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Three New Neolignans, Fargesones A, B and C, from the Flower Buds of *Magnolia fargesii*

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Three new neolignans, fargesone A (I), fargesone B (II) and fargesone C (III), together with two known compounds, denudatin B (IV) and syringin (V), have been isolated from the flower buds of *Magnolia fargesii*, and their structures determined.

Keywords——*Magnolia fargesii*; hsin-i; fargesone A; fargesone B; fargesone C; neolignan

The flower buds of *Magnolia fargesii* (Chinese name hsin-i) have been used for nasal empyema and headache. From this herb we have isolated four lignans: pinoresinol dimethyl ether, lirioresinol-B dimethyl ether, magnolin and fargesin.[1] Recently, we have been searching for Ca^{2+}-antagonizing activity in Chinese herbs. We found that the extract of hsin-i exhibited a Ca^{2+}-antagonizing activity on the taenia coli of the guinea pig. Meanwhile three new neolignans, fargesone A (I), fargesone B (II) and fargesone C (III), together with two known compounds, denudatin B (IV) and syringin (V), have been isolated from the $CHCl_3$ extracts of the herb,[2] and we present here the structural elucidation of the three new neolignans.

Fargesone A (I) was obtained as a viscous oil, $[\alpha]_D$ $-150°$ ($c=1.1$, $CHCl_3$), with a molecular weight of 372 as determined from the mass (MS) spectrum. Its ultraviolet (UV) spectrum (250, 270 nm) and infrared (IR) spectrum (1665, 1612, 1490 cm^{-1}) suggested the presence of a substituted benzene and an α,β-unsaturated carbonyl group. Fargesone A was considered to be a hydrobenzofuranoid neolignan on the basis of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum (Table I) and MS spectrum (*m/z* 162, 46%), which clearly indicated the presence of a 3,4-methylenedioxyphenyl function and an Me–$\underset{C}{CH}$–$\underset{O}{CH}$–Ar moiety with Ar and Me groups in a *trans*-relationship.[3-5] The chemical shift of the methyl group at δ 1.05 (d, $J=7$ Hz) also indicated a *trans*-relationship with the phenyl group.[3-5] Irradiation of the methyl doublet at δ 1.05 (H-9) caused the multiplet at δ 2.17—2.24 to collapse to a doublet δ 2.18 (d, $J_{H\text{-}7,H\text{-}8}=9.5$ Hz, H-8). Irradiation of the methine doublet at δ 4.67 (H-7) simplified the multiplet at δ 2.17—2.24 to a quartet at δ 2.18 ($J=7$ Hz, H-8). The additional C_6–C_3 unit could be accounted for by a cyclohexenone having two methoxyls (δ 3.20 and 3.76), one linked to the fully substituted sp^3-carbon and the other to the sp^2-carbon, and an allyl group (δ 2.51—2.58, m, H_A-7′; 2.66—2.76, m, H-1′ and H_B-7′; 5.06—5.16, 2H, m, H-9′; 5.81—5.90, m, H-8′) linked to the trisubstituted sp^3-carbon. The chemical shift of H-8 (δ 2.17—2.24) indicated OMe-3′ and H-8 to be in a *trans*-relationship.[6,7] The OMe-3′ must be in the β-orientation, due to the coupling constant of H-7 and H-8 being 9.5 Hz.[6] The presence of an nuclear Overhauser effect (NOE) between OMe-3′ and H-2′ established the *cis* junction of

TABLE I. ^{1}H-NMR Data for Fargesone A (I), Fargesone B (II) and Fargesone C (III) (300 MHz, $CDCl_3$)

Proton No.	I	II	III
2	6.78 br s		7.29 s
5	6.74 br s	6.65—6.72 m	6.76 d (8)[a]
6			7.47 d (8)[a]
7	4.67 d (10)[a]	4.20—4.23 m	
8	2.17—2.24 m	2.01—2.11 m	4.18 q (7)[a]
9	1.05 d (7)[a]	1.05 d (7)[a]	1.32 d (7)[a]
1′	2.66—2.76 m	2.63—2.70 m	
2′	4.40 d (9)[a]	4.20—4.23 m	6.42 s
5′	5.53 s	5.52 s	5.39 s
7_A′	2.51—2.58 m	2.29—2.39 m	3.13 d (6.6)[a]
7_B′	2.66—2.76 m	2.79—2.87 m	
8′	5.81—5.90 m	5.83—5.97 m	5.85—5.91 m
9′	5.06—5.16 m	5.03—5.15 m	5.10—5.12 m
O–CH_2–O	5.92 s	5.91 s	6.00 s
OMe-3′	3.20 s	3.29 s	3.06 s
OMe-4′	3.76 s	3.70 s	3.42 s

a) Figures in parentheses are coupling constants in Hz.

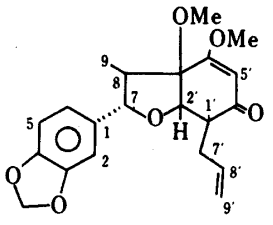
TABLE II. ^{13}C-NMR Data (δ Values) for Fargesone A (I), Fargesone B (II) and Fargesone C (III)

Carbon No.	I	II	III
1	134.06 s	133.68 s	131.65 s
2	105.35 d	103.21 d	105.46 d
3	147.74 s	147.65 s	151.76 s
4	147.26 s	147.19 s	148.08 s
5	106.47 d	106.47 d	107.48 d
6	120.12 d	119.81 d	124.33 d
7	86.94 d	85.79 d	197.36 s
8	51.00 d	49.24 d	47.82 s
9	8.56 q	10.99 q	12.50 q
1′	52.47 d	53.60 d	140.32 s
2′	79.70 d	80.89 d	138.07 d
3′	84.39 s	82.04 s	76.53 s
4′	172.12 s	173.12 s	170.84 s
5′	107.90 d	107.80 d	108.10 d
6′	196.07 s	196.59 s	185.97 s
7′	30.94 t	28.93 t	32.86 t
8′	135.20 d	136.13 d	135.09 d
9′	117.55 t	116.70 t	116.98 t
O–CH_2–O	100.92 t	100.99 t	101.01 t
OMe-3′	51.21 q	53.14 q	52.05 q
OMe-4′	56.11 q	55.92 q	55.41 q

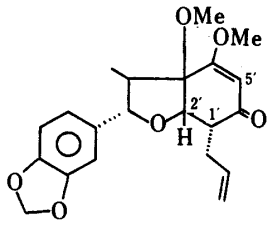
Run in $CDCl_3$ at 300 MHz. Assignment established by off-resonance and DEPT methods.

the two fused rings, and therefore H-2′ must be in the β-axial orientation. The chemical shift of the H-2′ doublet at δ 4.40 (J=9 Hz) confirmed the *trans*-diaxial relationship of H-1′ and H-2′. Therefore the allyl group must be in the β-equatorial orientation. The structure of I was further confirmed by carbon-13 nucler magnetic resonance (^{13}C-NMR) spectroscopy (Table

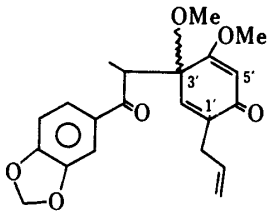
II); the methoxyl group, linked to the sp^2-carbon, located at the β-position (C-4′) from the carbonyl group showed a downfield singlet at δ 172.12.[8] Based on the above evidence, the structure of fargesone A can be unambiguously assigned as formula I.



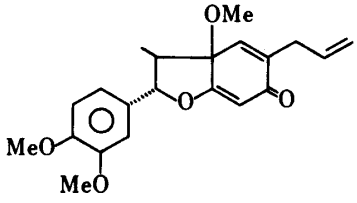
fargesone A (I)



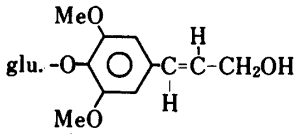
fargesone B (II)



fargesone C (III)



denudatin B (IV)



syringin (V)

Fargesone B (II) was also obtained as a viscous oil, $[\alpha]_D$ −190° (c=1.0, $CHCl_3$), with a molecular weight of 372. The UV, IR and ^{1}H-NMR (Table I) spectra of I and II were very similar. Fargesone B also had an α,β-unsaturated carbonyl group and the partial structure Me–CH(C)–CH(O)–Ar (Ar=3,4-methylenedioxyphenyl) with the Ar and Me group in a *trans*-relationship (δ 1.05, d, J=7 Hz, H-9).[3-5] This was confirmed by irradiation of the methyl double doublet at δ 2.66 (J=9.5 and 4.8 Hz). Irradiation at δ 2.06 (H-8) caused the H-7 signal (J=9 Hz, H-8). The multiplet at δ 4.20—4.23 (2H) was the overlapped signals of H-7 and H-2′. Since irradiation of the multiplet at δ 4.22 caused (i) the multiplet at δ 2.06 (H-8) to collapse to a quartet (J=7 Hz), and (ii) the multiplet at δ 2.63—2.70 (H-1′) to collapse to a double doublet at δ 2.66 (J=9.5 and 4.8 Hz). Irradiation at δ 2.06 (H-8) caused the H-7 signal to collapse to a singlet at δ 4.21 and H-2′ to appear as a doublet (J=4.2 Hz) at δ 4.22. Therefore the allyl group must be in the α-axial orientation due to the small coupling constant (J=4.2 Hz) between H-1′ and H-2′. The structure II was further confirmed by ^{13}C-NMR (Table II), and the evidence that the methoxyl group linked to the sp^2-carbon was located at the β-position (C-4′) from the carbonyl group. From the above evidence, fargesone B must be an epimer of fargesone A. Chemical correlation between fargesone A and fargesone B was achieved as follows. When fargesone B was treated with 1% methanolic NaOH at room temperature overnight, fargesone A was obtained quantitatively. This result also confirmed the orientation of the allyl group in fargesone A or fargesone B.

Fargesone C (III) was obtained as colorless prisms, mp 126—127 °C, $[\alpha]_D$ −206.5° (c=1.0, $CHCl_3$) with a molecular weight of 370 (from the MS spectrum). Its UV spectrum (234, 280, 310 nm) and IR spectrum (1670, 1642, 1610 cm^{-1}) suggested the presence of a substituted aromatic ketone and an α,β-unsaturated carbonyl group. The ^{1}H-NMR (δ 6.00, 6.76, 7.29 and 7.47) (Table I) and MS spectrum (m/z 149) clearly indicated the presence of a 3,4-methylenedioxyphenyl ketone. The chemical shifts at δ 1.32 (3H, d, J=7 Hz) and δ 4.18 (1H, q, J=7 Hz) were assigned to H-9 and H-8, respectively. The additional C_6–C_3 unit could be accounted for by a cyclohexadienone having two methoxyls (δ 3.06 and 3.42), one linked to the fully substituted sp^3-carbon and the other to the sp^2-carbon, and an allyl group [δ 3.13

(2H, d, H-7′); δ 5.12 (2H, m, H-9′); δ 5.91 (1H, m, H-8′)] linked to the sp^2-carbon, with two isolated olefinic proton signals at δ 5.39 and 6.42. The structure III was further confirmed by ^{13}C-NMR (Table II), and the evidence that the methoxyl group linked to the sp^2-carbon was located at the β-position (C-4′) from the carbonyl group. The gross structure of fargesone C can be assigned as formula III. An analysis of the stereochemistry is in progress.

In addition to the three new neolignans discussed above, two known compounds, namely denudatin B (IV) and syringin (V), were isolated from the same source. Their structures were confirmed by comparison of their spectral data with those in the literature.[4,9-11]

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-30 instrument. UV spectra were taken on a Hitachi 124 spectrophotometer. Optical rotations were measured with JASCO DIP-140 polarimeter. ^{1}H- and ^{13}C-NMR spectra were taken on a Brucker AM 300 at 300 MHz, using tetramethylsilane (TMS) as an internal standard.

Extraction and Isolation——Commercial Chinese crude drug (1.5 kg), the flower buds of *Magnolia fargesii* (hsin-i), was extracted with $CHCl_3$ (3 l × 2) and EtOH (3 l × 2), successively. The $CHCl_3$ extract (110 g) was chromatographed on a silica gel (800 g) column. The following fractions were eluted, in order, with the indicated solvent systems: Fr. I (*n*-hexane : EtOAc = 10 : 1), fr. II (EtOAc) and fr. III (MeOH). Fr. II was further chromatographed on a silica gel column, using a linear gradient of increasing concentrations of EtOAc in *n*-hexane, to give six fractions (fr. II-a→fr. II-f). Fr. II-a was purified by preparative thin layer chromatography (PTLC) to obtain denudatin B (IV). Fr. II-b was purified on a Lichroprep Si60 column (Merck Co.) with CH_2Cl_2. Two new compounds, fargesone A (I) and fargesone B (II), were isolated from this fraction. Fr. II-c was purified by PTLC to give a new crystalline compound, fargesone C (III). The EtOH extract was chromatographed on a silica gel column and eluted exhaustively with a $CHCl_3$–MeOH gradient, then further purified by PTLC to give a glucoside, syringin (V).

Fargesone A (I)——A viscous oil, $[\alpha]_D$ −150° (c = 1.1, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 250 (17798), 290 (4683) IR (KBr) cm^{-1}: 3000—2800, 1665, 1612, 1490, 1445, 1365, 1245, 1195, 1040, 930, 810, 750. MS *m/z* (%): 372 (100, M^+), 195 (60), 190 (50), 167 (48), 162 (46), 149 (98). ^{1}H-NMR: Table I. ^{13}C-NMR: Table II.

Fargesone B (II)——A viscous oil, $[\alpha]_D$ −196° (c = 1.0, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 245 (13924), 290 (2531). IR (KBr) cm^{-1}: 3000—2800. 1670, 1610, 1490, 1440, 1365, 1245, 1195, 1040, 932, 810, 750. MS *m/z* (%): 372 (100, M^+), 195 (60), 190 (60), 167 (48), 162 (46), 149 (98). ^{1}H-NMR: Table I. ^{13}C-NMR: Table II.

Conversion of II to I——Compound II (2 mg) was added to 10 ml of 1% methanolic NaOH and left to stand at room temperature overnight. Then the reaction mixture was diluted with H_2O (10 ml) and extracted with $CHCl_3$ (20 ml). The extracts were dried (Na_2SO_4), and the solvent was evaporated off under reduced pressure. The product was identical with compound I as judged by comparison with an authentic sample.

Fargesone C (III)——Colorless prisms, mp 126—127 °C, $[\alpha]_D$ −206.5° (c = 1.0, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 234 (22222), 280 (8994), 310 (9523). IR (KBr) cm^{-1}: 3100—2300, 1670, 1640, 1610, 1440, 1355, 1245, 1225, 1168, 1080, 1030, 995, 970, 920, 875, 830. MS *m/z*(%): 370 (19, M^+), 193 (100), 162 (26), 149 (57). ^{1}H-NMR: Table I. ^{13}C-NMR: Table II.

Denudatin B (IV)——A viscous oil, $[\alpha]_D$ +83.2° (c = 1.1, $CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 208 (18010), 235 (17820), 285 (6900), 300 (6350). IR (KBr) cm^{-1}: 3000—2800, 1675, 1645, 1625, 1505, 1460, 1350, 1275, 1180, 1140, 1060, 1030, 920. MS *m/z*: 356 (M^+), 341, 325, 178. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, J = 7 Hz, H-9), 2.16 (1H, m, H-8), 3.10 (3H, s, OMe-5′), 3.14 (2H, m, H-7′), 3.85 (6H, s, Ar-OMe), 5.08—5.14 (2H, m, H-9′), 5.32 (1H, d, J = 9.5 Hz, H-7). 5.78 (1H, s, H-3′), 5.81—5.92 (1H, m, H-8′), 6.23 (1H, s, H-6′), 6.72—6.88 (3H, m, Ar-H).

Syringin (V)——White prisms, mp 187—189 °C. IR (KBr) cm^{-1}: 3600—3100, 2900, 1640, 1589, 1505, 1415, 1240, 1130, 1090, 1025, 965. MS *m/z*: 210, 182, 167.

Syringin Pentaacetate (Va)——Acetylation of syringin (Ac_2O/pyr.) resulted in the formation of prisms, mp 110—111 °C. IR (KBr) cm^{-1}: 3000—2850, 1740, 1580, 1220, 1020. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s), 2.02 (6H, s), 2.05 (3H, s), 2.08 (3H, s), 3.66 (1H, m, H-5′), 3.81 (6H, s, Ar-OMe), 4.09 (1H, dd, J = 12, 3 Hz, H_A-6′), 4.22 (1H, dd, J = 12, 5 Hz, H_B-6′), 4.68 (2H, d, J = 6 Hz, =C–CH_2–O), 5.05 (1H, d, J = 7 Hz, H-1′), 5.18—5.31 (3H, m, H-2′, 3′ and 4′), 6.14—6.23 (1H, m, C=C<u>H</u>–CH_2), 6.54 (1H, d, J = 18 Hz, Ar-C<u>H</u>=C), 6.57 (2H, d, Ar-H).

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