Neolignans, a Coumarinolignan, Lignan Derivatives, and a Chromene: Anti-inflammatory Constituents from *Zanthoxylum avicennae*

Jih-Jung Chen,*[,†] Tzu-Ying Wang,[†] and Tsong-Long Hwang[‡]

Graduate Institute of Pharmaceutical Technology, Tajen University, Pingtung 907, Taiwan, Republic of China, and Graduate Institute of Natural Products, Chang Gung University, Taoyuan 333, Taiwan, Republic of China

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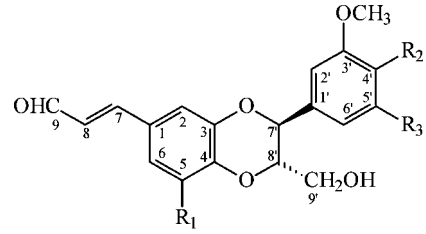
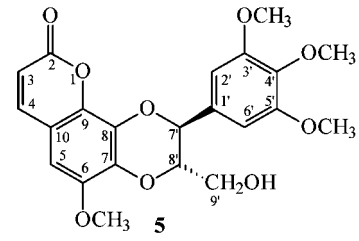
Eight new compounds, including four new neolignans, (7′*S*,8′*S*)-bilagrewin (**1**), (7′*S*,8′*S*)-5-demethoxybilagrewin (**2**), (7′*S*,8′*S*)-5-*O*-demethyl-4′-*O*-methylbilagrewin (**3**), and (7′*S*,8′*S*)-nocomtal (**4**), a new coumarinolignan, (7′*S*,8′*S*)-4′-*O*-methylcleomiscosin D (**5**), two new lignan derivatives, (+)-9′-*O*-(*Z*)-feruloyl-5,5′-dimethoxylariciresinol (**6**) and (+)-9′-*O*-(*E*)-feruloyl-5,5′-dimethoxylariciresinol (**7**), and a new chromene, (*E*)-3-(2,2-dimethyl-2*H*-chromen-6-yl)prop-2-enal (**8**), have been isolated from the stem wood of *Zanthoxylum avicennae*, together with 18 known compounds (**9**–**26**). The structures of these new compounds were determined through spectroscopic and MS analyses. (7′*S*,8′*S*)-4′-*O*-Methylcleomiscosin D (**5**), cleomiscosin D (**9**), skimmianine (**18**), robustine (**19**), and integrifoliolin (**23**) exhibited inhibition ($IC_{50} \leq 18.19$ μM) of superoxide anion generation by human neutrophils in response to formyl-L-methionyl-L-leucyl-L-phenylalanine/cytochalasin B (FMLP/CB). In addition, skimmianine (**18**) inhibited FMLP/CB-induced elastase release with an IC_{50} value of 19.15 ± 0.66 μM.

Human neutrophils are known to play crucial roles in host defense against microorganisms and in pathogenesis of various diseases such as rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), ischemia-reperfusion injury, and asthma.[1–5] In response to diverse stimuli, activated neutrophils secrete a series of cytotoxins, such as the superoxide anion radical ($O_2^{\bullet-}$), a precursor to other reactive oxygen species (ROS), granule proteases, and bioactive lipids.[2,6,7] Suppression of the extensive or inappropriate activation of neutrophils by drugs has been proposed as a way to ameliorate inflammatory diseases. Despite this, there are only a few currently available agents that directly modulate neutrophil proinflammatory responses in clinical practice. *Zanthoxylum avicennae* (Lam.) DC (Rutaceae) is an evergreen shrub distributed in Vietnam, Philippines, southern China, and Taiwan.[8] A decoction of its stems is used as a stomach tonic and as a counter-poison to snake bite.[9] Previous studies of this plant have reported the isolation of flavonoids, alkaloids, coumarins, and terpenoids.[10–15] In our studies on the anti-inflammatory constituents of Formosan plants, many species have been screened for *in vitro* anti-inflammatory activity, and *Z. avicennae* has been found to be one of the active species. The MeOH extract of *Z. avicennae* inhibited FMLP/CB-induced superoxide anion generation and elastase release in a concentration-dependent manner with IC_{50} values of 6.34 ± 0.56 and 15.32 ± 1.46 μg/mL, respectively. In our search for compounds with anti-inflammatory activities, four new neolignans, (7′*S*,8′*S*)-bilagrewin (**1**), (7′*S*,8′*S*)-5-demethoxybilagrewin (**2**), (7′*S*,8′*S*)-5-*O*-demethyl-4′-*O*-methylbilagrewin (**3**), and (7′*S*,8′*S*)-nocomtal (**4**), a new coumarinolignan, (7′*S*,8′*S*)-4′-*O*-methylcleomiscosin D (**5**), two new lignan derivatives, (+)-9′-*O*-(*Z*)-feruloyl-5,5′-dimethoxylariciresinol (**6**) and (+)-9′-*O*-(*E*)-feruloyl-5,5′-dimethoxylariciresinol (**7**), and a new chromene, (*E*)-3-(2,2-dimethyl-2*H*-chromen-6-yl)prop-2-enal (**8**), and 18 known compounds (**9**–**26**) have been isolated and identified from the stem wood of *Z. avicennae*. This paper describes the structural elucidation and anti-inflammatory activities of **1**–**8**.



1 $R_1 = R_3 = OCH_3$, $R_2 = OH$
2 $R_1 = H$, $R_2 = OH$, $R_3 = OCH_3$
3 $R_1 = OH$, $R_2 = R_3 = OCH_3$
4 $R_1 = OCH_3$, $R_2 = OH$, $R_3 = H$



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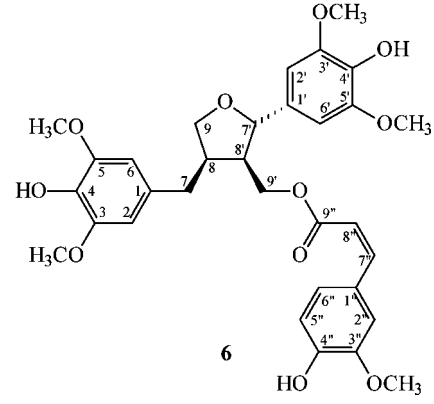

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Results and Discussion

Chromatographic purification of the EtOAc-soluble fraction of the stem wood of *Z. avicennae* on a Si gel column and preparative TLC afforded eight new (**1**–**8**) and 18 known compounds (**9**–**26**).

(7′*S*,8′*S*)-Bilagrewin (**1**) was obtained as a pale yellow, amorphous powder. Its molecular formula, $C_{21}H_{22}O_8$, was determined

* To whom correspondence should be addressed. Tel: +886-8-7624002, ext 332. Fax: +886-8-7625308. E-mail: jjchen@mail.tajen.edu.tw.
† Tajen University.
‡ Chang Gung University.

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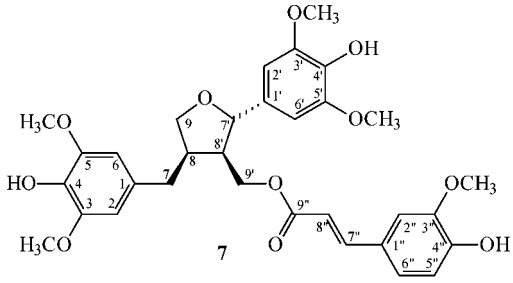

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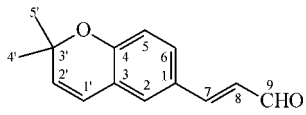

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on the basis of the positive HRESIMS at *m/z* 425.1210 $[M + Na]^+$ (calcd 425.1212) and supported by the ^1H, ^{13}C, and DEPT NMR data. The IR spectrum showed the presence of hydroxy (3432 cm^{-1}) and carbonyl (1665 cm^{-1}) groups. Comparison of the ^1H and ^{13}C NMR data of **1** with those of nocomtal (**4**)[16] suggested that their structures are closely related except that the 5′-methoxy group (δ 3.92) of **1** replaced H-5′ (δ 6.97) of nocomtal. This was supported by NOESY correlations (see Figure 1S in the Supporting Information) between OMe-5′ (δ 3.92) and H-6′ (δ 6.67). Compound **1** showed similar CD Cotton effects [225 ($\Delta\epsilon = -0.48$), 238 ($\Delta\epsilon = +0.55$), 287 ($\Delta\epsilon = +0.56$) nm] compared with analogous neolignans.[17] Thus, **1** possessed a 7′*S*,8′*S*-configuration. On the basis of the evidence above, the structure of **1** was elucidated as (7′*S*,8′*S*)-bilagrewin. Although the 7′*S*,8′*R* diastereomer, bilagrewin[18] was reported as a constituent from *Grewia bilamellata*,[18] this is the first isolation of the 7′*S*,8′*S* enantiomer from a natural source.

(7′*S*,8′*S*)-5-Demethoxybilagrewin (**2**) was isolated as an optically active, colorless oil ($[\alpha]^{25}_D = -19.7$). HRESIMS gave an $[M + Na]^+$ ion at *m/z* 395.1110 (calcd for $C_{20}H_{20}O_7Na$, 395.1107), consistent with a molecular formula of $C_{20}H_{20}O_7Na$. The IR spectrum showed a hydroxy absorption at 3402 cm^{-1} and a carbonyl function at 1665 cm^{-1}. The ^1H NMR spectrum of **2** was similar to that of bilagrewin (**1**),[18] except that H-5 [δ 7.03 (1H, d, $J = 8.0$ Hz)] of **2** replaced the 5-methoxy group [δ 3.95 (1H, s)] of bilagrewin. This was supported by both HMBC correlations between H-5 (δ 7.03) and both C-1 (δ 128.2) and C-3 (δ 143.8) and NOESY correlations between H-5 (δ 7.03) and H-6 (7.15). The 7′*S*,8′*S* configuration of **2** was evidenced by CD Cotton effects at 224 nm ($\Delta\epsilon = -0.45$), 235 nm ($\Delta\epsilon = +0.52$), and 284 nm ($\Delta\epsilon = +0.54$) in analogy with those of **1**. Thus, the structure of **2** was elucidated as (7′*S*,8′*S*)-5-demethoxybilagrewin. This was confirmed by COSY and NOESY data (see Figure 2S in the Supporting Information). The assignment of ^{13}C NMR resonances was confirmed by DEPT, HSQC, and HMBC (see Figure 2S in the Supporting Information) techniques.

(7′*S*,8′*S*)-5-*O*-Demethyl-4′-*O*-methylbilagrewin (**3**) was isolated as a pale yellow oil. The sodiated ion $[M + Na]^+$ (*m/z* 425.1208) in the HRESIMS of **3** was consistent with the formula $C_{21}H_{22}O_8Na$ (calcd 425.1212). A comparison of the ^1H and ^{13}C NMR data of **3** with those of bilagrewin (**1**)[18] suggested that their structures are closely related, except that the 5-hydroxy and 4′-methoxy groups of **3** replaced the 5-methoxy and 4′-hydroxy groups of bilagrewin.[18] This was supported by HMBC correlations observed between 5-OH (δ 5.62) and both C-5 (δ 148.0) and C-4 (δ 136.0) and between 4′-OMe (δ 3.89) and C-4′ (δ 137.3). The absolute configuration of **3** was assigned as 7′*S*,8′*S* by the CD Cotton effects at 225 nm ($\Delta\epsilon = -0.49$), 237 nm ($\Delta\epsilon = +0.56$), and 285 nm ($\Delta\epsilon = +0.57$) in analogy with previous CD observations.[17] On the basis of the above data, the structure of **3** was elucidated as (7′*S*,8′*S*)-5-*O*-demethyl-4′-*O*-methylbilagrewin. This was further confirmed by $^1H-^1H$ COSY and NOESY (see Figure 3S, Supporting Information) experiments. The full assignment of the carbon resonances was confirmed by DEPT, HSQC, and HMBC (see Figure 3S, Supporting Information) techniques.

(7′*S*,8′*S*)-Nocomtal (**4**) was obtained as a pale yellow oil, and the molecular formula was confirmed as $C_{20}H_{20}O_7$ from the sodiated ion peak at *m/z* 395.1111 $[M + Na]^+$ (calcd for $C_{20}H_{20}O_7Na$, 395.1107) obtained by HRESIMS. The ^1H NMR spectrum of **4** showed the resonances of a 4-hydroxy-3-methoxyphenyl group, a hydroxymethyl group, two oxymethine protons, two *meta*-coupled aromatic protons, a methoxy group, and an (*E*)-3-oxoprop-1-enyl group similar to those of bilagrewin (**1**), except that H-5′ [δ 6.97 (1H, d, $J = 8.0$ Hz)] of **4** replaced the 5′-OMe group (δ 3.92) of **1**. This was supported by NOESY correlations between H-5′ (δ 6.97) and H-6′ (δ 6.93). Compound **4** showed similar CD Cotton effects to those of **3**, and the absolute configuration of **4** has to be 7′*S*,8′*S*. On the basis of the above data, the structure of **4** was elucidated as (7′*S*,8′*S*)-nocomtal, which was further confirmed by the $^1H-^1H$ COSY, NOESY (see Figure 4S, Supporting Information), DEPT, HSQC, and HMBC (see Figure 4S, Supporting Information) experiments. Although the enantiomeric mixture (7′*R*,8′*R*/7′*S*,8′*S*)[16] of **4** was reported as a constituent from the xylem tissue of caffeic acid *O*-methyltransferase (COMT)-deficient poplar (*Populus* spp.),[16] this is the first isolation of the 7′*S*,8′*S* enantiomer from a natural source.

(7′*S*,8′*S*)-4′-*O*-Methylcleomiscosin D (**5**) was isolated as colorless needles with a molecular formula of $C_{22}H_{22}O_9$ as determined by positive-ion HRESIMS, showing an $[M + Na]^+$ ion at *m/z* 453.1166 (calcd for $C_{22}H_{22}O_9Na$, 453.1162). The presence of OH and carbonyl groups in **5** was revealed by the bands at 3395 and 1718 cm^{-1}, respectively, in the IR spectrum. The ^1H NMR spectrum of **5** showed the presence of a 3,4,5-trimethoxyphenyl group, two oxymethine protons, a hydroxymethyl group, a methoxy group, an aromatic proton, and two mutually coupled protons of a 2*H*-3,4-dehydropyran-2-one ring similar to signals described previously for cleomiscosin D (**9**),[19] except for the resonance of OMe-4′ (δ 3.93) in the spectrum of **5**, replacing that of OH-4′ (δ 5.65) of **9**. This was supported by HMBC correlations between OMe-4′ (δ 3.93) and C-4′ (δ 137.6). The absolute configurations at C-7′ and C-8′ were determined as 7′*S*,8′*S* by CD comparison with the analogous neolignan 7*S*,8*S*-nitidanin.[17] On the basis of the above data, the structure of **5** was elucidated as (7′*S*,8′*S*)-4′-*O*-methylcleomiscosin D. This was confirmed by $^1H-^1H$ COSY and NOESY (see Figure 5S, Supporting Information) experiments. The assignment of ^{13}C NMR resonances was confirmed by DEPT, HSQC, and HMBC (see Figure 5S, Supporting Information) techniques. This is the first isolation of the 7′*S*,8′*S* enantiomer of **5** from a natural source, although the 7′*R*,8′*R* enantiomer of **5** has been synthesized by Bhandari et al.[20]

(+)-9′-*O*-(*Z*)-Feruloyl-5,5′-dimethoxylariciresinol (**6**) was isolated as a colorless, amorphous, optically active powder ($[\alpha]^{25}_D = +23.4$). The molecular formula $C_{32}H_{36}O_{11}$ was deduced from the positive ion $[M]^+$ at *m/z* 596.2255 in the HREIMS. Comparison of the ^1H NMR data of **6** with those of (−)-9′-*O*-(*E*)-feruloyl-5,5′-dimethoxylariciresinol[21] suggested that their structures are related except that the 9′-*O*-(*Z*)-feruloyl moiety of **6** replaced a 9′-*O*-(*E*)-feruloyl moiety of (−)-9′-*O*-(*E*)-feruloyl-5,5′-dimethoxylariciresinol.[21] This was supported by the *cis*-coupling costant ($J = 12.8$ Hz) for H-7″ and H-8″ of **6**. NOESY correlations (see Figure 6S, Supporting Information) of **6** were observed between H-9′ (δ 4.26, 4.43) and both H-7 (δ 2.86) and H-7′ (δ 4.77) and between H-8′ (δ 2.62) and both H-8 (δ 2.72) and H-2′/6′ (δ 6.55). Moreover, NOESY correlations could not be detected between H-9′ (δ 4.26, 4.43) and both H-8 (δ 2.72) and H-2′/6′ (δ 6.55). Thus, the 8,8′-*cis*/7′,8′-*trans* configuration of **6** was established. The absolute configuration of **6** was assigned as 8*R*,7′*S*,8′*R* by the negative CD Cotton effect at 245 nm ($\Delta\epsilon = -0.75$) in analogy with previous

Table 1. Inhibitory Effects of **1**–**25** on Superoxide Radical Anion Generation and Elastase Release by Human Neutrophils in Response to fMet-Leu-Phe/Cytochalasin B[a]

compound	superoxide anion IC_{50} (μM)[b]	elastase IC_{50} (μM)[a]
(7′*S*,8′*S*)-bilagrewin (**1**)	48.65 ± 3.32***	>50
(7′*S*,8′*S*)-5-demethoxybilagrewin (**2**)	26.88 ± 2.41***	>50
(7′*S*,8′*S*)-5-*O*-demethyl-4′-*O*-methylbilagrewin (**3**)	>50	>50
(7′*S*,8′*S*)-nocomtal (**4**)	>50	>50
(7′*S*,8′*S*)-4′-*O*-methylcleomiscosin D (**5**)	14.72 ± 3.84***	>50
(+)-9′-*O*-(*Z*)-feruloyl-5,5′-dimethoxylariciresinol (**6**)	27.97 ± 3.65**	28.93 ± 5.43
(+)-9′-*O*-(*E*)-feruloyl-5,5′-dimethoxylariciresinol (**7**)	33.56 ± 3.31**	>50
(*E*)-3-(2,2-dimethyl-2*H*-chromen-6-yl)prop-2-enal (**8**)	>50	>50
cleomiscosin D (**9**)	13.08 ± 3.80***	>50
aesculetin dimethyl ether (**10**)	42.86 ± 6.07***	>50
scopoletin (**11**)	>50	>50
6,7,8,-trimethoxycoumarin (**12**)	49.52 ± 5.62***	>50
luvangetin (**13**)	>50	>50
avicennol (**14**)	>50	32.02 ± 4.21***
avicennol methyl ether (**15**)	48.43 ± 2.78***	>50
γ-fagarine (**16**)	31.31 ± 1.92***	>50
dictamnine (**17**)	>50	>50
skimmianine (**18**)	13.24 ± 1.35***	19.15 ± 0.66***
robustine (**19**)	18.19 ± 5.53***	>50
isodictamnine (**20**)	>50	>50
4-methoxy-1-methyl-2-quinolone (**21**)	>50	>50
edulitine (**22**)	37.95 ± 2.59***	>50
integrifoliolin (**23**)	18.19 ± 4.95***	32.55 ± 0.46
methyl (*E*)-4-(3′-methyl-2′-enyloxy)cinnamate (**24**)	49.28 ± 6.54*	>50
(-)-syringaresinol (**25**)	39.87 ± 6.24**	>50
diphenyleneiodonium	1.68 ± 0.79***	
phenylmethylsulfonyl fluoride		204.08 ± 33.07***

[a] Diphenyleneiodonium and phenylmethylsulfonyl fluoride were used as positive control. Results are presented as average ± SEM ($n = 4$). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with the control. [b] Concentration necessary for 50% inhibition (IC_{50}).

CD data.[22] According to the above data, the structure of **6** was elucidated as (+)-9′-*O*-(*Z*)-feruloyl-5,5′-dimethoxylariciresinol.

(+)-9′-*O*-(*E*)-Feruloyl-5,5′-dimethoxylariciresinol (**7**) was obtained as an amorphous powder ($[\alpha]^{25}_D = +20.8$). Its molecular formula was determined as $C_{32}H_{36}O_{11}$ using positive HRESIMS, which showed a sodiated ion peak at $m/z = 619.2153$ $[M + Na]^+$ (calcd for $C_{32}H_{36}O_{11}Na$, 619.2155). The ^1H and ^{13}C NMR data of **7** were similar to those of **6**, except that a 9′-*O*-(*E*)-feruloyl moiety of **7** replaced a 9′-*O*-(*Z*)-feruloyl moiety of **6**. Comparison of the CD data of **7** with that of **6** suggested that **7** also possessed an 8*R*,7′*S*,8′*R* configuration. The structure of **7** was thus elucidated as (+)-9′-*O*-(*E*)-feruloyl-5,5′-dimethoxylariciresinol. This was further confirmed by the $^1H-^1H$ COSY, NOESY (see Figure 7S, Supporting Information), DEPT, HSQC, and HMBC (see Figure 7S, Supporting Information) techniques. This is the first report of the occurrence of **7** in a natural source, although the enantiomeric (−)-9′-*O*-(*E*)-feruloyl-5,5′-dimethoxylariciresinol has been isolated by Hsiao et al.[21]

(*E*)-3-(2,2-Dimethyl-2*H*-chromen-6-yl)prop-2-enal (**8**) was isolated as a colorless oil. The HRESIMS of **8** showed an elemental composition of $C_{14}H_{14}O_2Na$ at m/z 237.0890 $[M + Na]^+$ (calcd 237.0891). The presence of a carbonyl group was revealed by a band at 1670 cm^{-1} in the IR spectrum, which was confirmed by the resonance at δ 194.0 in the ^{13}C NMR spectrum. The ^1H NMR spectrum of **8** showed the resonances for a 2,2-dimethyl-3,4-dehydropyrano moiety, three ABX-coupled aromatic protons, and an (*E*)-3-oxoprop-1-enyl group. On the basis of NOESY correlations between H-2 (δ 7.20) and H-7 (δ 7.37) and H-1′ (δ 6.34) and between H-6 (δ 7.34) and H-5 (δ 6.81) and H-7 (δ 7.37), the (*E*)-3-oxoprop-1-enyl group was assigned to C-1. According to the above data, the structure of **8** was elucidated as (*E*)-3-(2,2-dimethyl-2*H*-chromen-6-yl)prop-2-enal, which was confirmed by $^1H-^1H$ COSY and NOESY (see Figure 8S, Supporting Information) experiments. The assignment of ^{13}C NMR resonances was confirmed by DEPT, HSQC, and HMBC (see Figure 8S, Supporting Information) techniques.

The known isolates were readily identified by a comparison of physical and spectroscopic data (UV, IR, ^1H NMR, $[\alpha]_D$, and MS) with corresponding authentic samples or literature values, and this included a coumarinolignan, cleomiscosin D (**9**),[19] six coumarins, aesculetin dimethyl ether (**10**),[23] scopoletin (**11**),[24] 6,7,8,-trimethoxycoumarin (**12**),[25] luvangetin (**13**),[26] avicennol (**14**),[27] and avicennol methyl ether (**15**),[27] four furoquinolines, γ-fagarine (**16**),[28] dictamnine (**17**),[29] skimmianine (**18**),[30] and robustine (**19**),[31] a furo-4-quinolone, isodictamnine (**20**),[32] two 2-quinolones, 4-methoxy-1-methyl-2-quinolone (**21**)[31] and edulitine (**22**),[33] two phenylpropenoids, integrifoliolin (**23**)[34] and methyl (*E*)-4-(3′-methyl-2′-enyloxy)cinnamate (**24**),[35] a lignan, (−)-syringaresinol (**25**),[36] and a steroid, β-sitosterol (**26**).[37]

The anti-inflammatory effects of compounds isolated from the stem wood of *Z. avicennae* were evaluated by suppressing formyl-L-methionyl-L-leucyl-L-phenylalanine/cytochalasin B (FMLP/CB)-induced superoxide radical anion ($O_2^{\bullet-}$) generation and elastase release by human neutrophils. The anti-inflammatory activity data are shown in Table 1. Diphenyleneiodonium and phenylmethylsulfonyl fluoride were used as positive controls for $O_2^{\bullet-}$ generation and elastase release, respectively. From the results of our anti-inflammatory tests, the following conclusions can be drawn: (a) (7′*S*,8′*S*)-5-demethoxybilagrewin (**2**), (7′*S*,8′*S*)-4′-*O*-methylcleomiscosin D (**5**), (+)-9′-*O*-(*Z*)-feruloyl-5,5′-dimethoxylariciresinol (**6**), cleomiscosin D (**9**), γ-fagarine (**16**), skimmianine (**18**), robustine (**19**), and integrifoliolin (**23**) exhibited inhibitory activities ($IC_{50} \leq 27.97$ μM) on human neutrophil $O_2^{\bullet-}$ generation. (b) (+)-9′-*O*-(*Z*)-Feruloyl-5,5′-dimethoxylariciresinol (**6**), avicennol (**14**), skimmianine (**18**), and integrifoliolin (**23**) inhibited FMLP/CB-induced elastase release with IC_{50} values ≤ 32.55 μM. (c) Among the analogues (**16**–**19**), **18** (with 7,8-dimethoxy) and **19** (with 8-hydroxy) exhibited more effective inhibition than **16** (with 8-methoxy) and **17** (without 7- and 8-substituents) against $O_2^{\bullet-}$ generation and elastase release. (d) Coumarinolignans **5** and **9** showed stronger inhibition than the analogous neolignans **1**–**4** against FMLP-induced $O_2^{\bullet-}$ generation. (e) Cleomiscosin D (**9**) and skimmianine (**18**) are

the most effective among the isolated compounds, with IC_{50} values of 13.08 ± 3.80 and 13.24 ± 1.35 μM, respectively, against FMLP-induced superoxide anion generation. (f) Skimmianine (**18**) exhibited the most effective inhibition, with an IC_{50} value of 19.15 ± 0.66 μM against FMLP-induced elastase release.

Experimental Section

General Experimental Procedures. All melting points were determined on a Yanaco micromelting point apparatus and were uncorrected. Optical rotations were measured using a Jasco DIP-370 polarimeter in $CHCl_3$. UV spectra were obtained on a Jasco UV-240 spectrophotometer. IR spectra (KBr or neat) were recorded on a Perkin-Elmer system 2000 FT-IR spectrometer. NMR spectra, including COSY, NOESY, HMBC, and HSQC experiments, were recorded on a Varian Unity 400 or a Varian Inova 500 spectrometer operating at 400 and 500 MHz (^{1}H) and 100 and 125 MHz (^{13}C), respectively, with chemical shifts given in ppm (δ) using TMS as an internal standard. EI, ESI, and HR-ESI-mass spectra were recorded on a Bruker APEX II mass spectrometry. HREI-mass spectra were recorded on a JEOL JMX-HX 110 mass spectrometer. Si gel (70–230, 230–400 mesh) (Merck) was used for CC. Si gel 60 F-254 (Merck) was used for TLC and preparative TLC.

Plant Material. The stem wood of *Z. avicennae* was collected from Pakuashan, Changhua County, Taiwan, in June 2006 and identified by Dr. I. S. Chen. A voucher specimen (Chen 3007) was deposited in the Department of Pharmacy, Tajen University, Pingtung, Taiwan.

Extraction and Separation. The dried stem wood of *Z. avicennae* (16 kg) was extracted with cold MeOH, and the extract concentrated under reduced pressure. The MeOH extract (430 g), when partitioned between H_2O/EtOAc (1:1), afforded an EtOAc-soluble fraction (fraction A, 98.6 g). Fraction A (98.6 g) was chromatographed on Si gel (70–230 mesh, 3.8 kg), eluting with CH_2Cl_2, gradually increasing the polarity with MeOH to give 14 fractions: A1 (12.5 L, CH_2Cl_2), A2 (7 L, CH_2Cl_2/MeOH, 100:1), A3 (6 L, CH_2Cl_2/MeOH, 90:1), A4 (5 L, CH_2Cl_2/MeOH, 80:1), A5 (4 L, CH_2Cl_2/MeOH, 70:1), A6 (5 L, CH_2Cl_2/MeOH, 60:1), A7 (3 L, CH_2Cl_2/MeOH, 50:1), A8 (7 L, CH_2Cl_2/MeOH, 40:1), A9 (4 L, CH_2Cl_2/MeOH, 30:1), A10 (6 L, CH_2Cl_2/MeOH, 20:1), A11 (8 L, CH_2Cl_2/MeOH, 10:1), A12 (6 L, CH_2Cl_2/MeOH, 5:1), A13 (6 L, CH_2Cl_2/MeOH, 1:1), A14 (4 L, MeOH). Fraction A1 (5.8 g) was chromatographed further on Si gel (230–400 mesh, 203 g) eluting with $CHCl_3$/acetone (40:1) to give 12 fractions (each 500 mL, A1-1–A1-12). Fraction A1-4 (380 mg) was purified by MPLC (9.8 g Si gel, 40–63 mesh, *n*-hexane/EtOAc 10:1, 75 mL fractions) to obtain 16 subfractions: A1-4-1–A1-4-16. Fraction A1-4-4 (22 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 2:1) to obtain **24** (2.3 mg) (R_f = 0.36). Fraction A1-4-6 (28 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 10:1) to yield **23** (2.8 mg) (R_f = 0.43) and **8** (2.0 mg) (R_f = 0.44). Fraction A1-4-10 (26 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/MeOH, 50:1) to obtain **20** (3.5 mg) (R_f = 0.55). Fraction A1-4-12 (25 mg) was purified further by preparative TLC (Si gel, CH_2Cl_2/EtOAc, 40:1) to afford **13** (3.9 mg) (R_f = 0.45). Fraction A1-4-13 (25 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/acetone, 5:1) to obtain **14** (3.5 mg) (R_f = 0.72). Fraction A1-4-15 (32 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/acetone, 25:1) to yield **19** (3.3 mg) (R_f = 0.56). Fraction A1-5 (135 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/acetone, 40:1) to afford **26** (3.8 mg) (R_f = 0.44). Fraction A1-8 (2.0 g) was subjected to CC (72 g Si gel, 230–400 mesh; $CHCl_3$/acetone, 40:1, 1 L fractions) to give 10 subfractions: A1-8-1–A1-8-10. Fraction A1-8-3 (198 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 2:1) to afford **17** (4.3 mg) (R_f = 0.35). Fraction A1-8-4 (205 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 2:1) to obtain **12** (3.7 mg) (R_f = 0.20). Fraction A1-8-5 (188 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/EtOAc, 30:1) to yield **10** (6.9 mg) (R_f = 0.44) and **16** (4.6 mg) (R_f = 0.41). Fraction A2 (3.2 g) was chromatographed further on Si gel (230–400 mesh, 170 g) eluting with CH_2Cl_2/EtOAc (10:1) to give 10 fractions (each 1.0 L, A2-1–A2-10). Fraction A2-1 (178 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/acetone, 10:1) to obtain **11** (2.9 mg) (R_f = 0.38). Fraction A2-3 (198 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/EtOAc, 1:3) to obtain **15** (2.5 mg) (R_f = 0.65). Fraction A6 (4.3 g) was chromatographed further on Si gel (230–400 mesh, 235 g) eluting with CH_2Cl_2/MeOH (25:1) to give 11 subfractions (each 1.0 L, A6-1–A6-11). Fraction A6-2 (174 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/acetone, 20:1) to yield **18** (4.0 mg) (R_f = 0.40). Fraction A6-3 (166 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/MeOH, 30:1) to yield **21** (12.2 mg) (R_f = 0.38). Fraction A7 (5.2 g) was chromatographed further on Si gel (230–400 mesh, 175 g) eluting with $CHCl_3$/MeOH (25:1) to give 20 fractions (each 500 mL, A7-1–A7-20). Fraction A7-7 (207 mg) was purified further by preparative TLC (Si gel, CH_2Cl_2/acetone, 10:1) to yield **25** (122 mg) (R_f = 0.37). Fraction A7-9 (190 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/acetone, 5:1) to yield **5** (3.9 mg) (R_f = 0.48). Fraction A7-10 (538 mg) was purified by MPLC (18 g Si gel, 40–63 mesh, *n*-hexane/EtOAc 1:5, 50 mL fractions) to obtain eight subfractions: A7-10-1–A7-10-8. Fraction A7-10-2 (32 mg) was purified further by preparative TLC (Si gel, CH_2Cl_2/acetone, 10:1) to afford **4** (2.6 mg) (R_f = 0.49). Fraction A7-10-3 (35 mg) was purified further by preparative TLC (Si gel, CH_2Cl_2/acetone, 10:1) to afford **2** (3.2 mg) (R_f = 0.49). Fraction A7-10-4 (38 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 1:2) to obtain **6** (3.6 mg) (R_f = 0.13). Fraction A7-10-5 (48 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 1:2) to yield **3** (2.8 mg) (R_f = 0.17) and **7** (3.2 mg) (R_f = 0.12). Fraction A7-11 (191 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 1:3) to yield **1** (3.8 mg) (R_f = 0.37). Fraction A7-12 (184 mg) was purified further by preparative TLC (Si gel, $CHCl_3$/acetone, 5:1) to yield **9** (4.2 mg) (R_f = 0.39). Fraction A7-13 (175 mg) was purified further by preparative TLC (Si gel, *n*-hexane/EtOAc, 1:4) to yield **22** (2.7 mg) (R_f = 0.33).

Biological Assay. The anti-inflammatory effects of the isolated compounds from *Z. avicennae* were evaluated by inhibiting the generation of $O_2^{\bullet-}$ and the release of elastase in FMLP-activated human neutrophils in a concentration-dependent manner.

Preparation of Human Neutrophils. Human neutrophils from the venous blood of healthy, adult volunteers (20–28 years old) were isolated using a standard method of dextran sedimentation prior to centrifugation in a Ficoll Hypaque gradient and hypotonic lysis of erythrocytes.[38] Purified neutrophils containing >98% viable cells, as determined by the trypan blue exclusion method, were resuspended in a Ca^{2+}-free HBSS buffer at pH 7.4 and were maintained at 4 °C prior to use.

Measurement of $O_2^{\bullet-}$ Generation. The assay for measurement of $O_2^{\bullet-}$ generation was based on the SOD-inhibitable reduction of ferricytochrome *c*.[39,40] In brief, after supplementation with 0.5 mg/mL ferricytochrome *c* and 1 mM Ca^{2+}, neutrophils were equilibrated at 37 °C for 2 min and incubated with drugs for 5 min. Cells were activated with 100 nM FMLP for 10 min. When FMLP was used as a stimulant, CB (1 μg/mL) was incubated for 3 min before activation by peptide (FMLP/CB). Changes in absorbance with the reduction of ferricytochrome *c* at 550 nm were continuously monitored in a double-beam, six-cell positioner spectrophotometer with constant stirring (Hitachi U-3010, Tokyo, Japan). Calculations were based on differences in the reactions with and without SOD (100 U/mL) divided by the extinction coefficient for the reduction of ferricytochrome *c* (ϵ = 21.1/mM/10 mm).

Measurement of Elastase Release. Degranulation of azurophilic granules was determined by measuring elastase release as described previously.[40] Experiments were performed using MeO-Suc-Ala-Ala-Pro-Val-*p*-nitroanilide as the elastase substrate. Briefly, after supplementation with MeO-Suc-Ala-Ala-Pro-Val-*p*-nitroanilide (100 μM), neutrophils (6×10^5/mL) were equilibrated at 37 °C for 2 min and incubated with drugs for 5 min. Cells were stimulated with FMLP (100 nM)/cytochalasin B (0.5 μg/mL), and changes in absorbance at 405 nm were continuously being monitored in order to assay elastase release. The results were expressed as the percent of elastase release in the FMLP/cytochalasin B-activated, drug-free control system.

Statistical Analysis. Results are expressed as the mean ± SEM, and comparisons were made using Student's *t*-test. A probability of 0.05 or less was considered significant.

(7′*S*,8′*S*)-Bilagrewin (1): pale yellow, amorphous powder; $[\alpha]^{25}_D$ −20.2 (*c* 0.12, MeOH); UV (MeOH) λ_{max} (log ϵ) 276 (4.15), 332 (4.31) nm; CD (MeOH, $\Delta\epsilon$) 225 (−0.48), 238 (+0.55), 287 (+0.56) nm; IR (neat) ν_{max} 3432 (OH), 1665 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.43 (1H, br s, D_2O exchangeable, OH-9′), 3.58 (1H, m, H-9′), 3.92 (6H, s, OMe-3′ and OMe-5′), 3.93 (1H, m, H-9′), 3.95 (3H, s, OMe-5), 4.07 (1H, dt, *J* = 8.0, 3.0 Hz, H-8′), 4.97 (1H, d, *J* = 8.0 Hz, H-7′), 5.63 (1H, br s, D_2O exchangeable, OH-4′), 6.60 (1H, dd, *J* = 16.0, 7.6 Hz, H-8), 6.67 (2H, s, H-2′ and H-6′), 6.77 (1H, d, *J* = 2.0

Hz, H-6), 6.90 (1H, d, J = 2.0 Hz, H-2), 7.36 (1H, d, J = 16.0 Hz, H-7), 9.66 (1H, d, J = 7.6 Hz, CHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.5 (OMe-5), 56.7 (OMe-3′), 56.7 (OMe-5′), 61.6 (C-9′), 76.7 (C-7′), 79.2 (C-8′), 104.2 (C-6), 104.3 (C-2′), 104.3 (C-6′), 111.6 (C-2), 126.8 (C-1′), 126.9 (C-1), 127.6 (C-8), 135.7 (C-4′), 136.2 (C-4), 144.8 (C-3), 147.6 (C-3′), 147.6 (C-5′), 149.4 (C-5), 152.9 (C-7), 193.8 (C-9); ESIMS m/z (rel int) 425 ([M + Na]$^+$, 100); HRESIMS m/z 425.1210 [M + Na]$^+$ (calcd for $C_{21}H_{22}O_8Na$, 425.1212).

(7′*S*,8′*S*)-5-Demethoxybilagrewin (2): colorless oil; $[\alpha]^{25}_D$ −19.7 (c 0.13, MeOH); UV (MeOH) λ_{max} (log ϵ) 305 (4.27), 332 (4.33) nm; CD (MeOH, $\Delta\epsilon$) 224 (−0.45), 235 (+0.52), 284 (+0.54) nm; IR (neat) ν_{max} 3402 (OH), 1665 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.58 (1H, m, H-9′), 3.93 (1H, m, H-9′), 3.93 (6H, s, OMe-3′ and OMe-5′), 4.06 (1H, ddd, J = 8.4, 3.2, 2.8 Hz, H-8′), 5.01 (1H, d, J = 8.4 Hz, H-7′), 5.64 (1H, br s, D_2O exchangeable, OH-4′), 6.62 (1H, dd, J = 16.0, 8.0 Hz, H-8), 6.67 (2H, s, H-2′ and H-6′), 7.03 (1H, d, J = 8.0 Hz, H-5), 7.15 (1H, dd, J = 8.0, 2.0 Hz, H-6), 7.23 (1H, d, J = 2.0 Hz, H-2), 7.40 (1H, d, J = 16.0 Hz, H-7), 9.68 (1H, d, J = 8.0 Hz, CHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.7 (OMe-3′), 56.7 (OMe-5′), 61.8 (C-9′), 77.1 (C-7′), 78.4 (C-8′), 104.3 (C-2′), 104.3 (C-6′), 117.0 (C-2), 118.2 (C-5), 123.2 (C-6), 126.7 (C-1′), 127.5 (C-8), 128.2 (C-1), 135.8 (C-4′), 143.8 (C-3), 146.9 (C-4), 147.6 (C-3′), 147.6 (C-5′), 152.7 (C-7), 193.9 (C-9); ESIMS m/z (rel int) 395 ([M + Na]$^+$, 100); HRESIMS m/z 395.1110 [M + Na]$^+$ (calcd for $C_{20}H_{20}O_7Na$, 395.1107).

(7′*S*,8′*S*)-5-*O*-Demethyl-4′-*O*-methylbilagrewin (3): pale yellow oil; $[\alpha]^{25}_D$ −21.5 (c 0.10, MeOH); UV (MeOH) λ_{max} (log ϵ) 277 (4.13), 331 (4.22) nm; CD (MeOH, $\Delta\epsilon$) 225 (−0.49), 237 (+0.56), 285 (+0.57) nm; IR (neat) ν_{max} 3422 (OH), 1668 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.58 (1H, m, H-9′), 3.89 (3H, s, OMe-4′), 3.91 (6H, s, OMe-3′ and OMe-5′), 3.93 (1H, m, H-9′), 4.07 (1H, dt, J = 8.4, 3.0 Hz, H-8′), 4.98 (1H, d, J = 8.4 Hz, H-7′), 5.62 (1H, br s, D_2O exchangeable, OH-5), 6.62 (1H, dd, J = 15.6, 7.6 Hz, H-8), 6.67 (2H, s, H-2′ and H-6′), 6.78 (1H, d, J = 2.0 Hz, H-6), 6.90 (1H, d, J = 2.0 Hz, H-2), 7.38 (1H, d, J = 15.6 Hz, H-7), 9.68 (1H, d, J = 7.6 Hz, CHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.3 (OMe-3′), 56.3 (OMe-5′), 61.1 (OMe-4′), 61.6 (C-9′), 76.8 (C-7′), 79.1 (C-8′), 103.2 (C-2′), 103.2 (C-6′), 107.1 (C-6), 111.6 (C-2), 126.5 (C-1′), 127.3 (C-1), 127.6 (C-8), 136.0 (C-4), 137.3 (C-4′), 145.2 (C-3), 148.0 (C-5), 152.8 (C-7), 153.2 (C-3′), 153.2 (C-5′), 193.8 (C-9); ESIMS m/z (rel. int.) 425 ([M + Na]$^+$, 100); HRESIMS m/z 425.1208 [M + Na]$^+$ (calcd for $C_{21}H_{22}O_8Na$, 425.1212).

(7′*S*,8′*S*)-Nocomtal (4): pale yellow oil; $[\alpha]^{25}_D$ −23.8 (c 0.14, MeOH); UV (MeOH) λ_{max} (log ϵ) 275 (4.18), 334 (4.17) nm; CD (MeOH, $\Delta\epsilon$) 224 (−0.47), 236 (+0.54), 286 (+0.55) nm; IR (neat) ν_{max} 3420 (OH), 1670 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03 (1H, br s, D_2O exchangeable, OH-9′), 3.59 (1H, m, H-9′), 3.93 (1H, m, H-9′), 3.94 (3H, s, OMe-3′), 3.95 (3H, s, OMe-5), 4.08 (1H, dt, J = 8.0, 3.0 Hz, H-8′), 5.00 (1H, d, J = 8.0 Hz, H-7′), 5.73 (1H, br s, D_2O exchangeable, OH-4′), 6.60 (1H, dd, J = 16.0, 7.6 Hz, H-8), 6.77 (1H, d, J = 2.0 Hz, H-6), 6.89 (1H, d, J = 2.0 Hz, H-2), 6.93 (1H, dd, J = 8.0, 1.6 Hz, H-6′), 6.97 (1H, d, J = 1.6 Hz, H-2′), 6.97 (1H, d, J = 8.0 Hz, H-5′), 7.36 (1H, d, J = 16.0 Hz, H-7), 9.67 (1H, d, J = 7.6 Hz, CHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.4 (OMe-3′), 56.5 (OMe-5), 61.6 (C-9′), 76.6 (C-7′), 79.2 (C-8′), 104.1 (C-6), 110.6 (C-2′), 111.5 (C-2), 115.6 (C-5′), 121.5 (C-6′), 126.8 (C-1), 127.6 (C-8), 128.5 (C-1′), 136.3 (C-4), 145.0 (C-3), 145.7 (C-4′), 147.5 (C-3′), 149.5 (C-5), 152.9 (C-7), 193.8 (C-9); ESIMS m/z (rel int) 395 ([M + Na]$^+$, 100); HRESIMS m/z 395.1111 [M + Na]$^+$ (calcd for $C_{20}H_{20}O_7Na$, 395.1107).

(7′*S*,8′*S*)-4′-*O*-Methylcleomiscosin D (5): colorless needles ($CHCl_3$/MeOH); mp 252–254 °C; $[\alpha]^{25}_D$ −15.2 (c 0.11, $CDCl_3$); UV (MeOH) λ_{max} (log ϵ) 325 (4.26) nm; CD (MeOH, $\Delta\epsilon$) 226 (−0.43), 237 (+0.53), 286 (+0.55) nm; IR (neat) ν_{max} 3395 (OH), 1718 (C=O), 1618, 1510, 1457 (aromatic ring C=C stretch) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.59 (1H, m, H-9′), 3.92 (1H, m, H-9′), 3.93 (9H, s, OMe-3′, 4′, and 5′), 3.96 (3H, s, OMe-6), 4.02 (1H, dt, J = 8.0, 3.0 Hz, H-8′), 5.05 (1H, d, J = 8.0 Hz, H-7′), 6.22 (1H, d, J = 9.6 Hz, H-3), 6.55 (1H, s, H-5), 6.67 (2H, s, H-2′ and H-6′), 7.94 (1H, d, J = 9.6 Hz, H-4); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.7 (OMe-6), 56.7 (OMe-3′), 56.7 (OMe-5′), 60.9 (OMe-4′), 61.6 (C-9′), 77.5 (C-7′), 78.5 (C-8′), 93.1 (C-5), 103.4 (C-2′), 103.4 (C-6′), 103.7 (C-10), 112.4 (C-3), 126.3 (C-1′), 132.5 (C-8), 137.6 (C-4′), 138.3 (C-4), 140.0 (C-9), 149.9 (C-7), 152.5 (C-6), 153.0 (C-3′), 153.0 (C-5′), 161.3 (C-2); ESIMS m/z 453 [M + Na]$^+$; HRESIMS m/z 453.1166 [M + Na]$^+$ (calcd for $C_{22}H_{22}O_9Na$, 453.1162).

(+)-9′-*O*-(*Z*)-Feruloyl-5,5′-dimethoxylariciresinol (6): amorphous powder; $[\alpha]^{25}_D$ +23.4 (c 0.12, MeOH); UV (MeOH) λ_{max} (log ϵ) 287 (3.82), 299 (3.89), 325 (4.04) nm; CD (MeOH, $\Delta\epsilon$) 245 (−0.75) nm; IR (neat) ν_{max} 3422 (OH), 1711 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.51 (1H, dd, J = 13.6, 11.0 Hz, H-7), 2.62 (1H, m, H-8′), 2.72 (1H, m, H-8), 2.86 (1H, dd, J = 13.6, 4.8 Hz, H-7), 3.75 (1H, dd, J = 8.8, 6.4 Hz, H-9), 3.87 (12H, s, OMe-3, 5, 3′, and 5′), 3.95 (3H, s, OMe-3″), 4.06 (1H, dd, J = 8.8, 6.8 Hz, H-9), 4.26 (1H, dd, J = 11.6, 7.2 Hz, H-9′), 4.43 (1H, dd, J = 11.6, 7.2 Hz, H-9′), 4.77 (1H, d, J = 6.4 Hz, H-7′), 5.41 (1H, br s, D_2O exchangeable, OH-4), 5.47 (1H, br s, D_2O exchangeable, OH-4′), 5.77 (1H, d, J = 12.8 Hz, H-8″), 5.87 (1H, br s, D_2O exchangeable, OH-4″), 6.38 (2H, s, H-2 and H-6), 6.55 (2H, s, H-2′ and H-6′), 6.83 (1H, d, J = 12.8 Hz, H-7″), 6.88 (1H, d, J = 8.4 Hz, H-5″), 7.14 (1H, dd, J = 8.4, 2.0 Hz, H-6″), 7.78 (1H, d, J = 2.0 Hz, H-2″); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.8 (C-7), 42.6 (C-8), 49.1 (C-8′), 56.0 (OMe-3″), 56.3 (OMe-3), 56.3 (OMe-5), 56.3 (OMe-3′), 56.3 (OMe-5′), 62.3 (C-9′), 72.7 (C-9), 83.2 (C-7′), 102.4 (C-2′), 102.4 (C-6′), 105.2 (C-2), 105.2 (C-6), 112.8 (C-2″), 113.9 (C-5″), 115.8 (C-8″), 125.9 (C-6″), 127.0 (C-1″), 131.1 (C-1), 133.2 (C-4), 133.5 (C-1′), 134.1 (C-4′), 144.9 (C-7″), 145.8 (C-3″), 147.0 (C-3), 147.0 (C-5), 147.0 (C-3′), 147.0 (C-5′), 147.3 (C-4″), 166.2 (C-9″); EIMS m/z (rel int) 596 ([M]$^+$, 12), 581 (5), 402 (35), 235 (58), 194 (23), 181 (100), 167 (90); HREIMS m/z 596.2255 [M]$^+$ (calcd for $C_{32}H_{36}O_{11}$, 596.2258).

(+)-9′-*O*-(*E*)-Feruloyl-5,5′-dimethoxylariciresinol (7): amorphous powder; $[\alpha]^{25}_D$ +20.8 (c 0.10, MeOH); UV (MeOH) λ_{max} (log ϵ) 286 (3.85), 298 (3.89), 324 (4.03) nm; CD (MeOH, $\Delta\epsilon$) 246 (−0.73) nm; IR (neat) ν_{max} 3420 (OH), 1695 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.56 (1H, dd, J = 13.6, 10.8 Hz, H-7), 2.66 (1H, m, H-8′), 2.76 (1H, m, H-8), 2.90 (1H, dd, J = 13.6, 4.8 Hz, H-7), 3.79 (1H, dd, J = 8.8, 6.4 Hz, H-9), 3.87 (12H, s, OMe-3, 5, 3′, and 5′), 3.95 (3H, s, OMe-3″), 4.10 (1H, dd, J = 8.8, 6.8 Hz, H-9), 4.33 (1H, dd, J = 11.4, 7.4 Hz, H-9′), 4.53 (1H, dd, J = 11.4, 6.8 Hz, H-9′), 4.82 (1H, d, J = 6.8 Hz, H-7′), 5.41 (1H, br s, D_2O exchangeable, OH-4), 5.46 (1H, br s, D_2O exchangeable, OH-4′), 5.90 (1H, br s, D_2O exchangeable, OH-4″), 6.22 (1H, d, J = 16.0 Hz, H-8″), 6.41 (2H, s, H-2 and H-6), 6.59 (2H, s, H-2′ and H-6′), 6.92 (1H, d, J = 8.4 Hz, H-5″), 6.99 (1H, d, J = 2.0 Hz, H-2″), 7.05 (1H, dd, J = 8.4, 2.0 Hz, H-6″), 7.50 (1H, d, J = 16.0 Hz, H-7″); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.8 (C-7), 42.8 (C-8), 49.1 (C-8′), 56.0 (OMe-3″), 56.3 (OMe-3), 56.3 (OMe-5), 56.3 (OMe-3′), 56.3 (OMe-5′), 62.8 (C-9′), 72.8 (C-9), 83.7 (C-7′), 102.6 (C-2′), 102.6 (C-6′), 105.2 (C-2), 105.2 (C-6), 109.4 (C-2″), 114.8 (C-5″), 114.8 (C-8″), 123.0 (C-6″), 126.7 (C-1″), 131.1 (C-1), 133.2 (C-4), 133.5 (C-1′), 134.1 (C-4′), 145.4 (C-7″), 146.8 (C-3″), 147.0 (C-3), 147.0 (C-5), 147.0 (C-3′), 147.0 (C-5′), 148.2 (C-4″), 167.0 (C-9″); ESIMS m/z (rel int) 619 ([M + Na]$^+$, 100); HRESIMS m/z 619.2153 [M + Na]$^+$ (calcd for $C_{32}H_{36}O_{11}Na$, 619.2155).

(*E*)-3-(2,2-Dimethyl-2*H*-chromen-6-yl)prop-2-enal (8): colorless oil; UV (MeOH) λ_{max} (log ϵ) 295 (4.25), 320 (sh, 3.82) nm; IR (neat) ν_{max} 1670 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.46 (6H, s, H-4′ and H-5′), 5.69 (1H, d, J = 9.8 Hz, H-2′), 6.34 (1H, d, J = 9.8 Hz, H-1′), 6.59 (1H, dd, J = 15.6, 7.6 Hz, H-8), 6.81 (1H, d, J = 8.4 Hz, H-5), 7.20 (1H, d, J = 2.0 Hz, H-2), 7.34 (1H, dd, J = 8.4, 2.0 Hz, H-6), 7.37 (1H, d, J = 15.6 Hz, H-7), 9.64 (1H, d, J = 7.6 Hz, CHO); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.5 (C-4′), 28.5 (C-5′), 77.4 (C-3′), 117.3 (C-5), 121.4 (C-3), 121.7 (C-1′), 126.6 (C-2), 126.7 (C-8), 127.0 (C-1), 130.4 (C-6), 131.8 (C-2′), 153.0 (C-7), 156.3 (C-4), 194.0 (C-9); ESIMS m/z (rel int) 237 ([M + Na]$^+$, 100); HRESIMS m/z 237.0890 [M + Na]$^+$ (calcd for $C_{14}H_{14}O_2$ Na, 237.0891).

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Supporting Information Available: NOESY and HMBC correlations (Figures 1S−8S) for compounds **1**–**8**. This information is available free of charge via the Internet at http://pubs.acs.org.

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