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CLARAENONE, A NEW MERODITERPENE FROM BROWN ALGA.

Manuel Norte, Armando Sánchez and Antonio G. González

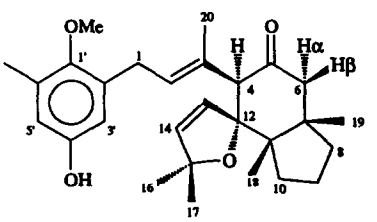
C.P.N.O. "Antonio González", Instituto Universitario de Bioorgánica. Universidad de La Laguna
38206 La Laguna, Tenerife, Spain.

Abstract: A new meroditerpene, claraenone **1**, having an unprecedented carbon skeleton with a [4,3,0] bicarbocyclic nonane ring system, has been isolated from the brown alga *Cystoseira sp.* Its structure and relative stereochemistry have been determined by spectroscopical methods.

Marine algae of the family *Cystoseiraceae* are among the most abundant along the Canary Islands coastline. This group, together with the algae belonging to the family *Sargassaceae*, is characterized by the production of a variety of tetraprenyl-hydroquinol derivatives which include regular and irregular examples with either acyclic or cyclic natures.[1)]

In this paper, we wish to report on the isolation and structural elucidation of a new meroditerpene, **1**, with a new carbon skeleton type, in which the terpenoid component has a bicarbocyclic [4,3,0] ring system.

This compound was isolated from an extract of *Cystoseira sp*, collected by scuba at -10m at Montaña Clara (Canary Islands) in September 1990. The alga was air-dried and subsequently extracted with acetone. Diterpenoids (3% of dry weight alga) were obtained by standard open-column silica gel and Sephadex LH-20 chromatographies, using n-Hex:EtOAc (70:30) and n-Hex:$CHCl_3$:MeOH (2:1:1), respectively, as eluents. After several chromatographies, compound **1** was isolated from the most polar diterpenoid fraction and purified by HPLC on μ-Porasil (20% Hex:EtOAc).



1

Compound **1** showed an optical rotation of $[\alpha]_D^{25}$ = -35.8 (c 0.52, $CHCl_3$) and it was analysed for $C_{28}H_{38}O_4$ in accordance with its molecular ion in the HRMS spectrum, m/z 438.2275 (calc. 438.2270). U.V. absorptions at 200.5 nm and 281 nm suggested a hydroquinol chromophore, while the IR bands at 3405, 1710 and 1600 cm^{-1} were indicative of hydroxyl, carbonyl and aromatic functions, respectively. Moreover, the nature of the first isoprene unit (C_1-C_4 + C_{20}), the presence of a cyclopentyl moiety and an isolated double bond with a Z geometry, were determined upon the basis of spectral analysis[2,3)].

Comparison of these data with those from related compounds[4)] clearly showed the lack in the ^1H NMR spectrum of the characteristic signals for the methylene group at C_4 in compound **1** which, in turn, were substituted by a signal from a deshielded methine at δ 3.78. Moreover, there was an isolated methylene group at C_6 (δ 2.64 and 2.13). These chemical shift values were consistent with the presence of a strained ketone at C_5 and imply the unprecedented involvement of carbon C_4 in the terpenoid moiety cyclization.

Support for the above conclusions, including the tricyclic nature of the terpenoid part of the molecule, was obtained from the 2D NMR spectra (Table 1). Thus, the proton connectivities observed in the COSY map established the presence of two small fragments, one identified with the isolated double bond and the other with the characteristic methylenic cyclopentyl portion. The positions of these fragments were assured through the HMBC correlation observed between the carbons C_7 and C_8, and the protons $H_{6\alpha}$, $H_{6\beta}$ and Me_{19} as well as between carbons C_{10}, C_{11} and C_{12} and the methyl group Me_{18}. On the other hand, C_{12} and C_{15} proved to be connected with H_{14} and H_{13}, while C_{13} was connected with H_4. These correlations established the presence and the position of a dihydrofuran ring in the cyclohexanone ring.

Table 1. NMR Spectral data of compound **1**

C #	^1H	^{13}C	HMBC (H#) J=4 Hz.	ROESY (H#)
1	3.35	28.2	3'	2, 16, 20, 3'
2	5.46	131.9	4, 20	1, 4, 3'
3	---	131.8	1, 4, 20	---
4	3.78	66.6	6β, 20	2, 6α, 10α
5	---	209.6	4, 6α, 6β	---
6	α 2.64 β 2.13	52.6	---	4, 6β, 8α, 10α 6α, 8α, 18, 19
7	---	45.6	6α, 6β, 18, 19	---
8	α 1.56 β 1.82	41.0	6α, 6β, 19	6α, 6β, 8β, 10α 8α
9	1.78	19.0	---	---
10	α 2.45 β 1.75	36.5	18	4, 6α, 8α, 10β 10α
11	---	52.0	6β, 18, 19	---
12	---	101.2	13, 14, 18	---
13	5.66	127.7	4, 14	18, 19, 20
14	5.71	135.5	16, 17	16, 17, 18, 20
15	---	86.7	13, 14, 16, 17	---
16	1.26	28.7	17	1, 14, 17
17	1.41	28.1	16	14, 16
18	1.01	20.8	---	6β, 13, 20
19	1.02	22.6	---	6β, 13, 20
20	1.78	18.9	4	1, 13, 18, 19
1'	---	150.2	1, Me-6'	---
2'	---	134.4	1	---
3'	6.62	114.1	1, 5'	1, 2
4'	---	151.8	3', 5'	---
5'	6.55	115.3	3', Me-6'	Me-6'
6'	---	130.8	Me-6'	---
Me-6'	2.27	16.2	5'	5'
-OMe	3.70	60.4	---	---
-OH	5.92	---	---	---

Chemical shifts are reported in ppm relative to TMS. NMR spectra were acquired using Bruker AMX -400 (400 MHz).

The relative stereochemistry was established on the basis of the observed ROE connectivities. Thus, protons H_2, H_4, $H_{6\alpha}$ and $H_{10\alpha}$ were on the same face of the molecule, while $H_{6\beta}$, Me_{18}, Me_{19} and Me_{20} were on the opposite one. On the other hand, the relative stereochemistry of the spiranic centre at C_{12} was fixed through the ROE connectivities observed between the vinylic proton H_{13} and the methyl groups Me_{18}, Me_{19} and Me_{20} (Fig. 1).

This compound showed in vitro antitumor activity (IC_{50}= 5 μg/ml) against P-388 mouse leukemia.

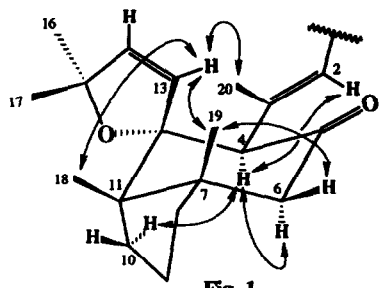


Fig. 1

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