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NOTE

Structure and absolute configuration of drimentine I, an alkaloid from *Streptomyces* sp. CHQ-64

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Actinomycetes are the producer of many secondary metabolites with novel structures and broad biological activities.[1–3] During our exploration for bioactive compounds from marine-derived actinomycetes, two classes of cytotoxic hybrid isoprenoid alkaloids and six new antifungal polyene-polyols (cultured under shaking condition) have been isolated from the marine-derived *Streptomyces* sp. CHQ-64.[4–6] Attracted by the amazing ability of this strain to produce diverse compounds, other fermentation conditions were attempted. Among them, we found that the HPLC-UV profile of the EtOAc extract from the liquid culture under static condition changed markedly. From the broth a new hybrid isoprenoid alkaloid named drimentine I (**1**) was isolated possessing a rare heptacyclic skeleton formed via two bridging linkages (Figure 1). The planar structure and absolute configuration of **1** were established by a combination of spectroscopic methods and X-ray diffraction analysis.

Compound **1** was obtained as optically active colorless crystals. Its molecular formula of $C_{32}H_{45}N_3O_2$ (12 degrees of unsaturation) was determined by high resolution electrospray ionization mass spectroscopy (HRESIMS). Interestingly, the molecular mass of **1** was consistent with those of drimentine F[4] and indotertine A,[4] which had been isolated from this strain, while ^{1}H-NMR spectra had many signals with larger deviations. Detailed comparison of the NMR data of **1** with those of the previously reported two compounds revealed the similarity of the resonance signals in the diketopiperazine unit and sesquitepene moiety. The 1D NMR data of **1** (Table 1) showed characteristic signals of diketopiperazine (δ_C 168.9 and 166.7 p.p.m., δ_H/δ_C 3.71/60.3, and 3.85/64.0 p.p.m.). The tetracyclic indol-diketopiperazine ring was further established by the HMBC correlations from H-11 (δ_H 2.68, 1.95) to C-1 (δ_C 168.9), C-5a (δ_C 88.1) and C-10a (δ_C 143.8), from H-5a (δ_H 5.21, s) to C-4 (δ_C 166.7), C-10a (δ_C 150.7) and C-6a (δ_C 47.6). The sesquitepene moiety was deduced by the interpretation of 1D NMR and 2D NMR spectra readily (Figure 2), mainly on the basis of HMBC correlations from the geminal dimethyls H_3-22 (δ_H 0.70, s) and H_3-23 (δ_H 0.73, s) to C-16a (δ_C 57.2), C-17 (δ_C 33.6), and C-18 (δ_C 42.1), together with the correlations from H_3-24 (δ_H 0.83, s) to C-20a (δ_C 37.5), C-16a (δ_C 57.2) and C-13 (δ_C 51.0), from H-16a (δ_H 0.26) to C-20 (δ_C 39.7), from H-13 (δ_H 0.38) to C-16a and C-14 (δ_C 62.0), from H_3-21 (δ_H 1.56) to C-14 and C-15 (δ_C 39.2).

A diketopiperazine unit composed of tryptophan and NMe valine and a sesquitepene moiety accounted for 11 of 12 degrees of unsaturation. Unlike one terminal double bond in drimentine F for the last unsaturation, compound **1** were attributed to correlations from H-5a to C-14 and C-12 (δ_C 27.8), and H-12 (δ_H 1.76, 1.65) to C-10b (δ_C 52.1) and C-13, which fully established the remaining substructures to give an unusual heptacyclic architecture. Therefore, the three isomers possessing the similar motifs but differed from the way of ring fusion (Figure 3). The pentacyclic product indotertine A was inspired by iminium-olefin cyclization, while tetracyclic product drimentine F could take place from amidic nitrogen by a nucleophilic addition to the α-position of the indole moiety.[4,7] However, cyclization of drimentine I (**1**) happened on indol-NH afford the linkage between C-14 and N-6.

The planar structure and absolute configuration of **1** has been confirmed by a single crystal X-ray diffraction analysis (Figure 4). The final refinement on the Cu Kα data resulted in a Flack parameter of −0.1, allowing an assignment of the absolute configurations as (3S, 5aS, 10bS, 11aS, 13R, 14R, 16aS, 20aS). Up to now only two reported natural compounds (drimentines D and E) with a hepacyclic terpenylated diketopiperazine, containing proline or leucine residues, were reported in a single patent[8] in which the determinations of the configurations were not clearly described. In our study, drimentine I (**1**), represents another rare bacterial terpenylated diketopiperazine with a heavily rearranged hepacyclic skeleton, which, was unambiguously assigned by X-ray.

Drimentine I (**1**) were evaluated in vitro for their cytotoxicities against two human tumor cell lines (A549 and HeLa) using the SRB method with adriamycin as positive control[9]. Among these, compound **1** was found to have weak activity against human cervical carcinoma cell line HeLa, with IC_{50} values of 16.73 μM.

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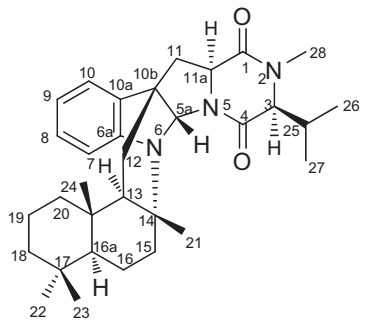


1, Drimentine I

Figure 1 Chemical structures of compound **1**.

Table 1 NMR data for compound 1 (600, 150 MHz, $CDCl_3$, TMS, δ p.p.m.)

No.	*δ_H (J in Hz)*	*δ_C*	*COSY*	*HMBC*
1		168.9, qC		
2				
3	3.85, d (1.5)	64.0, CH	25	4, 25, 26, 27
4		166.7 s		
5				
5a	5.21, s	88.1, CH		6a, 10a, 12, 4, 14
6				
6a		150.7, qC		
7	7.18, m	126.7, CH	8	
8	7.28, m	121.5, CH	7, 9	6a, 10
9	7.00, m	122.9, CH	8, 10	7, 10a
10	7.19, m	127.7, CH	9	
10a		143.8, qC		
10b		52.1, qC		
11	2.68, dd (5.8,11.8)	34.9, CH_2	11a	10a, 10b, 11a, 1, 5a
	1.95, t (11.0, 11.8)			
11a	3.71, dd (5.8,11.0)	60.3, CH	11	1, 11
12	1.76, t (12.1, 12.7)	27.8, CH_2	13	10b, 13, 10a, 5a, 14
	1.65, dd (3.8, 12.1)			
13	0.38, dd (3.8, 12.1)	51.0, CH	12	14, 16a
14		62.0, qC		
15	1.33, brd (12.6)	39.2, CH_2	16	
	0.33, dd (3.3,12.7)			
16	1.50, m,	19.8, CH_2	15, 16a	
	1.43, m			
16a	0.26, dd (2.2. 2.1)	57.2, CH	16	17, 20, 22, 23
17		33.6, qC		
18	1.21, m	42.1, CH_2	19	
	0.90, m			
19	1.59, m	18.5, CH_2	18, 20	
	1.26, m			
20	1.48, m	39.7, CH_2	19	
20a		37.5, qC		
21	1.56, s	24.8, CH_3		14,13,15
22	0.70, s	33.4, CH_3		16a, 17, 18, 23
23	0.73, s	21.5, CH_3		16a, 17, 18, 22
24	0.83, s	17.1, CH_3		13, 16a, 20a
25	2.57, m	29.0, CH	3, 26, 27	
26	1.10, d (6.6)	20.0, CH_3	25	3
27	0.94, d (6.6)	17.0, CH_3	25	3
28- NMe	2.79, s	31.6, CH_3		1, 3

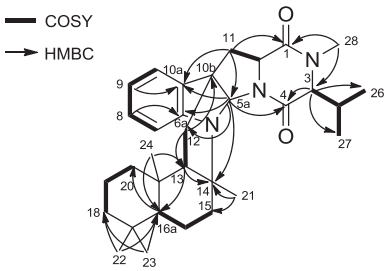
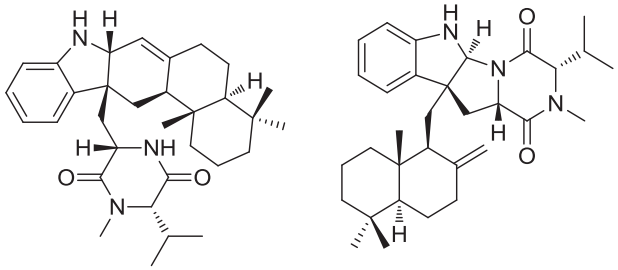


Figure 2 Key COSY and HMBC correlations of compound **1**.



Indotertine A **Drimentine F**

Figure 3 Structure of indotertine A and drimentine F

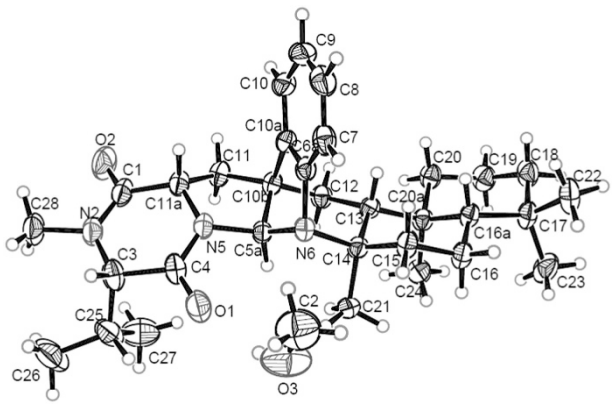


Figure 4 Chemical X-ray crystal structure of **1** (Cu Kα radiation). A full color version of this figure is available at *The Journal of Antibiotics* journal online.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on The Journal of Antibiotics website (http://www.nature.com/ja)