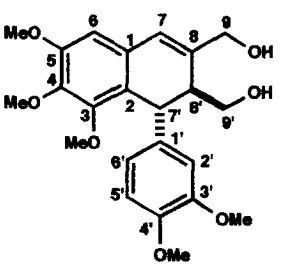
a) B_2H_6 / THF, 0°C *b*) 3*N* NaOH, 30% H_2O_2 *c*) 1*N* HCl / EtOH, Δ

EXPERIMENTAL

Isolation of (−)-magnofargesin and (+)-magnoliadiol. Dried and pulverized flower buds (6.86 kg) were extracted with CH_2Cl_2 which was partitioned by washing with 5% NaOH. The neutral portion was subjected to silica gel CC to give 1.37 g of (−)-magnofargesin (**1**) and 1.89 g of (+)-magnoliadiol (**2**).

Isomerization of **1** *to (+)-magnolin.* The acetate of **1** (116 mg) in THF (2 ml) was cooled to 0° and diborane in THF (1 M, 0.5 ml) was added dropwise with stirring. After 2 hr at 0° and 1 hr at 25°, the excess of hydride was destroyed by the careful addn of water in THF. The reaction mixt. was oxidized at 45° by adding of 3 M NaOH (0.5 ml) and 30% H_2O_2 (0.5 ml), after 1 hr the mixt. was saturated with K_2CO_3, the THF layer sepd, and the aq. phase extracted with Et_2O. The organic layers were combined, dried over $MgSO_4$, evapd under red. pres, and the extract subjected to silica gel CC with a solvent gradient of hexane/$CHCl_3$ to 100% $CHCl_3$ to afford 8′-hydro-7′-hydroxymagnofargesin (70 mg). 1 M HCl (0.1 ml) in EtOH (0.9 ml) was added to the diol (70 mg) in EtOH (1 ml) under stirring. This mixt. was refluxed for 0.5 hr, then cooled, diluted with water (20 ml), and extracted with Et_2O (10 ml × 2). The Et_2O layer was washed with water, dried with Na_2SO_4, and evapd to an oil (38 mg). Silica gel CC afforded (+)-epimagnolin A (5 mg) and (+)-magnolin (30 mg).

(−)-Magnofargesin (**1**). White crystals. HRMS *m/z*: 416.1815 $[M]^+$ (calcd for $C_{23}H_{28}O_7$: 416.1835); MS *m/z* (rel. int.): 416 $[M]^+$ (24), 282 (18), 220 (38), 212 (46), 196 (45), 195 (28), 189 (62), 181 (19), 167 (20), 151 (91), 57 (100); $[\alpha]_D$ − 33.33° ($CHCl_3$; *c* 2.8); $[\alpha]_D$ − 33.3° (*c* 2.8, $CHCl_3$); $IR_{\nu max}$ cm^{-1}: 3497, 3012, 2938, 1593, 1516, 1464, 1329, 1239, 1128, 1026, 1005; NMR: Table 1.



(+)-magnoliadiol (**2**)

8′-Hydro-7′-hydroxymagnofargesin (**3**). HRMS *m/z* 434.1946 $[M]^+$ (calcd for $C_{23}H_{30}O_8$: 434.1940); ^1H NMR (500.0 MHz, $CDCl_3$): δ 2.52 (*m*, H-8′), 2.77 (*m*, *J* = 15.5, 10.5, 8, H-8), 3.33 (*dd*, *J* = 9, 8, H-9a), 3.62 (*dd*, *J* = 9, 8, H-9b), 3.67 (*dd*, 11, 3.5, H-9′a), 3.74 (*s*, 4-OMe), 3.77 (*s*, 3,5-OMe), 3.80 (*s*, 3′,4′-OMe), 3.94 (*m*, H-9′b), 4.46 (*d*, *J* = 7, H-7′), 4.69 (*d*, *J* = 10, 5, H-7), 6.45 (*s*, H-2, 6), 6.74 (*d*, *J* = 8, H-5′), 6.78 (*dd*, 2, 8, H-6′), 6.82 (*d*, *J* = 2, H-2′); ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 48.8 (C-8′), 52.0 (C-8), 60.8 (C-9), 70.3 (C-9′), 73.2 (C-7′), 83.2 (C-7), 102.8 (C-2, 6), 109.3 (C-2′), 111.0 (C-5′), 118.8 (C-6′), 135.1 (C-1′), 137.4

Table 1. NMR spectral data for (−)-magnofargesin (**1**)

Position	^1H*	^{13}C†
1		136.9
2	6.63 (*s*)	103.1
3		153.3
4		137.4
5		153.3
6	6.63 (*s*)	103.1
7	4.86 (*d*, *J* = 6)	82.2
8	2.97 (*m*)	55.5
9	3.84‡	62.7
	3.95 (*dd*, *J* = 6, 11.5)	
1′		139.2
2′	6.70 (*d*, *J* = 2)	111.4
3′		148.1
4′		148.8
5′	6.87 (*d*, *J* = 8)	111.2
6′	6.72 (*dd*, *J* = 2, 8)	120.6
7′	6.39 (*dd*, *J* = 2, 4)	121.6
8′		129.9
9′ax	4.74 (*ddd*, *J* = 2, 2.5, 14)	70.1
9′eq	4.93 (*dd*, *J* = 2, 14)	
OMe		
3	3.85(*s*)	56.4
4	3.83 (*s*)	60.7
5	3.85 (*s*)	56.0
3′	3.89 (*s*)	55.8
4′	3.89 (*s*)	55.8
OH	2.01 (*s*)	

*^1H NMR recorded at 270.1 MHz in $CDCl_3$, *J* in Hz, and TMS as int. standard.

†^{13}C NMR at 67.8 MHz in $CDCl_3$, TMS as int. standard.

‡Overlapped with methoxyl protons.

Table 2. NMR spectral data for (+)-magnoliadiol (**2**)

Position	^{1}H*	^{13}C†
1		128.8
2		121.6
3		151.6
4		142.0
5		152.3
6	6.54 (*s*)	106.3
7	6.46 (*s*)	124.5
8		138.2
9	4.00 (*dd*, *J* = 1, 13)	66.2
	4.90 (*dd*, *J* = 1, 13)	
1′		136.5
2′	6.67 (*d*, *J* = 2)	111.0
3′		147.3
4′		148.6
5′	6.65 (*d*, *J* = 8)	110.8
6′	6.47 (*dd*, *J* = 2, 8)	119.4
7′	4.39 (*s*)	38.5
8′	2.67 (*dt*, *J* = 1, 1, 7)	47.0
9′	3.58 (*m*)	65.2
OMe		
3	3.35 (*s*)	55.7
4	3.85 (*s*)	60.8
5	3.88 (*s*)	56.0
3′	3.79 (*s*)	55.8
4′	3.78 (*s*)	55.8
OH	2.70 (*br s*)‡	

*^{1}H NMR recorded at 270.1 MHz in $CDCl_3$, TMS as int. standard, and *J* in Hz.

†^{13}C recorded at 67.8 MHz in $CDCl_3$, TMS as int. standard.

‡Two signals for hydroxyl groups were overlapped.

(C-1), 137.5 (C-4), 149.2 (C-4′), 148.9 (C-3′), 153.2 (C-3,5).

(+)-*Magnoliadiol* (**2**). Pale yellow oil. HRMS *m/z*: 416.1835 $[M]^+$ (calcd for $C_{23}H_{28}O_7$: 416.1835); MS *m/z* (rel. int.): 416 $[M]^+$ (20), 398 (100), 382 (24), 368 (25), 355 (21), 337 (19), 260 (27), 151 (12); $[\alpha]_D$ + 62.9° ($CHCl_3$; *c* 2.1); $IR_{\nu max}$ cm^{-1}: 3418, 3001, 2938, 1593, 1515, 1456, 1346, 1235, 1125, 1028; NMR: Table 2.

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