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Stellatolide H, a cytotoxic peptide lactone from a deep-sea sponge *Discodermia* sp.

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ABSTRACT

Stellatolide H (**1**) was isolated from a deep-sea sponge *Discodermia* sp. as the cytotoxic constituent. The planar structure of **1** was elucidated on the basis of the NMR spectroscopic and mass spectrometric data. The absolute configurations of the constituent amino acid residues were determined by the Marfey's method. Stellatolide H (**1**) is a peptide lactone of the callipeltin class with its N-terminus blocked by 3-hydroxy-6,8-dimethyldeca-(4*Z*,6*E*)-dienoic acid (Hdda).

Sessile marine organisms in the deep sea build unique communities which are different from those in shallow waters.[1] Only those physiologically adapted to the deep sea can survive there. Because secondary metabolites are compounds distributed species-specifically, it is reasonable to speculate that distinct natural products are present in the deep-sea organisms.[2] During our search for bioactive metabolites from deep-sea sponges,[3,4] we found that the extract of a sponge of the genus *Discodermia*, collected at a depth of 310 m in the East China Sea, exhibited cytotoxic activity. From the sponges of this genus a variety of biologically active natural products of polyketide synthase/non-ribosomal peptide synthetase origin have been discovered.[5,6] Bioassay-guided fractionation of the sponge afforded a peptide lactone of the callipeltin class named stellatolide H (**1**). In this paper, we report the isolation, structure elucidation, and biological activity of stellatolide H (**1**).

The EtOH extract of the sponge *Discodermia* sp. was partitioned between H_2O and $CHCl_3$, and the aqueous phase was further extracted with *n*-BuOH. The $CHCl_3$ and *n*-BuOH fractions, both of which exhibited cytotoxicity against HeLa cells, were combined and separated by ODS flash chromatography followed by reversed-phase HPLC to afford stellatolide H (**1**) as a colorless amorphous solid, together with the known cyclolithistide A.[7,8]

Stellatolide H (**1**) had the molecular formula of $C_{66}H_{106}N_{14}O_{21}$ as determined by HRESIMS. Preliminary analysis of the ^1H and ^{13}C NMR spectra measured in DMSO-d_6 (Table S1) revealed the presence of several amide protons and carbonyl carbons suggesting its peptide nature. Most of the NMR signals were doubled in this solvent, indicating the presence of conformational equilibrium. This signal duplication was not observed in CD_3OH (Table 1). Further analyses of the 2D NMR data mostly in CD_3OH disclosed the presence of seven usual amino acid residues, Ser, Gly, Leu, *N*-methylalanine (NMeAla), *N*-methylglutamine (NMeGln), and two residues of Thr or *allo*-Thr (*a*Thr) together with four unusual residues. The amidation of the side chain of the NMeGln residue was demonstrated by ROESY cross peaks between a pair of mutually coupled amide protons (δ_H 7.27 and 6.80) and the β-methylene protons at δ_H 1.67 (2H). There was a spin system reminiscent of a Ser residue with a deshielded β-methylene carbon (δ_C 71.4) which was coupled with an *O*-methyl proton signal at δ_H 3.37 in the HMBC spectrum, indicating the presence of an *O*-methylserine (OMeSer) residue.[9] The 2,3-diaminobutanoic acid (Dab) residue exhibited a spin system similar to that of a Thr residue, but with more shielded signals for the β-carbon (δ_C 48.8).[9] The presence of

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Table 1
^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) data for stellatolide H (**1**) in CD_3OH.

Position	δ_C	δ_H (J in Hz)	HMBC
Hdda			
1	174.6		
2a	44.9	2.51 m	1, 3, 4
2b		2.41 m	1
3	66.6	5.02 m	
4	131.0	5.31 dd (11.5, 9.6)	6
5	136.0	5.91 d (11.5)	3, 6-Me, 8
6	132.3		
6-Me	16.8	1.77 s	5, 6, 7
7	140.0	5.18 d (9.6)	5, 6-Me, 8, 8-Me, 9
8	35.5	2.34 m	6, 7, 8-Me, 9
8-Me	20.9	0.95 d (6.9)	7, 8, 9
9a	31.2	1.36 m	7, 8-Me, 9, 10
9b		1.25[a]	7, 8-Me, 9, 10
10	12.2	0.84 t (7.5)	8, 9
Ser			
11	ND[b]		
12	56.8	4.38 m	
13a	62.8	3.85 dd (4.8, 11.0)	
13b		3.79 m	
NH		8.29 brs	
Thr			
14	ND[b]		
15	60.1	4.40 m	
16	68.0	4.35 m	
17	20.1	1.19 d (6.2)	15, 16
NH		8.01 brs	
Dab			
18	ND[b]		
19	56.8	4.51[a]	
20	48.8	3.76 m	
NH_2		ND[b]	
21	16.8	1.33 d (6.2)	19, 20
NH		ND[b]	
Me_2Gln			
22	ND[b]		
23	58.9	4.09 d (8.25)	23, 24, 24-Me
24	37.1	2.38 m	23
24-Me	16.6	1.25[a]	24, 25
25	44.4	2.68 m	25-Me, 26
25-Me	13.1	1.26[a]	24, 25, 26
26	182.1		
NH_2		7.89 br s	
		7.07 br s	
NH		ND[b]	
*a*Thr			
27	ND[b]		
28	57.2	5.26 m	
29	71.7	5.58 m	54
30	14.8	1.17 d (6.2)	28, 29
NH		8.88 d (9.6)	
OMeSer			
31	173.6		
32	55.2	4.47 m	31
33a	71.4	3.80 m	31, 32, *O*Me
33b		3.72 dd (6.9, 9.6)	32, *O*Me
*O*Me	59.4	3.37 s	33
NH		8.42 br	
Gly			
34	ND[b]		
35a	44.0	3.92 d (17.2)	31
35b		3.50 d (17.2)	
NH		9.03 br	
Leu			
36	ND[b]		
37	49.2	4.75[a]	
38a	40.6	1.26[a]	37
38b		1.56 m	
39	25.8	1.62 m	
40	21.5	0.88 d (6.9)	38, 39, 41
41	23.3	0.92 d (6.9)	38, 39, 40
NH		7.20 br s	

(*continued on next page*)