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Cyclopiane-type diterpenes from the deep-sea-derived fungus *Penicillium commune* MCCC 3A00940

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ABSTRACT

Three new cyclopiane diterpenes (**1**–**3**) and one rare spirocyclolide (**5**) were isolated from the deep-sea-derived fungus *Penicillium commune* MCCC 3A00940, along with 11 known compounds. The planar structures of the new compounds were determined by extensive analysis of their NMR and HRESIMS spectra, and the absolute configurations were established on the basis of specific rotation data in association with calculated ECD spectra. Four of the cyclopiane diterpenes (**1**–**4**), with a rigid 6/5/5/5 fused tetracyclic ring framework, are rarely found in Nature. Notably, conidiogenone J (**1**) is the first naturally occurring enantiomer of the cyclopiane diterpenes. Additionally, penijanthine B (**6**) and 3-hydroxy-5-methoxystilbene (**14**) exhibited moderate antiallergic effects with IC_{50} values of 30 and 33 μM, respectively.

Introduction

Cyclopianes, a rare class of diterpenes bearing a rigid 6/5/5/5 tetracyclic skeleton, are exclusively isolated from the *Penicillium* genus, with potent bioactivities, such as conidiation-induction, cytotoxicity, and antibacterial properties. To date, only 10 congeners have been discovered in Nature, namely, conidiogenol, conidiogenone, and conidiogenones B–I.[1–3] The absolute configurations of conidiogenol, conidiogenone, and conidiogenone B were only recently determined unambiguously by total synthesis.[4] Consequently, the absolute configurations of conidiogenones C–G were revised as the corresponding enantiomers.[2,4] Very recently, a rearranged cyclopiane diterpene, spiroviolene, with a fused 5/5/5/5 ring system, was obtained from a bacterial terpene synthase.[5] Subsequently, spirograterpene, a C-4 diastereomer bearing the same carbon skeleton, was isolated from a fungal culture of *Penicillium granulatum*.[6] As part of our ongoing search for antiallergic compounds from deep-sea-derived microorganisms,[6,7] a chemical investigation of the fungal cultures of *Penicillium commune* MCCC 3A00940 led to the isolation of three new (**1**–**3**) and one known (**4**) cyclopiane-type diterpenes, as well as one rare spirocyclolide (**5**) and 10 known compounds (**6**–**15**; ESI). Remarkably, conidiogenone J (**1**) represents the first naturally occurring enantiomer of the cyclopiane diterpenes. Herein, the isolation, structural elucidation, and antiallergic activities of these compounds are described.

Results and discussion

The fungus *Penicillium commune* MCCC 3A00940 was cultured on a rice solid medium in 35 × 1 L Erlenmeyer flasks under static conditions. The EtOAc extract (28.6 g) was fractionated by column chromatography (CC) over silica gel, ODS, and Sephadex LH-20, which led to the isolation of four new (**1**–**3** and **5**, Fig. 1) and 11 known compounds.

Conidiogenone J[8] (**1**) was obtained as a colorless oil. The molecular formula $C_{20}H_{30}O_3$ was determined by its HRESIMS at *m*/*z* 319.2241 $[M+H]^+$, indicating six degrees of unsaturation. The ^1H NMR spectrum showed the presence of two singlet and one doublet methyls [δ_H 0.97 (3H, s, Me-19), 1.17 (3H, s, Me-17), and 1.26 (3H, d, *J* = 7.3 Hz, Me-16)], two oxygenated methylenes [δ_H 3.48 (1H, d, *J* = 10.8 Hz, H-18a), 3.39 (1H, d, *J* = 10.8 Hz, H-18b), and 3.28 (1H, d, *J* = 10.9 Hz, H-20a), 3.22 (1H, d, *J* = 10.9 Hz, H-20b)], and two olefinic protons [δ_H 7.15 (1H, dd, *J* = 10.1, 6.1 Hz, H-3) and 5.95 (1H, d, *J* = 10.1 Hz, H-2)]. The ^{13}C NMR spectrum, with the aid of the HSQC spectrum, provided 20 carbon resonance signals involving three methyls (δ_C 18.7 q, 21.8 q, 23.1 q; for

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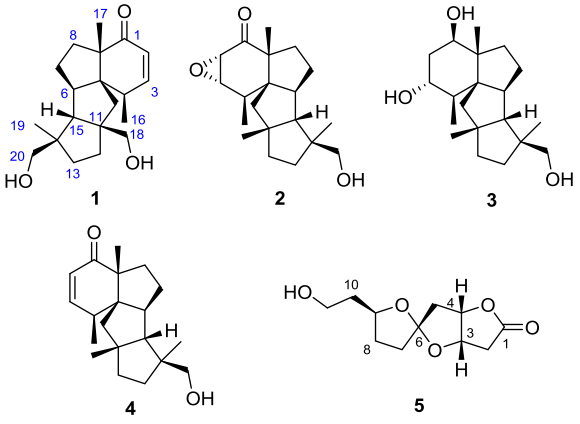

Fig. 1. Chemical structures of compounds **1**–**5**.

Me-16, 17, and 19, respectively), two oxygenated (δ_C 71.1 t, C-18 and 71.7 t, C-20) and five aliphatic methylenes, five methines including two sp^2 ones (δ_C 127.5 d, C-2 and 157.5 d, C-3), one ketone (δ_C 208.3), and four sp^3 quaternary carbons (Table 1). These signals were closely related to those of conidiogenone C (**4**), except for an additional hydroxy unit at C-18. This assumption was evidenced by the key COSY, HMBC, and NOESY correlations (Fig. 2).

To determine its absolute configuration, a computational modelling study was conducted using Gaussian 09. The (4*S*,5*S*,6*S*,9*R*,11*S*,14*S*,15*R*)-**1** (**1a**) and its enantiomer (**1b**) were optimized at the B3LYP/6-311G** level with the CPCM polarizable conductor calculation model after a conformational search using Confab with the MMFF94 force field. The calculated ECD spectra of **1a** and **1b** were obtained by time-dependent density functional theory (TD-DFT) at the B3LYP/6-311G** level in MeOH. The calculated ECD spectrum of **1b** was consistent with the experimental one (Fig. 3), confirming the absolute configuration of **1** to be 4*R*, 5*R*, 6*R*, 9*S*, 11*R*, 14*R*, and 15*S*, respectively. Therefore, **1** was determined to be 18,20-dihydroxy-*ent*-conidiogenone B, and named conidiogenone J.

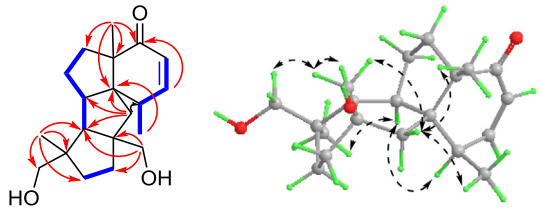

Fig. 2. Key COSY (▬), HMBC (⟶), and NOESY (⇢) correlations of **1**.

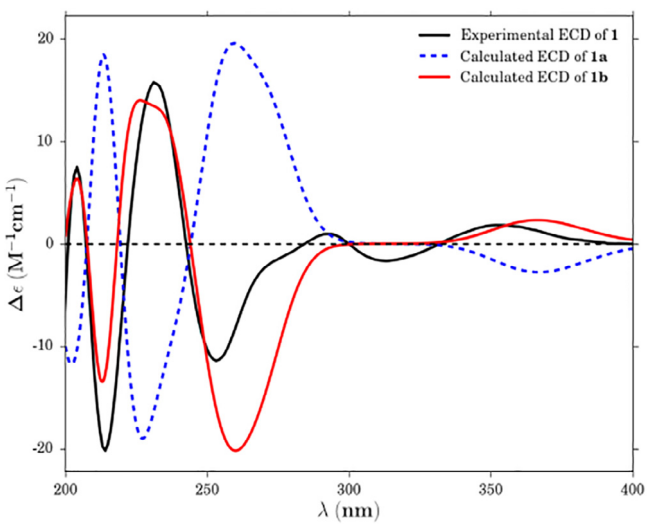

Fig. 3. Calculated and experimental ECD spectra of **1** in MeOH.

Conidiogenone K[9] (**2**) showed a protonated molecule peak at *m*/*z* 319.2246 $[M+H]^+$ in the positive HRESIMS, consistent with the molecular formula $C_{20}H_{30}O_3$, requiring six indices of hydrogen deficiency. The ^{13}C NMR spectrum exhibited 20 carbons, including four methyls, six methylenes (one oxygenated), five methines (two

Table 1
^1H(400 MHz) and ^{13}C (100 MHz) NMR spectroscopic data for **1**–**4** (δ in ppm, *J* in Hz within the parenthesis).

No.	**1**[a]		**2**[b]		**3**[a]		**4**[a]	
	δ_C, type	δ_H, mult (*J* in Hz)	δ_C, type	δ_H, mult (*J* in Hz)	δ_C, type	δ_H, mult (*J* in Hz)	δ_C, type	δ_H, mult (*J* in Hz)
1	208.3, C		212.6, C		75.4, CH	3.73, t (3.6)	208.3, C	
2	127.5, CH	5.95, d (10.1)	53.5, CH	3.34, d (4.1)	39.7, CH_2	1.89, m; 1.80, m	127.6, CH	5.94, d (10.1)
3	157.5, CH	7.15, dd (10.1, 6.1)	61.2, CH	3.53, t (3.8)	70.5, CH	3.44, td (10.7, 4.5)	157.4, CH	7.12, dd (10.1, 5.9)
4	38.9, CH	2.86, m	35.0, CH	2.65, dq (7.2, 3.1)	44.6, CH	1.54, m	39.2, CH	2.83, m
5	60.8, C		59.6, C		63.4, C		61.0, C	
6	55.2, CH	2.41, dt (10.7, 2.6)	55.7, CH	2.86, m	55.5, CH	2.51, m	56.1, CH	2.36, dd (9.8, 5.2)
7	35.0, CH_2	1.61, m; 1.24, m	34.0, CH_2	1.92, m; 1.26, m	30.5, CH_2	1.89, m; 1.55, m	35.1, CH_2	1.60, m; 1.25, m
8	39.4, CH_2	2.06, m; 1.80, m	40.1, CH_2	1.99, m; 1.52, m	39.8, CH_2	2.07, m; 1.42, m	39.8, CH_2	2.06, m; 1.73, m
9	59.0, C		56.8, C		50.0, C		58.7, C	
10	43.0, CH_2	1.99, d (14.8) 1.94, d (14.8)	48.0, C	1.88, d (14.6) 1.76, d (14.6)	42.5, CH_2	1.77, overlap	47.7, CH_2	2.06, d (15.1) 1.66, d (15.1)
11	60.3, C		52.1, C		55.9, C		53.9, C	
12	35.3, CH_2	1.72, m; 1.61, m	38.2, CH_2	1.67, m; 1.52, m	40.6, CH_2	1.80, m; 1.43, m	39.5, CH_2	1.73, m; 1.54, m
13	37.0, CH_2	1.69, m; 1.48, m	36.6, CH_2	1.67, m; 1.52, m	37.6, CH_2	1.61, m; 1.45, m	37.6, CH_2	1.71, m; 1.46, m
14	49.2, C		48.2, C		48.5, C		49.3, C	
15	63.7, CH	1.78, d (3.9)	65.6, CH	1.55, d (4.3)	68.2, CH	1.72, d (9.8)	69.3, CH	1.64, d (5.4)
16	18.7, CH_3	1.26, d (7.3)	15.1, CH_3	1.04, d (7.1)	13.7, CH_3	1.09, d (6.6)	18.8, CH_3	1.24, d (7.3)
17	21.8, CH_3	1.17, s	22.3, CH_3	1.16, s	24.2, CH_3	1.20, s	21.6, CH_3	1.17, s
18	71.1, CH_2	3.48, d (10.8) 3.39, d (10.8)	31.7, CH_3	1.20, s	29.4, CH_3	1.17, s	31.6, CH_3	1.22, s
19	23.1, CH_3	0.97, s	22.4, CH_3	1.10, s	22.9, CH_3	1.01, s	23.1, CH_3	0.97, s
20	71.7, CH_2	3.28, d (10.9) 3.22, d (10.9)	72.0, CH_2	3.42, s	72.6, CH_2	3.32, s	72.0, CH_2	3.32, s

[a] Recorded in CD_3OD.
[b] Recorded in $CDCl_3$.