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Gomerones A–C, halogenated sesquiterpenoids with a novel carbon skeleton from *Laurencia majuscula*

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ABSTRACT

The structures and relative sterochemistry of three halogenated sesquiterpenoids gomerones A–C, **1**–**3**, isolated from *Laurencia majuscula* are described. They are representative of a novel carbon skeleton, gomerane, biogenetically derived from cyclization of a β-chamigrene precursor. A biogenetic relationship with related sesquiterpenoids from lower terrestrial plants Hepaticae of genera *Bazzania*, *Mannia*, *Mylia*, and *Rebouli* as well as higher plants of genera *Cupressus* and *Juniperus* has been established.

1. Introduction

Sesquiterpene cyclases are among nature's most versatile catalysts. These enzymes are responsible for the formation of more than 15 distinct sesquiterpene carbon skeletons in *Laurencia* species.[1] Among them, chamigrene appears to be the most common with over 110 naturally occurring metabolites. Interestingly, they are all derivatives of α- and β-chamigrene in a ratio close to unity.[2]

In this work we describe compounds **1**–**3** isolated from *Laurencia majuscula* (Ceramiales, Rhodomelaceae), a red alga commonly found at the southern coast of La Gomera. These compounds are representative of gomerane, a novel carbon skeleton formed by intramolecular cyclization of a β-chamigrene backbone. The name of this structure alludes to the location where the alga was collected.

Seaweeds of genus *Laurencia*, lower terrestrial plants Hepaticae (Liverworts) of genera *Bazzania*, *Mannia*, *Mylia*, and *Rebouli* as well as higher plants Cupressaceae of genera *Cupressus* and *Juniperus* have in common the exclusive ability to biosynthesize polycyclic sesquiterpene networks by internal cyclization of a chamigrene backbone. To date, marine sources have provided rhodolaurane[3] and aplydactane[4] in addition to the gomerane framework, Figure 1.

Terrestrial environments have yielded myltaylane,[5] cyclomyltaylane[6] (Liverworts),[7] as well as junicedrane,[8] and chamipinane[9] skeletons (Cupressaceae). It is interesting to highlight that all three marine skeletons, grouped as Class I, appear to evolve exclusively from cyclization of the exocyclic methylene carbon of a β-chamigrene framework and never from an α-chamigrene, despite both α- and β-chamigrene derivatives occur in *Laurencia*. On the other hand, Class II skeletons from a terrestrial environment, Figure 1, are likely to come from a chamigrenyl cation,[10] and therefore the central isoprenic methyl group remains intact.

2. Results and discussion

Vacuum flash chromatography of the acetone extract of *L. majuscula* gave two fractions from which compounds **1**–**3** were obtained by standard chromatographic procedures involving gel filtration, Si gel chromatography and HPLC.

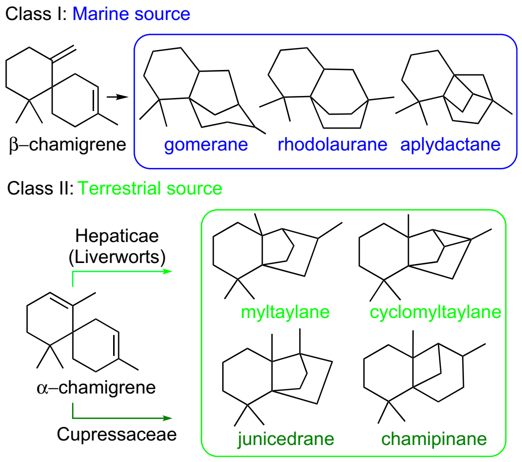

Figure 1. Class I and Class II of marine and terrestrial skeletons.

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Table 1
NMR Data of compounds **1**–**3** [500 MHz, d ppm, (*J*) Hz, $CDCl_3$ or C_6D_6]

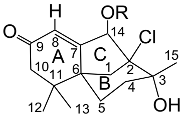
#	Compound **1**[b]			Compound **2**			Compound **3**	
	δ_H	δ_C	HMBC	δ_H	δ_C	HMBC	δ_H	δ_C
1	2.25 dd (*1.9*, *11.0*), 1.99 dd (*2.8*, *11.0*)	39.0	C-2, C-3, C-5, C-7, C-14	2.96 d (*12.4*), 2.18 dd (*3.1*, *12.4*)	43.9	C-2, C-3, C-5, C-6, C-7, C-14	2.95 d (*12.3*), 2.14 dd (*3.0*, *12.3*)	42.0
2	—	72.9		—	79.9[a]		—	79.4[a]
3	—	85.6		—	70.8[a]		—	73.6[a]
4	0.74 m, 1.45 ddd (*1.6*, *5.1*, *14.5*)	34.5	C-2, C-3	2.46 ddd (*1.8*, *4.9*, *15.9*), 1.72 ddd (*4.9*, *12.8*, *15.9*)	40.2	C-2, C-3, C-6	2.26 m 1.70 ddd (*5.4*, *12.8*, *12.8*)	39.0
5	1.56 ddd (*5.0*, *12.3*, *13.6*), 1.04 m	28.9	C-1, C-4, C-11	2.31 ddd (*4.9*, *13.3*, *13.3*), 1.98 dddd (*2.4*, *2.4*, *4.9*, *13.3*)	29.9		2.32 m 1.97 m	29.4
6	—	51.4		—	48.0		—	47.9
7	—	168.2		—	155.0		—	154.3
8	6.20 s	125.3	C-6, C-10, C-14	6.57 br s	125.0	C-6, C-14	6.57 s	125.1
9	—	197.4		—	204.6		—	199.8
10	1.93 d (*17.3*), 2.21 d (*17.3*)	48.7	C-6, C-8, C-9, C-11, C-12	2.21 d (*16.8*), 2.67 d (*16.8*)	48.9	C-9, C-11, C-13	2.21 d (*17.4*), 2.67 d (*17.4*)	49.0
11	—	37.5		—	38.4		—	38.4
12	0.55 s	24.8	C-6, C-10, C-11, C-13	1.14 s	24.3	C-6, C-10, C-11, C-13	1.13 s	24.3
13	0.74 s	22.9	C-6, C-10, C-11, C-12	0.99 s	24.0	C-6, C-10, C-11, C-12	0.99 s	23.9
14	3.69 s	73.8	C-8, C-6, C-1, C-2	—	196.3		—	198.2
15	0.96 s	25.6	C-2, C-3, C-4	1.90 s	29.7	C-2, C-3, C-4	1.70 s	27.8
OH_3	1.45 br s							
OH_{14}	1.83 d (*2.5*)							

[a] Interchangeable.

[b] NMR data recorded in C_6D_6.

Gomerone A (**1**) was a colorless oil. Its EIMS spectrum showed peaks at *m*/*z* 284/286, with relative intensities suggestive of a chlorine atom, which correspond to the empirical formula $C_{15}H_{21}O_3Cl$ $[M]^+$ (HREIMS) requiring five sites of unsaturation. Absorptions for an α,β-unsaturated carbonyl and hydroxyl groups at 1658 and 3433 cm^{-1}, respectively, were observed in the IR spectrum. Its NMR experiments acquired in C_6D_6 provided better resolution than in $CDCl_3$, avoiding overlapped signals. The ^{13}C NMR spectrum of **1**, Table 1, showed signals for 15 carbons whose multiplicities were determined from the DEPT spectral data: three methyl groups, four methylenes, two methines (one bearing a heteroatom and one olefinic), and six quaternary carbons (two bearing a heteroatom, one olefinic, and one ketone).

The ^1H NMR spectrum, Table 1, showed signals for only one olefinic proton at δ 6.20 indicative of the presence of a trisubstituted enone system. Therefore, the remaining three sites of unsaturation indicated that the molecule must be tricyclic. One proton geminal to a heteroatom at δ 3.69, eight methylene protons between δ 2.25 and 0.74, and upfield signals for three methyl groups at δ 0.55, 0.74, and 0.96 account for the remaining protons bonded to carbons. The presence of a quaternary carbon at δ 51.4, characteristic of a spiro-carbon,[2] suggested that this compound could be a chamigrene derivative and the absence of an additional methyl group expected for a sesquiterpene skeleton indicated that it has to be involved in the formation of the third cycle of the chamigrene-like skeleton. Formation of the monoacetylated derivative **1a** proved the presence of a secondary alcohol in **1**.



1: R = H
1a: R = COMe

A ^1H–^1H-COSY experiment established the presence of a single discrete spin system H_2-4–H_2-5. In the HMBC experiment, the mutual correlations of H_3-12/C-13, H_3-13/C-12 and their long-range correlations with an isolated C-10 methylene and with the quaternary carbons C-6 and C-11 secured the *gem*-dimethyl group. The correlations of H-14 with C-6 and C-8 and H-8 with C-10 established ring A whereas the H_3-15/C-2, C-3, C-4 correlations placed Me-15 at C-3 and the H_2-5/C-11 and H_2-1/C-2, C-3, C-5, C-7 correlations established ring B and the connection of both rings through the spiro-carbon C-6. The third ring of the molecule was confirmed by the long-range correlation of H-14 with C-1 and C-2 configuring the planar structure of **1**. Since the ^1H NMR singlet at δ 0.96 corresponds to a methyl group on a carbon bearing oxygen, the regiochemistry of the heteroatoms was established as depicted in **1**.

Gomerone B (**2**) and gomerone C (**3**) were colorless. Their EIMS spectra showed the same molecular ion at *m*/*z* 300/302/304 $[M]^+$ with relative intensities indicative of the presence of two chlorine atoms in the empirical formula $C_{15}H_{18}O_2Cl_2$ (HREIMS) and six sites of unsaturation for each molecule. Absorptions for α,β-unsaturated carbonyl groups were observed in their IR spectra. ^{13}C NMR data corresponding to **2** and **3**, Table 1, indicated the presence of 15 carbon atoms whose multiplicities were determined from the DEPT experiments: three methyl groups, four methylenes, only one methine (olefinic), and seven quaternary carbons (two bearing a heteroatom, one olefinic, and two ketones). Since the two oxygens given by the molecular formula of each product are ketones both molecules must be tricyclic.

Comparison of the NMR data of **2** and **3** with those of compound **1** (Table 1) showed the absence of any signal for a proton geminal to oxygen in the ^1H NMR spectra of **2** and **3** that suggested that the secondary hydroxyl group in **1** (C-14) was oxidized to a ketone in compounds **2** and **3**. ^{13}C chemical shifts of the carbonyl carbons and the presence of a single vinyl proton suggested that these ketones are involved in a dienone system. Hence, their planar structures are as depicted in **2** and **3**. These structures were corroborated by HMBC experiments. Structurally, compounds **2** and **3** contain six contiguous quaternary carbons of different nature: two sp^3 substituted by carbons, two sp^2 and two