JOURNAL OF NATURAL PRODUCTS

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Antibacterial Polyketides from the Jellyfish-Derived Fungus *Paecilomyces variotii*

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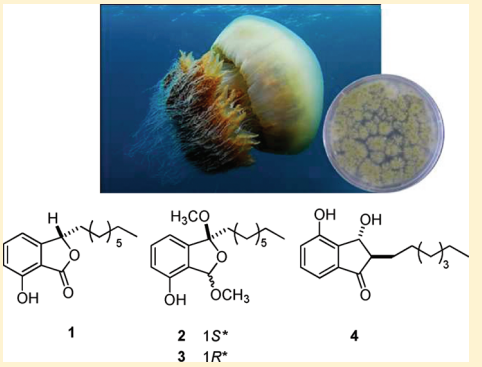
Supporting Information

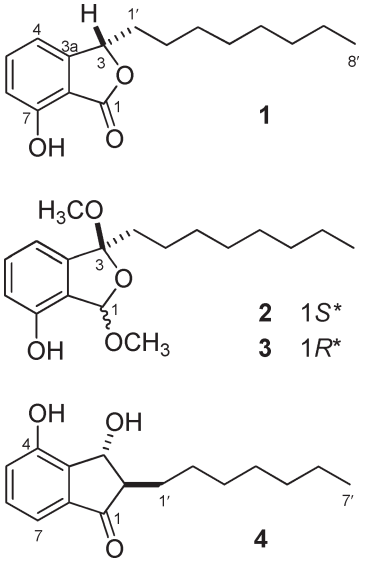
ABSTRACT: Four new polyketides (**1**−**4**) were isolated from the fungus *Paecilomyces variotii*, which was derived from the jellyfish *Nemopilema nomurai*. The planar structures and relative configurations of these polyketides were elucidated on the basis of spectroscopic analyses, including 2D NMR experiments. The compounds showed inhibitory activity against pathogenic bacteria including methicillin-resistant *Staphylococcus aureus* 3089 and multi-drug-resistant *Vibrio parahemolyticus* 7001 with MIC values in the range 5−40 μg/mL.



Marine microorganisms are an important source of bioactive secondary metabolites, and the interest in marine microorganisms continues to grow every year, with fungi being a consistent source of active metabolites. Endozoic microorganisms inhabit the inner tissues of animals as specific microbial biota, and ecological interactions have evolved not only between the host and their endozoic microorganisms but also between the endozoic microorganisms such as bacteria and fungi, either in a symbiotic or competitive manner.[1] Unlike free-living marine microorganisms, they biosynthesize unique secondary metabolites in a special ecological niche and often have interesting pharmacological properties.[2] Marine invertebrates such as sponges, tunicates, and jellyfish are known to host diverse endozoic microorganisms.[3]

Our aim was to identify bioactive metabolites from jellyfish-derived microorganisms. To this end, we investigated the chemical components of a fungus derived from the giant jellyfish *Nemopilema nomurai*.[4,5] The extract of the fungal strain *Paecilomyces variotii*, which was isolated from the inner tissue of the jellyfish, showed significant brine shrimp lethality (LD_{50} 2 μg/mL) and antibacterial activity against several pathogens (see Experimental Section). The fungal strain *P. variotii* was known to produce various secondary metabolites, such as sphingofungins,[6] semiviriditoxin derivatives,[7] cornexistin,[8] and a tricarboxylic acid.[9] The semiviriditoxin derivatives and tricarboxylic acid showed antibacterial activity against a number of bacterial strains.[7,10]

Guided by antibacterial activity, four new polyketides (**1**−**4**) were isolated from the crude extract of *P. variotii*. Compounds **1**−**3** were then further evaluated for antibacterial activity against methicillin-resistant *Staphylococcus aureus* 3089 (MRSA) and multi-drug-resistant (MDR) *Vibrio parahemolyticus* 7001. Herein we describe the structure elucidation and the biological evaluation of these compounds.



Received: April 24, 2011
Published: July 11, 2011

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Table 1. ^{1}H and ^{13}C NMR Data of Compounds 1−4 (in CD_3OD)

	paecilocin A (1)		paecilocin B (2)		paecilocin C (3)		paecilocin D (4)	
position	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
1	172.0		106.1	6.17, s	105.3	5.90, s	207.3	
2							57.6	2.48, ddd (7.5, 5.0, 2.0)
3	82.8	5.47, dd (8.0, 4.0)	115.1		114.2		72.2	5.13, d (2.0)
3a	153.7		143.1		142.3		140.1	
4	113.8	6.95, d (8.0)	114.1	6.71, d (8.0)	114.0	6.70, d (8.0)	156.0	
5	137.6	7.53, t (8.0)	132.6	7.27, t (8.0)	132.6	7.28, t (8.0)	121.2	7.08, d (8.0)
6	116.6	6.86, d (8.0)	117.0	6.79, d (8.0)	116.9	6.79, d (8.0)	130.9	7.33, t (8.0)
7	158.3		154.4		154.4		113.5	7.16, d (8.0)
7a	112.7		126.6		126.8		137.7	
1′	35.7	2.04, 1.71, m	41.2	1.92, 1.89, m	40.7	1.94, 1.87, m	29.7	1.83, 1.54, m
2′	25.7	1.45, 1.35, m	24.5	1.48, 1.21, br s	24.7	1.28, 1.26, m	27.1	1.32, br s
3′							29.5	
4′	30.3−30.5		30.3−30.8		30.3−30.7		29.0	
5′		1.28, br s		1.26, br s		1.21, br s	31.8	
6′	33.0		33.0		33.0		22.5	
7′	23.7		23.7		23.7		13.2	0.89, t (7.0)
8′	14.4	0.88, t (7.0)	14.4	0.88, t (6.8)	14.4	0.87, t (7.0)		
1-OCH_3			55.6	3.51, s	56.3	3.57, s		
3-OCH_3			50.0	2.86, s	50.8	3.01, s		

The molecular formula of compound **1** was assigned as $C_{16}H_{22}O_3$ on the basis of HRFABMS, $[M + H]^+$ at m/z 263.1634, and NMR data (Table 1). The ^{1}H and ^{13}C NMR data of compound **1** were almost identical to those of 3-butyl-7-hydroxyphthalide, which was isolated previously from a culture broth of *Penicillium vulpinum*.[11] However, compound **1** contained a longer (C_8) alkyl chain. The 1,2,3-trisubstitution pattern of the aromatic ring [δ 7.53 (t), 6.95 (d), and 6.86 (d)] suggested that the OH group should be attached to either C-4 or C-7. With regard to the oxygenation pattern of known phthalides from plants and microorganisms, mono-OH substitution has been observed at C-7, C-5, or C-4.[11−13] The OH group of compound **1** was suggested to be at C-7 (δ 158.3) after comparing the ^{13}C NMR data with that of model compounds.[11−13] This suggestion was corroborated by HMBC correlations of H-3/C-4 (δ_C 113.8) and H-4/C-3 (δ_C 82.8). The oxymethine proton (H-3) also showed a correlation to the carbonyl carbon (C-1, δ 172.0). The absolute configuration at C-3 was defined as *S* by comparison of the optical rotation ($[\alpha]^{25}_D$ −8.6, $CHCl_3$) with that of (−)-3-butyl-7-hydroxyphthalide ($[\alpha]^{25}_D$ −45.5, $CHCl_3$).[14] Therefore, the structure of compound **1** was determined to be (*S*)-7-hydroxy-3-octylphthalide, and it was given the trivial name paecilocin A.

Compound **2** ($C_{18}H_{28}O_4$, by HRFABMS) was isolated as a yellow oil, and it partially converted to an isomeric molecule (compound **3**) after several days at room temperature. The conversion established an equilibrium ratio of approximately 1:1.5 (of **2** to **3**). The ^{1}H NMR spectrum of **2** also showed the presence of a 1,2,3-trisubstituted aromatic ring (δ 7.27, 6.79, and 6.71). Notable was the presence of two OCH_3 groups (δ_H 2.86 and 3.51; δ_C 50.0 and 55.6). The DEPT spectrum of compound **2** showed two dioxygenated carbons [δ_C 106.1 (C-1) and 115.1 (C-3)]. In the HMBC spectrum, OCH_3 signals at δ_H 3.51 and 2.86 showed correlations with C-1 and C-3, respectively (Supporting Information, Figure S1). The correlation of H-1 (δ_H 6.17) to C-3 supported the presence of a cyclic ether. HMBC correlation between H-4 (δ 6.71) and C-3 (δ 115.1) indicated that the OH group was located at C-7 (δ 154.4) as in compound **1**. A correlation was observed in the NOESY spectrum between H-1 (δ_H 6.17) and the 3-OCH_3 (δ_H 2.86) protons, indicating that they were on the same face of the molecule. On the basis of biosynthetic considerations, the configuration at C-3 was presumed to be the same as that of compound **1**. The absolute configuration of **2** remains to be confirmed; however, the relative configuration of **2** was defined as (1*S**,3*S**), and compound **2** was given the trivial name paecilocin B.

Compound **3** ($C_{18}H_{28}O_4$, by HRFABMS) was isolated as a yellow oil, and when left standing at room temperature, it formed an equilibrium mixture of **2** and **3**. As observed in the case of compound **2**, the FABMS spectrum of **3** also showed the $[M + Na]^+$ and $[M - OCH_3]^+$ ions at m/z 331 and 277, respectively. In the negative ion mode, the FABMS spectrum of compound **3** showed the $[M - H]^-$ and $[M - H - OCH_3 - CH_3]^-$ ions at m/z 307 and 261, respectively (Figure 1). The ^{1}H NMR data were almost identical to those of compound **2**, with differences in the chemical shifts of the two OCH_3 groups (compound **3**, δ_H 3.01 and 3.57; compound **2**, δ_H 2.86 and 3.51) and the methine group (compound **3**, δ_H 5.90; compound **2**, δ_H 6.17) (Table 1). The ^{13}C NMR data of compound **3** were distinct for C-1, -1′, -3, -3a, and the two OCH_3 carbons, indicating that the configuration at one of the chiral centers was reversed in compound **3**.[15] The relative configuration of the OCH_3 groups was defined as *cisoid* by the NOE correlation between them. The configuration at C-3 in compound **3** was presumed to be the same as that in compound **2**, and the relative configuration of **3** was defined as (1*R**,3*S**). Compound **3** was given the trivial name paecilocin C. Compounds **2** and **3** are presumed to be interconverted by ketalization of the tentative precursor **A** (Supporting Information, Figure S2). The ketal form **B** might be reversibly transformed to

dx.doi.org/10.1021/np200350b |*J. Nat. Prod.* 2011, 74, 1826–1829

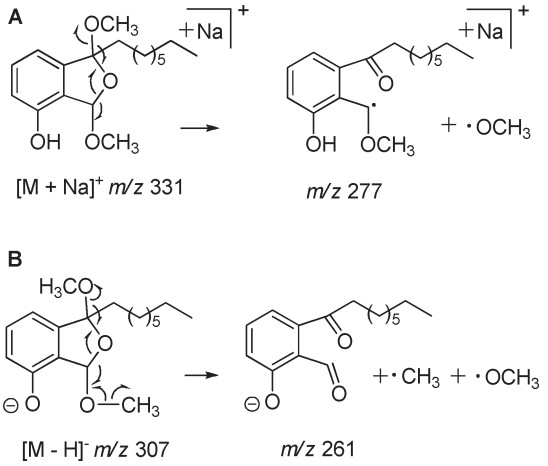

Figure 1. Key mass fragmentations of the pseudomolecular ions of compound **3** in positive (**A**) and negative (**B**) FABMS.

the methyl ether form (**2** and **3**). We cannot exclude the possibility that compounds **2** and **3** are artifacts, although we did not isolate the presumed precursor **A** from the fractions.

Compound **4** had the molecular formula $C_{16}H_{22}O_3$ on the basis of HRFABMS and NMR data. The ^{1}H NMR spectrum of **4** was similar to that of compound **1**. However, the splitting pattern of the oxymethine proton (H-3, δ_H 5.13) was a doublet, suggesting that it was coupled with a vicinal methine proton (H-2, δ 2.48). This methine carbon (C-2, δ 57.6) was apparent in the DEPT spectrum. Because the difference in the chemical shift between C-3a and C-7a was negligible (Δ 2.4 ppm),[11−13] we assumed that the OH group was located at C-4. This assumption was supported by a HMBC correlation between the aromatic proton H-7 (δ 7.16, doublet) and the ketone carbon C-1 (δ 207.3). In the HMBC spectrum, the methine protons (δ_H 2.48 and 5.13) showed correlations to the ketone carbon (C-1), indicating the presence of a cyclopentanone moiety. The relative configuration was defined as *trans* on the basis of the small coupling constant between H-2 and H-3 ($J_{2,3}$ 2.0 Hz).[16,17] The absolute configuration at C-3 was studied using Mosher's method. However, the reaction was unsuccessful probably due to weak reactivity of the OH group trapped in intramolecular hydrogen bonding. Therefore, the absolute configuration at C-3 was proposed as 3*R* by comparison of the CD data with that of model compounds.[16] Compound **4** showed a Cotton effect that was almost identical to that of (2*R*,3*R*)-3-hydroxy-2-methylindan-1-one.[18] Thus, the structure of compound **4** was determined as (2*R*,3*R*)-2-heptyl-3,4-dihydroxyindan-1-one, and it was given the trivial name paecilocin D. On the basis of its structural relevance to compound **1**, compound **4** could be biosynthesized from the same octaketide precursor.[19] Although indanones are an important class of natural compounds, no long-chain analogues of phthalide-like polyketide origin were reported.[16]

Polyketides **1**−**3** were isolated as major components from the fraction that suppressed the growth of *Staphylococcus aureus* SG 511 strain with a zone of inhibition of 10 mm at 30 μg/disk. Compounds **1**−**3** were evaluated for their antibacterial activity against three human pathogens using a microtiter plate-based minimum inhibitory concentration (MIC) assay. Compounds **2** and **3** showed moderate antibacterial activity against *Staphylococcus aureus* SG 511 and MRSA 3089 with MIC values ranging from 5 to 40 μg/mL (Table 2). The difference in potency between stereoisomers **2** and **3** suggests that the stereochemistry of these compounds modulates their biological activity.

EXPERIMENTAL SECTION

General Experimental Procedures. 1D and 2D NMR spectra were recorded on Varian UNITY 400 and Varian INOVA 500 spectrometers. Chemical shifts were reported with reference to the respective residual solvent or deuterated solvent peaks (δ_H 3.30 and δ_C 49.0 for CD_3OD). FABMS data were obtained on a JEOL JMS SX-102A. HRFABMS data were obtained on a JEOL JMS-700 M station mass spectrometer. FAB accurate mass measurements were carried out at a resolution of 10 000. The CD spectra were recorded on a JASCO J-715 instrument in acetonitrile; $\Delta\varepsilon$ values are expressed in L·mol^{-1} cm^{-1}. The UV spectrum was obtained in MeOH using an OPTIZEN 3220UV spectrophotometer, and the IR spectrum was recorded on a JASCO FT/IR-410 spectrometer. HPLC was performed using a Gilson 370 pump with an YMC packed J'sphere ODS-H80 column (250 × 10 mm, 4 μm, 80 Å) using a Shodex RI-71 detector.

Fungal Materials. The fungus *Paecilomyces variotii* was isolated from the jellyfish *Nemopilema nomurai* collected off the southern coast of Korea in June 2007. The specimen was deposited at the Marine Natural Product Laboratory, PNU. Following a rinse with sterile seawater, the jellyfish tissue was homogenized and then inoculated on malt extract agar (MEA), which was prepared with 75% seawater, containing glucose (20 g/L), malt extract (20 g/L), agar (20 g/L), peptone (1 g/L), and antibiotics (10 000 units/mL penicillin and 10 000 μg/mL streptomycin, 5 mg/L). Fungi growing out of the jellyfish tissue were separated on the same MEA medium until a pure culture was obtained. Twelve pure fungal strains (J08NF-1−J08NF-12) were isolated from the jellyfish. The fungal strain J08NF-1 was selected on the basis of significant antibacterial activity against the Gram-positive strain *Staphylococcus aureus* SG 511 (zone of inhibition 14 mm at 400 μg/disk), and it was identified as *Paecilomyces variotii* by one of the authors (K.S.B.) using morphological and biochemical analyses. *P. variotii* was then cultured in MEA medium (prepared with 75% seawater) containing glucose (20 g/L), malt extract (20 g/L), and peptone (1 g/L) at 30 °C on a shaker platform at 155 rpm for 21 days, in a total of 22 L.

Extraction and Isolation. The culture medium and mycelia were extracted with EtOAc at room temperature. The antibacterial activity of the crude EtOAc extract of *P. variotii* was tested against a panel of human pathogens (*Staphylococcus aureus* SG 511, *Salmonella typhimurium*, *Klebsiella aerogenes* 1522 E, *Escherichia coli* 078, and *Enterobacter cloacae* 1321 E) and marine pathogens (*Edwardsiella tarda* FP 5060, *Listonella anguillarum* FP 5208, *Streptococcus iniae* FP 5228, and *Vibiro ichthyoenteri* FP 4004) by the disk diffusion method. The results showed that *Staphylococcus aureus* SG 511 and two marine strains, *Streptococcus iniae* FP 5228 and *Vibrio ichthyoenteri* FP 4004, were sensitive at an exact concentration of 400 μg/disk. Guided by lethality to brine shrimp larvae (LD_{50} 2 μg/mL) and antibacterial activity against these strains, the EtOAc extract (10.2 g) was partitioned between aqueous MeOH and *n*-hexane, whose zones of inhibition against *Staphylococcus aureus* SG 511 were 13 and 7 mm at 30 μg/disk, respectively. The aqueous MeOH layer was subjected to step-gradient MPLC (ODS-A, 120 Å, S-30/50 mesh) eluting with 50% to 100% MeOH to afford 21 fractions. Each fraction was tested for lethality to brine shrimp larvae and for antibacterial activity against *Staphylococcus aureus* SG 511, *Streptococcus iniae* FP 5228, and *Vibiro ichthyoenteri* FP 4004. Fraction 7 (275.8 mg), one of the active fractions, was subjected to RP-HPLC (YMC ODS-H80, 250 × 10 mm i.d., 4 μm, 80 Å) eluting with 85% MeOH to afford compounds **1** (9.1 mg), **2** (33.8 mg), and **3** (49.1 mg). Compound **4** (5.6 mg) was isolated from fraction 4 by RP-HPLC (YMC ODS-H80, 250 × 10 mm i.d., 4 μm, 80 Å) eluting with 70% MeOH + 0.3% HCOOH (v/v).

Paecilocin A (***1***): white, amorphous powder; $[\alpha]^{25}_D$ −8.6 (*c* 0.25, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 262 (4.00), 270 (4.00), 300 (2.64), 316 (2.68) nm; IR ν_{max} 3485, 2924, 2855, 1728, 1631, 1601, 1475, 1385, 1307, 1206, 1050, 980, 803 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see

Table 2. MICs (μg/mL) of Compounds 1−3 and Standard Antibiotics

compound	*Staphylococcus aureus* SG 511	MRSA 3089	MDR *Vibrio parahemolyticus* 7001
1	>40	>40	>40
2	5	20	>40
3	20	40	>40
antibiotics[a]	1.25	0.625	0.156

[a] Tetracycline, vancomycin, and levofloxacin were employed as positive controls for the strains *Staphylococcus aureus* SG 511, methicillin-resistant *Staphylococcus aureus* (MRSA) 3089, and MDR *Vibrio parahemolyticus* 7001, respectively.

Tables 1 and 2; (+) FABMS m/z 263 $[M + H]^+$, 245 $[M + H - H_2O]^+$; HRFABMS m/z 263.1634 $[M + H]^+$ (calcd for $C_{16}H_{23}O_3$, 263.1647).

*Paecilocin B (**2**):* yellow oil; $[\alpha]^{25}_D$ −4.1 (c 0.10, CH_3OH); ^1H NMR and ^{13}C NMR data, see Tables 1 and 2; (+) FABMS m/z 331 $[M + Na]^+$, 299 $[M + Na - OCH_3 - H]^+$, 277 $[M - OCH_3]^+$; HRFABMS m/z 331.1882 $[M + Na]^+$ (calcd for $C_{16}H_{23}O_3Na$, 331.1885).

*Paecilocin C (**3**):* yellow oil; $[\alpha]^{25}_D$ −12.6 (c 0.10, CH_3OH); ^1H NMR and ^{13}C NMR data, see Tables 1 and 2; (+ve) FABMS m/z 331 $[M + Na]^+$, 299 $[M + Na - OCH_3 - H]^+$, 277 $[M - OCH_3]^+$; (−ve) FABMS m/z 307 $[M - H]^-$, 261 $[M - H - CH_3 - OCH_3]^-$.

*Paecilocin D (**4**):* yellow oil; $[\alpha]^{25}_D$ −10.8 (c 0.25, CH_3OH); CD (c 1.3×10^{-4} M, acetonitrile) $\Delta\varepsilon$ (nm) −0.66 (338.5), 0 (267.0), +0.71 (252.5), +2.00 (226.5), 0 (213.0), −0.90 (208.0); ^1H NMR and ^{13}C NMR data, see Tables 1 and 2; (−ve) FABMS m/z 261 $[M - H]^-$, 243 $[M - H - H_2O]^-$; HRFABMS m/z 261.1489 $[M - H]^-$ (calcd for $C_{16}H_{21}O_3$, 261.1491).

Bacterial Strains and Antibiotics. The human pathogens *Staphylococcus aureus* SG 511, *Salmonella typhimurium*, *Klebsiella aerogenes* 1522 E, *Escherichia coli* 078, and *Enterobacter cloacae* 1321 E were donated by the Korea Institute of Science and Technology. The marine strains *Edwardsiella tarda* FP 5060, *Listonella anguillarum* FP 5208, *Streptococcus iniae* FP 5228, and *Vibiro ichthyoenteri* FP 4004 were provided by National Fisheries Research & Development Institute, Korea. Methicillin-resistant *Staphylococcus aureus* 3089 and multidrug-resistant *Vibrio parahemolyticus* 7001 were purchased from the Korea National Reasearch Resource Bank. All standard antibiotics were purchased from Sigma Aldrich Co.

Antibacterial Assay. MIC values of the compounds were determined by the modified 0.5 Mcfarland standard method.[20] Twofold dilutions of the compounds in the range 40−0.31 μg/mL were prepared in 0.5% MeOH. Antibiotics were similarly diluted in 0.5% MeOH to generate a series of concentrations ranging from 40 to 0.31 μg/mL per well. The turbidity of the bacterial suspensions was measured at 600 nm and adjusted with medium to match the 0.5 McFarland standards (10^5−10^6 colony forming units/mL). Subsequently, 180 μL of bacterial culture was inoculated into each well, and the test solutions (20 μL) were added to 96-well plates. Finally, the plates were incubated at 36 °C for 24 h, and the MIC values were determined in triplicates and re-examined at appropriate times. To ensure that these vehicles had significant effect on the bacterial growth, each bacterial species was additionally cultured in a blank solution containing LB broth media at concentrations equivalent to those of the test solutions.

■ ASSOCIATED CONTENT

Supporting Information. Key HMBC correlations, plausible biogenetic pathways, and selected 1D and 2D NMR spectra of compounds **1**−**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This study was supported by a grant from the Marine Biotechnology Program, Ministry of Land, Transport, and Maritime Affairs, and a grant from the National Research Foundation (No. 20090083538), Korea. The authors acknowledge Dr. W. D. Yoon (National Fisheries Research & Development Institute) for the collection of the jellyfish *Nemopilema nomurai*. Thanks are due to Dr. Y. M. Lee of PNU for performing the antibacterial assay.

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