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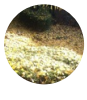

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Penicillipyrones A and B, Meroterpenoids from a Marine-Derived *Penicillium* sp. Fungus

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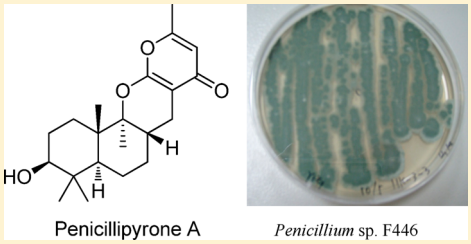
Supporting Information

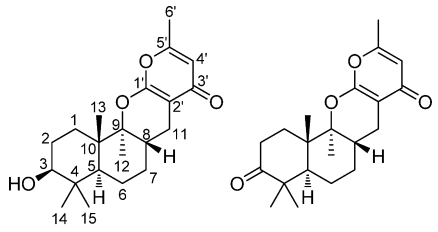
ABSTRACT: Penicillipyrones A (**1**) and B (**2**), two novel meroterpenoids, were isolated from the marine-derived fungus *Penicillium* sp. On the basis of the results of combined spectroscopic analyses, these compounds were structurally elucidated to be sesquiterpene γ-pyrones from a new skeletal class derived from a unique linkage pattern between the drimane sesquiterpene and pyrone moieties. Compound **2** elicited significant induction of quinone reductase.



Fungi from marine environments are widely recognized as prolific sources of biologically active and structurally unique secondary metabolites.[1] Although studies on these organisms began much later than their counterparts in terrestrial environments, more than a hundred novel compounds have been found annually since the late 1990s.[2] Consequently, fungi, along with actinomycete bacteria, from marine environments are regarded as a new frontier for research into natural products.

In our search for novel bioactive compounds from marine fungi, we reported acremostrictin, a highly oxygenated metabolite of a new structural class from *Acremonium strictum*.[3] In addition, there have been recent reports of novel polyaromatic compounds and hydroxybenzolactones from marine-derived *Penicillium* sp.[4] and *Chrysosporium articulatum*, respectively.[5] In our continued search, a strain of *Penicillium* sp. was isolated from a Korean marine sediment, whose organic extract showed a mild cytotoxicity (LC_{50} 192 μg/mL) against the K562 human leukemia cell line. More importantly the LC-ESIMS profile of the *Penicillium* sp. extract suggested the presence of novel compounds, which prompted us to investigate its metabolites in detail. Large-scale culture of the strain followed by the extraction of the broth and chromatographic separation led to the isolation of two new meroterpenoids. Here, we report the structural determinations of penicillipyrones A (**1**) and B (**2**), sesquiterpene γ-pyrones of a novel skeletal class. These compounds were inactive against the K562 and A549 cell lines, but compound **2** exhibited significant induction of quinone reductase in Hepa 1c1c7 murine hepatoma cells.

The molecular formula of penicillipyrone A (**1**) was deduced to be $C_{21}H_{30}O_4$ by HRFABMS analysis. The ^{13}C NMR data of this compound showed signals from a carbonyl carbon at δ_C 180.2 and four olefinic carbons at δ_C 163.3, 160.6, 111.8, and 98.0 (Table 1). The highly differentiated chemical shifts of the olefinic carbons, in conjunction with the seven degrees of unsaturation inherent in the molecular formula, suggested the presence of a conjugated cyclic lactone or ketone moiety, such as an α- or γ-pyrone. The strong absorption band at 1665 cm^{-1} in the IR data as well as the absorption maxima at 210, 243, and 257 nm in the UV data were indicative of the latter, a γ-pyrone moiety.[6] In addition to the downfield carbon signals, the ^{13}C NMR data also showed signals of two oxygenated carbons at δ_C 89.5 and 78.6 and 14 upfield carbon atoms: 2 × C, 2 × CH, 5 × CH_2, and 5 × CH_3. The high occurrence of methyl groups in the NMR data revealed the meroterpenoid nature of this compound.



Given this information, the planar structure of compound **1** was determined by a combination of the $^1H-^1H$ COSY, HSQC, and HMBC experiments. In particular, the HMBC correlations between the upfield methyl protons and their neighboring carbons were crucial to defining the sesquiterpenoid portion of compound **1** (Figure 1). The two singlet

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Table 1. NMR Data of Compounds 1 and 2 in $CDCl_3$[a]

	1			2		
position	δ_C, type	δ_H, mult (J in Hz)	HMBC[b]	δ_C, type	δ_H, mult (J in Hz)	HMBC
1	29.7, CH_2	α 1.67, m	2, 5, 10, 13	30.8, CH_2	α 2.02, m	2, 5, 9, 10, 13
		β 1.75, m	3, 10, 13		β 2.03, m	2, 5, 9, 10, 13
2	27.1, CH_2	α 1.73, m	4, 10	34.5, CH_2	α 2.42, dt (15.6, 4.5)	1, 3
		β 1.66, m	4, 10		β 2.70, ddd (15.6, 12.1, 7.3)	3, 10
3	78.6, CH	3.22, dd (10.0, 3.0)	1, 2, 14, 15	215.5, C		
4	39.1, C			47.8, C		
5	47.6, CH	1.23, dd (12.9, 3.2)	1, 4, 6, 13, 14	48.8, CH	1.70, dd (10.8, 5.1)	3, 4, 6, 10, 13, 14
6	20.9, CH_2	α 1.64, m	5, 7, 10	22.1, CH_2	α 1.62, m	5, 7, 8, 10
		β 1.47, dq (12.9, 4.7)	5, 7, 10		β 1.61, m	5, 7, 8, 10
7	28.9, CH_2	α 1.14, dq (12.9, 4.7)	8	28.7, CH_2	α 1.21, dq (12.9, 4.4)	6, 8, 11
		β 1.88, m	6, 8		β 1.94, m	6
8	33.5, CH	2.01, dddd (11.7, 9.0, 4.7, 4.7)	7, 9, 11, 12	28.7, CH	2.10, dddd (12.0, 9.3, 5.2, 4.4)	6, 7, 9, 12
9	89.5, C			88.8, C		
10	41.8, C			41.5, C		
11	22.0, CH_2	α 1.93, dd (15.9, 11.7)	8, 9, 1′, 2′, 3′	22.0, CH_2	α 1.95, dd (16.4, 12.0)	8, 9, 1′, 2′, 3′
		β 2.53, dd (15.9, 4.7)	7, 8, 1′, 2′		β 2.58, dd (16.4, 5.2)	1′, 2′
12	13.1, CH_3	1.22, s	8, 9, 10	13.2, CH_3	1.27, s	8, 9, 10
13	14.5, CH_3	1.08, s	1, 5, 9, 10	14.1, CH_3	1.29, s	1, 5, 9, 10
14	28.4, CH_3	1.00, s	3, 4, 5, 15	26.2, CH_3	1.11, s	3, 4, 5, 15
15	15.3, CH_3	0.84, s	3, 4, 5, 14	21.8, CH_3	1.09, s	3, 4, 5, 14
1′	163.3, C			163.0, C		
2′	98.0, C			98.1, C		
3′	180.2, C			180.1, C		
4′	111.8, CH	5.96, br s	2′, 3′, 5′, 6′	111.9, CH	5.98, br s	2′, 5′, 6′
5′	160.6, C			160.7, C		
6′	19.2, CH_3	2.19, br s	4′, 5′	19.3, CH_3	2.21, br s	4′, 5′

[a]Data were measured at 500 and 125 MHz for ^1H and ^{13}C NMR, respectively. [b]HMBC correlations are from the proton(s) stated to the indicated carbon.

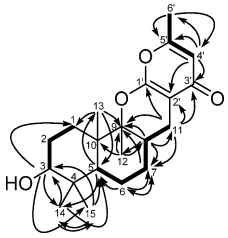

Figure 1. COSY (bold line) and selected gHMBC (arrows) correlations of compound **1**.

methyl protons at δ_H 1.00 and 0.84 showed long-range correlations to the neighboring carbons at δ_C 78.6, 39.1, and 47.6 as well as the mutual correlations with their carbons at δ_C 15.3 and 28.4, revealing that these are the terminal *gem*-dimethyl head of the sesquiterpene-derived ring system. Starting from the methine protons at δ_H 3.22 and 1.23, which are attached at the carbons at δ_C 78.6 (C-3) and 39.1 (C-4), respectively, and are also neighbors to the isopropyl moiety, the COSY NMR data revealed the presence of two linear proton spin systems (Figure 1). The C-1 and C-5 carbons at δ_C 29.7 and 47.6, which contained the protons belonging to each of the spin systems, showed long-range correlations with a singlet methyl proton at δ_H 1.08 (H-13) in the HMBC data. Thus, a six-membered carbocycle was constructed from these data and an additional correlation between H-13 and a quaternary carbon at δ_C 41.8 (C-10). Meanwhile, a carbon bearing an oxygen at δ_C 89.5 was placed at the neighboring C-9 position by its HMBC correlation with the H-13 methyl proton. Another six-membered ring was also established by the HMBC correlations of a singlet methyl proton at δ_H 1.22 (H-12) with the prepositioned C-9 and C-10 atoms as well as a methine carbon at δ_C 33.5 (C-8), whose proton at δ_H 2.01 was determined to belong to a linear spin system starting from the H-5 methine proton.

The terminus of the sesquiterpenoid portion was deduced to be the C-11 methylene, whose carbon and proton signals were assigned to be those at δ_C 22.0 and δ_H 2.53 and 1.93 by the COSY data of the linear proton spin system starting from H-5 as well as from the carbon−proton correlations of H-8/C-11, H-11/C-7, and H-11/C-9 in the HMBC data (Figure 1). The characteristic shifts of the carbon atom and protons of this methylene group indicated the direct attachment of an aromatic moiety, the γ-pyrone, at this position, which was confirmed by the long-range correlations of the methylene protons with the carbons at δ_C 180.2 (C-3′), 163.3 (C-1′), and 98.0 (C-2′). The remaining carbons at δ_C 160.6 (C-5′) and 111.8 (C-4′) were also placed in this pyrone by the HMBC correlations between H-4′/C-2′, H-4′/C-3′, and H-4′/C-5′, while the attachment of a methyl group (C-6′, δ_C 19.2, δ_H 2.19) was secured by the correlations between H-4′/C-6′, H-6′/C-4′, and H-6′/C-5′. Meanwhile, 2D NMR based carbon assignments, in conjunction with the molecular formula, confirmed the presence of a γ-pyrone moiety by the downfield shifts of the C-1′ and C-5′ carbons at δ_C 163.3 and 160.6, respectively.[6] Although the lack of protons at these positions prohibited direct evidence, the downfield shift of C-9 at δ_C 89.5 showed an ether bridge between this and carbon atom C-1′.[6,7] Thus, the planar

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structure of penicillipyrone A (**1**) was unambiguously determined.

Penicillipyrone A possesses asymmetric carbon centers at C-3, C-5, C-8, C-9, and C-10. The relative configurations at these centers were determined by a combination of 1D NMR data and NOESY analysis (Figure 2). First, the H-3 and H-5 protons

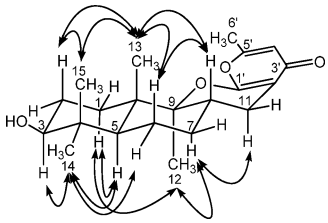


Figure 2. Selected NOE correlations of compound **1**.

were assigned axial orientations by the large vicinal proton−proton couplings (10.0 and 12.9 Hz). Starting from these protons, those axially oriented to the same side of the rings were found by NOESY cross-peaks to be H-1α (δ_H 1.67)/H-5, H-1α/H-12, H-3/H-14, H-5/H-14, H-6α (δ_H 1.64)/H-14, H-7α (δ_H 1.14)/H-11α (δ_H 1.93), and H-7α/H-12. Those axially oriented to the opposite side of H-3 and H-5 were also determined by the NOESY data to be H-2β (δ_H 1.66)/H-13, H-2β/H-15, H-6β (δ_H 1.47)/H-13, H-6β/H-15, H-6/H-8, H-8/H-13, and H-13/H-15. Overall, these data determined that the orientations for both the A/B and B/C ring junctures were *trans*, which was supported by the characteristic upfield shifts of the bridgehead methyl groups and the downfield shifts of the ring juncture methines in the ^{13}C NMR data.

Having the relative configurations through the NMR data, the absolute configurations were assigned by Mosher's analysis in which the *S* configuration at the hydroxy-bearing C-3 was deduced from $\Delta\delta$ values between the MTPA esters (Figure 3).

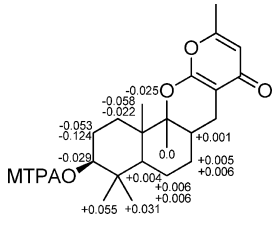
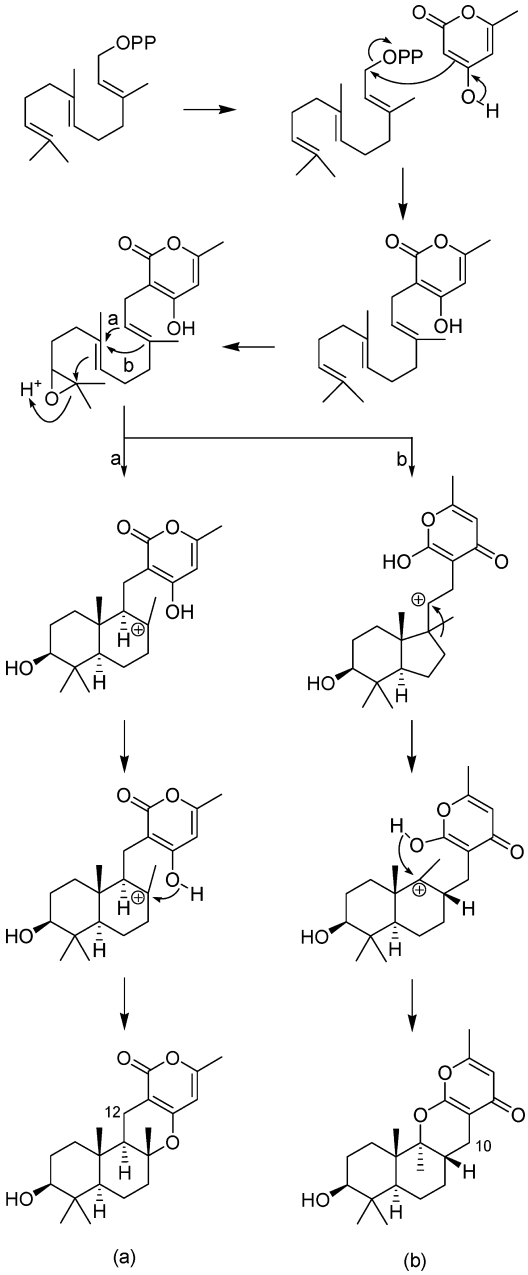


Figure 3. $\Delta\delta$ ($\delta_{(S\text{-ester})}$-$\delta_{(R\text{-ester})}$) values of MTPA esters for compound **1**.

Therefore, the overall absolute configurations were assigned as 3*S*, 5*S*, 8*S*, 9*S*, and 10*S*. Thus the structure of penicillipyrone A (**1**) was determined to be that of a sesquiterpene γ-pyrone meroterpenoid of a new skeletal class.

A literature survey showed that structurally related prenylated α- and/or γ-pyrones are found from diverse organisms,[8−12] such as sponges, fungi, and plants, and have also been synthetically prepared.[13] However, the cyclization pattern connecting the sesquiterpene to the γ-pyrone of **1** significantly differed from the other known meroterpenoids in both the linkage and orientation of the pyrone moiety to the terpene unit. As depicted in Scheme 1a, the biosynthesis of meroterpenoids initializes at the ionization of the allylic diphosphate, promoting the farnesylation of the pyrone ring. Then sequential epoxidation, ring-opening, and cyclization can occur in the carbon framework of the sesquiterpenoid moiety.[14]

Scheme 1. Comparison of Biosynthetic Pathways of Meroterpenoids



However, the unique skeleton of **1** required an alternative biosynthetic pathway because the vinyl methyl group (C-10) of the third isoprene unit seemed to be directly linked to the pyrone moiety in **1** instead of the terminal methylene carbon (C-12) of the sesquiterpene portion, as seen in the ordinary linkage. A plausible mechanism is that, after the farnesylation of the pyrone ring and epoxidation, cyclization might occur to form not a six- but a five-membered ring. Then the sequential charge accommodation by the adjacent carbon and pyrone oxygen might form compound **1** (Scheme 1b). Despite the same appearance with ordinary meroterpenoids, these processes grossly displaced the carbons of the third isoprene unit of the farnesyl moiety from their original positions. This is an unprecedented linkage among the pyrone-containing meroterpenoids.

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The molecular formula of penicillipyrone B (**2**) was deduced to be $C_{21}H_{28}O_4$ by HRFABMS analysis. The NMR data of this compound were very similar to those of **1**, with the most noticeable difference being the replacement of the C-3 oxymethine, which had signals at δ_C 78.6 and δ_H 3.22, with a carbonyl carbon having a signal at δ_C 215.5. This interpretation was readily confirmed by a combination of 2D NMR experiments, in which all of the proton−proton and carbon−proton correlations obtained supported the placement of a ketone group at C-3. NOESY data showed the same cross-peaks among the ring juncture protons as **1**, allowing the assignment of the 5*R*, 8*S*, 9*S*, and 10*S* configurations, which were also supported by the comparison of the specific rotations ($[\alpha]_D^{25}$ = +51 and +26 for **1** and **2**, respectively). Thus penicillipyrone B (**2**) was elucidated to be a 3-keto derivative of **1**.

In our bioactivity measurement, **1** and **2** were inactive toward the K562 (LC_{50} 28 and 50 μM for **1** and **2**, respectively; doxorubicin was used as a positive control with an LC_{50} 0.99 μM) and A549 (LC_{50} 15, 17, and 1.2 μM for **1**, **2**, and doxorubicin, respectively) cell lines. Compounds **1** and **2** were also inactive (MIC > 100 μg/mL) against various Gram-positive and Gram-negative bacteria and pathogenic fungi.

Compound **2** exhibited significant induction of quinone reductase (QR) in a dosage-dependent manner in murine Hepa 1c1c7 cells over the concentration range 5−40 μM. At a concentration of 40 μM, the induction was 1.9 times that of a blank control (0.1% DMSO), which was comparable with that of β-NF (2 μM), a positive control (Supporting Information). In contrast compound **1**, which possesses a 3-hydroxy group, failed to show noticeable induction at a concentration of 40 μM, implying that the ketone moiety at C-3 of **2** plays a crucial role in its QR-inducing activity. QR, a representative detoxification enzyme, is known to play an important anticancer role through the reduction of electrophilic quinones.[15] Therefore, the significant induction of QR by penicillipyrone B (**2**) may be suggestive of a potential role in cancer prevention.

EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured on a JASCO P-1020 polarimeter using a 1 cm cell. UV spectra were acquired with a Hitachi U-3010 spectrophotometer. IR spectra were recorded on a Jasco 4200 FT-IR spectrometer, using a ZnSe cell. NMR spectra were recorded on a Bruker Avance 500 and 600 spectrometer. Proton and carbon NMR spectra of **1** and **2** were measured in $CDCl_3$ solution at 500 and 125 MHz, respectively. For MTPA esters of **1**, proton NMR spectra were recorded in $CDCl_3$ solution at 600 MHz. High-resolution fast-atom bombardment mass spectrometry (HRFABMS) data were acquired using a Jeol JMS 700 mass spectrometer with *meta*-nitrobenzyl alcohol as a matrix at the Korea Basic Science Institute (Daegu, Korea). HPLC were performed on a Spectrasystem p2000 equipped with a refractive index detector (Spectrasystem RI-150). All solvents used were spectroscopic grade or distilled from glass prior to use.

Isolation and Identification of the Fungal Strain. The fungal strain *Penicillium* sp. (strain number F446) was isolated from marine sediments at the depth of 25 m collected from Geomun-do (Island), Korea, in October 2011. F446 was identified using standard molecular biological protocols by DNA amplification and sequencing of the ITS region. Genomic DNA extraction was performed using Intron's i-genomic BYF DNA extraction mini kit according to the manufacturer's protocol. The nucleotide sequence of F446 has been deposited in the GenBank database under the accession number JF901804. The 18S rDNA sequence of this strain showed 99% identity with *Penicillium citrinum* a2s6-6 (GenBank accession number KF146984).

Fermentation and Isolation. The isolated strain was cultured on a marine broth agar plate (37.4 g of Difco marine broth 2216, 20.0 g of glycerol, 16.0 g of agar in 1 L of artificial seawater) for 7 days. Agar plugs (1 cm × 1 cm, 10 pieces for 1 L) were inoculated into 2.8 L glass Fernbach flasks, 24 flasks in all, containing MB media (37.4 g of Difco marine broth 2216 and 20.0 g of glycerol in 1 L of artificial seawater). The fermentation was conducted at 28 °C on a rotary shaker at 150 rpm for 3 weeks. The mycelia and culture broth were separated by filtration, and the broth was extracted with EtOAc. The solvent was evaporated to obtain an organic extract (1.4 g). The extract was separated by C_{18} reversed-phase vacuum flash chromatography using a sequential mixture of MeOH and H_2O as eluents (seven fractions in gradient, H_2O−MeOH, from 60:40 to 0:100), acetone, and finally EtOAc. On the basis of the results of ^{1}H NMR analysis, the fraction that eluted with H_2O−MeOH (30:70) (96 mg) was chosen for separation. The fraction that eluted with H_2O−MeOH (30:70) was separated by semipreparative reversed-phase HPLC (H_2O−MeCN, 70:30, 1.0 mL/min) to afford compounds **1** (8.9 mg) and **2** (4.5 mg).

*Penicillipyrone A (**1**):* pale yellow, amorphous solid; $[\alpha]_D^{25}$ +51 (*c* 0.5, acetone); UV (MeOH) λ_{max} (log ε) 210 (3.83), 243 (3.83), 257 (3.85) nm; IR (ZnSe) ν_{max} 3394 (br), 2942, 2874, 1665, 1572, 1449 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRFABMS, *m*/*z* 347.2224 $[M + H]^+$ (calcd for $C_{21}H_{31}O_4$, 347.2222).

*Penicillipyrone B (**2**):* pale yellow, amorphous solid; $[\alpha]_D^{25}$ +26 (*c* 0.5, acetone); UV (MeOH) λ_{max} (log ε) 210 (3.80), 243 (3.81), 256 (3.82) nm; IR (ZnSe) ν_{max} 2944, 2876, 1666, 1579, 1431 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HRFABMS, *m*/*z* 345.2064 $[M + H]^+$ (calcd for $C_{21}H_{29}O_4$, 345.2066).

MTPA Esterifications of 1. To a solution of **1** (2.0 mg) in 1.0 mL of pyridine (distilled over CaH_2) were added 10 μL of triethylamine and 20 μL of (−)-(*R*)-MTPA chloride. The mixture was stirred under N_2 for 1 h at room temperature. After the consumption of the starting material was confirmed by thin-layer chromatography, the solvent was removed under vacuum and the residue was purified by analytical HPLC (YMC-ODS column, 4.6 × 250 mm; H_2O−MeOH, 15:85, 1.0 mL/min) to afford the (*S*)-MTPA ester of **1**, **1S**. The corresponding (*R*)-MTPA ester of **1**, **1R**, was also obtained from the same esterification reaction with (+)-(*S*)-MTPA chloride. ^{1}H NMR ($CDCl_3$, 600 MHz) of **1S**: δ_H 7.533−7.417 (5H, m, aromatic), 6.143 (1H, s, H-4′), 4.708 (1H, dd, *J* = 11.2, 4.4 Hz, H-3), 3.521 (3H, s, OMe), 2.567 (1H, dd, *J* = 15.9, 4.7 Hz, H-11), 2.234 (3H, s, H-6′), 2.031 (1H, dddd, *J* = 11.7, 9.0, 4.7, 4.7 Hz, H-8), 1.971 (1H, dd, *J* = 15.9, 11.7 Hz, H-11), 1.910 (1H, m, H-7), 1.885 (1H, m, H-2), 1.783 (1H, m, H-1), 1.730 (1H, m, H-1), 1.711 (1H, m, H-2), 1.662 (1H, m, H-6), 1.490 (1H, dq, *J* = 12.9, 4.7 Hz, H-6), 1.347 (1H, dd, *J* = 12.9, 3.2 Hz, H-5), 1.260 (3H, s, H-12), 1.181 (1H, m, H-7), 1.103 (3H, s, H-13), 0.921 (3H, s, H-15), 0.871 (3H, s, H-14); ESIMS *m*/*z* 563.2 $[M + H]^+$. ^{1}H NMR ($CDCl_3$, 600 MHz) of **1R**: δ_H 7.554−7.410 (5H, m, aromatic), 6.113 (1H, s, H-4′), 4.737 (1H, dd, *J* = 11.0, 4.4 Hz, H-3), 3.576 (3H, s, OMe), 2.562 (1H, dd, *J* = 15.9, 4.6 Hz, H-11), 2.230 (3H, s, H-6′), 2.030 (1H, dddd, *J* = 11.7, 9.0, 4.6, 4.6 Hz, H-8), 1.965 (1H, dd, *J* = 15.9, 11.7 Hz, H-11), 1.938 (1H, m, H-2), 1.905 (1H, m, H-7), 1.835 (1H, m, H-2), 1.805 (1H, m, H-1), 1.788 (1H, m, H-1), 1.656 (1H, m, H-6), 1.484 (1H, dq, *J* = 12.9, 4.7 Hz, H-6), 1.343 (1H, dd, *J* = 12.9, 3.2 Hz, H-5), 1.259 (3H, s, H-12), 1.175 (1H, m, H-7), 1.128 (3H, s, H-13), 0.866 (3H, s, H-15), 0.840 (3H, s, H-14); ESIMS *m*/*z* 563.2 $[M + H]^+$.

Biological Assays. Quinone reductase activity in Hepa 1c1c7 murine hepatoma cells was assayed in accordance with literature protocols.[16] Antimicrobial and cytotoxicity assays were also carried out in accordance with the primary literature.[17,18]

ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, including spectroscopic and analytical data, along with the ^{1}H NMR, ^{13}C NMR, and 2D

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NMR spectra of compounds **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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