Paecilomycines A and B, Novel Diterpenoids, Isolated from Insect-Pathogenic Fungi *Paecilomyces* sp. ACCC 37762

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Two new diterpenoids, named paecilomycine A (**1**) and paecilomycine B (**2**), including a novel skeleton with a five-membered lactone ring, together with three known labdane diterpenoids, *rel*-(1*R*,3*S*,4a*S*,5*R*,8a*S*)-5-[(3*E*)-4-carboxy-3-methylbut-3-en-1-yl]decahydro-3-hydroxy-1,4a-dimethyl-6-methylidenenaphthalene-1-carboxylic acid (**3**), botryosphaerin E (**4**), and agathic acid (**5**), were isolated from solid culture of the insect pathogenic fungi strain *Paecilomyces* sp. The structures of all compounds were established on the basis of comprehensive spectroscopic studies. The relative configurations of **1** and **2** were determined by single-crystal X-ray diffraction analyses.

Introduction. – Insect-pathogenic fungi constitute an ecologically highly specialized group of microorganisms. More than 700 known fungal species from 100 genera have adopted an entomopathogenic lifestyle [1]. Fungi belonging to the genus *Paecilomyces* are pathogens against insects like Homoptera, Lepidoptera, and Coleoptera. This group of fungi has been the source of a wide range of bioactive compounds [2–5]. Recently, many new compounds have been isolated from the genus *Paecilomyces*. Paecilodepsipeptide A, an antimalarial and antitumor cyclohexadepsipeptide, together with its linear analogs, paecilodepsipeptides B and C, were isolated from the insect-pathogenic fungus *Paecilomyces cinnamomeus* BCC 9616 [6]. Variotin and three novel compounds, formosusins A, B, and C, were isolated from cultures of the fungus *Paecilomyces formosus*. Among these compounds, formosusin B showed selective inhibitory activity of mammalian DNA polymerase β (pol β) *in vitro* with an IC_{50} value of 35.6 μM [7]. Paecilomide, a new acetylcholinesterase inhibitor, was isolated from *Paecilomyces lilacinus* [8]. Therefore, interest in searching for bioactive compounds from insect-pathogenic fungi has recently increased considerably [9].

In our continuing studies, we investigated the secondary metabolites produced by the solid-cultured *Paecilomyces* sp. and isolated two new diterpenoids, named paecilomycines A and B (**1** and **2**, resp.), one new diterpenoid with a novel C-atom skeleton and one new labdane-type diterpenoid, together with three known compounds, **3**–**5** (*Fig. 1*). Herein, the isolation and structure elucidation of these compounds are reported.

Results and Discussion. – Paecilomycine A (**1**) was obtained as colorless crystals. The molecular formula was determined as $C_{19}H_{26}O_6$ (seven degrees of unsaturation) on

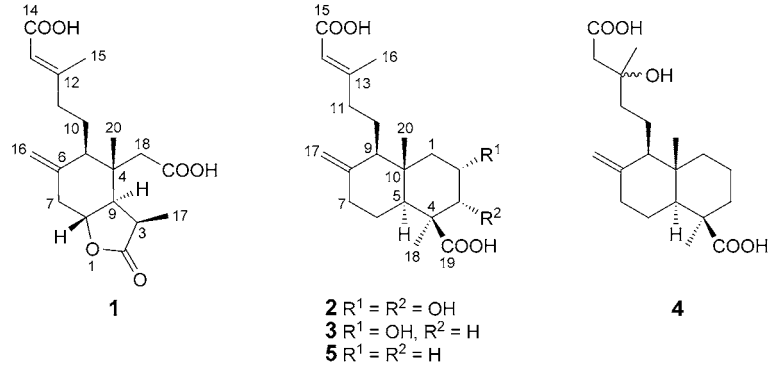

Fig. 1. *Structures of compounds* **1**–**5** *isolated from* Paecilomyces *sp.*

the basis of HR-APCI-MS data (*m/z* 351.1796 ($[M+H]^+$; calc. 351.1802). The ^{1}H-NMR spectrum (*Table 1*) indicated three Me signals at δ(H) 0.93 (*s*), 1.29 (*d*, $J=$ 7.8), and 2.19 (*d*, $J=1.2$), three olefinic H-atom signals at 4.90 (*s*), 5.26 (*s*), 5.68 (*s*), and a CH–O signal at 4.41 (*dt*, $J=11.4, 4.8$). ^{13}C-NMR and DEPT data (*Table 1*) of **1** exhibited 19 C-atoms signals, including those of three C=O units (δ(C) 168.9, 170.0, and 180.5), three C_q-atoms (40.1, 142.3, and 160.2), three Me (11.1, 16.8, and 17.6), four sp^3 CH_2 groups (22.5, 39.3, 41.6, and 42.5), one sp^2 CH_2 (113.0), and one sp^2 CH group (115.4), and four sp^3 CH groups (38.8, 50.7, 52.9, and 77.4). The HMBC spectrum displayed the following long-range correlations (*Fig. 2*): H–C(3)/C(2), C(9), and C(17); CH_2(7)/C(6), C(8), and C(16); Me(20)/C(4), C(5), C(9), and C(18); CH_2(18)/C(4), C(9), C(19), and C(20); and H–C(9)/C(3), C(17), and C(20). Based on these findings and key ^{1}H,^{1}H-COSY correlations (*Fig. 2*), the planar structure of **1** was thus elucidated as shown in *Fig. 1*. The relative configuration of **1** was established by a

Table 1. *^{1}H- and ^{13}C-NMR Data of* **1** (600 and 150 MHz, resp.; in CD_3OD). δ in ppm, *J* in Hz. Arbitrary atom numbering as indicated in *Fig. 1*.

Position	δ(H)	δ(C)	Position	δ(H)	δ(C)
2		180.5 (*s*)	12		160.2 (*s*)
3	2.97–3.03[a])	38.8 (*d*)	13	5.68 (*s*)	115.4 (*d*)
4		40.1 (*s*)	14		168.9 (*s*)
5	2.20–2.22[a])	50.7 (*d*)	15	2.19 (*d*, $J=1.2$)	17.6 (*q*)
6		142.3 (*s*)	16	5.26 (*s*), 4.90 (*s*)	113.0 (*t*)
7	2.97–3.03[a]), 2.20–2.22[a])	42.5 (*t*)	17	1.29 (*d*, $J=7.8$)	11.1 (*q*)
8	4.41 (*dt*, $J=11.4, 4.8$)	77.4 (*d*)	18	2.59 (*d*, $J=13.8$), 2.44 (*d*, $J=13.8$)	41.6 (*t*)
9	2.54 (*dd*, $J=11.4, 7.2$)	52.9 (*d*)	19		170.0 (*s*)
10	1.85–1.91 (*m*), 1.62–1.68 (*m*)	22.5 (*t*)	20	0.93 (s)	16.8 (*q*)
11	2.30–2.35 (*m*), 2.03–2.10 (*m*)	39.3 (*t*)			

[a]) Partially overlapped by other resonances.

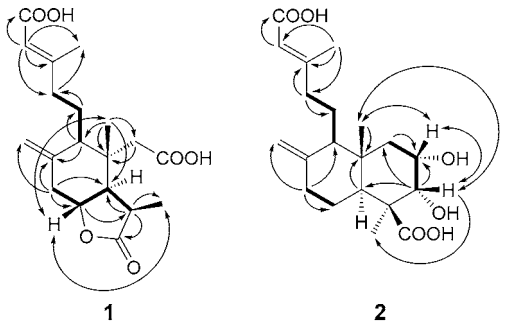

Fig. 2. *Key* $^1H,^1H$*-COSY* (—), *HMB* (H → C), *and ROESY* (H ↔ H) *correlations of* **1** *and* **2**

ROESY experiment (*Fig. 2*), which showed significant correlations between H–C(8) and Me(17) and Me(20). The structural assignments were confirmed by single-crystal X-ray diffraction (*Fig. 3*), which established the relative configuration of **1**. Thus, from the above data, **1** was determined to be *rel*-(2*E*)-5-[(3*R*,3a*R*,4*S*,5*R*,7a*R*)-4-(carboxymethyl)-octahydro-3,4-dimethyl-6-methylidene-2-oxo-1-benzofuran-5-yl]-3-methylpent-2-enoic acid, named paecilomycine A.

Table 2. ^1H*-NMR Data of* **2**–**5** (600 MHz; in CD_3OD). δ in ppm, *J* in Hz. Arbitrary atom numbering as indicated in *Fig. 1*.

Position	**2**	**3**	**4**	**5**
1	1.49 (*t*, *J* = 12.2, H_α), 1.74–1.80 (H_β)[a])	1.00–1.05 (H_α)[a]), 2.38–2.42 (*m*, H_β)	1.16 (*t*, *J* = 13.2, H_α), 1.85–1.95 (H_β)[a])	1.08–1.15 (H_α)[a]), 1.86–1.98 (H_β)[a])
2	4.15–4.19 (*m*)	4.11–4.14 (*m*)	1.53 (*d*, *J* = 11.8, H_α), 1.85–1.95 (H_β)[a])	1.52–1.58 (H_α)[a]), 1.86–1.98 (H_β)[a])
3	3.97 (*d*, *J* = 2.52)	1.00–1.05 (H_α)[a]), 2.13–2.15 (*m*, H_β)	1.09 (*t*, *J* = 13.2, H_α), 2.16 (*d*, *J* = 12.8, H_β)	1.08–1.15 (H_α)[a]), 2.15–2.16 (H_β)[a])
5	1.71–1.80[a])	1.37 (*dd*, *J* = 12.6, 3.0)	1.32–1.38[a])	1.37 (*d*, *J* = 11.4)
6	1.90–1.95 (*m*)	1.82–1.88 (*m*, H_α), 2.02–2.08 (H_β)[a])	1.85–1.95 (H_α)[a]), 2.00 (*d*, *J* = 10.7, H_β)	1.86–1.98 (H_α)[a]), 2.00–2.05 (H_β)[a])
7	1.93–2.00 (H_α)[a]), 2.44–2.45 (*m*, H_β)	1.94–1.99 (*m*, H_α), 2.44–2.47 (*m*, H_β)	1.85–1.95 (H_α)[a]), 2.40 (*d*, *J* = 10.4, H_β)	1.86–1.98 (H_α)[a]), 2.43–2.44 (*m*, H_β)
9	1.71–1.80[a])	1.72 (*d*, *J* = 10.8)	1.59 (*d*, *J* = 10.3)	1.65 (*d*, *J* = 11.4)
11	1.57–1.61 (*m*, H_α), 1.71–1.80 (H_β)[a])	1.56–1.62 (*m*, H_α), 1.78–1.82 (*m*, H_β)	1.42–1.45 (*m*, H_α), 1.67–1.71 (*m*, H_β)	1.52–1.58 (H_α)[a]), 1.73–1.79 (*m*, H_β)
12	2.02–2.08 (*m*, H_α), 2.31–2.36 (*m*, H_β)	2.02–2.08 (H_α)[a]), 2.31–2.35 (*m*, H_β)	1.32–1.38 (H_α)[a]), 1.78–1.82 (*m*, H_β)	2.00–2.05 (H_α)[a]), 2.30–2.35 (*m*, H_β)
14	5.63 (*s*)	5.64 (*d*, *J* = 0.6)	2.47 (*s*)	5.63 (*s*)
16	2.16 (*d*, *J* = 1.08)	2.16 (*s*)	1.30 (*s*)	1.14 (*s*)
17	4.59 (*s*, H_α), 4.98 (*s*, H_β)	4.60 (*s*, H_α), 4.95 (*d*, *J* = 1.2, H_β)	4.59 (*s*, H_α), 4.86 (*s*, H_β)	4.56 (*s*, H_α), 4.90 (*s*, H_β)
18	1.32 (*s*)	1.28 (*s*)	1.22 (*s*)	1.22 (*s*)
20	0.69 (*s*)	0.68 (*s*)	0.67 (*s*)	0.67 (*s*)

[a]) Partially overlapped by other resonances.

Paecilomycine B (**2**) was isolated as colorless crystals. Its molecular formula was established as $C_{20}H_{30}O_6$ based on its positive-ion-mode HR-EI-MS data (*m/z* 366.2048 (M^+; calc. 366.2042), implying eight degrees of unsaturation. The ^{1}H- and ^{13}C-NMR spectra of **2** (*Tables 2* and *3*) were similar to those of agathic acid (**5**) [10], suggesting that **2** possessed the same labdane diterpenoid skeleton. The key differences were that the signals of C(2) and C(3) in the spectrum of **2** (δ(C) 66.3 (*d*) and 73.7 (*d*)) were shifted downfield compared to those of **5** (19.8 (*t*) and 38.0 (*t*)). These characteristic differences were caused by replacement of two H-atoms (one at C(2) and one at C(3)) of **5** by OH groups, respectively. The presence of the two OH groups at C(2) and C(3) was determined by the key HMBCs (*Fig. 2*). HMBCs (H–C(3)/C(1), C(2), C(5), and C(18)) and ^{1}H,^{1}H-COSY correlations (H–C(3)/H–C(2); H–C(2)/CH_2(1) and H–C(3)) further revealed the planar structure of **2**. The relative configuration of **2** could not be established unambiguously by ROESY experiments, because the signals of H–C(5) and H–C(9) overlapped at δ(H) 1.71 – 1.80. Fortunately, crystals of **2** were obtained from MeOH. Consequently, the relative configuration of **2** was determined by single-crystal X-ray diffraction (*Fig. 3*), and **2** was identified as *rel*-(1*R*,2*S*,3*R*,4a*R*,5*S*,8a*R*)-5-[(3*E*)-4-carboxy-3-methylbut-3-en-1-yl]decahydro-2,3-dihydroxy-1,4a-dimethyl-6-methylidenenaphthalene-1-carboxylic acid, named paecilomycine B.

Compounds **3** – **5** were identified as *rel*-(1*R*,3*S*,4a*S*,5*R*,8a*S*)-5-[(3*E*)-4-carboxy-3-methylbut-3-en-1-yl]decahydro-3-hydroxy-1,4a-dimethyl-6-methylidenenaphthalene-1-carboxylic acid (**3**), botryosphaerin E (**4**) [11], and agathic acid (**5**) [10]. In addition, the NMR assignments for **3** were completed.

Table 3. *^{13}C-NMR Data of* **2** – **5** (150 MHz; in CD_3OD). δ in ppm. Arbitrary atom numbering as indicated in *Fig. 1*.

Position	**2**	**3**	**4**	**5**
1	40.4 (*t*)	46.2 (*t*)	39.1 (*t*)	39.1 (*t*)
2	66.3 (*d*)	64.2 (*d*)	19.9 (*t*)	19.8 (*t*)
3	73.7 (*d*)	47.0 (*t*)	38.1 (*t*)	38.0 (*t*)
4	48.4 (*s*)	44.6 (*s*)	43.8 (*s*)	43.8 (*s*)
5	47.6 (*d*)	55.3 (*d*)	56.2 (*d*)	56.1 (*d*)
6	25.3 (*t*)	25.7 (*t*)	26.2 (*t*)	26.2 (*t*)
7	38.3 (*t*)	38.2 (*t*)	38.6 (*t*)	38.5 (*t*)
8	147.6 (*s*)	147.4 (*s*)	148.2 (*s*)	148.1 (*s*)
9	55.0 (*d*)	55.2 (*d*)	56.7 (*d*)	55.1 (*d*)
10	40.4 (*s*)	40.9 (*s*)	43.4 (*s*)	40.1 (*s*)
11	21.6 (*t*)	21.6 (*t*)	17.7 (*t*)	21.5 (*t*)
12	39.3 (*t*)	39.3 (*t*)	40.9 (*t*)	39.4 (*t*)
13	160.4 (*s*)	160.3 (*s*)	70.1 (*s*)	160.5 (*s*)
14	115.5 (*d*)	115.4 (*d*)	45.2 (*t*)	115.4 (*d*)
15	168.8 (*s*)	168.9 (*s*)	174.2 (*s*)	168.9 (*s*)
16	17.5 (*q*)	17.5 (*q*)	25.7 (*q*)	17.5 (*q*)
17	106.0 (*t*)	106.2 (*t*)	105.9 (*t*)	105.4 (*t*)
18	23.6 (*q*)	28.1 (*q*)	28.3 (*q*)	28.2 (*q*)
19	178.9 (*s*)	179.2 (*s*)	180.0 (*s*)	179.8 (*s*)
20	12.8 (*q*)	12.8 (*q*)	12.1 (*q*)	12.0 (*q*)

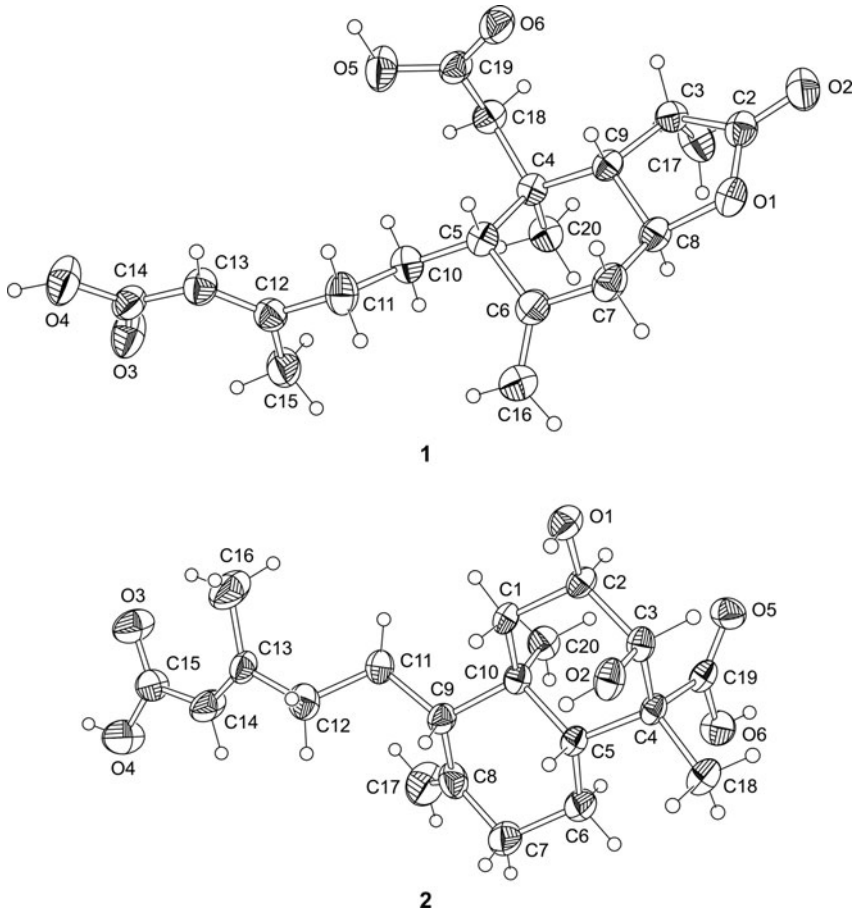

Fig. 3. *Crystall structures of* **1** *and* **2**

Compound **1**, for which we propose the name 'paecilomycine A', possesses a previously unknown C-atom skeleton. From a biogenetic point of view, the precursor of **1** may be agathic acid (**5**). We propose a possible biosynthetic pathway from **5** to **1** as outlined in the *Scheme*, in which hydration, dehydration, oxidation, and decarboxylation reactions are potentially responsible for the transformation.

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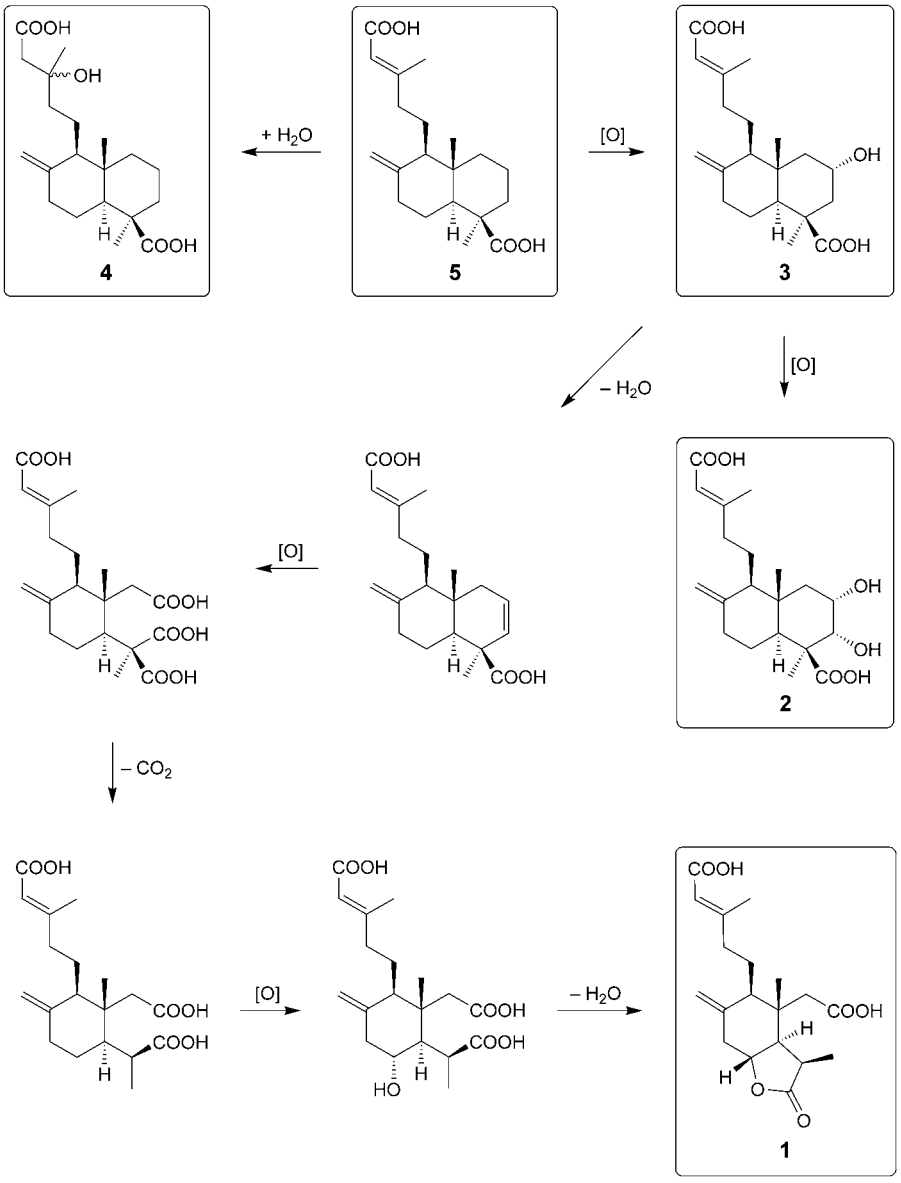
Experimental Part

General. TLC: Silica gel GF_{254} plates (SiO_2; *Yantai Zhifu Chemical Co., Ltd.*, P. R. China). Column chromatography (CC): SiO_2 (200–300 mesh; *Yantai Zhifu Chemical Co., Ltd.*, P. R. China) and

Scheme. *Proposed Biogenetic Pathway of* **5** *to* **1**–**4**



Sephadex LH-20 gel (25–100 mm, *GE Healthcare Co., Ltd.*, Sweden). Optical rotations: *PerkinElmer 341* spectropolarimeter. UV Spectra: *Shimadzu UV-210* spectrometer; λ_{max} (log ε) in nm. IR Spectra: *PerkinElmer 577* spectrometer; KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker AM-600* spectrometer; δ in ppm rel. to Me_4Si as internal standard, J in Hz. FT-MS Spectra: *Bruker Apex-Ultra 7.0 T* spectrometer; in m/z.

Fungal Material and Cultivation Conditions. Paecilomyces sp. was isolated from an unidentified Lepidopteran collected in Hebei Province, P. R. China, and identified by Prof. *Yong-Chun Niu*. It has been cataloged as strain ACCC 37762 in the culture collection of the Key Laboratory of Medicinal Chemistry and Molecular Diagnosis of Ministry of Education, Hebei University. The fungal strain was cultured on slants of potato dextrose agar (PDA; modified) at 26° for 7 d and then inoculated into a 500-ml *Erlenmeyer* flask containing 100 ml of modified PDA medium (20.0 g of glucose, 200.0 g of potato (peeled), 3.0 g of KH_2PO_4, 1.5 g of $MgSO_4$, 0.1 g of citric acid, and 10.0 mg of thiamine hydrochloride, in 1 l of deionized H_2O). The final pH of the mixture was adjusted to 6.5 before sterilization. After 7 d of incubation at 26° on rotary shakers at 150 rpm, samples of culture liquid were transferred into 50 500-ml *Erlenmeyer* flasks containing 180.0 g of rice medium (88 g of rice and 100 ml of dist. H_2O), and the fermentation was carried out at 26° under light for 30 d.

Extraction and Isolation. The fermented material was extracted four times with AcOEt (soaking for 2 d in 15 l each), and the org. layer was concentrated *in vacuo* to yield a yellow oily residue (30.0 g). This residue was subjected to CC (SiO_2; petroleum ether (PE)/AcOEt 100:0, 95:5, 90:10, 90:15, 80:20, 60:30, and 50:50) to furnish seven fractions, *Frs. 1–7. Fr. 4* (3.2 g; eluted with PE/AcOEt 90:15) was repeatedly purified by CC (SiO_2; PE/AcOEt 20:1) and recrystallized from MeOH to afford **5** (40 mg). *Fr. 5* (6.5 g, eluted with PE/AcOEt 80:20) was further purified by CC (SiO_2; PE/acetone 50:1 → 1:1) to give eight subfractions, *Frs. 5.1–5.8*. *Fr. 5.3* (55 mg) and *Fr. 5.5* (50 mg) were subjected to CC (*Sephadex LH-20*; MeOH) to afford **3** (20 mg) and **4** (18 mg). Compounds **1** (20 mg) and **2** (15 mg) were obtained from *Fr. 6* by CC (SiO_2; PE/AcOEt 8:1 and 6:1) and recrystallization from MeOH.

Paecilomycine A (= rel-*(2*E*)-5-[(3*R*,3a*R*,4*S*,5*R*,7a*R*)-4-(Carboxymethyl)-octahydro-3,4-dimethyl-6-methylidene-2-oxo-1-benzofuran-5-yl]-3-methylpent-2-enoic Acid*; **1**). Colorless crystals. M.p. 215–216°. $[\alpha]_D^{25} = -22.93$ ($c = 0.15$, MeOH). UV (MeOH): 202 (4.02), 216 (4.00). IR: 3449, 2973, 1776, 1691, 1637, 1255, 1176, 980. ^{1}H- and ^{13}C-NMR: see *Table 1*. HR-APCI-MS (pos.): 351.1796 ($[M+H]^+$, $C_{19}H_{27}O_6^+$; calc. 351.1802).

X-Ray Crystallographic Analysis of **1**[1]). Upon crystallization from MeOH by the vapor-diffusion method, colorless crystals were obtained for **1**. A crystal (0.24 × 0.17 × 0.14 mm) was separated from the sample and mounted on a glass fiber, and data were collected with a *Bruker-SMART-1000-CCD* diffractometer and graphite-monochromated MoK_α radiation (λ 0.71073 Å) at 296(2) K. Crystal data: $C_{19}H_{26}O_6$; M_r 350.41, monoclinic; space group $P2_12_12_1$; $Z = 4$; unit cell parameters $a = 27.977(12)$, $b = 6.789(3)$, $c = 9.838(4)$ Å; $V = 1854.9(14)$ Å^3; D_x (calc.) = 1.255 Mg m^{-3}; $\mu = 0.093$ mm^{-1}; $F(000) = 752$. The structure was solved by direct methods with SHELXL-97 [12] and refined by full-matrix least-squares difference *Fourier* techniques. All non-H-atoms were refined with anisotropic displacement parameters, and all H-atoms were placed in idealized positions and refined as riding atoms with the relative isotropic parameters. Absorption corrections were applied with the *Siemens* area detector absorption program (SADABS) [13]. The 6829 reflections collected yielded 4287 independent reflections after equivalent data had been averaged, and *Lorentz* and polarization corrections had been applied. The final refinement gave $R_f = 0.0454$ and $R_w = 0.0912$ ($I > 2\sigma(I)$).

Paecilomycine B (= rel-*(1*R*,2*S*,3*R*,4a*R*,5*S*,8a*R*)-5-[(3*E*)-4-Carboxy-3-methylbut-3-en-1-yl]-decahydro-2,3-dihydroxy-1,4a-dimethyl-6-methylidenenaphthalene-1-carboxylic Acid*; **2**). Colorless crystals. M.p. 240–241°. $[\alpha]_D^{25} = 6.73$ ($c = 0.10$, MeOH). UV (MeOH): 203 (3.71), 216 (3.64). IR: 3441, 2952, 2862, 1690, 1640, 1637, 1262, 1182. ^{1}H- and ^{13}C-NMR: see *Tables* 1 and 2, resp. HR-EI-MS (pos.): 366.2048 (M^+, $C_{20}H_{30}O_6^+$; calc. 366.2042).

X-Ray Crystallographic Analysis of **2**[1]). Upon crystallization from MeOH by vapor-diffusion method, colorless crystals were obtained for **2**. A crystal (0.28 × 0.16 × 0.11 mm) was separated from the sample and mounted on a glass fiber, and data were collected with a *Bruker-SMART-1000-CCD* diffractometer and graphite-monochromated MoK_α radiation ($\lambda = 0.71073$ Å) at 296(2) K. Crystal data:

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[1]) Crystallographic data for **1** and **2** have been deposited in the *Cambridge Crystallographic Data Centre* (deposition Nos.: CCDC-1017518 and 1017519, resp.). Copies of these data can be obtained, free of charge, *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the *Cambridge Crystallographic Data Centre*, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

$C_{20}H_{30}O_6$, M_r 366.45, monoclinic, space group $P2_12_12_1$, $Z=4$; unit cell parameters $a=9.509(3)$ Å, $b=30.601(8)$ Å, $c=6.8466(18)$ Å; $V=1992.3(9)$ Å^3, D_x (calc.) $=1.222$ Mg m^{-3}, $\mu=0.089$ mm^{-1}, $F(000)=792$. The structure was solved by direct methods with SHELXL-97 [12] and refined by full-matrix least-squares difference *Fourier* techniques. All non-H-atoms were refined with anisotropic displacement parameters, and all H-atoms were placed in idealized positions and refined as riding atoms with the relative isotropic parameters. Absorption corrections were applied with SADABS [13]. The 6412 reflections collected yielded 1881 independent reflections after equivalent data had been averaged, and *Lorentz* and polarization corrections had been applied. The final refinement gave $R_f=0.0380$ and $R_w=0.0947$ ($I>2\sigma(I)$).

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