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Naupliolide, a sesquiterpene lactone with a novel tetracyclic skeleton from *Nauplius graveolens* subsp. *odorus*

Mohamed Akssira,[a,*] Fouad Mellouki,[a] Ali Salhi,[a] Hakim Alilou,[a] Abderrahmane Saouf,[a] Fadwa El Hanbali,[a] Jesús F. Arteaga[b] and Alejandro F. Barrero[b,*]

[a] *Laboratoire de Chimie Bioorganique et Analytique UFR C35/97. F. S. T. Université Hassan II-Mohammedia BP 146, 20800 Mohammedia, Morocco*
[b] *Department of Organic Chemistry, Institute of Biotechnology, University of Granada, Avda. Fuentenueva, 18071 Granada, Spain*

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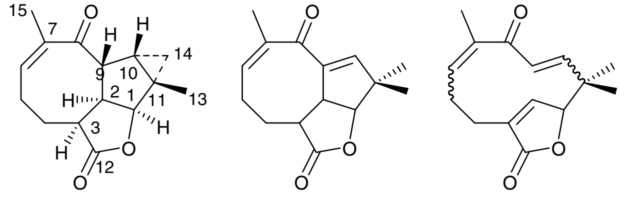
Abstract—The aerial parts of *Nauplius graveolens* subsp. *odorus* (*Schousb*) *Wikl.* afforded a novel sesquiterpene lactone (**1**) named naupliolide together with the known 6,7,9,10-tetradehydroasteriscanolide **2** and asteriscunolides A–D **3a**–**d**. The structure of compound **1** corresponds to a novel skeleton of 14,15-dimethyl-7,13-dioxotricyclic[6.4.0.0^{9,11}]dodeca-12,13-olide, and was established on the basis of spectroscopic methods including 2D-NMR. The coexistence of naupliolide **1** together with the structurally related sesquiterpene lactones asterisculolides A–D (**3a**–**d**) and 6,7,9,10-tetradehydroasteriscanolide **2**, seems to indicate their biosynthetic relationship.

Over the past twenty years, considerable attention has been given to *Asteriscus* genus from which mainly sesquiterpenes have been reported. Asteriscunolides A–D (**3a**–**d**) were previously isolated from the aerial parts of *Asteriscus aquaticus*,[1] *Asteriscus graveolens*,[2] *Asteriscus sericeus*,[3] and *Asteriscus vogelii*.[4] From the extract of *Nauplius intermedius*, asteriscunolides and their corresponding free hydroxyacids were also obtained.[5] Other sesquiterpene lactones such as asteriscanolide and aquatolide were obtained from the extract of *Asteriscus aquaticus*.[6] Flavonoids,[7] bisabolone hydroperoxides,[9] as well as farnesol and thymol derivatives,[10] were also described as constituents of extracts from plants of the Asteriscus genus. *Asteriscus graveolens* is reported to possess antimicrobial and hypoglycemic activities,[7] whereas Asteriscunolides C and D have shown phytotoxic activities and the last also showed citotoxic ones.[4]

Nauplius graveolens subsp. *odorus* (*Schousb.*) *Wikl.* is an endemic species from Morocco (synonym: *Odontospermum odorum*, familly: Asteraceae, tribe Inuleae). In our knowledge, this plant has never been studied.

In the present study, we report the isolation of a new sesquiterpene lactone named Naupliolide (**1**) with a novel tetracyclic skeleton, together with several known compounds (Fig. 1) as 6,7,9,10-tetradehydroasteriscanolide (**2**) and asteriscunolides A–D (**3a**–**d**).[1b,2]

The plant material[8] (1 kg) was extracted with chloroform in a soxhlet apparatus. The extract (120 g) diluted into $CHCl_3$ was separated into acidic and neutral fractions after treatment by aqueous sodium carbonate. Column chromatography (silica gel) of neutral part (37 g) only gave four important fractions starting with hexane/EtOAc (1:0) and ending with hexane/EtOAc (0:1).



1 **2**

	Δ^6	Δ^9		Δ^6	Δ^9
3a	*Z*	*Z*	**3c**	*Z*	*E*
3b	*E*	*Z*	**3d**	*E*	*E*

Figure 1.

Keywords: *Nauplius graveolens* subsp. *odorus*; Asteraceae; Sesquiterpenes lactones.

[*] Corresponding authors. Tel./fax: +34 958243318 (A.F.B.); e-mail: afbarre@ugr.es

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Column chromatography (CC) of fraction-1 (1.37 g) eluted with CH_2Cl_2/EtOAc (9:1) yielded **1** (20 mg) and **3b** (11.6 mg). From the medium polar fraction-2 (1.5 g), compounds **2** (62.9 mg), and **3a** (59.3 mg) were isolated after CC using petroleum ether/Et_2O (3:2). Fraction-3 (3.5 g) eluting with hexane/Et_2O (1:1) gave compound **3c** (345.4 mg). Finally, fraction-4 (0.85 g) was separated with CH_2Cl_2/EtOAc (4.95:0.05) to give compound **3d** (111.7 mg). Spectral data of **2** and **3a–d** are in good agreement with those previously reported.[1b,2]

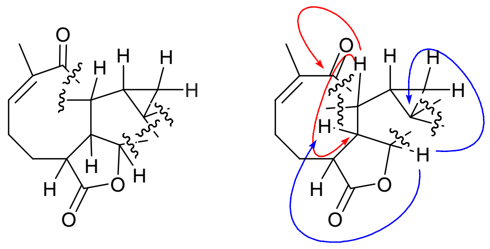
Compound **1** was isolated as an amorphous white powder $[\alpha]_D$ +80 (*c* 0.11, $CHCl_3$). Its molecular formula was determined as $C_{15}H_{18}O_3$ by HREIMS, *m/z* 246.1336 indicating 7 degrees of unsaturation. Its IR spectra shows two bands of absorption by the presence of carbonyl groups at 1765 and 1660 cm^{-1} corresponding to γ-lactone and α,β-unsaturated ketone, respectively. The ^{13}C NMR spectra (Table 1) show 15 signals, two of them at δ_C 177.0 and 203.8 ppm confirming the presence of these oxygenated functions, whereas the presence of a trisubstituted double bond can be established by those at 136.2 ppm (singlet) and 138.7 ppm (doublet).

The remaining signals present a multiplicity corresponding to two CH_3, three CH_2, five CH and one quaternary carbon their δ values being characteristic of non-functionalized sp^3 carbons. Thus **1** contains three unsaturated functions and possesses four cycles in its structure. The ^1H NMR spectra present signals at 6.34 ppm (1H, ddq, $J = 8.9$, 7.7, and 1.3 Hz) and 1.84 ppm (3H, s) of the trisubstituted double bond conjugated with a ketone and at 1.34 ppm (3H, s) of a second methyl group.

Furthermore, a signal at 4.66 ppm (1H, d, $J = 4.2$ Hz) was assigned to a proton linked to an oxygenated carbon. Other signals at 0.57 ppm (1H, dd, $J = 6.0$ and 8.0 Hz), 0.64 ppm (1H, dd, $J = 6.0$ and 4.0 Hz), and 1.61 ppm (1H, ddd, $J = 8.4$ and 4.0 Hz) can be attributed to a cyclopropane ring. The interpretation of the remaining signals with the help of the 2D-NMR experiments, HSQC, and ^1H–^1H COSY permitted us to establish the partial structure **I** (Fig. 2). All the protons in **I** have been connected via direct correlations except those of the methyl group at 1.34 ppm in ^1H NMR.

HMBC correlations (Fig. 2) permit joining to **I** the remaining methyl and determining the connections among the rest of the structural fragments. Thus, the carbonated structure for **1** has been established. The stereochemistry of the double bond was determined being *Z* by the NOE effect observed for H6 and Me-C7 in 1D-NOESY spectra. Relative configurations of the six stereogenic carbons were established also through 1D-NOESY spectra (Fig. 3) and $J_{H2-H9} = 9.9$ Hz, confirming the anti relationship between those protons. Additionally, the NOE effects observed for H5β–H9 and H4β–H9 are in accordance with a boat conformation for the cyclooctene ring (Fig. 3). Thus, the structural characterization of compound **1**, named naupliolide and possessing a novel tetracyclic sesquiterpenic skeleton was completed.

The coexistence of asterisculolides A–D (**3a–d**) together with the structurally related sesquiterpene lactone, naupliolide **1** and 6,7,9,10-tetradehydroasteriscanolide **2**, in *Nauplius graveolens* subsp. *odorus* seems to indicate their biosynthetic relationship. Thus, we propose the biosynthetic steps depicted in Scheme 1. The acid-induced

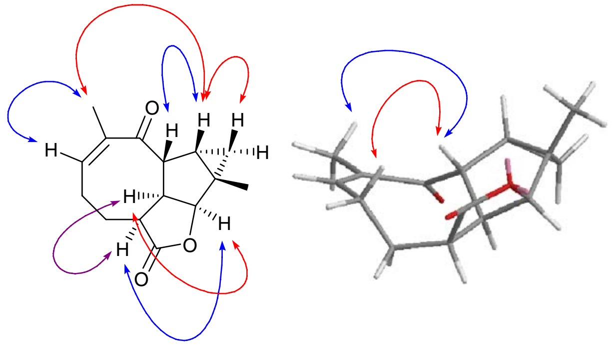


I

Figure 2. Partial structure and selected HMBC correlations for **1**.

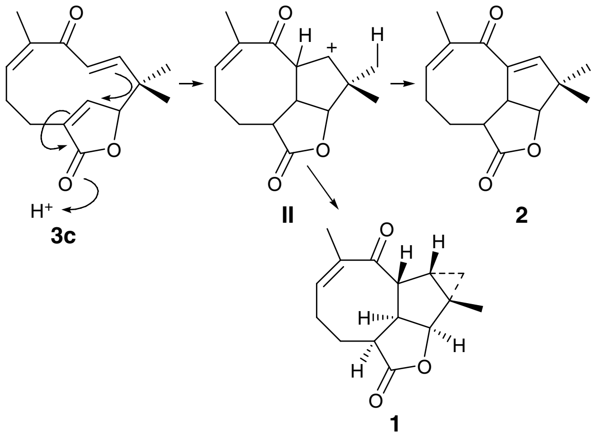
Table 1. ^1H, ^{13}C NMR DEPT data of 1 ($CDCl_3$, TMS)

No.	δ_H	δ_C	DEPT
1α	4.66 (1H, d, $J = 4.2$ Hz)	89.1	CH
2α	2.59 (1H, ddd, $J = 9.9$, 6.7, 4.2 Hz)	42.0	CH
3α	2.94 (1H, ddd, $J = 6.6$, 6.4, 4.2 Hz)	43.4	CH
4α	1.79 (1H, dddd, $J = 15.0$, 10.3, 6.2, 6.2 Hz)	23.0	CH_2
4β	2.39 (1H, dddd, $J = 15.0$, 9.0, 4.0, 1.3 Hz)		
5α	2.30 (1H, dddd, $J = 15.5$, 9.0, 8.9, 6.2 Hz)	25.3	CH_2
5β	2.54 (1H, ddddq, $J = 15.5$, 10.2, 7.5, 1.3, 1.3 Hz)		
6	6.34 (1H, dddq, $J = 8.9$, 7.7, 1.3 Hz)	138.7	CH
7	—	136.1	C
8	—	203.8	C
9β	3.66 (1H, dd, $J = 9.9$, 4.2 Hz)	51.9	CH
10β	1.61 (1H, ddd, $J = 8.1$, 4.0, 4.0 Hz)	28.4	CH
11	—	25.3	C
12	—	177.0	C
13	1.84 (3H, sa)	21.0	CH_3
14α	0.57 (1H, dd, $J = 6.0$, 4.0 Hz)	13.2	CH_2
14β	0.64 (1H, dd, $J = 7.9$, 6.0 Hz)		
15	1.34 (3H, s)	16.1	CH_3



1

Figure 3. NOESY correlations for compound **1**.



Scheme 1. Biosynthetic pathway to compound **1**.

cyclization of asteriscunolide C (**3c**) leads to the intermediate carbocation **II** which can evolve toward **1** or **2** losing H9 or H14, respectively. Thus, the presence of compound **1** constitutes a strong evidence of the biogenetic relation between asteriscunolides and the tricyclic sesquiterpene lactones such as asteriscanolide and related compounds.

In summary, besides five known compounds, a new sesquiterpene lactone naupliolide **1** was isolated from *Nauplius graveolens* subsp. *odorus*. The main novelty of this compound is the presence of one new tetracyclic skeleton possessing a cyclopropane ring in its structure.

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References and notes

1. (a) San Feliciano, A.; Barrero, A. F.; Medarde, M.; del Corral, J. M.; Ledesma, E.; Sánchez-Ferrando, F. *Tetrahedron Lett.* **1982**, *23*, 3097–3100; (b) San Feliciano, A.; Barrero, A. F.; Medarde, M.; del Corral, J. M.; Aizpiri, A. A.; Sánchez-Ferrando, F. *Tetrahedron* **1984**, *40*, 873–878; (c) San Feliciano, A.; Barrero, A. F.; Medarde, M.; del Corral, J. M.; Aramburu, A.; Perales, A.; Sánchez-Ferrando, F. *Tetrahedron* **1985**, *41*, 5711–5717.
2. El-Dahmy, S.; Jakupovic, J.; Bohlmann, F.; Sarg, T. M. *Tetrahedron* **1985**, *41*, 309–316.
3. Jakupovic, J.; Lehmann, L.; Bohlmann, F.; Hogdson, A. A. *Phytochemistry* **1987**, *26*, 2854–2855.
4. Rauter, A. P.; Branco, I.; Bermejo, J.; González, A. G.; García-Grávalos, M. D.; San Feliciano, A. *Phytochemistry* **2001**, *56*, 167–171.
5. Bohlmann, F.; Pauls, A. *Phytochemistry* **1992**, *31*, 1663–1665.
6. (a) San Feliciano, A.; Barrero, A. F.; Medarde, M.; del Corral, J. M.; Aramburu, A.; Perales, A.; Fayos, J. *Tetrahedron Lett.* **1985**, *26*, 2369–2372; (b) San Feliciano, A.; Medarde, M.; del Corral, J. M.; Aramburu, A.; Gordaliza, M.; Barrero, A. F. *Tetrahedron Lett.* **1989**, *30*, 2851–2854.
7. (a) Ahmed, A. A.; Ishak, M. S.; Micheal, H. N.; El-Ansari, M. A.; El-Sissi, H. I. *J. Nat. Prod.* **1991**, *54*, 1092–1093; (b) Youssef, S. A.; Ibraheim, Z. Z.; Attia, A. A. *Bull. Pharm. Sci. Assiut. Univ.* **1995**, *18*, 33–38.
8. *Nauplius graveolens* subsp. *odorus* was collected between Chichaoua and Marrakech (arid region in south Morocco) in March 2003. The plant was kindly identified by Dr. A. Ouyahya at Scientific Institute (Rabat, Morocco). A voucher specimen was deposited at the Herbarium of this Institute.
9. Sarg, T. M.; El Dahmy, S. I.; Ateya, A. M.; Abdel-Fattah, H. A. *Fitoterapia* **1994**, *65*, 241–244.
10. Ahmed, A. A. J. *Nat. Prod.* **1992**, *55*, 824–827.