Antimicrobial Resveratrol Tetramers from the Stem Bark of *Vatica oblongifolia* ssp. *oblongifolia*

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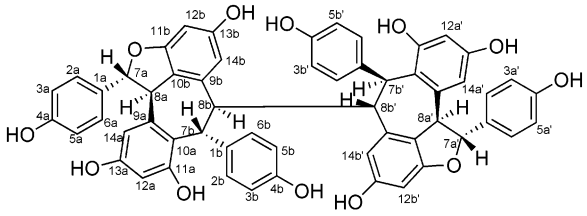
Two new resveratrol tetramers, hopeaphenol A (**1**) and isohopeaphenol A (**2**), along with the known vaticaphenol A (**3**), were isolated from the stem bark of *Vatica oblongifolia* ssp. *oblongifolia* through bioassay-guided fractionation. The structures and their relative stereochemistry were determined by spectroscopic techniques. Compounds **1** and **3** demonstrated moderate activity against methicillin-resistant *Staphylococcus aureus* and *Mycobacterium smegmatis.*

Vatica oblongifolia ssp. *oblongifolia* Hook. (Dipterocarpaceae) is a plant native to Sarawak, Malaysia, and no reports have appeared in the literature describing the phytochemistry or biological activity of the plant. The genus *Vatica* consists of over 60 species distributed primarily in Kalimantan and the Malay Peninsula.[1] Over the last two decades, several resveratrol oligomers have been isolated from various *Vatica* species, and plants belonging to the Dipterocarpaceae are well known to be an abundant source of such compounds.[1−9] Resveratrol oligomers are also found in the Cyperaceae, Gnetaceae, Vitaceae, and Fabaceae.[9] They exhibit diverse biological activities including antibacterial,[5,9−12] antifungal,[9,13] antiinflammatory,[14] cytotoxic,[1,2] and HIV-inhibitory activities.[15]

In the course of our investigation of over one thousand organic plant extracts from the Natural Product Repository of the National Cancer Institute for antimicrobial activity,[16] an EtOAc-soluble extract of the stem bark of *V. oblongifolia* ssp. *oblongifolia* was found to exhibit moderate activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Mycobacterium smegmatis* (a model for pathogenic mycobacteria). Bioassay-guided fractionation of this extract using a 96-well plate microdilution assay[17] led to the isolation of three resveratrol tetramers, hopeaphenol A (**1**), isohopeaphenol A (**2**), and vaticaphenol A (**3**).[1] Compounds **1** and **2** are novel stereoisomers of the previously reported hopeaphenol[18−20] and isohopeaphenol,[21] respectively, while vaticaphenol A (**3**) has been previously reported from the stems of *Vatica diospyroides*.[1] The structures of compounds **1** and **2** were elucidated entirely by spectral means. All compounds were evaluated for their antimicrobial activity, and compounds **1** and **3** were found to be moderately active against MRSA and *M. smegmatis.*



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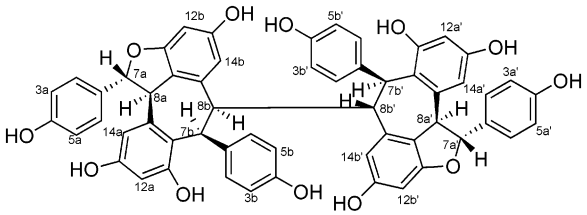

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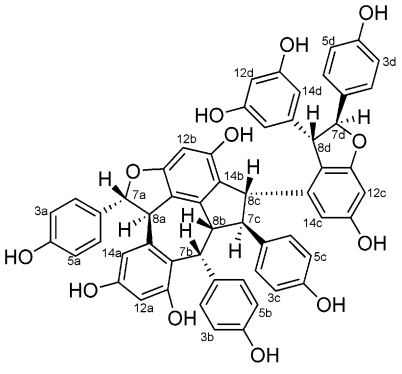

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Results and Discussion

The positive ESMS of compound **1** showed an $[M + H]^+$ ion at *m/z* 907, and on the basis of NMR and HRMS data, the molecular formula of **1** was determined to be $C_{56}H_{42}O_{12}$, indicating 36 degrees of unsaturation. The ESMS-MS of the *m/z* 907 $[M + H]^+$ ion contained fragments at *m/z* 453 ($C_{28}H_{21}O_6$) and *m/z* 451 ($C_{28}H_{19}O_6$), suggesting that the compound was a symmetrical dimer. When a deuterated mobile phase was used, the ESMS of **1** showed an $[M + D]^+$ ion at *m/z* 918, indicating that 10 exchangeable hydrogens were present in the molecule.

Eight aliphatic multiplets, 15 aromatic multiplets integrating for 24 protons in total, and 10 phenolic singlets were observed in the ^{1}H NMR spectrum of compound **1**. On the basis of the COSY data, 16 of the aromatic protons formed four discrete A_2B_2 spin systems (J = 8.6 Hz), suggesting the presence of four 1,4-disubstituted aromatic rings in **1**. In similar fashion the remaining eight aromatic protons were ascribed to four sets of 1,2,3,5-tetrasubsti-

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tuted aromatic rings, implying the presence of four additional aromatic rings, each bearing two *meta*-coupled protons ($J = 2.1$ Hz). The COSY data further indicated that the eight aliphatic protons in the ^{1}H NMR spectrum of compound **1** were dispersed among three separate spin systems. Two of the three aliphatic spin systems consisted of two vicinal methine doublets [H-7a and H-8a ($J = 12.8$ Hz) and H-7a′ and H-8a′ ($J = 8.6$ Hz)], and the third spin system contained four contiguous methine multiplets [H-7b ($J = 5.0$ Hz), H-8b ($J = 10.8$, 5.0 Hz), H-8b′ ($J = 10.8$, 4.4 Hz), and H-7b′ ($J = 4.4$ Hz)].

The ^{13}C GASPE NMR spectrum of compound **1** contained 48 unique carbon NMR signals, 24 of which represented methine carbons and 24 of which represented quaternary carbons. Eight of the aromatic methine carbon signals were approximately twice as intense as the other 16 methine carbon signals because they each represented two equivalent carbon atoms. This observation was consistent with the presence of four 1,4-disubstituted aromatic rings (implied by the ^{1}H NMR data) as well as with the C_{56} molecular formula. No methylene or methyl carbons were observed.

The eight aromatic rings, proposed from the ^{1}H and ^{13}C NMR data described above, accounted for 32 out of the 36 degrees of unsaturation required for compound **1**. Due to the lack of any additional double bonds, the remaining four degrees of unsaturation could only be accounted for by the presence of four additional rings.

It was concluded that each of the four 1,4-disubstituted aromatic rings bore a phenolic hydroxyl group, as evidenced by their HMBC (Table 1) and NOE interactions. For instance, the OH-4a singlet at δ_H 8.46 shared mutual NOE interactions with the adjacent H-3a(5a) aromatic protons. The OH-4b singlet at δ_H 7.88 showed similar interactions with H-3b(5b) as did the OH-4a′ singlet at δ_H 8.52 with H-3a′(5a′) and the OH-4b′ singlet at δ_H 7.59 with H-3b′-(5b′).

The H-7a and H-8a proton doublets, comprising one of the three aliphatic spin systems delineated above, exhibited a mutual 12.8 Hz coupling constant, but saturation of H-8a produced no NOE enhancement of H-7a, suggesting that these two protons were situated *trans*-periplanar to one another. The chemical shifts of H-7a at δ_H 5.81 and its corresponding carbon at δ_C 88.8 suggested that C-7a was attached to a dihydrofuran oxygen linkage. A HMBC correlation between H-8a and the quaternary aromatic carbon C-10b at δ_C 116.2 (see Table 1) further indicated that H-7a and H-8a were a part of a dihydrobenzofuran entity. The H-12b doublet that shared a 2.1 Hz *meta*-coupling with H-14b exhibited HMBC correlations with C-10b, C-11b, and C-14b, while the H-14b doublet shared HMBC correlations with C-10b and C-12b (see Table 1), thus confirming the presence of a dihydrobenzofuran moiety. It was further determined that the OH singlet at δ_H 7.67 shared indicative HMBC correlations with C-12b and C-14b (Table 1) and NOE interactions with their corresponding protons. This phenolic substituent was therefore placed at C-13b.

Additional HMBC correlations between H-7a and C-2a-(6a) indicated that one of the previously described *p*-phenolic aromatic rings was attached at C-7a. Mutual NOEs between H-7a and H-2a(6a) supported this proposal.

In similar fashion HMBC correlations observed between both H-7a and H-8a and the quaternary C-9a aromatic carbon at δ_C 141.1 suggested that C-8a bore an aromatic ring substituent, as did C-7a. The H-14a doublet of doublets at δ_H 6.18, which shared a 2.1 Hz *meta*-coupling with H-12a at δ_H 6.30 and a long-range coupling with H-8a, exhibited HMBC correlations with C-8a, C-10a, C-12a, and C-13a. The H-12a doublet shared HMBC correlations with C-10a, C-11a, C-13a, and C-14a (see Table 1). In addition, H-12a showed NOE enhancements to two phenol singlets, OH-11a at δ_H 7.51 and OH-13a at δ_H 7.98, whereas H-14a showed a NOE enhancement with the OH-13a singlet.

One of the terminal proton doublets in the four-proton contiguous aliphatic spin system described above, H-7b at δ_H 5.04, showed HMBC interactions with C-9a, C-10a, and C-11a, indicating that this proton was positioned adjacent to C-10a. The HMBC and NOE data for H-8b at δ_H 4.29, the methine doublet of doublets vicinal to H-7b, correlated to C-10a on one side as well as to C-9b, C-10b, and C-14b of the originally described dihydrobenzofuran on the other side, thus describing a central seven-membered ring.

Additional HMBC correlations between H-7b and C-2b-(6b) indicated that a second *p*-phenolic aromatic ring was attached at C-7b. Mutual NOEs between H-7b and H-2b-(6b) supported this proposal.

At this point, a $C_{28}H_{21}O_6$ moiety encompassing four aromatic and two aliphatic rings was accounted for, as well as half of the molecular formula and half the total degrees of unsaturation. On the basis of the MS-MS fragmentation data that suggested that compound **1** was a symmetrical dimer, these two fused resveratrol moieties, which collectively formed a central seven-membered ring, constituted one complete monomer unit of a larger dimer.

Proton H-8b, the second hydrogen in the four-proton contiguous aliphatic spin system, shared a 10.8 Hz coupling constant with the vicinal H-8b′, which was in turn coupled to H-7b′ ($J = 4.4$ Hz), the terminal methine doublet in the spin system. The large coupling constant and the lack of a NOE enhancement between H-8b and H-8b′ suggested that these protons were positioned in a *trans* conformation.

The remaining ^{1}H, ^{13}C, HMBC, and NOE NMR data suggested that the second half of this dimeric molecule was very similar in structure to the first half and that the two halves of the dimer were connected by a single aliphatic bond between C-8b and C-8b′. Thus dimer **1**, which contained four resveratrol moieties in all, was recognized as a $C_{56}H_{42}O_{12}$ structural analogue of the previously described hopeaphenol and isohopeaphenol.[18−21] In the cases of hopeaphenol and isohopeaphenol, only 24 carbon NMR signals and half the number of proton NMR signals were observed due to stereoequivalence between the two halves of each dimer. This was clearly not the case for compound **1**, and therefore, the stereochemistries of the two monomers comprising compound **1** differed from one another, unlike hopeaphenol and isohopeaphenol.

Each of the two monomers comprising compound **1** possessed four chiral centers for a total of eight stereocenters in the parent dimer. As was the case for hopeaphenol, a NOE enhancement between H-8a and H-8b was observed in **1**, indicating that these two protons were cofacial about the central seven-membered ring.[18−20] As previously indicated, H-8a shared a 12.8 Hz coupling constant with H-7a but no mutual NOE enhancement, suggesting that these two protons were *trans*-periplanar. H-8b displayed a NOE with H-7b, but since these two vicinal protons resided on a seven-membered ring, the stereochemical implications of this result were not clear. Additionally, H-8a showed a significant NOE with the H-2b(6b) protons of the pendant aromatic ring attached to C-7b, thus clearly establishing that proton H-7b was on the opposite side of the ring, co-facial to H-7a. The relative stereochemistry thus established for the first half of

Table 1. NMR Assignments for Hopeaphenol A (**1**) in Acetone-d_6

position	δ_C	δ_H (int., mult., J in Hz)	COSY	HMBC
1a	130.8			
2a, 6a	130.4	7.23 (2H, dm, J = 8.6)	H-3a, 5a	C-1a, 2a, 4a, 6a, 7a
3a, 5a	116.0	6.81 (2H, dm, J = 8.6)	H-2a, 6a	C-1a, 3a, 4a, 5a
4a	158.6			
7a	88.8	5.81 (1H, d, J = 12.8)	H-8a	C-2a, 6a, 9a
8a	50.7	4.38 (1H, d, J = 12.8)	H-7a	C-1a, 7a, 9a, 10b
9a	141.1			
10a	118.7			
11a	158.9			
12a	101.8	6.30 (1H, d, J = 2.1)	H-14a	C-10a, 11a, 13a, 14a
13a	157.2			
14a	105.9	6.18 (1H, dd, J = 0.6, 2.1)	H-12a	C-8a, 10a, 12a, 13a
1b	133.9			
2b, 6b	128.9	6.90 (2H, dm, J = 8.6)	H-3b, 5b	C-1b, 2b, 4b, 6b
3b, 5b	115.4	6.53 (2H, dm, J = 8.6)	H-2b, 6b	C-1b, 3b, 4b, 5b
4b	155.7			
7b	41.8	5.04 (1H, d, J = 5.0)	H-8b	C-9a, 10a, 11a, 1b, 2b, 6b, 8b, 9b
8b	45.9	4.29 (1H, dd, J = 5.0, 10.8)	H-7b, 8b′	C-10a, 7b, 9b, 10b, 14b, 8b′
9b	142.0			
10b	116.2			
11b	160.2			
12b	96.0	6.01 (1H, d, J = 2.1)	H-14b	C-10b, 11b, 13b, 14b
13b	157.9			
14b	111.7	5.88 (1H, d, J = 2.1)	H-12b	C-8b, 10b, 12b, 13b
1a′	134.6			
2a′, 6a′	130.3	7.50 (2H, dm, J = 8.6)	H-3a′, 5a′	C-2a′, 4a′, 6a′, 7a′
3a′, 5a′	116.4	6.90 (2H, dm, J = 8.6)	H-2a′, 6a′	C-1a′, 3a′, 5a′
4a′	158.5			
7a′	93.7	5.71 (1H, d, J = 8.6)	H-8a′	C-2a′, 6a′, 9a′
8a′	53.5	5.41 (1H, d, J = 8.6)	H-7a′	C-1a′, 7a′, 9a′, 10b′
9a′	141.7			
10a′	120.0			
11a′	158.0			
12a′	102.7	6.34 (1H, d, J = 2.1)	H-14a′	C-10a′, 11a′, 13a′, 14a′
13a′	156.9			
14a′	106.6	6.38 (1H, dd, J = 0.6, 2.1)	H-12a′	C-8a′, 10a′, 12a′, 13a′
1b′	138.1			
2b′, 6b′	129.9	6.31 (2H, m)	H-3b′, 5b′	C-2b′, 4b′, 6b′, 7b′
3b′, 5b′	114.5	6.31 (2H, m)	H-2b′, 6b′	C-1b′, 3b′, 4b′, 5b′
4b′	155.0			
7b′	45.1	4.71 (1H, d, J = 4.4)	H-8b′	C-9a′, 10a′, 1b′, 2b′, 6b′, 8b′, 9b′
8b′	59.2	2.62 (1H, dd, J = 4.4, 10.8)	H-8b, 7b′	C-8b, 10a′, 9b′, 10b′
9b′	140.4			
10b′	116.8			
11b′	160.2			
12b′	94.9	5.86 (1H, d, J = 2.1)	H-14b′	C-10b′, 14b′
13b′	158.2			
14b′	112.7	4.98 (1H, d, J = 2.1)	H-12b′	C-8b′, 10b′, 12b′
OH-4a		8.46 (1H, s)		C-3a, 5a
OH-11a		7.51 (1H, s)		C-10a
OH-13a		7.98 (1H, s)		C-12a, 14a
OH-4b		7.88 (1H, s)		C-3b, 5b
OH-13b		7.67 (1H, s)		C-12b, 14b
OH-4a′		8.52 (1H, s)		C-3a′, 5a′
OH-11a′		7.80 (1H, s)		C-10a′
OH-13a′		8.07 (1H, s)		C-12a′, 14a′
OH-4b′		7.59 (1H, s)		C-3b′, 5b′
OH-13b′		7.49 (1H, s)		C-12b′, 14b′

compound **1** was consistent with the stereochemistry presented for hopeaphenol (established by X-ray).[19,20] A summary of the pertinent NOEs for compound **1** is presented in Figure 1.

In the second half of compound **1**, doublets H-7a′ and H-8a′ shared a coupling constant of 8.6 Hz but displayed no mutual NOE enhancements, suggesting that they were *trans*-periplanar, as were their counterparts in the first half. A moderately intense mutual NOE was observed between H-8b in the first monomer and H-8a′ in the second monomer. In a two-dimensional structural representation, this NOE was confusing owing to the apparent great distance between H-8b on one monomer and H-8a′ on the remote side of the second monomer. However, after modeling studies were performed on the structure of **1** (see Figure 1), this initially surprising NOE result was readily explained. This particular NOE enhancement proved to be a crucial constraint on the three-dimensional structure of **1**.

In addition, a mutual NOE between H-14b in the first monomer and H-7b′ in the second monomer confirmed that the second monomer was rotated approximately 180° about the C-8b/C-8b′ bond with respect to the first monomer, as depicted in Figure 1. This inversion of the second monomer was consistent with the *trans* conformation between H-8b and H-8b′.

As depicted in the model, H-8b′ shared a NOE with the aromatic H-2b′(6b′) protons, indicating that H-7b′ was cofacial with H-8a′. This stereochemical conclusion was

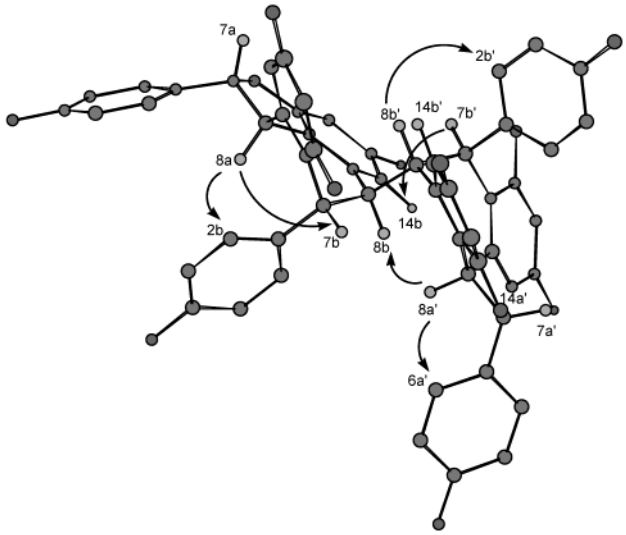

Figure 1. 3D model of hopeaphenol A (**1**) showing pertinent NOE correlations.

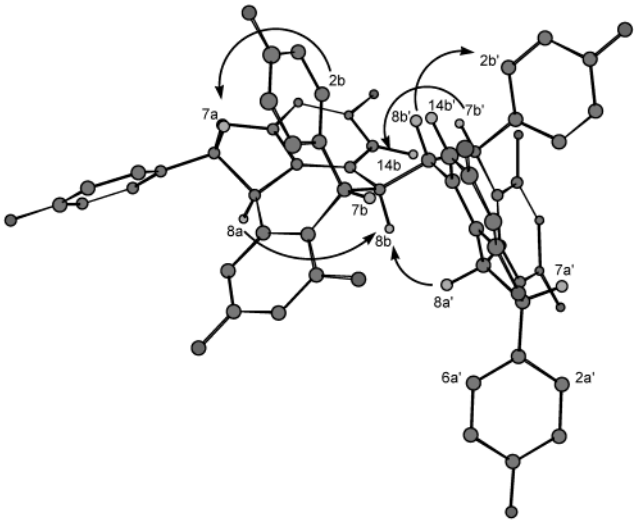

Figure 2. 3D model of isohopeaphenol A (**2**) showing pertinent NOE correlations.

readily supported by the relative upfield chemical shift of H-8b′ (δ_H 2.62) owing to its position in the shielding cone of the adjacent aromatic ring.

Although the absolute stereochemistry of compound **1** was not determined, it was clear that the four chiral centers in the first monomer possessed the same relative stereochemistry as hopeaphenol. The four chiral centers in the second monomer possessed different stereochemistry at centers H-7b′ and H-8b′, making this monomer unique. This difference rendered the two halves of the dimer nonequivalent, thus accounting for observation of the full complement of carbon and proton signals in the NMR spectra.

The UV spectrum of compound **1** was typical of resveratrol tetramers with absorption maxima at 284, 228, and 203 nm.[20] Therefore, compound **1**, a novel resveratrol tetramer, was determined to be a stereoisomer of hopeaphenol and was accordingly named hopeaphenol A.

On the basis of the HRMS and NMR spectral data, the molecular formula of compound **2** was deduced to be $C_{56}H_{42}O_{12}$, making it an isomer of hopeaphenol A. The positive ESMS of **2** showed an $[M + H]^+$ ion at *m*/*z* 907, as well as a mass fragment at *m*/*z* 465 ($C_{29}H_{21}O_6$). The positive ion ESMS-MS of *m*/*z* 907 $[M + H]^+$ contained mass fragments at *m*/*z* 453 and 451, as in the case of hopeaphenol A. The presence of 10 exchangeable hydrogens was also confirmed by the ESMS in a deuterated mobile phase.

The ^{1}H and ^{13}C NMR spectra of compound **2** were very similar to those observed for compound **1**, containing 42 protons and 48 carbons. The ^{1}H NMR spectrum revealed the presence of one aliphatic singlet, six aliphatic multiplets, 16 aromatic multiplets, and 10 phenolic singlets. As with **1**, the ^{13}C GASPE NMR spectrum of compound **2** contained 48 unique carbon NMR signals, 24 of which represented methine carbons and 24 of which represented quaternary carbons. Eight of the 24 aromatic methine carbon signals represented two equivalent carbon atoms each, again confirming the presence of four 1,4-disubstituted aromatic rings as well as the C_{56} molecular formula. No methylene or methyl carbons were observed.

Analysis of the spectroscopic data revealed that compound **2** had the same skeletal structure and was isomeric with compound **1**. Additionally, observation of the full complement of carbon and proton NMR signals indicated that compound **2** was not hopeaphenol or isohopeaphenol, which would have revealed only 24 carbon NMR signals and half the number of proton NMR signals.

Similar to the case for hopeaphenol A, the H-7a (at δ_H 5.61) and H-8a (at δ_H 4.63) doublets in compound **2** shared a 8.5 Hz coupling constant but no mutual NOE enhancement, indicating that H-7a and H-8a were *trans*-periplanar. Also, as was the case for hopeaphenol A, a mutual NOE observed between H-8a and H-8b indicated that these two protons were co-facial about the central seven-membered ring. The coupling constant shared between the vicinal H-7b and H-8b protons was nearly zero, but since these two vicinal protons resided on a seven-membered ring, once again the relative stereochemistry at C-7b was unclear. As seen in Figure 2, H-7a showed a significant NOE with the H-2b(6b) protons of the pendant aromatic ring attached to C-7b, thus clearly establishing that proton H-7b was on the opposite side of the ring, co-facial to both H-8a and H-8b. Therefore, the relative stereochemistry for the first half of compound **2** differed from that of hopeaphenol A only at stereocenter C-7b. This relative stereochemistry was similar to that ascribed to isohopeaphenol in the literature.[21] A summary of the pertinent NOEs for compound **2** is presented in Figure 2.

As with hopeaphenol A, the H-8b doublet at δ_H 4.44 shared a 12.1 Hz coupling constant with the vicinal H-8b′ doublet of doublets at δ_H 3.53 in compound **2**. The lack of NOE enhancement between H-8b and H-8b′ suggested that these protons shared a *trans* conformation.

In the second half of compound **2**, doublets H-7a′ and H-8a′ shared a coupling constant of 9.3 Hz but displayed no mutual NOE enhancements, suggesting that they were *trans*-periplanar, as were their counterparts in the first half. As shown in Figure 2, the crucial NOE observed between H-8b in the first monomer and H-8a′ in the second monomer for hopeaphenol A was also observed for compound **2**. In addition, a mutual NOE between H-14b in the first monomer and H-7b′ in the second monomer once again confirmed that the second monomer in compound **2** was rotated approximately 180° about the C-8b/C-8b′ bond with respect to the first monomer as depicted in Figure 2. This rotation was consistent with the *trans* relationship previously attributed to H-8b and H-8b′. Last, H-8b′ shared a NOE with the aromatic H-2b′(6b′) protons, indicating that H-7b′ was co-facial with H-8a′.

Thus, it was concluded that compound **2** is a diastereomer of hopeaphenol A, in which the first monomer

Table 2. NMR Assignments for Isohopeaphenol A (**2**) in Acetone-d_6

position	δ_C	δ_H (int., mult., J in Hz)	COSY	HMBC
1a	133.8			
2a, 6a	130.1	7.16 (2H, dm, J = 8.6)	H-3a, 5a	C-1a, 2a, 4a, 6a, 7a
3a, 5a	116.4	6.81 (2H, dm, J = 8.6)	H-2a, 6a	C-1a, 3a, 4a, 5a
4a	158.4			
7a	93.3	5.61 (1H, d, J = 8.5)	H-8a	C-2a, 6a, 9a
8a	52.6	4.63 (1H, d, J = 8.5)	H-7a	C-1a, 7a, 9a, 10a, 9b, 10b, 11b
9a	140.8			
10a	123.9			
11a	157.2			
12a	101.8	6.30 (1H, d, J = 2.1)	H-14a	C-10a, 13a, 14a
13a	156.7			
14a	106.9	6.05 (1H, dd, J = 0.6, 2.1)	H-12a	C-8a, 10a, 12a, 13a
1b	135.1			
2b, 6b	130.7	6.64 (2H, dm, J = 8.6)	H-3b, 5b	C-2b, 3b, 4b, 5b, 6b, 7b
3b, 5b	114.3	6.41 (2H, dm, J = 8.6)	H-2b, 6b	C-1b, 3b, 4b, 5b
4b	155.5			
7b	43.4	4.90 (1H, s)		C-9a, 10a, 11a, 1b, 2b, 6b, 8b, 9b, 8b′
8b	47.7	4.44 (1H, d, J = 12.1)	H-8b′	C-10a, 1b, 7b, 9b, 10b, 14b, 7b′, 8b′
9b	140.7			
10b	118.7			
11b	159.6			
12b	94.7	5.91 (1H, d, J = 2.1)	H-14b	C-10b, 11b, 13b, 14b
13b	159.4			
14b	105.2	6.18 (1H, d, J = 2.1)	H-12b	C-8b, 10b, 11b, 12b, 13b
1a′	133.5			
2a′, 6a′	130.5	7.06 (2H, dm, J = 8.6)	H-3a′, 5a′	C-2a′, 4a′, 6a′, 7a′
3a′, 5a′	116.5	6.76 (2H, dm, J = 8.6)	H-2a′, 6a′	C-1a′, 3a′, 4a′, 5a′
4a′	158.4			
7a′	93.4	5.61 (1H, d, J = 9.3)	H-8a′	C-2a′, 6a′
8a′	52.5	4.99 (1H, d, J = 9.3)	H-7a′	C-1a′, 7a′, 9a′, 10a′, 9b′, 10b′, 11b′
9a′	141.4			
10a′	118.6			
11a′	158.3			
12a′	102.1	6.16 (1H, d, J = 2.1)	H-14a′	C-10a′, 11a′, 13a′, 14a′
13a′	156.6			
14a′	106.4	5.94 (1H, dd, J = 0.6, 2.1)	H-12a′	C-8a′, 10a′, 12a′, 13a′
1b′	138.2			
2b′, 6b′	129.9	6.73 (2H, dm, J = 8.6)	H-3b′, 5b′	C-2b′, 4b′, 6b′, 7b′
3b′, 5b′	114.8	6.48 (2H, dm, J = 8.6)	H-2b′, 6b′	C-1b′, 3b′, 4b′, 5b′
4b′	155.3			
7b′	44.6	5.27 (1H, d, J = 4.8)	H-8b′	C-9a′, 10a′, 11a′, 1b′, 2b′, 6b′, 8b′, 9b′
8b′	51.5	3.53 (1H, dd, J = 4.8, 12.1)	H-8b, 7b′	C-8b, 10a′, 7b′, 9b′, 10b′, 14b′
9b′	141.2			
10b′	117.7			
11b′	160.9			
12b′	95.4	5.97 (1H, d, J = 2.1)	H-14b′	C-10b′, 11b′, 13b′, 14b′
13b′	158.8			
14b′	111.4	6.00 (1H, d, J = 2.1)	H-12b′	C-8b′, 10b′, 12b′
OH-4a		8.45 (1H, s)		C-3a, 5a
OH-11a		7.72 (1H, s)		C-10a
OH-13a		8.08 (1H, s)		C-12a, 14a
OH-4b		7.76 (1H, s)		C-3b, 5b
OH-13b		7.94 (1H, s)		C-12b, 14b
OH-4a′		8.49 (1H, s)		C-3a′, 5a′
OH-11a′		7.62 (1H, s)		C-10a′
OH-13a′		7.98 (1H, s)		C-12a′
OH-4b′		7.77 (1H, s)		C-3b′, 5b′
OH-13b′		7.98 (1H, s)		C-12b′, 14b′

possesses the same relative stereochemistry as does isohopeaphenol, and the second monomer possesses the same relative stereochemistry as does its counterpart in hopeaphenol A. Consequently, compound **2**, a second resveratrol tetramer, was named isohopeaphenol A. Although the absolute stereochemistry of isohopeaphenol A was not determined, hopeaphenol A and isohopeaphenol A differ only in their relative C-7b stereochemistry, as do hopeaphenol and isohopeaphenol.

The bioassay-guided fractionation of the *V. oblongifolia* stem bark extract also led to the isolation of the known resveratrol oligomer, vaticaphenol A (**3**), which was biologically active in the antimicrobial bioassays. To our knowledge, this is the first report of the biological activity for this compound. Physical and spectral data of compound **3** were in agreement with the literature values.[1]

Antimicrobial testing on compounds **1**−**3** was performed using an established 96-well plate microdilution method.[17] The minimum inhibitory concentrations (MICs) of hopeaphenol A (**1**) and vaticaphenol A (**3**) were determined to be 100 and 50 μg/mL against MRSA, respectively, with vancomycin being used as a positive control (MIC of 0.8 μg/mL).[22] The MIC values of **1** and **3** against *M. smegmatis* were 50 and 25 μg/mL, respectively, and the MIC of the positive control, isoniazid, was 0.8−1.6 μg/mL.[17] Isohopeaphenol A (**2**) was inactive against both of these microorganisms (MIC > 100 μg/mL).

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. UV spectra were recorded on a Varian Cary 100 Bio UV−visible spectrophotometer in MeOH at 0.01 mg/mL concentration. FT-IR spectra were obtained on a salt plate using a Perkin-Elmer Spectrum 1000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-400 spectrometer in acetone-d_6 using the solvent as a secondary reference standard (^{1}H, 2.04 ppm, and ^{13}C, 29.8 ppm). ^{1}H, NOE difference, ^{13}C GASPE, COSY, HMQC, and HMBC spectra were recorded using standard Bruker pulse sequences. HRMS were recorded on a Finnigan FT/MS Newstar T70 mass spectrometer, and the ESMS (positive mode) were recorded on a HP/Bruker Esquire ion trap. HPLC was performed on a Dionex P580 system equipped with a Dionex UVD340S photodiode array detector, and HPLC grade solvents were used throughout.

Plant Material. *Vatica oblongifolia* ssp. *oblongifolia* was collected in Sarawak, Malaysia, by Dr. John Burley of the Harvard University Arnold Arboretum under NCI subcontract to the University of Illinois at Chicago (UIC) and by Mr. Bernard Lee of the Sarawak State Department of Forests under UIC contract to NCI, in September 1987. A voucher specimen (Q66O1958) has been deposited at the Smithsonian Museum of Natural History Botany Department.

Extraction and Isolation. The dried bark (825.0 g) was extracted with MeOH−CH_2Cl_2 (1:1) to yield 119.25 g of a crude extract. A portion of the crude extract (1.02 g) was fractionated by flash chromatography on diol resin and eluted with hexane (3.30 mg), CH_2Cl_2 (7.70 mg), EtOAc (591.5 mg), acetone (213.7 mg), and MeOH (156.0 mg). The EtOAc fraction was confirmed to be active against MRSA and *M. smegmatis* in the 96-well plate microdilution assay.[17] A portion of the EtOAc fraction (204.3 mg) was further fractionated by Sephadex LH-20 column chromatography (2.5 cm i.d. × 60 cm) and eluted with MeOH−CH_2Cl_2 (1:1), affording fractions 1−6. Active fractions 2−5 were further purified by gradient HPLC on a YMC C_{18} column (5 μm, 1 × 25 cm) using CH_3CN with 0.05% TFA−H_2O with 0.05% TFA (40:60 → 60:40 over 10 min at 3 mL/min) as the mobile phase. Fractions 2 and 3 yielded compounds **1** (5.4 mg) and **2** (4.3 mg), and fractions 4 and 5 yielded compound **3** (4.0 mg).

Hopeaphenol A (1): yellowish amorphous powder; $[\alpha]^{25}_D$ −87.5° (*c* 0.229, MeOH); UV (MeOH) λ_{max} (log ϵ) 284 (4.22), 228 (4.86), 203 (5.17) nm; IR (NaCl) ν_{max} 3351, 1614, 1512, 1354, 1174, 1132, 835 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) and ^{13}C NMR (acetone-d_6, 100 MHz), see Table 1; ESMS (positive-ion mode) *m/z* 907 [M + H$^+$] (100), 359 (9), 282 (4); ESMS-MS of *m/z* 907 → *m/z* 906 (100), 453 (23), 452 (43); ESMS (deuterated mobile phase, positive-ion mode) *m/z* 918 [M + D$^+$] (100); HREIMS *m/z* 906.2676, calcd for $C_{56}H_{42}O_{12}$, 906.2676.

Isohopeaphenol A (2): yellowish amorphous powder; $[\alpha]^{25}_D$ −7.37° (*c* 0.543, MeOH); UV (MeOH) λ_{max} (log ϵ) 284 (4.18), 228 (4.81), 203 (5.13) nm; IR (NaCl) ν_{max} 3353, 1613, 1512, 1455, 1365, 1236, 1173, 1134, 834 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz) and ^{13}C NMR (acetone-d_6, 100 MHz), see Table 2; ESMS (positive-ion mode) *m/z* 907 [M + H$^+$] (21), 813 (2), 465 (100), 322 (17), 282 (36); ESMS-MS of *m/z* 907 → *m/z* 906 (100), 453 (49), 452 (46); ESMS (deuterated mobile phase, positive-ion mode) *m/z* 918 [M + D$^+$] (100); HREIMS *m/z* 906.2670, calcd for $C_{56}H_{42}O_{12}$, 906.2676.

Vaticaphenol A (3): yellowish amorphous powder; $[\alpha]_D$, UV, IR, ^{1}H NMR (acetone-d_6, 400 MHz), and ^{13}C NMR (acetone-d_6, 100 MHz) data were in agreement with the literature values[1]; ESMS (positive-ion mode) *m/z* 907 [M + H$^+$] (100); ESMS (deuterated mobile phase, positive-ion mode) *m/z* 918 [M + D$^+$] (100).

Bioassay Evaluation. Compounds **1**−**3** were evaluated for antimicrobial activity against methicillin-resistant *Staphylococcus aureus* and *M. smegmatis* according to an established protocol for screening natural products for activity against bacteria and fungi.[17]

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