Pergamon

Tetrahedron Letters 39 (1998) 5635–5638

TETRAHEDRON
LETTERS

Hodgsonal, a new drimane sesquiterpene from the mantle of the Antarctic nudibranch *Bathydoris hodgsoni*

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Received 20 March 1998; accepted 26 May 1998

Abstract

A new drimane sesquiterpene, hodgsonal (**1**), has been isolated from the mantle extract of the Antarctic opisthobranch mollusc *Bathydoris hodgsoni.* The structure of **1**, including the absolute stereochemistry, has been elucidated by spectroscopic and chemical methods.The localization of **1** in the mantle and the analogies with related drimane compounds may indicate a defensive role against predators.

Keywords: Natural Products; Terpenes; Aldehydes; Molluscs;

The High Antarctic marine ecosystem is particularly characterized by low temperatures, a pronounced seasonality and a strong limitation of food resources. These environmental conditions cause strong inter- and intraspecific competitions among organisms [1]. Accordingly, effective defense mechanisms come to be crucial for the survival of the species. Opisthobranch molluscs have been largely investigated for their ability to defend themselves against predators by using chemicals [2-4]. Despite the large number of ecological studies on molluscs from temperate and tropical areas, little is known about the presence of defensive chemicals in Antarctic opisthobranchs [5-7]. Here we report the structural elucidation of the drimane sesquiterpene **1**, isolated from the mantle extract of the nudibranch *Bathydoris*

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[1] Associated to the National Institute for the Chemistry of Biological Systems (CNR).

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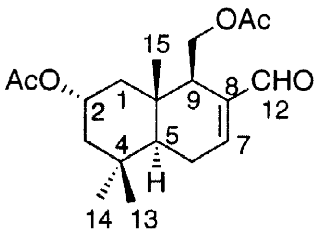
PII: S0040-4039(98)01095-8



1

hodgsoni Eliot, 1907 collected by trawling in the Weddell Sea (Antarctica) in 1996.[2] Six frozen specimens of *B. hodgsoni* were dissected into mantle and viscera and separately extracted with acetone. Chromatographic comparison of the diethyl ether soluble material from the acetone extracts revealed a similar pattern of secondary metabolites in all animals and the presence of a few products exclusively located in the mantle. Sequential SiO_2 columns of the combined mantle extracts of four animals (620 mg) gave **1**, that we are naming hodgsonal (light petroleum/diethyl ether 6:4, R*f* 0.35), together with minor compounds featured by the same drimane skeleton.

Hodgsonal (**1**),[3] $[\alpha]_D = -6.45°$ (c = 1.2, $CHCl_3$) showed a molecular formula $C_{19}H_{28}O_5$

Table 1

^1H- and ^{13}C-NMR data[a,b] for compound **1**

Position	δ ^1H	m	J (Hz)	δ ^{13}C	m[c]	long-range connectivities[d]
1	1.15	bdt		44.7	t	H_3-15
	2.26	bt				
2	5.01	m		67.9	d	H_2-1, H_2-3, H_3-14
3	1.25	m		46.5	t	
	1.89	bdt				
4				34.4	s	H_3-13, H_3-14
5	1.21	dd	4.0 and 11.8	48.5	d	H_3-13, H_3-14, H_3-15
6	2.23	bd		24.5	t	H-5, H-7
	2.43	bdt				
7	6.94	bd		152.5	d	H_2-6
8				139.8	s	H_2-6, H_2-11
9	2.48	bs		48.4	d	H_3-15
10				37.7	s	H_2-1, H-5, H-9, H_3-15
11	4.40	dd	1.5 and 11.9	59.9	t	
	4.63	dd	6.0 and 11.9			
12	9.43	s		193.7	d	H-7
13	1.04	s		22.7	q	H_3-14
14	0.98	s		33.1	q	H_3-13
15	0.94	s		15.3	q	H_2-1, H-5
OAc	1.95	s		170.5	s	
OAc	2.03	s		170.6	s	H_2-11

[a] All spectra were recorded at 500 MHz in $CDCl_3$; δ values are referred to $CHCl_3$ (δ ^1H 7.26 and δ ^{13}C 77.0).

[b] Assignments supported by COSY, HMQC, HMBC, HOHAHA and homodecoupling experiments.

[c] determined by DEPT; [d] J $_{^1H-^{13}C}$ = 10 Hz.

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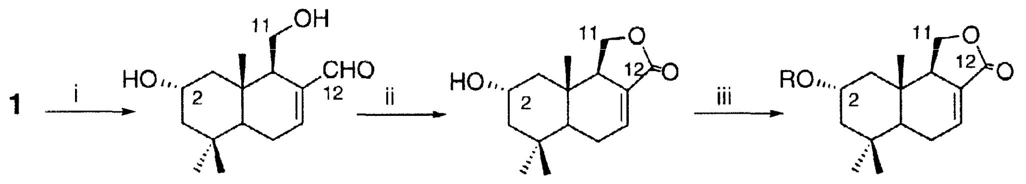
[2] Eleven specimens of *B. hodgsoni* were collected during the German Antarctic expedition ANT XIII/3 (EASIZ I) to the Eastern Weddell Sea. The specimens were found at five different localities between 246-620m depth. [3] Hodgsonal (**1**) was isolated as colorless oil, $[\alpha]_D = -6.4°$ (c=1.2, $CHCl_3$); IR (liquid film) ν_{max} 2965, 1737, 1689 cm^{-1}; UV (MeOH) λ_{max} 224 (9200) nm; EIMS *m/z* 336 (5), 276 (80), 216 (85), 201 (82), 107 (100). HREIMS *m/z* 336.1935 (- 0.0002 uma, $C_{19}H_{28}O_5$).

deduced by MS and ^{13}C-NMR data. The EIMS spectrum exhibited peaks at *m/z* 276 and 216 due to the successive losses of two molecules of acetic acid from the parent ion (*m/z* 336). Besides the strong absorption at 1737 cm^{-1} due to the acetyl groups, the IR spectrum revealed a third carbonyl moiety, 1689 cm^{-1}, assigned to an α,β unsaturated aldehyde on the basis of the proton signal a δ 9.43 (H-12) and the ^{13}C-NMR resonance at δ 193.7. The diacetate drimane skeleton of **1** was inferred by analysis of the ^1H NMR spectrum which showed signals for two acetyl groups (δ 1.95 and 2.03), three methyl singlets (δ 1.04, H_3-13; 0.98, H_3-14; 0.94, H_3-15) and an AB system at δ 4.63 (H-11a) and 4.40 (H-11b). The olefin proton at δ 6.94 (H-7) exhibited both a long range correlation with the aldehydic signal (H-12) and a stronger coupling with the methylene hydrogens at δ 2.43 and 2.23 (H_2-6), both in turn coupled to the bridgehead H-5 (δ 1.21). In addition, correlations of the down-shifted signal at δ 5.01 (H-2, ^{13}C NMR 67.9) with two distinct methylene groups at δ 2.26 and 1.15 (H_2-1), and 1.89 and 1.25 (H_2-3) led us to assign an acetoxy substituent at C-2. The equatorial orientation of this group was determined on the basis of NOEs between H-2 and both CH_3-15 (δ 0.94) and CH_3-13 (δ 1.04). The spectral data analysis of **1** was completed by the correlation of the hydroxymethylene group at C-11 (δ 4.63 and 4.40) with the allylic proton at δ 2.48 (H-9). A strong NOE between this latter hydrogen and H-5 supported the equatorial substituent at C-9 and established the relative stereochemistry of the drimane skeleton confirming the *trans* fused decalin ring.



2 **3** **4** R = (*S*) - MTPA
5 R = (*R*) - MTPA

Scheme 1. *i.* KOH in dry MeOH, 4h, r.t.; *ii.* MnO_2 in CH_2Cl_2, overnight, r.t.; *iii.* (*S*)- or (*R*)- MTPA Cl in dry pyridine, overnight, r.t.

Hodgsonal (**1**) contains four chiral carbons and, on biogenetic and spectral grounds, its structure is assumed to be that shown. In order to ascertain the absolute stereochemistry, however, **1** was converted into the lactone **3** by a two step process based on cyclization of the deacetylated product **2** with MnO_2 (scheme1). Treatment of **3** with Mosher's chlorides [8] gave the corresponding esters (**4** and **5**), of which $\Delta\delta$ values (Table 2) indicated the *S* absolute configuration at C-2 of **3** and confirmed the drimane skeleton for the native hodgsonal (**1**). Furthermore, the CD curve of **3** was in well agreement with that reported for the drimane ring of cinnamolide [9].

Table 2
Selected ^{1}H-NMR chemical shifts^a and $\Delta\delta^b$ for the MTPA esters of **3**

H	**4**	**5**	$\Delta\delta$
H_3-15	0.95	0.94	+ 0.01
H-9	2.91	2.89	+ 0.02
H-11a	4.06	4.04	+ 0.02
H-11b	4.40	4.36	+ 0.04
H_3-13	1.08	1.09	- 0.01
H_3-14	1.00	1.03	- 0.03
H-6	2.48	2.49	- 0.01

[a] Bruker AMX 500 MHz, $CDCl_3$, δ values are referred to $CHCl_3$ (δ 7.26); [b] $\Delta\delta$ ($\delta_{(S)\text{-ester}} - \delta_{(R)\text{-ester}}$) values are given in ppm.

At the best of our knowledge, hodgsonal (**1**) is the first example of a 2-substituted drimane sesquiterpene from marine organisms. Levels of **1** in individual animals are very similar and independent on both locality and depth. In absence of biosynthetic studies, this suggests a possible *de novo* synthesis as previously reported for the drimane sesquiterpenes isolated from other dorid nudibranchs [10]. Furthermore, the structural analogies with bioactive compounds from molluscs of the genus *Dendrodoris* [10,11], and the exclusive presence in the mantle of *B. hodgsoni*, may support the defensive role of **1**.

Acknowledgments

Thanks are due to T. Brey for collecting the specimens, to G. Scognamiglio for spectrophotometric measurements, and to W. Arntz and A. Ramos for financial support. This project was partially supported by the Italian National Research Program in Antarctica (PNRA) of CNR. C.A. thanks the M.E.C. (Spain) for a contract within the project ANT96-1011. This is A.W.I. publication No. 1406.

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