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

Jih-Jung Chen,*,† Po-Hou Chen,† Chang-Hui Liao,‡ Shi-Yu Huang,† and Ih-Sheng Chen§

Graduate Institute of Pharmaceutical Technology, Tajen University, Pingtung 907, Taiwan, Republic of China, Graduate Institute of Natural Products, Chang Gung University, Taoyuan 333, Taiwan, Republic of China, and Faculty of Pharmacy, College of Pharmacy, Kaohsiung Medical University, Kaohsiung 807, Taiwan, Republic of China

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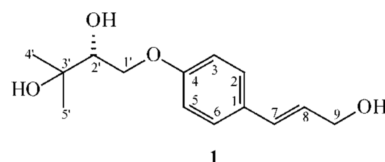
Five new compounds, including two new phenylpropenoids, (*R,E*)-1-[4-(3-hydroxyprop-1-enyl)phenoxy]-3-methylbutane-2,3-diol (**1**) and 4-hydroxy-3-(3-methyl-2-butenyl)cinnamyl alcohol (**2**), two new bis(1-phenylethyl)phenols, 2,6-bis(1-phenylethyl)phenol (**3**) and 2,4-bis(1-phenylethyl)phenol (**4**), 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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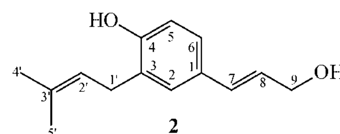

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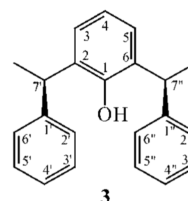

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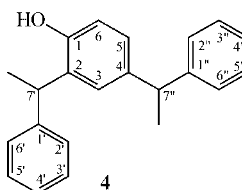

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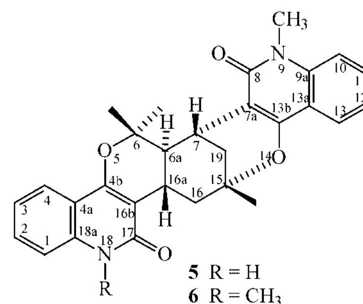

5 R = H
6 R = CH_3

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 =

* 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.
§ Kaohsiung Medical University.

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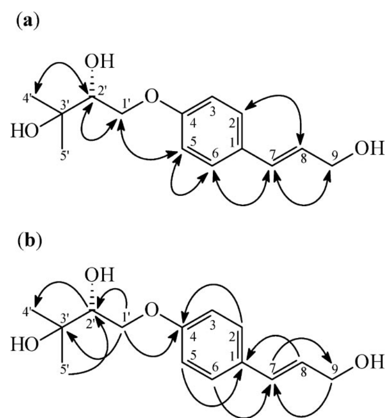

Figure 1. NOESY (a) and HMBC (b) correlations of **1**.

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-hydroxy-prop-1-enyl)phenoxy]-3-methylbutane-2,3-diol. This was confirmed by ^1H–^1H 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 ^1H 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 ^1H 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 ^1H–^1H 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 ^1H NMR spectrum. Analysis of the ^1H 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

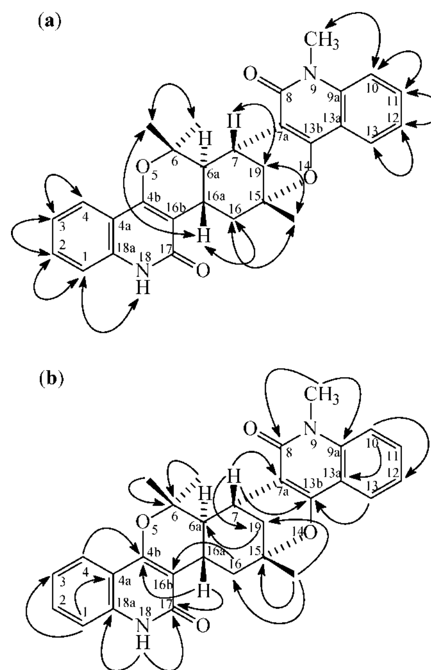

Figure 2. NOESY (a) and HMBC (b) correlations of **5**.

2,6-bis(1-phenylethyl)phenol. This was confirmed by ^1H–^1H 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 ^1H 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 ^1H–^1H 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 ^1H 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 ^1H–^1H 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}. ^{1}H 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}. ^{1}H 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}. ^{1}H 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}. ^{1}H 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}. ^{1}H 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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