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(−)-Wistarin from the marine sponge *Ircinia* sp.: the first case of enantiomeric sesterterpenes

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Abstract

The sestertepene (−)-wistarin has been isolated from a Red Sea sponge of the genus *Ircinia*. This metabolite is the enantiomer of (+)-wistarin, a tetracyclic metabolite previously isolated from the sponge *Ircinia wistarii*. The enantiomeric relationship was proved by comparison of the CD spectrum of (−)-wistarin with that of a synthetic sample of the (+)-isomer. A hypothetical biosynthesis of (−)-wistarin is discussed starting from a putative linear precursor.

Natural products are usually enantiomerically pure compounds, although the occurrence of enantiomeric pairs from different organisms has been reported occasionally. Some examples of this surprising finding are described among the terpenes. This is the case of (+)- and (−)-isomers of the sesquiterpenoids furodysin[1,2] and pallescensin,[3,4] or the terpenoic part of a few glyceryl esters isolated from dorid nudibranchs.[5,6] These examples seem to be episodic and, to the best of our knowledge, no case of enantiomeric pairs has been described for sesterterpenoids. Here we report the finding of a natural sesterterpene **1** enantiomeric to (+)-wistarin **2**, isolated from the sponge *Ircinia wistarii*[7] and more recently synthesized by Prof. Uenishi of Okoyama University.[8]

The (−)-isomer **1** of wistarin was isolated from a taxonomically new sponge of the genus *Ircinia* collected at Hurgada (Red Sea, Egypt) in March 1998. During the work-up the soft body of the sponge dissolved to give a mucous residue that was extracted with acetone. The high-density solution was centrifuged (3000 rpm) to separate the viscous part from the acetone soluble material. This latter fraction was transferred into a flask and concentrated at reduced pressure. The resulting aqueous residue was diluted with fresh water and extracted three times with diethyl ether. The organic layers were combined and evaporated to give 915 mg of diethyl ether extract. Silica gel column fractionation of half the extract gave 8 mg of **1**.

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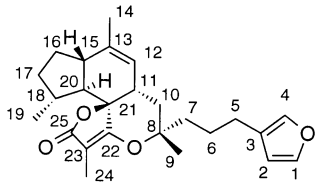

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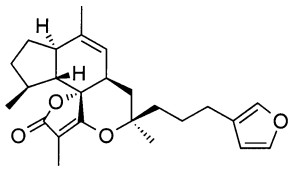

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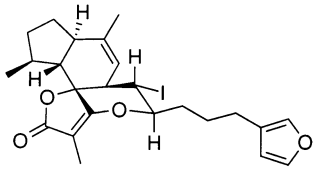

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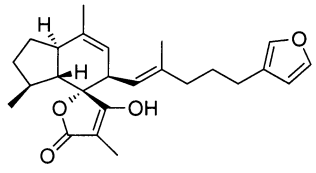

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The structure of (+)-wistarin **2** had been suggested by Gregson and Ouvrier in 1982[7] and recently revised on the basis of the synthesis carried out by Uenishi and co-workers.[8] The sesterterpene **1** isolated from the Red Sea sponge had identical spectroscopic properties to **2**, except for the polarimetric rotation that resulted to be opposite to that reported previously ($[\alpha]_D$ −112.2 (c 0.7, $CHCl_3$) and +132 (c 0.25, $CHCl_3$), respectively, for **1** and **2**[8]). Comparison (Fig. 1) of the CD spectrum of the natural product **1** with that of a synthetic sample† of (+)-wistarin **2**[8] proved unambiguously the enantiomeric relationship between the two sesterterpenes. A complete NMR assignment of **1** is reported in Table 1. These data are

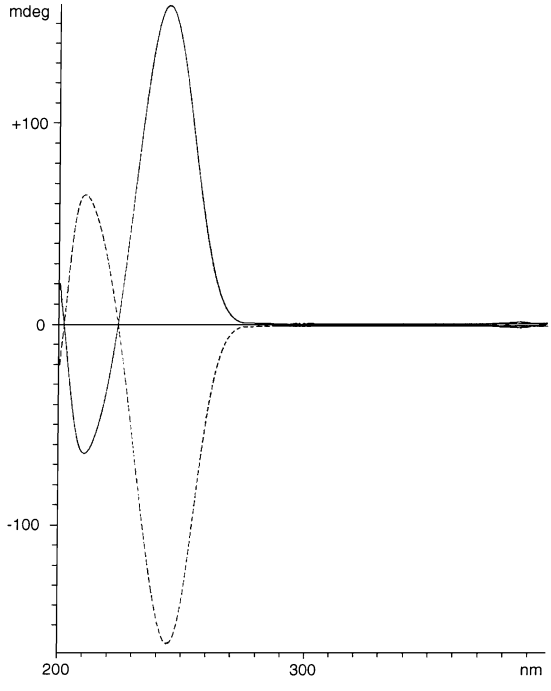


Figure 1. Comparison of the CD spectrum (MeOH) of (−)-wistarin **1** with that of a synthetic sample of (+)-wistarin **2**. Dotted line=**1**; single line=**2**

† The synthetic sample of (+)-wistarin was kindly supplied by Prof. J. Uenishi, Okayama University of Sciences, Japan.

Table 1
NMR assignment for (−)-wistarin (500 MHz). Chemical shifts are referred to $CHCl_3$ (δ 7.26 and 77.0) or C_6D_5H (δ 7.14 and 128.0)

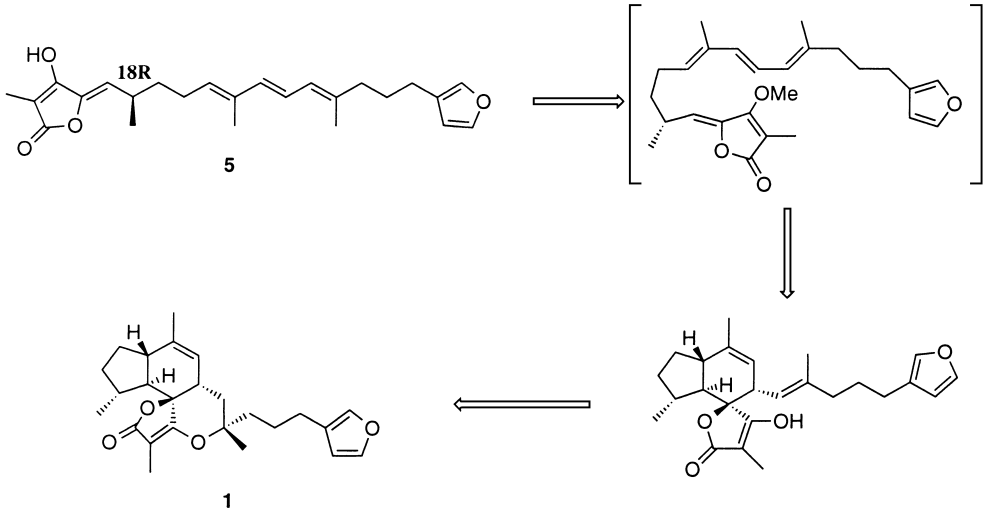
	$CDCl_3$		C_6D_6	
	δ_{1H}, *m*, Hz	δ_{13C}, m	δ_{1H}, *m*, Hz	δ_{13C}, *m*
1	7.35, *bs*	142.8, d	7.11, *s*	143.1, d
2	6.24, *bs*	110.8, d	6.00, *s*	110.9, d
3	-	124.5, s	-	124.7, s
4	7.23, *s*	138.9, s	7.02, *s*	139.2, d
5	2.52, *m*	23.6, t	2.17, *bm*	24.0, t
6	1.75, *m*	24.7, t	1.43, *m*	25.1, t
7	1.75, *m*	40.5, t[a]	1.43, *m*	40.9, t
8	-	80.7, s	-	80.1, s
9	1.19, *s*	23.3, q	0.69, *s*	22.7, q
10	1.75, m	41.7, t[a]	1.43, *m*	42.2, t
			1.17, *dd*, 11.8 and 3.9	
11	2.52, *m*	39.7, d	2.26, *m*	40.3, d
12	5.12, *bs*	121.1, d	4.97, *bs*	121.9, d
13	-	138.4, s	-	138.4, s
14	1.72, *s*	20.5, q	1.75, *s*	20.9, q[b]
15	2.52, *m*	44.7, d	2.56, *bm*	45.0, d
16	1.86, *bdd*, 9.8 and 4.1	26.5, t	1.56, *m*	26.8, t
	1.24, *m*		1.06, *m*	
17	1.97, *m*	31.7, t	1.69, *m*	32.2, t
	1.24, *m*		1.06, *m*	
18	1.63, *m*	30.3, d	1.69, *m*	30.8, d
19	0.83, *d*, 6.6	20.6, q	0.83, *d*, 6.7	20.7, q[b]
20	1.53, *m*	51.1, d	1.43, *m*	51.6, d
21	-	86.1, s	-	85.5, s
22	-	175.1, s	-	172.9, s
23	-	107.0, s	-	107.8, s[c]
24	1.68, *s*	6.1, q	1.62, *s*	6.4, q
25	-	175.2, s	-	174.2, s[c]

[a,b,c] = assignments with the same superscripted letters are interchangeable

in agreement with the revision of the stereochemistry at C-8 of **2** suggested on the basis of mechanistic considerations about the cyclization route of the synthetic intermediate **3**.[8] In particular, NOESY spectra (C_6D_6, 800 ms) of **1** showed cross-correlation between CH_3-9 (δ 0.69) and H-11 (δ 2.26), thus supporting a 1,3-diaxial interaction between these two substituents.

In conclusion, this work provides the first evidence for the natural occurrence of pairs of enantiomeric sesterterpenes. Uenishi and co-workers proved the stereoselective formation of **2** starting from (−)-ircinianin **4** via a base catalyzed mechanism.[8] A similar process could take place in nature and explain the co-occurrence of **2** and **4** in *I. wistarii*. Also, it is noteworthy that ircinianin **4** may derive from a linear precursor by a Diels–Alder cyclization. Both the racemate[9] and the (−)-isomer[8] of ircinianin have been synthesized following this approach. Consequently, it is likely that the (−)-isomer of wistarin **1** may derive from a putative linear precursor **5**, or its sulfate analog, through a similar biosynthetic pathway (Scheme 1). Whether this process is spontaneous or enzymatic remains to be thoroughly investigated.

The extract of the Red Sea *Ircinia* sp. also contained another compound characterized by an R_f value lower than that of **1**. Unfortunately our attempts to purify this product have been unsuccessful to date. In agreement with other authors,[10] however, it is reasonable to believe that the linear sesterterpene **5**, or its unstable sulfate analog, may occur in the living sponge.



Scheme 1. Hypothetical biosynthesis of (−)-wistarin **1** from a putative linear precursor

Acknowledgements

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