



Pergamon

Tetrahedron Letters 41 (2000) 1979–1982

TETRAHEDRON
LETTERS

Structure and absolute configuration of a new rearranged chamigrane-type sesquiterpenoid from the sea hare *Aplysia* sp.

Sergei N. Fedorov, Larisa K. Shubina, Anatoly I. Kalinovsky, Ekaterina G. Lyakhova and
Valentin A. Stonik *

Laboratory of the Chemistry of Marine Natural Products, Pacific Institute of Bioorganic Chemistry of the Russian
Academy of Sciences, Vladivostok-22, Russia

Received 9 November 1999; accepted 11 January 2000

Abstract

(6*S*,10*S*)-3,10-Dimethyl-7,11-dimethylidenespiro[5,5]undec-2-en-4-one (**1**), a new rearranged chamigrane-type sesquiterpenoid with two sp^2 -hybridized carbons in α -positions to the spiro-atom, was isolated from the alcoholic extract of the sea hare *Aplysia* sp. and its structure and absolute configuration were established by chemical transformations, NMR, EIMS, IR, UV and CD spectroscopy. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: marine metabolites; terpenes; spectroscopy.

A plethora of halogenated chamigrane sesquiterpenoids with skeleton system **A** have been isolated from red algae^{1–12} and opisthobranch molluscs which feed on such algae.^{1,13–15} Related rearranged chamigrane-type compounds, having skeleton system **B**, are much rarer natural products. So far these compounds have been found only from an undescribed species of red algae belonging to the genus *Laurencia*¹⁶ and the sea hare *Aplysia dactylomela*.¹⁷ We have isolated a new unusual non-halogenated sesquiterpene (**1**) with the skeleton system **B** from the alcoholic extract of the sea hare *Aplysia* sp.[†] by silica gel column chromatography in hexane:ethyl acetate, 15:1, followed by HPLC on an Ultrasphere Si column in hexane:ethyl acetate, 25:1.

Sesquiterpene (**1**), has a molecular formula of $C_{15}H_{20}O$, and is a colorless oil, 0.0072% based on net weight, $[\alpha]_D^{20} +15^\circ$ (c 0.1, EtOH). From its NMR data (Table 1) it is evident that the functionality within **1** consists of a ketone [197.4 (s) ppm], one olefinic and one secondary methyl group [1.75 (q, $J=1.8$ Hz, 3H) and 1.04 ppm (d, $J=6.4$ Hz, 3H)], and three carbon–carbon double bonds, two *exo* [4.57 (bs, 1H), 4.76 (bt, $J=1.1$ Hz, 1H), 4.7 (bd, $J=1.2$ Hz, 1H), 4.77 ppm (d, $J=1.9$ Hz, 1H)] and one *endo* [6.79 ppm (m, 1H)]. The molecule is thus bicyclic.

* Corresponding author. E-mail: piboc@stl.ru (V. A. Stonik)

† The sea hare was collected in the northern point of Madagascar in October, 1986, SCUBA, from a depth of 3–5 m.

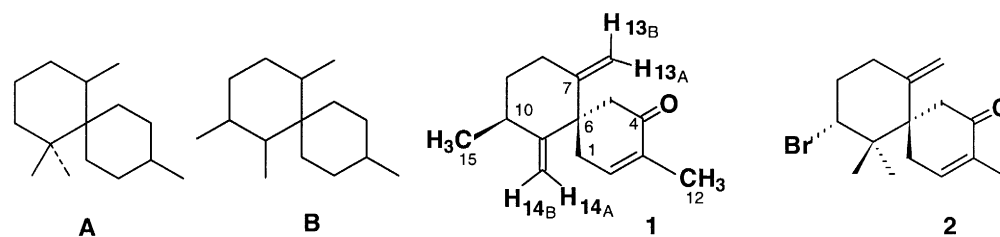


Table 1
NMR data for compound **1***

Position	δ_C	m	δ_H	m	J (Hz)	NOE
1	34.6	t	2.75, 2H	m		
2	143.1	d	6.79, 1H	m		H-2→H-1, 3H-12
3	134.7	s	-			-
4	197.4	s	-			-
5	48.5	t	2.79, 2H	bs		-
6	50.9	s	-			-
7	151.8	s	-			-
8ax	32.0	t	2.50	m		H-8ax→H-5, H-8eq, H-9eq
8eq			2.21	ddd	14.0, 4.9, 2.5	H-8eq→H-13 _B
9ax	38.1	t	1.05	qd	12.6, 4.9	-
9eq			1.93	dtd	12.6, 4.9, 2.5	H-9eq→H-9ax
10	32.9	d	2.50, 1H	m		H-10→H-5, 3H-15
11	155.7	s	-			-
12	15.2	q	1.75, 3H	q	1.8	-
13 _A	108.3	t	4.57, 1H	bs		H-13 _A →H-13 _B , H-1, H-2
13 _B			4.76, 1H	bt	1.1	-
14 _A	106.1	t	4.70, 1H	bd	1.2	H-14 _A →H-1, H-14 _B
14 _B			4.77, 1H	d	1.9	-
15	19.0	q	1.04, 3H	d	6.4	3H-15→H-10, H-14 _B

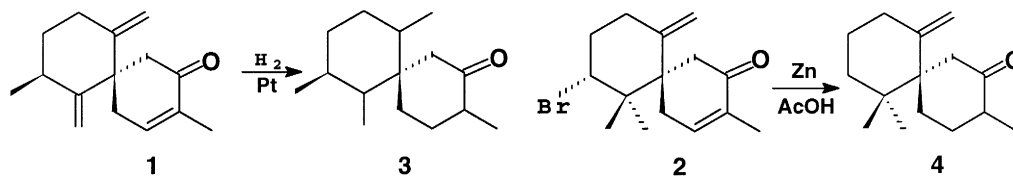
*¹H NMR experiments were performed at 250 MHz in CDCl₃ and ¹³C NMR experiments were performed at 62.5 MHz in CDCl₃.

The presence of δ_C at 50.9 (s) ppm for a spiro-atom confirms that **1** is closely related to chamigrane sesquiterpenes. The structure of the ketone-containing ring in **1** is identical to that in sesquiterpene **2**, previously described by us from the same mollusc.¹⁸ Really, both compounds have similar corresponding resonances in the ¹H and ¹³C NMR spectra, UV and IR spectral data [for **1** UV: λ_{\max} (EtOH) 240 nm (ϵ 3850); IR: (CHCl₃) $\nu_{C=O}$ 1667 cm⁻¹] (Table 1).

The structure of the other ring of **1** was proven by NMR spectroscopy, including NOE experiments, to be a chair form bearing two *exo*-methylene groups in the α -positions and one methyl group in the β -position to the spiro-atom. In fact, irradiation of either H-13_A or H-14_A (δ 4.57 and 4.70 ppm, respectively) enhances the same signal of 2H-1 (δ 2.75 ppm), while irradiation of 3H-15 (δ 1.04 ppm) enhances the signal of H-14_B (δ 4.77 ppm). The fact that the coupling constant between H-10 and H-9ax is 12.6 Hz clearly places CH₃-15 as equatorial. These data show that this ring has a conformation of a 7 β ,10 α -chair (see the perspective drawing of **1**).

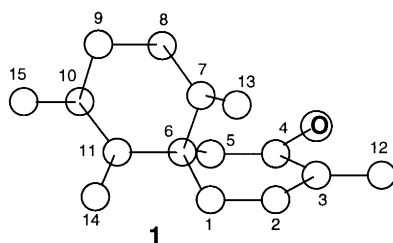
Previously the X-ray analysis showed that the absolute configuration of **2** is 6*S*,10*R*.¹⁸ In order to

determine the absolute configuration in **1** we obtained the saturated ketone **3**[‡] by catalytic hydrogenation of **1** and another saturated ketone **4**[§] by treatment of **2** with Zn in a mixture of acetic acid and methanol, refluxing for 2 h. The 6*S* configuration of **1** was suggested by comparison of the CD spectra of **3** and **4** (Scheme 1).

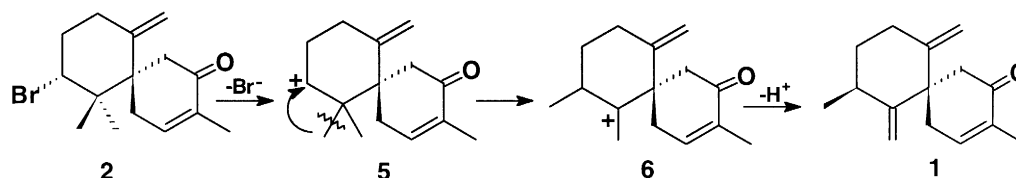


Scheme 1.

Both CD spectra showed negative Cotton effects with $[\theta]_{290} = -12.9 \times 10^4$ and $[\theta]_{288} = -29.3 \times 10^4$, respectively. Application of the octant rule to compound **3** confirmed that **3**, and therefore **1**, have 6*S*-configurations. On the basis of this and NMR data, taking into consideration the equatorial position of the CH₃-15, the structure of **1** was determined as (6*S*,10*S*)-3,10-dimethyl-7,11-dimethylenespiro[5,5]undec-2-en-4-one.

The perspective drawing of **1**.

The presence of **1** and **2**, having the same configurations at C-6, in the extracts from *Aplysia* sp. suggests that **1** could be a product of metabolism of **2** in this mollusc and is formed from **2** as a result of the elimination of a bromide ion followed by 1,2 shift of a methyl group and the loss of a proton from CH₃-14 in the intermediate carbonium ion (**6**) (Scheme 2).



Scheme 2.

Studies on the chemical constituents of opisthobranch molluscs have established that these animals do not themselves biosynthesize sesquiterpenes but ingest them with their algal diet,¹ very often with resulting loss of bromine atoms. Rearrangements of the same type with migration of a methyl group from

[‡] Oil, $[\alpha]_D^{20} = -6^\circ$ (*c* 0.1, EtOH); EIMS, *m/z*: 222 (*M*⁺, 15), 207 (10), 177 (15), 150 (100), 135 (40), 111 (75), 95 (70); ¹H NMR: 0.845 (d, 6.8, 3H), 0.891 (d, 7.5, 3H), 0.942 (d, 7.5, 3H), 1.021 (d, 6.5, 3H), 2.17 (m, 1H), 2.33 (m, 1H), 2.98 (dd, 13.5; 2.8, 1H).

[§] Mp 93–95°C (EtOH), $[\alpha]_D^{20} = -13^\circ$ (*c* 0.1, EtOH) EIMS, *m/z*: 220 (*M*⁺, 100), 205 (12), 177 (10), 164 (18), 151 (55), 138 (13), 123 (27), 109 (45), 95 (33); ¹H NMR: 0.84 (s, 3H), 0.98 (s, 3H), 1.01 (d, 7.0, 3H), 4.59 (s, 1H), 4.95 (s, 1H).

C-11 to C-10, fostered by the loss of a bromine atom at C-10, were earlier implicated in the biogenesis of other rearranged terpenoid carbon skeletons found in red algae.¹⁹

References

1. Martin, J. D.; Darias, J. In *Marine Natural Products Chemical and Biological Perspectives*; Scheuer, P. J., Ed. Algal sesquiterpenoids. Academic Press: New York, 1978; Vol. 1, pp. 125–173.
2. Ojika, M.; Shizuri, Y.; Yamada, K. *Phytochemistry* **1982**, *21*, 2410–2411.
3. Suzuki, T.; Kikuchi, H.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1561–1563.
4. Furusaki, A.; Katayama, C.; Matsumoto, T.; Suzuki, M.; Suzuki, T.; Kikuchi, H.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3398–3402.
5. Suzuki, M.; Segawa, M.; Suzuki, T.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3824–3826.
6. Suzuki, M.; Segawa, M.; Suzuki, T.; Kurosawa, E. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2435–2436.
7. Brennan, M. R.; Erickson, K. L.; Minott, D. A.; Pascoe, K. O. *Phytochemistry* **1987**, *26*, 1053–1057.
8. Kennedy, D. J.; Selby, I. A.; Thomson, R. H. *Phytochemistry* **1988**, *27*, 1761–1766.
9. Juagdan, E. G.; Kalidindi, R.; Scheuer, P. *Tetrahedron* **1997**, *53*, 521–528.
10. Konig, G. M.; Wright, A. D. *J. Nat. Prod.* **1997**, *60*, 967–970.
11. Guella, G.; Oztune, A.; Mancini, I.; Pietra, F. *Tetrahedron Lett.* **1997**, *38*, 8261–8264.
12. Francisco, M. E. Y.; Turnbull, M. M.; Erickson, K. L. *Tetrahedron Lett.* **1998**, *39*, 5289–5292.
13. Pitombo, L. F.; Kaiser, C. R.; Pinto, A. C. *Bol. Soc. Chil. Quim.* **1996**, *41*, 433–436.
14. Faulkner, D. J. *Tetrahedron* **1977**, *33*, 1421–1443.
15. Schmitz, F. J.; Michaud, D. P.; Schmidt, P. G. *J. Am. Chem. Soc.* **1982**, *104*, 6415–6423.
16. Bittner, M. L.; Silva, M.; Paul, V. J.; Fenical, W. *Phytochemistry* **1985**, *24*, 987–989.
17. Sakai, R.; Higa, T.; Jefford, C.; Bernardinelli, G. *Helv. Chim. Acta* **1986**, *69*, 91–105.
18. Fedorov, S. N.; Reshetnyak, M. V.; Schedrin, A. P.; Ilyin, S. G.; Struchkov, J. T.; Stonik, V. A.; Elyakov, G. B. *Dokl. AN SSSR.* **1990**, *307*, 877–879.
19. Fenical, W. In *Recent Advances in Phytochemistry*; Swain, T.; Waller, G. R., Eds. Topics in the biochemistry of natural products. Plenum Press: New York, 1979; Vol. 13, pp. 219–253.