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NEOLIGNANS FROM THE SEEDS OF *MYRISTICA FRAGRANS* HOUTT.

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Abstract. *Myristica fragrans* Houtt. is an aromatic evergreen tree that belongs to the Myristicaceae family. The seeds of this plant have been widely used in culinary field as a spice and in folk medicine for treating several diseases such as stomachic, stimulant, carminative, intestinal catarrh and colic, headaches, and diarrhea, and so on. In this study, seven neolignans including one new, maceneolignan L (**1**), and six known neolignans: *erythro*-(7*S*,8*R*)-$\Delta^{8,}$-4,7-dihydroxy-3,3',5'-trimethoxy-8-*O*-4'-neolignan (**2**), rhaphidecursinol B (**3**), maceneolignan H (**4**), maceneolignan F (**5**), (+)-(4-hydroxy-3-methoxy-1'-allyl-3',5'-dimethoxy)-8-*O*-4'-neolignan (**6**), (±) licarin A (**7**) were isolated from the seeds of *M. fragrans* Houtt. The structures of the compounds were determined by comprehensive spectroscopic analyses of their 1D-, 2D- NMR and high-resolution mass spectrometry (HR-EI-MS).

Keywords. Myristica fragrans Houtt., neolignans.

Classification numbers: 1.1.1, 1.1.6.

1. INTRODUCTION

Myristica fragrans Houtt., known in Vietnam as Nhuc Dau Khau, belongs to the Myristicaceae family and is widespread in tropical countries such as Vietnam, Indonesia, India, Mauritius, Singapore, Sri Lanka, and South Africa, etc. [1]. The seeds of this plant are reported to be useful in food processing and therapeutics. Traditionally, they have been used to treat rheumatic diseases, cholera, mental disorders, tuberculosis, stomach cramps, nausea, and diarrhea [1]. Previous phytochemical investigations have reported the isolation of essential oils [2 - 4], lignans [5 - 7], neolignans [1, 8 - 10], and diarylnonanoids [11 - 13], and they showed various pharmacological effects such as anti-inflammatory, analgesic [14 - 16], antioxidant [17, 18], antibacterial and antifungal [19, 20], anti-obesity, antidiabetic [6, 21, 22], anticancer, chemopreventive [23 - 25], hepatoprotective [26], and neuropharmacological activities [17, 27],

etc. In this paper, we reported the isolation and structural elucidation of one new neolignan (**1**) and six known ones (**2**−**7**) (Figure 1).

2. MATERIALS AND METHODS

2.1. General experimental procedures

HR-EI-MS spectra were recorded on a JEOL JMS-700 mass spectrometer (Jeol, Tokyo, Japan). ^{1}H-(500 MHz), ^{13}C-(125 MHz) NMR, and 2D-NMR spectra were recorded on a Bruker Advance Digital 500 MHz NMR spectrometer (Bruker, Karlsruhe, Germany). Thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel $60F_{254}$ and RP-18 F_{254s} (Merck, Darmstadt, Germany). Compounds were detected under UV light and then visualized by spraying the plates with a 10 % sulfuric acid reagent followed by heating to 110 °C for 1 min. Column chromatography (CC) was performed on Merck silica gel (60-200 μm) or Merck Lichroprep RP-18 gel (40 - 63 μm).

2.2. Plant material

The seeds of *M. fragrans* were purchased in an oriental medicinal market in Ha Noi, Viet Nam and identified by Dr. Do Thanh Tuan, Thai Binh University of Medicine and Pharmacy. The sample (NDK-2021) was deposited at the Center for Research and Technology Transfer, Vietnam Academy of Science and Technology.

2.3. Extraction and isolation

The dried seeds of *M. fragrans* (1.2 kg) were powdered and extracted with MeOH by ultrasonic (2h) three times. The extract was concentrated under low pressure to give MeOH residue (90.0 g), which was suspended in distilled water (0.5 L) and partitioned with *n*-hexane (3 × 1.0 L) and ethyl acetate (EtOAc, 3 × 1.0 L) to give *n*-hexane (30.0 g), EtOAc (20.5 g), and water layers. The EtOAc extract (20.5 g) was introduced to a silica gel CC and eluted with *n*-hexane/ EtOAc (2/1, v/v) to yield six fractions (1A-1F). Fraction 1A (2.5 g) was further chromatographed on a silica gel CC and eluted with *n*-hexane/ EtOAc (4/1, v/v) to give compound **2** (90.0 mg) and five fractions (2A-2E). Fraction 2C (0.5 g) was subjected to a silica gel CC and eluted with *n*-hexane/ EtOAc (3/1, v/v) to yield compound **3** (50.5 mg). Fraction 1C (3.3 g) was further subjected to a silica gel CC eluting with *n*-hexane/ EtOAc (10/1, v/v) to get six fractions (3A-3F). Compound **4** (70.0 mg) was recrystallized from the fraction 3B (0.61 g) in methylene chloride. Fraction 3D (0.45 g) was further subjected to a silica gel CC and eluted with *n*-hexane/ EtOAc (4/1, v/v) to obtain compound **5** (50.7 mg). Fraction 1E (3.2 g) was separated on a silica gel CC with elution solvent *n*-hexane/ EtOAc (15/1, v/v) to afford eight fractions (4A-4H). Fraction 4B (0.5 g) was chromatographed on an RP-18 gel CC and eluted with MeOH/ H_2O (4/1, v/v) to obtain compounds **6** (30.5 mg) and **7** (40.0 mg). Compound **1** (2.5 mg) was obtained from fraction 4D (0.1 g) using a RP-18 gel CC eluted with MeOH/ H_2O (1.5/1, v/v).

Maceneolignan L (1): colorless oil; $[\alpha]_D^{20}$ + 12.3 (c 0.05, $CHCl_3$); ^{1}H-NMR and ^{13}C-NMR data: see Table 1; HR-EI-MS *m/z* 376.1890 $[M]^+$ (calculated for $C_{21}H_{28}O_6$, 376.1890 $[M]^+$).

***Erythro*-(7*R*,8*S*)-$\Delta^{8'}$-4,7-Dihydroxy-3,3',5'-trimethoxy-8-*O*-4'-neolignan (2)**: colorless oil; $[\alpha]_D^{25}$ − 15.9 (c 0.05, $CHCl_3$); ^{1}H-NMR (500 MHz, CD_3OD): δ_H 7.01 (1H, d, *J* = 1.7 Hz, H-2), 6.81 (1H, d, *J* = 8.1 Hz, H-5), 6.75 (1H, dd, *J* = 1.7, 8.1 Hz, H-6), 6.56 (2H, s, H-2', H-6'), 6.01 (1H, ddt, *J* = 6.7, 10.0, 16.8 Hz, H-8'), 5.12 (2H, m, H-9'), 4.83 (1H, d, *J* = 3.3 Hz, H-7), 4.35

(1H, qd, *J* = 3.3, 6.4 Hz, H-8), 3.86 (3H, s, 3-OCH_3), 3.85 (6H, s, 3'-OCH_3, 5'-OCH_3), 3.37 (2H, d, *J* = 6.7 Hz, H-7'), and 1.16 (3H, d, *J* = 6.4 Hz, H-9); ^{13}C-NMR (125 MHz, CD_3OD): δ_C 154.6 (C-3', C-5'), 148.6 (C-3), 146.5 (C-4), 138.6 (C-8'), 137.6 (C-1'), 134.6 (C-4'), 133.3 (C-1), 120.0 (C-6), 116.2 (C-9'), 115.7 (C-5), 111.0 (C-2), 106.8 (C-2', C-6'), 83.7 (C-8), 75.3 (C-7), 56.3 (3-OCH_3), 56.6 (3'-OCH_3, 5'-OCH_3), 41.3 (C-7'), and 13.8 (C-9).

Rhaphidecursinol B (3): colorless oil; $[\alpha]_D^{20}$ − 21.2 (c 0.05, $CHCl_3$); ^{1}H-NMR (500 MHz, CD_3OD): δ_H 6.72 (2H, s, H-2, H-6), 6.59 (2H, s, H-2', H-6'), 6.04 (1H, ddt, *J* = 6.7, 10.0, 16.8 Hz, H-8'), 5.15 (2H, m, H-9'), 4.87 (1H, d, *J* = 3.3 Hz, H-7), 4.41 (1H, qd, *J* = 3.3, 6.4 Hz, H-8), 3.89 (6H, s, 3-OCH_3, 5-OCH_3), 3.87 (6H, s, 3'-OCH_3, 5'-OCH_3), 3.81 (3H, s, 4-OCH_3), 3.40 (2H, d, *J* = 6.7 Hz, H-7'), and 1.20 (3H, d, *J* = 6.4 Hz, H-9); ^{13}C-NMR (125 MHz, CD_3OD): δ_C 154.6 (C-3, C-5), 154.2 (C-3', C-5'), 138.7 (C-8'), 138.1 (C-4), 138.0 (C-1), 137.6 (C-4'), 134.7 (C-1'), 116.2 (C-9'), 111.0 (C-2), 106.8 (C-2', C-6'), 104.7 (C-2, C-6), 83.4 (C-8), 75.6 (C-7), 61.1 (4-OCH_3), 56.5 (3'-OCH_3, 5'-OCH_3), 56.3 (3-OCH_3, 5-OCH_3), 41.4 (C-7'), and 14.0 (C-9).

Maceneolignan H (4): colorless oil; $[\alpha]_D^{20}$ − 30.5 (c 0.05, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 6.87 (1H, d, *J* = 1.3 Hz, H-2), 6.83 (1H, dd, *J* = 1.3, 8.4 Hz, H-6), 6.78 (1H, d, *J* = 8.4 Hz, H-5), 6.38 (2H, s, H-2', H-6'), 5.94 (1H, ddt, *J* = 6.7, 10.0, 16.8 Hz, H-8'), 5.85 (1H, d, *J* = 3.3 Hz, H-7), 5.07 (2H, m, H-9'), 4.43 (1H, m, H-8), 3.83 (3H, s, 3-OCH_3), 3.81 (3H, s, 4-OCH_3), 3.75 (6H, s, 3'-OCH_3, 5'-OCH_3), 2.15 (3H, s, $C\underline{H}_3COO$), and 1.27 (1H, d, *J* = 6.5 Hz, H-9); ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 170.2 ($CH_3\underline{C}OO$), 153.3 (C-3', C-5'), 148.7 (C-3), 148.5 (C-4), 137.2 (C-8'), 135.7 (C-4'), 133.7 (C-1'), 130.5 (C-1), 119.2 (C-6), 115.9 (C-9'), 110.8 (C-5), 110.2 (C-2), 105.5 (C-2', C-6'), 80.0 (C-8), 76.6 (C-7), 55.9 (3'-OCH_3, 5'-OCH_3), 55.8 (3-OCH_3, 4-OCH_3), 40.4 (C-7'), 21.2 ($\underline{C}H_3COO$), and 14.4 (C-9).

Maceneolignan F (5): colorless oil; $[\alpha]_D^{20}$ + 13.5 (c 0.05, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 6.53 (2H, s, H-2, H-6), 6.44 (2H, s, H-2', H-6'), 5.95 (1H, ddt, *J* = 6.8, 10.0, 16.8, H-8'), 5.10 (2H, m, H-9'), 4.77 (1H, d, *J* = 2.4 Hz, H-7), 4.30 (1H, dd, *J* = 2.4, 6.4 Hz, H-8), 3.83 (6H, s, 3'-OCH_3, 5'-OCH_3), 3.81 (6H, s, 3-OCH_3, 5-OCH_3), 3.33 (2H, d, *J* = 6.8 Hz, H-7'), and 1.09 (3H, d, *J* = 6.4 Hz, H-9); ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 153.4 (C-3', C-5'), 146.9 (C-3, C-5), 137.0 (C-8'), 136.1 (C-4'), 133.6 (C-4), 132.9 (C-1'), 131.0 (C-1), 116.1 (C-9'), 105.4 (C-2', C-6'), 102.7 (C-2, C-6), 82.3 (C-8), 73.0 (C-7), 56.2 (3-OCH3, 5-OCH3), 56.0 (3'-OCH_3, 5'-OCH_3), 40.5 (C-7'), and 12.7 (C-9).

(+)-(4-Hydroxy-3-methoxy-l'-allyl-3',5'-dimethoxy)-8-*O*-4'-neolignan (6): Yellow oil; $[\alpha]_D^{20}$ + 35.0 (c 0.05, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 6.82 (1H, d, *J* = 8.0 Hz, H-5), 6.77 (1H, d, *J* = 1.8 Hz, H-2), 6.70 (1H, dd, *J* = 1.8, 8.0 Hz, H-6), 6.41 (2H, s, H-2', H-6'), 5.97 (1H, ddt, *J* = 6.8, 10.0, 16.8 Hz, H-8'), 5.10 (2H, m, H-9'), 4.34 (1H, m, H-8), 3.85 (3H, s, 3-OCH_3), 3.80 (6H, s, 3'-OCH_3, 5'-OCH_3), 3.34 (2H, d, *J* = 6.8 Hz, H-7'), 3.12 (1H, dd, *J* = 5.2, 13.5 Hz, H-7), 2.73 (1H, dd, *J* = 8.2, 13.5 Hz, H-7), and 1.20 (3H, d, *J* = 6.2 Hz, H-9); ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 153.7 (C-3', C-5'), 146.3 (C-3), 143.9 (C-4), 137.4 (C-8'), 135.5 (C-4'), 134.4 (C-1), 131.1 (C-1'), 122.2 (C-6'), 116.0 (C-9'), 114.1 (C-5), 112.3 (C-2), 105.7 (C-2', C-6'), 80.1 (C-8), 56.1 (3'-OCH_3, 5'-OCH_3), 56.0 (3-OCH_3), 43.0 (C-7), 40.6 (C-7'), and 19.6 (C-9).

(±) Licarin A (7): white powder; $[\alpha]_D^{20}$ + 0.0 (c 0.02, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ_H 6.98 (1H, s, H-2), 6.90 (2H, overlapped, H-5, H-6), 6.80 (1H, s, H-6'), 6.77 (1H, s, H-2'), 6.37 (1H, dd, *J* = 1.5, 15.7 Hz, H-7'), 6.11 (1H, dq, *J* = 6.6, 15.7 Hz, H-8'), 5.11 (1H, d, *J* = 9.4 Hz, H-7), 3.90 (3H, s, 3'-OCH_3), 3.88 (3H, s, 3-OCH_3), 3.45 (1H, dq, *J* = 6.7, 9.4 Hz, H-8), 1.88 (3H, dd, *J* = 1.5, 6.6 Hz, H-9'), and 1.38 (3H, d, *J* = 6.7 Hz, H-9); ^{13}C-NMR (125 MHz, $CDCl_3$): δ_C 146.8 (C-4'), 146.7 (C-3), 145.9 (C-5'), 144.3 (C-4), 133.4 (C-3'), 132.3 (C-1), 132.2 (C-1'), 131.1 (C-7'), 123.6 (C-8'), 120.1 (C-6), 114.2 (C-5), 113.4 (C-2'), 109.4 (C-6'), 109.1 (C-2), 93.9

(C-7), 56.1 (3-OCH_3, 3'-OCH_3), 45.7 (C-8), 18.5 (C-9'), and 17.7 (C-9).

3. RESULTS AND DISCUSSION

Compound **1** was isolated as colorless amorphous, its molecular formula was established as $C_{21}H_{28}O_6$ by the HR-EI-MS which produced a molecular ion peak at *m/z* 376.1890 $[M]^+$ (calculated. for $C_{21}H_{28}O_6$, 376.1890). The ^{1}H-NMR spectrum (Table 1) of **1** displayed signals of a 1,3,4-trisubstituted benzene ring at δ_H 6.76 (1H, d, *J* = 2.1 Hz, H-2), 6.81 (1H, d, *J* = 8.0 Hz, H-5), and 6.70 (1H, dd, *J* = 2.1, 8.0 Hz, H-6); a 1,3,4,5-tetrasubstituted benzene ring at δ_H 6.56 (2H, s, H-2', H-6'); two oxygenated methine protons at δ_H 4.52 (1H, dd, *J* = 6.0, 12.4 Hz, H-7') and 4.36 (1H, m, H-8); two methylene groups at δ_H 3.10 (1H, dd, *J* = 5.2, 13.6 Hz, H-7), 2.73 (1H, dd, *J* = 8.1, 13.6 Hz, H-7), 1.77 (2H, m, H-8'); two methyl groups at δ_H 1.20, (3H, d, *J* = 6.2 Hz, H-9) and 0.93 (3H, t, *J* = 7.4 Hz, H-9'); and three methoxy groups at δ_H 3.81 (6H, s, 2'-OCH_3, 6'-OCH_3), and 3.86 (3H, s, 3-OCH_3).

Table 1. NMR data of compound **1** in $CDCl_3$

Position	δ_H mult., (*J* in	δ_C, type[b]	COSY	HMBC
1		131.1, C		
2	6.76, d (2.1)	112.3, CH		C-4, C-6, C-7
3		146.3, C		
4		144.0, C		
5	6.81, d (8.0)	114.1, CH	H-6	C-3, C-1
6	6.70, dd (2.1, 8.0)	122.2, CH	H-5	C-2, C-4, C-7
7	3.10, dd (5.2, 13.6)	43.1, CH_2	H-8	C-2, C-6, C-8, C-9
	2.73, dd (8.1, 13.6)			
8	4.36, m	80.1, CH	H-7, H-9	C-1, C-7, C-9, C-4'
9	1.20, d (6.2)	19.7, CH_3	H-8	C-7, C-8
1'		140.2, C		
2'	6.56, s	103.1, CH		C-4', C-6', C-7'
3'		153.8, C		
4'		135.4, C		
5'		153.8, C		
6'	6.56, s	103.1, CH		C-2', C-4', C-7'
7'	4.52, dd (6.0, 12.4)	76.5, CH	H-8'	C-2', C-6', C-8' C-9'
8'	1.77, m	32.1, CH_2	H-7', H-9'	C-1', C-7', C-9'
9'	0.93, t (7.4)	10.4, CH_3	H-8'	C-8', C-7'
3-OCH_3	3.86, s	56.0, OCH_3		C-3
3'-OCH_3	3.81, s	56.2, OCH_3		C-3'
5'-OCH_3	3.81, s	56.2, OCH_3		C-5'

Recorded at [a]500 MHz and [b]125 MHz. [a, b] Assigned by HSQC, ^{1}H-^{1}H COSY, and HMBC.

These proton signals were connected to the carbons resonating at δ_C 112.3 (C-2), 114.1 (C-5), 122.2 (C-6), 103.1 (C-2', C-6'), 76.5 (C-7'), 80.1 (C-8), 43.1 (C-7), 32.1 (C-8'), 19.7 (C-9), 10.4 (C-9'), and 56.2 (3'- OCH_3, 5'-OCH_3) in the HSQC spectrum. In addition, the ^{13}C NMR and

HSQC of **1** also exhibited seven non-protonated carbons at δ_C 131.1 (C-1), 146.3 (C-3), 144.0 (C-4), 135.4 (C-4'), 153.8 (C-3', C-5'), 140.2 (C-1') (Table 1). The 1D NMR data were similar to those of (+)-(4-hydroxy-3-methoxy-l'-allyl-3',5'-dimethoxy)-8-*O*-4'-neolignan (**6**) [29], except for the replacement of an allyl moiety by a 1-hydroxypropyl moiety. This was further confirmed by the COSY correlation between H-8' (δ_H 4.52) and H-7' (δ_H 1.77)/ H-9' (δ_H 0.93) as well as the HMBC correlation between H-9' and C-7' (δ_C 76.5)/ C-8' (δ_C 32.9). The absolute configuration of **1** was retained due to its small amount. Thus, the chemical structure of new compound **1** was elucidated as (4-hydroxy-3-methoxy-l'-(1-hydroxypropyl)-3',5'-dimethoxy)-8-*O*-4'-neolignan and named maceneolignan L (Figure 1).

Six known compounds were identified to be *erythro*-(7*R*,8*S*)-$\Delta^{8'}$-4,7-dihydroxy-3,3',5'-trimethoxy-8-*O*-4'-neolignan (**2**) [28], rhaphidecursinol B (**3**) [9], maceneolignan H (**4**) [10], maceneolignan F (**5**) [10], (+)-(4-hydroxy-3-methoxy-l'-allyl-3',5'-dimethoxy)-8-*O*-4'-neolignan (**6**) [29], and (±) licarin A (**7**) [30] by the consistency of their NMR spectral data with those reported in the literature (Figure 1).

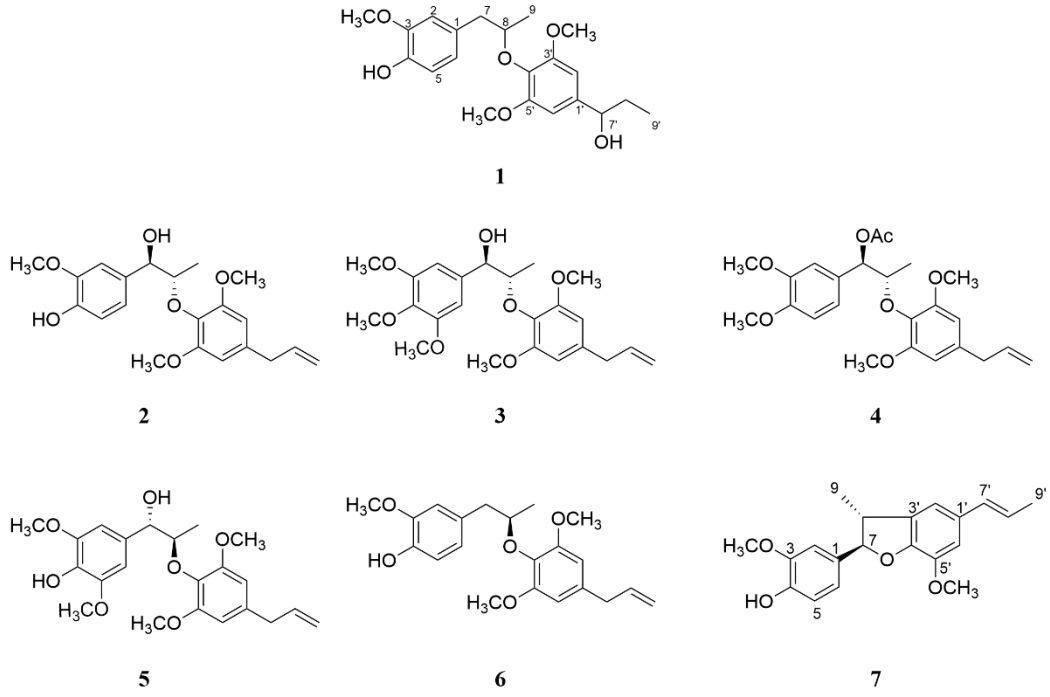

Figure 1. The chemical structures of compounds **1**–**7**

4. CONCLUSION

From the seeds of *M. fragrans* Houtt., one new neolignan, maceneolignan L (**1**), and six known compounds were isolated including *erythro*-(7*S*,8*R*)-$\Delta^{8'}$ -4,7-dihydroxy-3,3' ,5' -trimethoxy-8-*O*-4' -neolignan (**2**), rhaphidecursinol B (**3**), maceneolignan H (**4**), maceneolignan F (**5**), (+)-(4-hydroxy-3-methoxy-1'-allyl-3',5'-dimethoxy)-8-*O*-4'-neolignan (**6**), and (±) licarin A (**7**). Their structures were elucidated using spectroscopic analysis and comparing them with those previously reported in the literature.

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Declaration of competing interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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