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New Phenylpropenoids, Bis(1-phenylethyl)phenols, Bisquinolinone Alkaloid, and Anti-inflammatory Constituents from *Zanthoxylum integrifoliolum*

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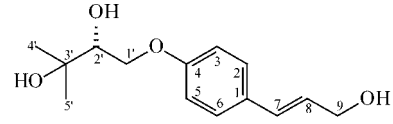
Five new compounds, including two new phenylpropenoids, (*R,E*)-1-[4-(3-hydroxyprop-1-enyl)phenoxy]-3-methylbutane-2,3-diol (**1**) and 4-hydroxy-3-(3-methyl-2-butenyl)cinnamyl alcohol (**2**), two new bis(1-phenylethyl)phenols, 2,6-bis(1-phenylethyl)phenol (**3**) and 2,4-bis(1-phenylethyl)phenol (**4**), and a new bisquinolinone alkaloid, 18-demethylparaensidimerin C (**5**), together with 17 known compounds have been isolated from the stem wood of *Zanthoxylum integrifoliolum*. The structures of these new compounds were determined through spectral analyses including extensive 2D nuclear magnetic resonance data. Among the isolates, *N*-methylflindersine (**7**), (–)-simulanol (**10**), and evofolin-C (**16**) exhibited potent inhibition against *N*-formylmethionylleucylphenylalanine-induced superoxide production with IC_{50} values less than 12 μM.

Zanthoxylum integrifoliolum (Merr.) Merr. (Rutaceae) is an evergreen tree distributed in northern Philippine and on Lanyu Island in Taiwan.[1] Previous chemical studies of this plant (fruit, bark, root, wood, and leaves) have indicated the isolation of several components, including isobutylamides, benzo[*c*]phenanthridines, quinolines, indolopyridoquinazolines, berberines, lignans, and triterpenoids.[2–9] Antiplatelet aggregation,[4,8] vasorelaxing,[4] and cytotoxic[9] activities have been demonstrated for some of these compounds. In our studies on the anti-inflammatory constituents of Formosan plants, many species have been screened for *in vitro* anti-inflammatory activity and *Z. integrifoliolum* has been found to be one of the active species. Investigation of the EtOAc-soluble fraction of the stem woods of *Z. integrifoliolum* has led to the isolation of five new compounds, including two phenylpropenoids, (*R,E*)-1-[4-(3-hydroxyprop-1-enyl)phenoxy]-3-methylbutane-2,3-diol (**1**) and 4-hydroxy-3-(3-methyl-2-butenyl)cinnamyl alcohol (**2**), two bis(1-phenylethyl)phenols, 2,6-bis(1-phenylethyl)phenol (**3**) and 2,4-bis(1-phenylethyl)phenol (**4**), and a bisquinolinone alkaloid, 18-demethylparaensidimerin C (**5**), along with 17 known compounds. This paper describes the structural elucidation of **1**–**5** and the anti-inflammatory activities of the isolates.



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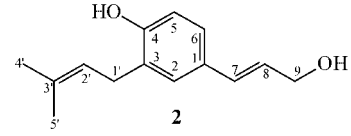

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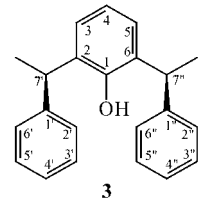

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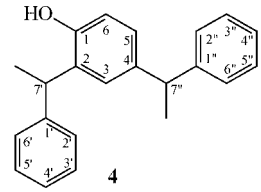

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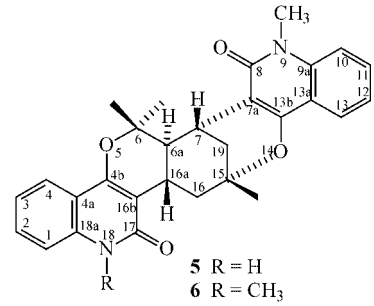

5 R = H
6 R = CH_3

Results and Discussion

Extensive chromatographic purification of the EtOAc-soluble fraction of the stem woods of *Z. integrifoliolum* on a silica gel column and preparative thin-layer chromatography (TLC) afforded five new compounds (**1–5**) and 17 known compounds (**6**–**22**).

(*R,E*)-1-[4-(3-Hydroxyprop-1-enyl)phenoxy]-3-methylbutane-2,3-diol (**1**) was isolated as a colorless oil. The high-resolution electrospray ionization mass spectrometry (HRESIMS) gave an $[M + Na]^+$ ion at *m/z* 275.1257 (calcd for $C_{14}H_{20}O_4Na$, 275.1259), consistent with a molecular formula of $C_{14}H_{20}O_4Na$. In the IR spectrum, absorptions for hydroxy (3380 cm^{-1}) and aromatic olefinic (1602, 1510, and 1458 cm^{-1}) functions were observed. The ^1H nuclear magnetic resonance (NMR) spectrum of **1** showed the presence of a 3-hydroxyprop-1-enyl group [δ 4.31 (2H, dd, J = 6.0, 1.2 Hz, H-9), δ 6.25 (1H, dt, J = 15.8, 6.0 Hz, H-8), δ 6.56 (1H, br d, J = 15.8 Hz, H-7)], a 2,3-dihydroxy-3-methylbutoxy group [δ 1.28, 1.33 (each 3H, each s, H-4′ and H-5′), δ 3.81 (1H, dd, J = 7.4, 2.8 Hz, H-2′), δ 4.03 (1H, dd, J = 9.6, 7.4 Hz, H-1′), δ 4.15 (1H, dd, J = 9.6, 2.8 Hz, H-1′)], and an AA′BB′ spin system [δ 6.88 (2H, d, J = 8.8 Hz, H-3 and H-5) and δ 7.33 (2H, d, J =

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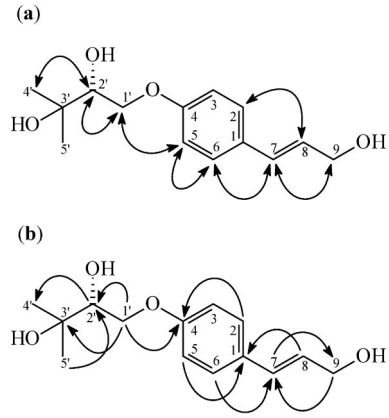

Figure 1. NOESY (a) and HMBC (b) correlations of **1**.

8.8 Hz, H-2 and H-6)]. Nuclear Overhauser effect spectrometry (NOESY) correlations (Figure 1) were between H-2/H-6 (δ 7.33) and H-7 (δ 6.56), H-3/H-5 (δ 6.88), and between H-3/H-5 (δ 6.88) and H-1′ (δ 4.03 and 4.15) of the 2,3-dihydroxy-3-methylbutoxy group. This group was assigned to reside at C-4. Compound **1** showed a dextrorotatory optical activity with $[\alpha]_D^{25} = +16.2$ as in the cases of (*R*)-heraclenol ($[\alpha]_D^{23} = +16$),[10] and the absolute configuration of C-2′ in **1** has to be *R*.[10] On the basis of the evidence above, the structure of **1** was elucidated as (*R*,*E*)-1-[4-(3-hydroxyprop-1-enyl)phenoxy]-3-methylbutane-2,3-diol. This was confirmed by ^{1}H–^{1}H correlation spectroscopy (COSY) and NOESY experiments (Figure 1). The assignment of ^{13}C NMR resonances was confirmed by distortionless enhancement by polarization transfer (DEPT), heteronuclear single-quantum coherence (HSQC), and heteronuclear multiple-bond correlation (HMBC) (Figure 1) techniques.

4-Hydroxy-3-(3-methyl-2-butenyl)cinnamyl alcohol (**2**) was isolated as a yellowish solid. The ESIMS afforded the sodiated ion $[M + Na]^+$ at *m*/*z* 241, implying a molecular formula of $C_{14}H_{18}O_2$, which was confirmed by the HRESIMS (*m*/*z* 241.1207 $[M + Na]^+$, calcd for $C_{14}H_{18}O_2Na$, 241.1204). The IR spectrum showed a hydroxy absorption at 3385 cm^{-1} and an aromatic ring C=C stretch at 1601, 1492, and 1454 cm^{-1}. The ^{1}H NMR spectrum of **2** was similar to that of precolpuchol,[11] except that a 3-methyl-2-butenyl group of **2** replaced the 3-methylbut-1,3-dienyl group of precolpuchol.[11] Analysis of the ^{1}H NMR spectrum of **2** showed resonances for a 3-methyl-2-butenyl group, a 3-hydroxyprop-1-enyl group, and three ABX-coupled protons. In the NOESY spectrum of **2**, H-2 (δ 7.14) showed correlations with H-7 (δ 6.53) and H-1′ (δ 3.34) and H-6 (δ 7.15) showed correlations with H-5 (δ 6.76) and H-7 (δ 6.53). Thus, the hydroxy group was assigned to reside at C-4. On the basis of the above data, the structure of **2** was elucidated as 4-hydroxy-3-(3-methyl-2-butenyl)cinnamyl alcohol. This was further confirmed by ^{1}H–^{1}H COSY and NOESY experiments. This is the first report of the occurrence of **2** in a natural source, although it has been synthesized by Menon et al.[12]

2,6-Bis(1-phenylethyl)phenol (**3**) was isolated as a colorless oil with a molecular formula of $C_{22}H_{22}O$ as determined by positive-ion high-resolution electron impact mass spectrometry (HREIMS), showing an $[M]^+$ ion at *m*/*z* 302.1673 (calcd for $C_{22}H_{22}O$, 302.1671). The presence of a hydroxy group was revealed by a band at 3424 cm^{-1} in the IR spectrum, which was confirmed by the resonances at δ 4.54 (1H, br s, D_2O exchangeable) in the ^{1}H NMR spectrum. Analysis of the ^{1}H NMR spectrum of **3** showed resonances for two 1-phenylethyl groups and three mutually coupled aromatic protons. In the NOESY spectrum of **3**, the proton at δ 7.11 (H-3/H-5) showed correlations with the resonances at δ 6.94 (H-4) and 4.33 (H-7′/H-7″). Thus, the hydroxy group (δ 4.54) was assigned to C-1. Compound **3** is a meso compound, $[\alpha]_D^{25} = \pm 0$. According to the above data, the structure of **3** was elucidated as

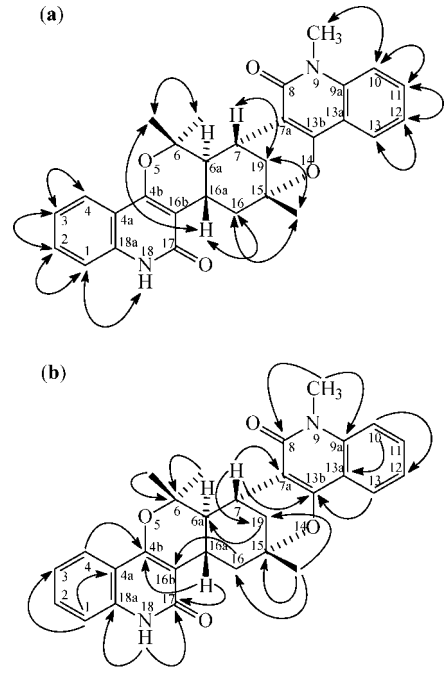

Figure 2. NOESY (a) and HMBC (b) correlations of **5**.

2,6-bis(1-phenylethyl)phenol. This was confirmed by ^{1}H–^{1}H COSY and NOESY experiments. The assignment of ^{13}C NMR resonances was confirmed by DEPT, HSQC, and HMBC techniques. This is the first report of the occurrence of **3** in a natural source, although it has been synthesized by Kuts et al.[13]

2,4-Bis(1-phenylethyl)phenol (**4**) was obtained as an amorphous solid, and the molecular formula was confirmed to be $C_{22}H_{22}O$ from the sodiated ion peak at *m*/*z* = 325.1564 $[M + Na]^+$ (calcd for $C_{22}H_{22}ONa$, 325.1568) obtained by HRESIMS. In the IR spectrum, absorptions for hydroxy (3395 cm^{-1}) and aromatic olefinic (1598, 1491, and 1450 cm^{-1}) functions were observed. The ^{1}H NMR spectrum of **4** showed the resonances for two 1-phenylethyl groups, a hydroxy group, and three ABX-coupled aromatic protons. On the basis of NOESY correlations between H-5 (δ 6.96) and H-6 (δ 6.67), H-7″ (δ 4.11), and between H-3 (δ 7.13) and H-7″ (δ 4.32), Me-7″ (δ 1.62), the hydroxy group was assigned to C-1. The structure of **4** was thus elucidated as 2,4-bis(1-phenylethyl)phenol. This was further confirmed by ^{1}H–^{1}H COSY and NOESY experiments. The assignment of ^{13}C NMR resonances was confirmed by DEPT, HSQC, and HMBC techniques. This is the first report of the occurrence of **4** in a natural source, although it has been synthesized by Casiraghi et al.[14]

18-Demethylparaensidimerin C (**5**) was isolated as a colorless powder. The molecular formula $C_{29}H_{28}N_2O_4$ was deduced from the sodiated ion at *m*/*z* 491.1948 $[M + Na]^+$ in the HRESI mass spectrum. The presence of carbonyl groups was revealed by a band at 1634 cm^{-1} in the IR spectrum, which was confirmed by the resonances at δ 162.8 and 163.6 in the ^{13}C NMR spectrum. A comparison of the IR and ^{1}H and ^{13}C NMR data of **5** with those of paraensidimerin C[15] suggested that their structures are closely related, except that the NH group of **5** replaced the N–Me group of paraensidimerin C.[15] This was supported by both HMBC correlations observed between NH (δ 11.25) and C-1 (δ 115.9), C-17 (163.6) and NOESY correlations between NH (δ 11.25) and H-1 (δ 7.32). According to the above data, the structure of **5** was elucidated as (±)-18-demethylparaensidimerin C. This was further confirmed by ^{1}H–^{1}H COSY and NOESY (Figure 2) experiments. The assignment of ^{13}C NMR resonances was confirmed by DEPT, HSQC, and HMBC (Figure 2) techniques.

Paraensidimerin C (**6**) was isolated as colorless needles. The structure of **6** was readily identified by a comparison of its

Table 1. IC_{50} Values of Compounds Isolated from the Stem Wood of *Z. integrifoliolum* in the Inhibition on fMLP-Induced Superoxide Generation in Human Neutrophils

compound	IC_{50} (μM)[a]
(*R*,*E*)-1-[4-(3-hydroxyprop-1-enyl)phenoxy]-3-methylbutane-2,3-diol (**1**)	32.55 ± 7.54
4-hydroxy-3-(3-methyl-2-butenyl)cinnamyl alcohol (**2**)	75.14 ± 8.13
2,6-bis(1-phenylethyl)phenol (**3**)	>100
2,4-bis(1-phenylethyl)phenol (**4**)	>100
18-demethylparaensidimerin C (**5**)	>100
paraensidimerin C (**6**)	>100
N-methylflindersine (**7**)	4.28 ± 0.89
γ-fagarine (**8**)	>100
haplopine (**9**)	57.32 ± 6.12
(–)-simulanol (**10**)	11.83 ± 5.23
(–)-balanophonin (**11**)	31.94 ± 16.28
(–)-5-methoxybalanophonin (**12**)	19.30 ± 3.87
isoscopoletin (**13**)	77.52 ± 6.04
aesculetin dimethyl ether (**14**)	>100
6,7,8-trimethoxycoumarin (**15**)	47.10 ± 7.10
evofolin-C (**16**)	9.64 ± 4.48
1-[(3-methylbut-2-enyl)oxyl]-2-methoxy-4-(prop-1-en-3-ol)benzene (**17**)	>100
syringaldehyde (**18**)	>100
mixture of β-sitostenone (**19**) and stigmasta-4,22-dien-3-one (**20**)	>100
mixture of β-sitosterol (**21**) and stigmasterol (**22**)	>100
ibuprofen[b]	27.33 ± 3.28

[a] The IC_{50} values were calculated from the slope of the dose–response curves. Values are expressed as mean ± standard error of the mean (SEM) of three independent experiments. [b] Ibuprofen was used as a positive control.

spectroscopic data (^{1}H NMR, IR, and mass spectrometry data) with literature values,[15] except for the proton resonances of H-7, H-16, H-16a, H-19, and Me-15. The original assignments of H-7 (δ 3.27), H_{ax}-16 (δ 1.45), H_{eq}-16 (δ 3.89), H-16a (δ 2.66), H_{ax}-19 (δ 2.17), H_{eq}-19 (δ 1.48), and Me-15 (δ 1.90) of **6**[15] are erroneous and not confirmed by the NOESY and HMBC techniques. This is now corrected as follows: H-7 (δ 2.68), H_{ax}-16 (δ 2.17), H_{eq}-16 (δ 1.48), H-16a (δ 3.28), H_{ax}-19 (δ 1.46), H_{eq}-19 (δ 3.89), and Me-15 (δ 1.72) by our ^{1}H–^{1}H COSY, NOESY, HSQC, and HMBC experiments on compound **6**. The following correlations were evident: (a) ^{1}H–^{1}H COSY correlations were observed between H-16_{ax} (δ 2.17) and H-16_{eq} (δ 1.49), H-16a (δ 3.27) and between H-19_{eq} (δ 3.89) and H-19_{ax} (δ 1.47), H-7 (δ 2.66); (b) NOESY correlations were observed between H-16a (δ 3.27) and H-16_{eq} (δ 1.49) and between H-19_{eq} (δ 3.89) and H-7 (δ 2.66), Me-15 (δ 1.73); and (c) HMBC correlations were observed between H-16a (δ 3.27), N–Me (δ 3.70), and C-17 (δ 161.7) and between H-7 (δ 2.66), H-13 (δ 7.93), and C-13b (δ 155.9).

The known isolates were readily identified by a comparison of physical and spectroscopic data (UV, IR, ^{1}H NMR, $[\alpha]_D$, and MS) with corresponding authentic samples or literature values, and this included a bisquinolinone alkaloid, paraensidimerin C (**6**),[15] a quinolinone alkaloid, *N*-methylflindersine (**7**),[16] two furoquinoline alkaloids, γ-fagarine (**8**)[17] and haplopine (**9**),[18] three neolignans, (–)-simulanol (**10**),[19] (–)-balanophonin (**11**),[20] and (–)-5-methoxybalanophonin (**12**),[21] three coumarins, isoscopoletin (**13**),[22] aesculetin dimethyl ether (**14**),[23] and 6,7,8-trimethoxycoumarin (**15**),[24] two phenylpropenoids, evofolin-C (**16**)[25] and 1-[(3-methylbut-2-enyl)oxyl]-2-methoxy-4-(prop-1-en-3-ol)benzene (**17**),[26] a benzenoid, syringaldehyde (**18**),[27] and four steroids, a mixture of β-sitostenone (**19**)[28] and stigmasta-4,22-dien-3-one (**20**)[29] and a mixture of β-sitosterol (**21**)[28] and stigmasterol (**22**).[29]

The anti-inflammatory effects of the isolates from the stem woods of *Z. integrifoliolum* were evaluated by suppressing *N*-formylmethionylleucylphenylalanine (fMLP)-induced production of superoxide anion, an inflammatory mediator produced by neutrophils. The anti-inflammatory activity data are shown in Table 1. The clinically used anti-inflammatory agent, ibuprofen, was used as the positive control. From the results of our anti-inflammatory tests, the following conclusions can be drawn: (a) *N*-methylflindersine (**7**), (–)-simulanol (**10**), (–)-5-methoxybalanophonin (**12**), and evofolin-C (**16**) exhibited more potent inhibition ($IC_{50} \leq 19.30$ μM) than ibuprofen ($IC_{50} = 27.33$ μM) on fMLP-induced superoxide generation; (b) (–)-simulanol (**10**) with a 3-hydroxyprop-1-enyl group exhibited more effective inhibition than its analogue, (–)-5-methoxybalanophonin (**12**) with a 3-oxoprop-1-enyl group; (c) (–)-5-methoxybalanophonin (**12**) with a 5-methoxy group exhibited more effective inhibition than its analogue, (–)-balanophonin (**11**) without a 5 substituent; (d) *N*-methylflindersine (**7**) showed strong anti-inflammatory activity, but its corresponding dimer, paraensidimerin C (**6**), was inactive; and (e) *N*-methylflindersine (**7**) is the most effective among the isolates, with an IC_{50} of 4.28 ± 0.89 μM against the fMLP-induced production of superoxide anion by neutrophils.

Experimental Section

General Experimental Procedures. All melting points were determined on a Yanaco micro-melting 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. 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 tetramethylsilane (TMS) as an internal standard. EI, ESI, and HRESI-mass spectra were recorded on a Bruker APEX II mass spectrometry. HREI, fast atom bombardment (FAB), and HRFAB-mass spectra were recorded on a JEOL JMX-HX 110 mass spectrometer. Silica gel (70–230, 230–400 mesh) (Merck) was used for CC. Silica gel 60 F-254 (Merck) were used for TLC and preparative TLC.

Plant Material. The stem wood of *Z. integrifoliolum* was collected from Lanyu Island, Taitung County, Taiwan, in July 2002 and identified by Dr. I. S. Chen. A voucher specimen (Chen 5528) was deposited in the herbarium of the Faculty of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan, Republic of China.

Extraction and Separation. The dried stem wood of *Z. integrifoliolum* (10.3 kg) was extracted with cold MeOH, and the extract was concentrated under reduced pressure. The MeOH extract (240 g), when partitioned between H_2O/EtOAc (1:1), afforded an EtOAc-soluble fraction (fraction A, 79.5 g). Fraction A (79.5 g) was chromatographed on silica gel (70–230 mesh, 2.9 kg), eluting with CH_2Cl_2, gradually increasing the polarity with MeOH to give 11 fractions: A1 (5 L, CH_2Cl_2), A2 (3 L, CH_2Cl_2/MeOH, 100:1), A3 (3 L, CH_2Cl_2/MeOH, 90:1), A4 (3 L, CH_2Cl_2/MeOH, 80:1), A5 (4 L, CH_2Cl_2/MeOH, 60:1), A6 (4 L, CH_2Cl_2/MeOH, 50:1), A7 (4 L, CH_2Cl_2/MeOH, 40:1), A8 (5 L, CH_2Cl_2/MeOH, 20:1), A9 (4 L, CH_2Cl_2/MeOH, 5:1), A10 (4 L,

CH_2Cl_2/MeOH, 1:1), and A11 (4 L, MeOH). Fraction A3 (5.33 g) was chromatographed further on silica gel (230–400 mesh, 180 g) eluting with CH_2Cl_2/MeOH (80:1) to give 12 fractions (each 1.5 L, A3-1–A3-12). Fraction A3-2 (222 mg) was purified further by preparative TLC (*n*-hexane/acetone, 7:1) to obtain a mixture of **19** and **20** (16.4 mg) ($R_f = 0.53$). Fraction A3-4 (185 mg) was purified further by preparative TLC (*n*-hexane/acetone, 3:1) to obtain a mixture of **21** and **22** (25.4 mg) ($R_f = 0.73$). Fraction A4 (5.81 g) was chromatographed further on silica gel (230–400 mesh, 185 g) eluting with CH_2Cl_2/MeOH (80:1) to give 10 fractions (each 1.5 L, A4-1–A4-10). Fraction A4-4 (223 mg) was purified further by preparative TLC (*n*-hexane/acetone, 2:1) to obtain **5** (2.5 mg) ($R_f = 0.61$). Fraction A4-6 (213 mg) was purified further by preparative TLC ($CHCl_3$/MeOH, 15:1) to obtain **10** (3.7 mg) ($R_f = 0.26$). Fraction A4-7 (201 mg) was purified further by preparative TLC (*n*-hexane/EtOAc, 20:1) to obtain **3** (2.7 mg) ($R_f = 0.55$). Fraction A5 (6.8 g) was chromatographed further on silica gel (230–400 mesh, 225 g) eluting with CH_2Cl_2/MeOH (60:1) to give 12 fractions (each 1.5 L, A5-1–A5-12). Fraction A5-2 (226 mg) was purified further by preparative TLC (*n*-hexane/EtOAc, 2:1) to obtain **16** (2.9 mg) ($R_f = 0.55$). Fraction A5-3 (198 mg) was purified further by preparative TLC (*n*-hexane/EtOAc, 1:1) to obtain **8** (3.5 mg) ($R_f = 0.27$). Fraction A5-4 (244 mg) was purified further by preparative TLC (*n*-hexane/EtOAc, 1:1) to obtain **14** (2.6 mg) ($R_f = 0.39$). Fraction A5-8 (265 mg) was purified further by preparative TLC ($CHCl_3$/MeOH, 15:1) to obtain **12** (3.2 mg) ($R_f = 0.7$). Fraction A6 (7.3 g) was chromatographed further on silica gel (230–400 mesh, 245 g) eluting with CH_2Cl_2/MeOH (30:1) to give 8 fractions (each 1.5 L, A6-1–A6-8). Fraction A6-1 (216 mg) was purified further by preparative TLC (*n*-hexane/EtOAc, 1:1) to obtain **13** (3.4 mg) ($R_f = 0.58$). Fraction A6-2 (231 mg) was purified further by preparative TLC (*n*-hexane/actone, 3:2) to obtain **6** (2.7 mg) ($R_f = 0.54$). Fraction A6-3 (235 mg) was purified further by preparative TLC (*n*-hexane/EtOAc, 1:1) to obtain **15** (3.8 mg) ($R_f = 0.45$). Fraction A6-5 (218 mg) was purified further by preparative TLC (*n*-hexane/EtOAc, 1:1) to obtain **17** (3.2 mg) ($R_f = 0.67$). Fraction A6-8 (207 mg) was purified further by preparative TLC (*n*-hexane/acetone, 4:1) to obtain **4** (2.6 mg) ($R_f = 0.41$). Fraction A8 (2.3 g) was chromatographed further on silica gel (230–400 mesh, 140 g) eluting with CH_2Cl_2/MeOH (20:1) to give 10 fractions (each 1.0 L, A8-1–A8-10). Fraction A8-6 (187 mg) was purified further by preparative TLC (*n*-hexane/acetone, 10:1) to obtain **9** (3.9 mg) ($R_f = 0.49$). Fraction A9 (3.3 g) was chromatographed further on silica gel (230–400 mesh, 185 g) eluting with CH_2Cl_2/MeOH (5:1) to give 12 fractions (each 1.3 L, A9-1–A9-12). Fraction A9-1 (210 mg) was purified further by preparative TLC (*n*-hexane/acetone, 1:1) to obtain **18** (3.5 mg) ($R_f = 0.42$). Fraction A9-2 (187 mg) was purified further by preparative TLC (CH_2Cl_2/acetone, 7:1) to obtain **2** (1.8 mg) ($R_f = 0.72$). Fraction A9-3 (196 mg) was purified further by preparative TLC (*n*-hexane/acetone, 1:1) to obtain **7** (3.8 mg) ($R_f = 0.49$). Fraction A9-4 (228 mg) was purified further by preparative TLC ($CHCl_3$/MeOH, 10:1) to obtain **1** (2.4 mg) ($R_f = 0.70$). Fraction A9-8 (235 mg) was purified further by preparative TLC (*n*-hexane/acetone, 1:1) to obtain **11** (3.7 mg) ($R_f = 0.51$).

Anti-inflammatory Activity Assay—Evaluation of $O_2^{\bullet-}$ Release by Human Neutrophils. Superoxide anion production was tested by using a continuous spectrophotometric assay of ferryicytochrome *c* reduction by isolated neutrophils. Briefly, neutrophils were isolated from the venous blood[30] of consenting healthy volunteers (20–35 years old) by double-gradient Ficoll–Hypaque centrifugation and hypotonic lysis of contaminating red blood cells as previously described.[31] Neutrophils (1×10^6 cells/mL) pretreated with the various test agents (100 μmol/L) at 37 °C for 5 min were stimulated with fMLP (1 μmol/L) in the presence of ferryicytochrome *c* (0.5 mg/mL). Extracellular $O_2^{\bullet-}$ production was assessed with a UV spectrophotometer at 550 nm (Hitachi; UV-3010). The percentage of superoxide inhibition of the test compound was calculated as the percentage of inhibition = {(control – resting) – (compound – resting)}/(control – resting) × 100.

***(R,E)*-1-[4-(3-Hydroxyprop-1-enyl)phenoxy]-3-methylbutane-2,3-diol (1):** colorless oil. $[\alpha]_D^{25}$ +16.2 (*c* 0.11, $CHCl_3$). UV (MeOH) λ_{max} (log ε): 263 (3.96) nm. IR (KBr) υ_{max}: 3380 (OH), 1602, 1510, 1458 (aromatic ring C=C stretch) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.28 (3H, s, H-5′), 1.33 (3H, s, H-4′), 3.81 (1H, dd, J = 7.4, 2.8 Hz, H-2′), 4.03 (1H, dd, J = 9.6, 7.4 Hz, H-1′), 4.15 (1H, dd, J = 9.6, 2.8 Hz, H-1′), 4.31 (2H, dd, J = 6.0, 1.2 Hz, H-9), 6.25 (1H, dt, J = 15.8, 6.0 Hz, H-8), 6.56 (1H, br d, J = 15.8 Hz, H-7), 6.88 (2H, d, J = 8.8 Hz, H-3 and H-5), 7.33 (2H, d, J = 8.8 Hz, H-2 and H-6). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 24.0 (C-5′), 25.6 (C-4′), 62.8 (C-9), 68.2 (C-1′), 70.7 (C-3′), 74.6 (C-2′), 113.7 (C-3 and C-5), 125.7 (C-8), 126.7 (C-2 and C-6), 129.1 (C-1), 129.7 (C-7), 157.1 (C-4). ESIMS *m/z* (relative intensity): 275 ($[M + Na]^+$, 100). HRESIMS *m/z*: 275.1257 $[M + Na]^+$ (calcd for $C_{14}H_{20}O_4Na$, 275.1259).

4-Hydroxy-3-(3-methyl-2-butenyl)cinnamyl Alcohol (2): yellowish needles ($CHCl_3$/MeOH), mp 88–90 °C (literature[12] mp 87–90 °C). UV (MeOH) λ_{max} (log ε): 219 (4.40), 263 (4.31) nm. IR (KBr) υ_{max}: 3385 (OH), 1601, 1492, 1454 (aromatic ring C=C stretch) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.78 (6H, s, H-4′ and H-5′), 3.34 (2H, d, J = 7.6 Hz, H-1′), 4.29 (2H, dd, J = 6.0, 1.2 Hz, H-9), 5.31 (1H, br t, J = 7.6 Hz, H-2′), 6.22 (1H, dt, J = 15.8, 6.0 Hz, H-8), 6.53 (1H, br d, J = 15.8 Hz, H-7), 6.76 (1H, d, J = 8.8 Hz, H-5), 7.14 (1H, d, J = 2.0 Hz, H-2), 7.15 (1H, dd, J = 8.8, 2.0 Hz, H-6). ESIMS *m/z* (relative intensity): 241 ($[M + Na]^+$, 100). HRESIMS *m/z*: 241.1207 $[M + Na]^+$ (calcd for $C_{14}H_{18}O_2Na$, 241.1204).

2,6-Bis(1-phenylethyl)phenol (3): colorless oil. $[\alpha]_D^{25}$ ±0 (*c* 0.13, $CHCl_3$). UV (MeOH) λ_{max} (log ε): 275 (4.01) nm. IR (KBr) υ_{max}: 3424 (OH), 1594, 1487, 1451 (aromatic ring C=C stretch) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.59 (6H, d, J = 7.2 Hz, Me-7′ and Me-7′), 4.33 (2H, q, J = 7.2 Hz, H-7′ and H-7′), 4.54 (1H, br s, OH-1, D_2O exchangeable), 6.94 (1H, t, J = 7.6 Hz, H-4), 7.11 (2H, d, J = 7.6 Hz, H-3 and H-5), 7.19 (2H, t, J = 7.8 Hz, H-4′ and H-4′), 7.20 (4H, d, J = 7.8 Hz, H-2′, H-6′, H-2′, and H-6′), 7.28 (4H, t, J = 7.8 Hz, H-3′, H-5′, H-3′, and H-5′). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.8 (Me-7′ and Me-7″), 39.0 (C-7′ and C-7″), 120.7 (C-4), 126.3 (C-3 and C-5), 126.7 (C-4′ and C-4″), 127.7 (C-2′, C-6′, C-2″, and C-6″), 128.9 (C-3′, C-5′, C-3″, and C-5″), 132.6 (C-2 and C-6), 145.5 (C-1′ and C-1″), 151.4 (C-1). EIMS *m/z* (relative intensity): 302 ($[M]^+$, 90), 287 (100), 271 (15), 224 (58), 223 (76), 209 (89), 197 (61), 165 (61), 105 (64), 77 (59). HREIMS *m/z*: 302.1673 $[M]^+$ (calcd for $C_{22}H_{22}O$, 302.1671).

2,4-Bis(1-phenylethyl)phenol (4): colorless amorphous solid. $[\alpha]_D^{25}$ –41.7 (*c* 0.11, $CHCl_3$). UV (MeOH) λ_{max} (log ε): 282 (4.00) nm. IR (KBr) υ_{max}: 3395 (OH), 1598, 1491, 1450 (aromatic ring C=C stretch) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.60 (3H, d, J = 7.2 Hz, Me-7′), 1.62 (3H, d, J = 7.2 Hz, Me-7″), 4.11 (1H, q, J = 7.2 Hz, H-7″), 4.32 (1H, q, J = 7.2 Hz, H-7′), 4.55 (1H, br s, OH-1, D_2O exchangeable), 6.67 (1H, d, J = 8.4 Hz, H-6), 6.96 (1H, dd, J = 8.4, 2.0 Hz, H-5), 7.13 (1H, d, J = 2.0 Hz, H-3), 7.19 (1H, t, J = 7.8 Hz, H-4″), 7.20 (1H, t, J = 7.8 Hz, H-4′), 7.21 (2H, d, J = 7.8 Hz, H-2″ and H-6″), 7.22 (2H, d, J = 7.8 Hz, H-2′ and H-6′), 7.28 (4H, t, J = 7.8 Hz, H-3′, H-5′, H-3″, and H-5″). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.3 (Me-7′), 22.5 (Me-7″), 39.3 (C-7′), 44.4 (C-7″), 116.2 (C-6), 126.1 (C-4′), 126.7 (C-5), 126.7 (C-4′), 127.6 (C-3), 127.7 (C-2′, C-6′, C-2″, and C-6″), 128.5 (C-3″ and C-5″), 128.9 (C-3′ and C-5′), 131.7 (C-2), 138.9 (C-4), 145.5 (C-1′), 147.1 (C-1″), 151.8 (C-1). ESIMS *m/z* (relative intensity): 325 ($[M + Na]^+$, 100). HRESIMS *m/z*: 325.1564 $[M + Na]^+$ (calcd for $C_{22}H_{22}ONa$, 325.1568).

18-Demethylparaensidimerin C (5): colorless needles $CHCl_3$/MeOH), mp 197–199 °C. $[\alpha]_D^{25}$ ±0 (*c* 0.12, $CHCl_3$). UV (MeOH) λ_{max} (log ε): 228 (4.65), 276 (3.85), 285 (3.84), 318 (3.86) nm. IR (KBr) υ_{max}: 3315 (NH), 1634 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.33 (3H, s, Me-6), 1.46 (1H, dd, J = 14.7, 12.5 Hz, H_{ax}-19), 1.48 (1H, d, J = 10.8 Hz, H_{eq}-16), 1.63 (1H, dd, J = 12.4, 3.7 Hz, H-6a), 1.72 (3H, s, Me-15), 1.90 (3H, s, Me-6), 2.17 (1H, dd, J = 10.8, 3.5 Hz, H_{ax}-16), 2.68 (1H, ddd, J = 12.5, 12.4, 4.3 Hz, H-7), 3.28 (1H, dd, J = 3.7, 3.5 Hz, H-16a), 3.64 (3H, s, N–CH_3), 3.89 (1H, dd, J = 14.7, 4.3 Hz, H_{eq}-19), 7.17 (1H, t, J = 8.0 Hz, H-12), 7.19 (1H, dd, J = 8.1, 7.8 Hz, H-3), 7.28 (1H, br d, J = 8.4 Hz, H-10), 7.32 (1H, br d, J = 8.4 Hz, H-1), 7.48 (1H, ddd, J = 8.4, 7.8, 1.6 Hz, H-2), 7.50 (1H, ddd, J = 8.4, 8.0, 1.8 Hz, H-11), 7.89 (1H, dd, J = 8.1, 1.6 Hz, H-4), 7.92 (1H, dd, J = 8.0, 1.8 Hz, H-13), 11.25 (1H, br s, NH, D_2O exchangeable). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.6 (Me-6), 25.6 (C-16a), 26.5 (C-7), 28.4 (Me-6), 29.0 (N–Me), 29.3 (Me-15), 31.1 (C-16), 39.7 (C-19), 52.2 (C-6a), 78.5 (C-15), 81.6 (C-6), 107.6 (C-7a), 113.7 (C-10), 114.6 (C-16b), 115.9 (C-1), 116.1 (C-4a), 116.5 (C-13a), 121.4 (C-12), 121.9 (C-3), 122.5 (C-4), 123.3 (C-13), 130.3 (C-11), 130.4 (C-2), 138.0 (C-18a), 138.8 (C-9a), 155.9 (C-13b), 156.9 (C-4b), 162.8 (C-8), 163.6 (C-17). ESIMS *m/z* (relative intensity): 491 ($[M + Na]^+$, 100). HRESIMS *m/z*: 491.1948 $[M + Na]^+$ (calcd for $C_{29}H_{28}N_2O_4Na$, 491.1947).

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