

## Jaspolides G and H, unique bisomalabaricanes from the Chinese marine sponge *Jaspis* sp.

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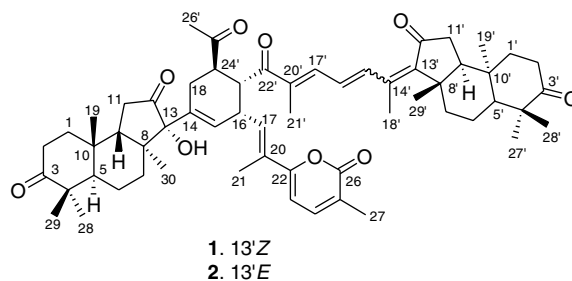
**Abstract**—Two unique bisomalabaricanes jaspolides G (**1**) and H (**2**) were isolated from the marine sponge *Jaspis* sp. Their structures were elucidated on the basis of extensive spectroscopic data (IR, MS, and 1D and 2D NMR) analyses. A possible biogenetic pathway via Diels–Alder dimerization for jaspolides G and H was also proposed.

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The trivial name malabaricane or isomalabaricane describes a class of unique triterpenes or nortriterpenes containing a tricyclic core and a polyene conjugated side chain. The first malabaricane-type derivative was isolated from the wood of the *Alianthus malabarica*,<sup>1,2</sup> and later on this rare structural pattern was discovered frequently from marine sponges. Thus far, more than 100 isomalabaricane derivatives have been isolated from sponge genera *Stelletta*,<sup>3</sup> *Jaspis*,<sup>4</sup> *Geodia*,<sup>5</sup> and *Rhabdastrella*<sup>6</sup> (order Astrophorida) as the principal metabolites. With the exception of ring A, the structural variety was predominated by the polyene system, and was classified into three groups (stelletins, stelliferins, globostellatic acids) according to side chain variation. The genus *Jaspis* has been investigated extensively,<sup>4</sup> and was shown to be a rich source of biologically active and structurally novel natural products. The isomalabaricane skeleton is one type of remarkable marine natural products from the genus *Jaspis*. Majority of them showed promising anti-tumor activity. Besides, macrolides such as jaspisamide derivatives<sup>7</sup> are another group of the secondary metabolites showing potential anti-fungal, antiproliferative anthelmintic, cytotoxic, selective antimicrobial, insecticidal and ichthyotoxic activities. Bengamides<sup>8</sup> are a group of unusual structures containing nitrogen elements which showed interesting anti-parasitic, antimicrobial, and cytotoxic activities, while

the cytotoxicity of shingosine derivatives was evaluated against A549 lung tumor cell lines. Bengazole alkaloids<sup>9</sup> have shown in vitro potency against human tumor cell lines. Our previous examination of *Jaspis* sp. from South China Sea resulted in the isolation and characterization of tricyclic core based triterpenes, sesterpenes, diterpenes, and nortriterpenes.<sup>4a,b</sup> In addition to the previous work, two unique bisomalabaricanes named jaspolides G–H (**1–2**) were now isolated from the same sponge.<sup>10</sup> This report describes the structural elucidation of the novel metabolites (see Fig. 1).

Jaspolide G (**1**),<sup>11</sup> a yellow amorphous solid, possessed a molecular formula of C<sub>59</sub>H<sub>76</sub>O<sub>9</sub> as determined by HRFABMS (*m/z* 928.5458 [M]<sup>+</sup>, Calcd: 928.5459) and NMR data, implying 22° of unsaturation. The IR absorption bands at 3419, 1738, 1702, and 1656 cm<sup>-1</sup> suggested the presence of hydroxy and conjugated



**Figure 1.** Structures of jaspolides G (**1**) and H (**2**).

**Keywords:** Sponge; *Jaspis* sp.; Jaspolide G; Jaspolide H.

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**Table 1.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of jaspolides G (**1**) and H (**2**)

No.	<b>1</b>		<b>2</b>		No.	<b>1</b>		<b>2</b>	
	$\delta_{\text{H}}$	$\delta_{\text{C}}$	$\delta_{\text{H}}$	$\delta_{\text{C}}$		$\delta_{\text{H}}$	$\delta_{\text{C}}$	$\delta_{\text{H}}$	$\delta_{\text{C}}$
1	1.50 (m)	31.3 (CH <sub>2</sub> )	1.50 (m)	31.5 (CH <sub>2</sub> )	1'	1.50 (m)	31.5 (CH <sub>2</sub> )	1.50 (m)	31.4 (CH <sub>2</sub> )
	2.15 (m)		2.15 (m)			2.15 (m)		2.15 (m)	
2	2.40 (m)	33.3 (CH <sub>2</sub> )	2.40 (m)	33.3 (CH <sub>2</sub> )	2'	2.40 (m)	33.4 (CH <sub>2</sub> )	2.40 (m)	33.5 (CH <sub>2</sub> )
	2.75 (m)		2.77 (m)			2.75 (m)		2.77 (m)	
3		219.2 (C)		219.0 (C)	3'		218.9 (C)		218.9 (C)
4		46.9 (C)		46.8 (C)	4'		46.8 (C)		46.9 (C)
5	2.44 (m)	43.5 (CH)	2.44 (m)	43.7 (CH)	5'	2.31 (m)	46.2 (CH)	2.31 (m)	45.5 (CH)
6	1.48 (m)	19.7 (CH <sub>2</sub> )	1.46 (m)	19.7 (CH <sub>2</sub> )	6'	1.48 (m)	19.6 (CH <sub>2</sub> )	1.50 (m)	19.5 (CH <sub>2</sub> )
	1.62 (m)		1.60 (m)			1.67 (m)		1.70 (m)	
7	2.29 (m)	36.9 (CH <sub>2</sub> )	2.25 (m)	36.6 (CH <sub>2</sub> )	7'	2.12 (m)	37.1 (CH <sub>2</sub> )	2.10 (m)	38.6 (CH <sub>2</sub> )
8		46.8 (C)		46.1 (C)	8'		45.0 (C)		45.6 (C)
9	2.43 (m)	45.4 (CH)	2.50 (m)	45.4 (CH)	9'	1.94 (dd, 9.5, 11.8)	47.8 (CH)	1.94 (dd, 9.0, 11.5)	47.7 (CH)
10		34.7 (C)		34.5 (C)	10'		34.8 (C)		34.8 (C)
11	2.40 (m)	28.9 (CH <sub>2</sub> )	21.5 (m)	29.2 (CH <sub>2</sub> )	11'	2.10 (m)	34.5 (CH <sub>2</sub> )	2.10 (m)	34.9 (CH <sub>2</sub> )
	2.60 (m)		2.35 (m)			2.30 (m)		2.30 (m)	
12		215.1 (C)		216.3 (C)	12'		206.2 (C)		207.4 (C)
13		84.6 (C)		85.0 (C)	13'		148.0 (C)		148.9 (C)
14		133.9 (C)		133.1 (C)	14'		141.2 (C)		140.2 (C)
15	5.42 (d, 4.0)	127.1 (CH)	5.30 (d, 4.0)	127.0 (CH)	15'	8.43 (d, 15.0)	139.2 (CH)	7.07 (d, 15.0)	139.4 (CH)
16	3.74 (ddd, 4.0, 5.5, 10.5)	37.5 (CH)	3.79 (ddd, 4.0, 5.7, 10.5)	37.5 (CH)	16'	6.92 (dd, 15.0, 11.0)	129.3 (CH)	7.00 (dd, 15.0, 11.0)	130.7 (CH)
17	6.00 (d, 10.5)	129.5 (CH)	6.00 (d, 10.5)	129.0 (CH)	17'	7.26 (d, 11.0)	138.6 (CH)	7.19 (d, 11.0)	137.3 (CH)
18	2.10 (dd, 11.5, 17.0)	28.1 (CH <sub>3</sub> )	2.12 (dd, 11.0, 16.5)	27.7 (CH <sub>3</sub> )	18'	2.11 (s)	15.9 (CH <sub>3</sub> )	2.38 (s)	14.5 (CH <sub>3</sub> )
	2.50 (dd, 4.5, 17.0)		2.43 (dd, 5.0, 16.5)						
19	0.89 (s)	24.3 (CH <sub>3</sub> )	0.90 (s)	24.3 (CH <sub>3</sub> )	19'	0.90 (s)	23.5 (CH <sub>3</sub> )	0.90 (s)	23.5 (CH <sub>3</sub> )
20		127.1 (C)		127.0 (C)	20'		137.1 (C)		137.6 (C)
21	1.70 (s)	12.6 (CH <sub>3</sub> )	1.71 (s)	12.6 (CH <sub>3</sub> )	21'	1.80 (s)	12.2 (CH <sub>3</sub> )	1.83 (s)	12.3 (CH <sub>3</sub> )
22		159.1 (C)		158.6 (C)	22'		201.5 (C)		201.4 (C)
23	6.03 (d, 6.7)	101.8 (CH)	6.03 (d, 6.7)	102.0 (CH)	23'	3.92 (dd, 5.5, 11.4)	46.4 (CH)	3.91 (dd, 5.7, 11.0)	46.3 (CH)
24	7.09 (d, 6.7)	139.5 (CH)	7.11 (d, 6.7)	139.1 (CH)	24'	3.35 (ddd, 4.5, 11.4, 11.5)	44.1 (CH)	3.40 (ddd, 5.0, 11.0, 11.0)	43.5 (CH)
25		124.2 (C)		124.5 (C)	25'		211.4 (C)		211.8 (C)
26		163.0 (C)		163.0 (C)	26'	2.36 (s)	29.9 (CH <sub>3</sub> )	2.39 (s)	29.3 (CH <sub>3</sub> )
27	2.10 (s)	16.7 (CH <sub>3</sub> )	2.10 (s)	16.7 (CH <sub>3</sub> )	27'	1.14 (s)	29.2 (CH <sub>3</sub> )	1.14 (s)	29.2 (CH <sub>3</sub> )
28	1.15 (s)	29.2 (CH <sub>3</sub> )	1.16 (s)	29.2 (CH <sub>3</sub> )	28'	1.09 (s)	19.4 (CH <sub>3</sub> )	1.09 (s)	19.4 (CH <sub>3</sub> )
29	1.09 (s)	19.4 (CH <sub>3</sub> )	1.09 (s)	19.3 (CH <sub>3</sub> )	29'	1.43 (s)	24.6 (CH <sub>3</sub> )	1.56 (s)	26.3 (CH <sub>3</sub> )
30	1.09 (s)	23.9 (CH <sub>3</sub> )	1.10 (s)	24.3 (CH <sub>3</sub> )					

In CDCl<sub>3</sub>;  $\delta_{\text{H}}$  500 MHz;  $\delta_{\text{C}}$  125 MHz.

carbonyl groups (lactone and ketone). The  $^1\text{H}$  NMR spectrum exhibited eight aliphatic methyl resonances at  $\delta$  0.89 (3H, s, Me-19), 0.90 (3H, s, Me-19'), 1.09 (9H, s, Me-28', Me-29, Me-30), 1.14 (3H, s, Me-27'), 1.15 (3H, s, Me-28), and 1.43 (3H, s, Me-29'), which were assigned to the tertiary methyls of two tricyclic nuclei by comparison with those of known isomalabaricanes from this sponge.<sup>4a,b</sup> Four olefinic methyls at  $\delta$  1.70 (3H, s, Me-21), 1.80 (3H, s, Me-21'), 2.10 (3H, s, Me-27), and 2.11 (3H, s, Me-18') were assigned to the side chain. An ABX coupling system at  $\delta$  8.43 (1H, d,  $J = 15.0$  Hz, H-15'), 6.92 (1H, dd,  $J = 11.0$ , 15.0 Hz, H-16'), and 7.26 (1H, d,  $J = 11.0$  Hz, H-17') was assigned to a conjugated diene, while two vicinal protons at  $\delta$  6.03 (1H, d,  $J = 6.7$  Hz, H-23) and 7.09 (1H, d,  $J = 6.7$  Hz, H-24) were in agreement with  $\beta$ - and  $\gamma$ -protons of an unsaturated  $\delta$ -lactone as described in stelletin A.<sup>3g</sup> In addition, the coupling constants of two olefinic protons at  $\delta$  5.42 (1H, d,  $J = 4.0$  Hz, H-15) and 6.00 (1H, d,  $J = 10.5$  Hz, H-17) indicated the presence of trisubstituted vinyl bonds. The remaining proton resonances were observed in aliphatic range  $\sim\delta$  1.0–2.5 ppm. Their corresponding carbons were assigned through HMQC correlations. The  $^{13}\text{C}$  NMR spectrum exhibited 59 carbon resonances, of which the peaks of the aliphatic range appeared in duplicate or twice (Table 1). The  $^1\text{H}$  and  $^{13}\text{C}$  data in association with the molecular composition highly suggested the structure of **1** to be a dimeric isomalabaricane. Interpretation of 2D NMR (COSY, HMQC, and HMBC) data enabled the assignment of two substructures of tricyclic 3,12-dione, which were closely related to known isomalabaricanes stelletin A and also jaspolides C and D from the same sponge.<sup>4a</sup> The connection of tricyclic units was supposed to be realized through side chain inter-reaction. A comparison of NMR data revealed the partial side chain of **1** from C-13' to C-22' to be in agreement with that of geoditin A,<sup>5</sup> as indicated by the presence of an ABX coupling system from H-15' to H-17', and the HMBC correlations between Me-18' and C-13' ( $\delta$  148.0, s), C-14' ( $\delta$  141.2, s), and C-15' ( $\delta$  139.2, d), between Me-21' and C-17' ( $\delta$  138.6, d), C-20' ( $\delta$  137.1, s), and C-22' ( $\delta$  201.5, s), and between Me-29' and C-13', C-8' ( $\delta$  45.0, s), and C-9' ( $\delta$  47.8, d) (Fig. 2). With respect to the second part of isomalabaricane unit, the NMR data of the side chain were compatible to those of stelletin A,<sup>3g</sup> as indicated by the presence of an AB coupling system ( $\delta$  6.03, d; 7.09, d), and the  $^{13}\text{C}$  resonances at  $\delta$  159.1 (s, C-22), 101.8 (d, C-23), 139.5 (d, C-24), 124.2 (s, C-25), 163.0 (s, C-26), and 16.7 (q, C-27) for a conjugated  $\alpha$ -methyl- $\delta$ -lactone.

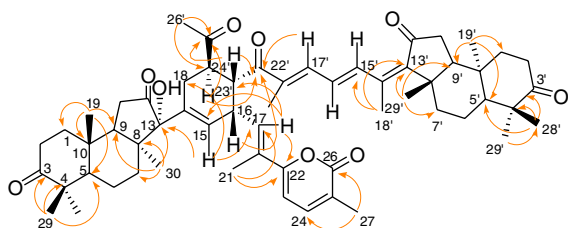


Figure 2. HMBC correlations of jaspolides G (**1**).

A double bond at C-17/C-20 of stelletin A was also detected in **1** based on the HMBC relationship from Me-21 to C-17 ( $\delta$  129.5, d), C-20 ( $\delta$  127.1, s), and C-22. However, the side chain of **1** from C-13 to C-16 consisted of an oxygen-bearing quaternary carbon ( $\delta$  84.6, s), a methine ( $\delta$  37.5, d), and a double bond ( $\delta$  133.9, s; 127.1, d) instead of the conjugated double bonds C-13/C-14 and C-15/C-16 of stelletin A. The COSY correlations between H-15/H-16 ( $\delta$  3.74, ddd,  $J = 4.0$ , 5.5, 10.5 Hz) and H-16/H-17 indicated that an additional double bond was positioned at C-14/C-15, which was confirmed by the HMBC correlations from H-15 to C-13 ( $\delta$  84.6, s), C-16 ( $\delta$  37.5, d), and C-17. These data also designated a hydroxy group linking to C-13, which was further supported by the HMBC data between Me-30 and C-13. An interpretation of COSY correlations between H<sub>2</sub>-18 ( $\delta$  2.10, dd; 2.50, dd)/H-24' ( $\delta$  3.35, ddd,  $J = 4.5$ , 11.4, 11.5 Hz), H-24'/H-23' ( $\delta$  3.92, dd,  $J = 5.5$ , 11.4 Hz), and H-23'/H-16 connected a subunit from C-16 to C-18 via C-23' and C-24'. The HMBC correlations from H-15 to C-18 ( $\delta$  28.1, t) and C-23' ( $\delta$  46.4, d), and from H<sub>2</sub>-18 and H-15 to C-13 allowed the assignment of a cyclohexene linking to C-13. Consequently, an acetyl group [ $\delta$  29.9 (q, C-26'), 211.4 (s, C-25'), and 2.36 (3H, s, Me-26')] was deduced to be positioned at C-24' by the HMBC correlation between Me-26' and C-25' and C-24' ( $\delta$  44.1, d), and in turn between H-23' and H-24' and C-25' (Fig. 2). The linkage of terminal ketone C-22' to C-23' was based on the HMBC correlations from H-24', H-23', and H-16 to C-22'.

The relative stereochemistry of **1** was determined on the basis of NOESY data and coupling constants. NOE effects were observed between H-5/Me-30, H-5'/Me-29', H-9/Me-19, and H-9'/Me-19' (Fig. 3), which confirmed the presence of the *trans-syn* ring junction in both tricyclic units typical for the isomalabaricane nucleus. The remarkable downfield resonance of H-15' was indicative of 13'*Z* as similar in jaspolides A and F.<sup>4a</sup> The  $J$  values of H-16' and the NOE correlations between H-18'/H-29', H-18'/H-16', H-21'/H-16', and H-15'/H-17' were consistent with 15'-*E* and 17'-*E*. The geometry of the double bond at C-17/C-20 was assigned as 17'-*E* since no NOE effect was observed between H-17/Me-21. The NOE correlation between OH-13 ( $\delta$  5.33, s) and Me-30 suggested an  $\alpha$ -orientation of the hydroxy group. The coupling constants  $J_{\text{H-23'}/\text{H-24'}}$  (11.4 Hz) and  $J_{\text{H-23'}/\text{H-16}}$  (5.5 Hz) were in agreement with axial–axial (*trans*) and axial–equatorial (*cis*) between H-23'/H-24' and H-23'/H-16 when the cyclohexene adopts a

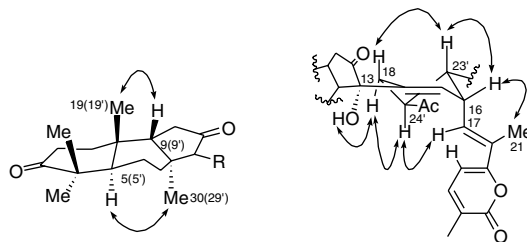
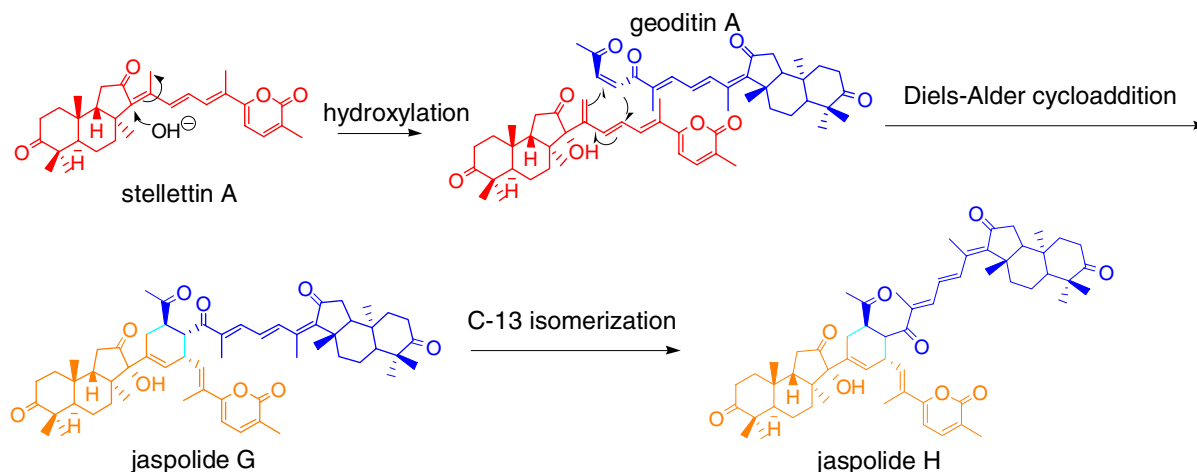


Figure 3. Partial NOESY correlations of **1** and **2**.



**Scheme 1.** Proposed biogenetic pathway for jaspolides G (1) and H (2).

favorable chair form. Thus, the NOE effects between OH-13/H-18 $\alpha$  ( $\delta$  2.50, dd), H-18 $\alpha$ /H-24', H-24'/H-17 ( $\delta$  6.00, d), and H-23'/H-16 ( $\delta$  3.74, ddd) (Fig. 3) allowed the assignment of H-16 $\beta$ , H-23' $\beta$ , and H-24' $\alpha$ .

Jaspolidide H (2)<sup>12</sup> had the same molecular formula as that of jaspolidide G, as determined by HRFABMS and NMR data. The 1D and 2D NMR spectroscopic data analyses revealed the gross structure of 2 to be identical to that of 1, with the exception of the conjugated polyene side chain. The proton resonance of 2 at Me-18' shifted downfield at  $\delta$  2.38 (3H, s), whereas H-15' shifted upfield at  $\delta$  7.07 (1H, d,  $J$  = 15.2 Hz), in contrast to those of 1 (Table 1), indicating the presence of 13'*E*-geometry. This finding was also supported by the NOE correlation between H-15' and Me-29' ( $\delta$  1.56, s). Therefore, the structure of 2 was determined to be a geometrical isomer at C-13' of 1.

The isomalabaricane based dimers were discovered for the first time from marine derived metabolites. The hypothesis of a biogenetic pathway to generate compounds 1 and 2 was depicted (Scheme 1). The structure of 1 might be derived from a triterpene and a nortriterpene of isomalabaricanes as the precursors which were closely related to stellettin A<sup>3g</sup> for left moiety and geoditin A<sup>5</sup> for right moiety. A possible hydroxylation occurring at C-13 of stellettin A could provide an intermediate with a new double bond at C-14/C-18 due to the double bond transformation. A Diels–Alder cycloaddition between C-23/C-24 of geoditin A and C-15/C-16 and C-14/C-18 of the intermediate could result in the formation of a cyclohexene. Compound 2 could be derived from 1 through geometrical isomerization at C-13'. The co-existence of C-13 isomers of isomalabaricanes was frequently found from marine sponges.

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10. The sponge specimen (2.0 kg) was extracted by using EtOH to give a residue (150 g), which was portioned between water and CHCl<sub>3</sub> to give a CHCl<sub>3</sub> extract (40.0 g). This extract (1.0 g) was chromatographed on a silica gel column eluting with CHCl<sub>3</sub>–acetone (5:1) to yield **1** (4.5 mg) and **2** (3.2 mg).
11. Jaspolide G (**1**): Yellow amorphous solid;  $[\alpha]_D^{25} +110.3$  (*c* 0.4, acetone); IR (KBr)  $\nu_{\max}$  3419, 1738, 1702, 1656 cm<sup>-1</sup>; ESIMS *m/z* 946 [M+NH<sub>4</sub>]<sup>+</sup>, 929 [M+1]<sup>+</sup>, 504; HRFAB-MS *m/z* [M]<sup>+</sup>, 928.5458 [M]<sup>+</sup> (Calcd for C<sub>59</sub>H<sub>76</sub>O<sub>9</sub>, 928.5459).
12. Jaspolide H (**2**): Yellow amorphous solid;  $[\alpha]_D^{25} +37.5$  (*c* 0.3, acetone); IR (KBr)  $\nu_{\max}$  3453, 1740, 1705, 1659 cm<sup>-1</sup>; ESIMS *m/z* 946 [M+NH<sub>4</sub>]<sup>+</sup>, 929 [M+1]<sup>+</sup>; HRFAB-MS *m/z* [M]<sup>+</sup>, 928.5494 (Calcd for C<sub>59</sub>H<sub>76</sub>O<sub>9</sub>, 928.5459).