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Paecilonic acids A and B, bicyclic fatty acids from the jellyfish-derived fungus *Paecilomyces variotii* J08NF-1

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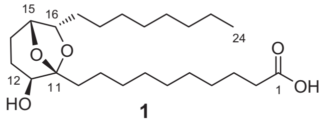
ABSTRACT

Two new bicyclic fatty acids, paecilonic acids A and B (**1** and **2**), were isolated from the culture broth of the marine fungus *Paecilomyces variotii* derived from the jellyfish *Nemopilema nomurai*. Compounds **1** and **2** share the same molecular formula and possess a 6,8-dioxabicyclo[3.2.1]octane core skeleton. The planar structures of compounds **1** and **2** were established by spectroscopic analysis, which included NMR and ESI-MS/MS. Relative and absolute configurations were determined by analyzing coupling constants, NOESY correlations, and optical rotations.

Marine microorganisms, especially marine fungi, represent a rich source of bioactive compounds due to their abilities to produce structurally unique, biologically active secondary metabolites.[1,2]

In our ongoing search for bioactive metabolites from the fungus *Paecilomyces variotii* derived from the inner tissues of the jellyfish *Nemopilema nomurai*, we isolated a series of new phthalide derivatives with moderate antibacterial activities.[3] The fungal strain *Paecilomyces variotii* has been previously reported to produce various metabolites, such as, alkaloids and butenolide and nonanolide derivatives.[4–6] Our chemical investigation of this fungus led to the isolation of two new bicyclic fatty acids (compounds **1** and **2**), which are probably derived by ketal formation in the middle of a fatty acid chain, and share a 6,8-dioxabicyclo[3.2.1]octane core skeleton. Several relevant metabolites, including didemniserinolipids,[7] cyclodidemniserinol trisulfate,[8] siladenoserinols,[9] and attenol B[10] have been isolated from marine invertebrates like tunicates and bivalves. Herein, we describe the isolation and structure elucidation of these two bicyclic fatty acids.



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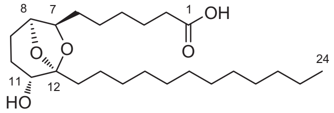

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Paecilonic acid A (**1**)[11] was isolated as a brown amorphous powder. Subsequent NMR and (−)-HRFABMS data indicated a molecular formula of $C_{24}H_{44}O_5$. The pseudomolecular ion at m/z 411.3108 $[M-H]^-$ (calcd, m/z 411.3111) well matched its expected formula and indicated the presence of three degrees of unsaturation. An initial analysis of ^{13}C and DEPT NMR data (Table 1) showed that compound **1** contained one carbonyl carbon (δ_c 176.5), a dioxygenated and nonprotonated carbon (δ_c 108.3), three oxymethine carbons (δ_c 80.3, 76.6, 68.1), several methylenes (δ_c 20.3–34.2), and one methyl group (δ_c 13.2). Its COSY spectrum showed the presence of two spin systems. Straightforward connections from H-12 (δ_H 3.44) to H-17 (δ_H 1.58/1.75) and from H-10 (δ_H 1.66/1.82) to H-9

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Table 1
^{1}H (900/500 MHz) and ^{13}C (100 MHz) NMR data for **1** and **2** (CD_3OD)[*]

Pos.	**1**[a]		**2**[b]	
	δ_C type	δ_H (*J* in Hz)	δ_C type	δ_H (*J* in Hz)
1	176.5, C		178.8, C	
2	34.2, CH_2	2.29, t (7.2)	34.4, CH_2	2.25, t (7.0)
3	25.1, CH_2	1.62, quint	25.2, CH_2	1.58, m
4	29.0–29.8, CH_2	1.30–1.36, m	29.0–29.8, CH_2	1.28–1.35, m
5	29.0–29.8, CH_2	1.30–1.36, m	26.7, CH_2	1.30, 1.51, m
6	29.0–29.8, CH_2	1.30–1.36, m	29.1, CH_2	1.53, 1.72, m
7	29.0–29.8, CH_2	1.30–1.36, m	80.3, CH	3.94, m
8	29.0–29.8, CH_2	1.30–1.36, m	76.6, CH	4.19, m
9	22.0, CH_2	1.45, quint	20.2, CH_2	1.51, 2.05, m
10	33.7, CH_2	1.66, dt (15.2, 7.2), 1.82, dt (15.2, 7.2)	25.9, CH_2	1.51, 2.13, m
11	108.3, C		68.1, CH	3.42, m
12	68.1, CH	3.44, br d (4.8)	108.3, C	
13	25.9, CH_2	1.54, m 2.16, tdd (14.4, 7.2, 4.8)	33.6, CH_2	1.63, 1.78, m
14	20.2, CH_2	1.53, m 2.05, tdd (14.4, 6.4, 4.8)	22.0, CH_2	1.41, m
15	76.6, CH	4.22, br t (4.0)	29.0–29.8, CH_2	1.28–1.35, m
16	80.3, CH	3.96, dt (4.0, 7.2)	29.0–29.8, CH_2	1.28–1.35, m
17	29.1, CH_2	1.58, 1.75, m	29.0–29.8, CH_2	1.28–1.35, m
18	26.7, CH_2	1.36, 1.51, m	29.0–29.8, CH_2	1.28–1.35, m
19–21	29.0–29.8, CH_2	1.30–1.36, m	29.0–29.8, CH_2	1.28–1.35, m
22	31.8, CH_2	1.28, m	31.8, CH_2	1.28, m
23	22.5, CH_2	1.31, m	22.5, CH_2	1.31, m
24	13.2, CH_3	0.92, t (7.2)	13.2, CH_3	0.90, t (7.0)

[*] Some overlapped or crowded ^{1}H signals were assigned based on HSQC data.
[a] ^{1}H NMR data of compound **1** measured by 900 MHz NMR.
[b] ^{1}H NMR data of compound **2** measured by 500 MHz NMR.

(δ_H 1.45) were detected. In addition, HMBC correlations were observed between the ketal carbon (C-11, δ_C 108.3) and H-15 (δ_H 4.22) and H-13 (δ_H 1.54), and between C-11 and H-10 (δ_H 1.82) (Fig. 1). The three degrees of unsaturation and the ^{13}C chemical shift of C-11 (δ_C 108.3), which corresponded to a dioxygenated and nonprotonated carbon, indicated that either C-12 or C-16 (both oxymethine carbons) should be linked to C-11 via an ether bridge. The upfield carbon chemical shift of C-12 (δ_C 68.1) indicated it bore a free hydroxy group, and that C-16 was linked to C-11 via an ether bridge. These findings indicated that compound **1** contained a bicyclo-ketal ring system. H_2-17 signals showed coupling to methylene protons, indicating an alkyl chain connected to the bicyclo-ketal ring system at C-16. The HMBC cross peak between H-10 and ketal carbon C-11 suggested that another linear alkyl chain was connected at C-11. These NMR data indicated that compound **1** was composed of a 6,8-dioxabicyclo[3.2.1]octane core with two alkyl chains, one of which had a terminal carboxy group. The 6,8-dioxabicyclo[3.2.1]octane moiety has been previously reported in several fatty acid derivatives, such as, didemniserinolipids,[7] cyclodidemniserinol trisulfate,[8] siladenoserinols,[9] and attenol B.[10] Unfortunately, the location of the carboxyl terminal and the lengths of the two alkyl chains could not be determined by 2D NMR because of methylene signal (δ_H 1.35) overlap, and thus, we resorted to ESI-MS/MS. Analysis of fragmentations of compound **1** revealed prominent peaks at *m*/*z* 157, 169, 197, 225, 241, and 253, which were attributed to cleavages in the vicinity of the ketal moiety (Fig. 2), and enabled the location of the carboxy group and the length of each alkyl chain to be established.

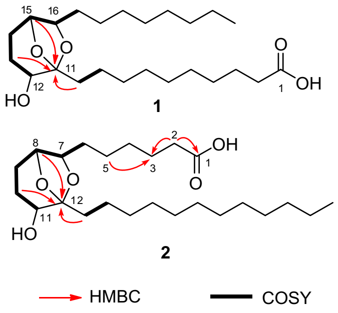

Figure 1. Key HMBC and COSY correlations for compounds **1** and **2**.

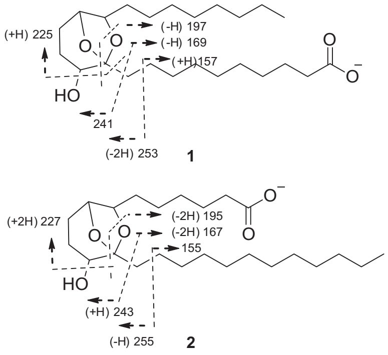

Figure 2. Key ESI-MS/MS fragmentations of $[M-H]^-$ (*m*/*z* 411) of compounds **1** and **2**.

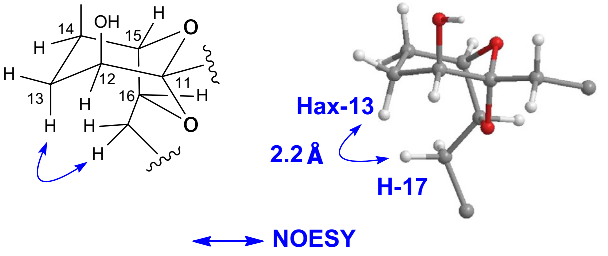

Figure 3. Key NOESY correlation of compound **1** and the interproton distance of the energy-minimized conformation (side chains were omitted).