

GRACIOSIN AND GRACIOSALLENE, TWO BROMOETHERS FROM *LAURENCIA OBTUSA*

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Key Word Index—*Laurencia obtusa*, Rhodomelaceae, Rhodophyta, marine natural products, bromo ether

Abstract—Two new bromo ethers possessing a bromo propargylic and bromo allenic moieties, graciosin and graciosallene, were isolated from the red alga *Laurencia obtusa* and their structures determined by X-ray crystallography and chemical methods.

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The secondary metabolites elaborated by the marine red algae of the genus *Laurencia* include a group of C₁₅ acetylenic cyclic ethers with a remarkable structural variation [1]. In our continuing studies on samples of this genus collected in the Canary Islands, we have reported the isolation and structural determination of several C₁₅ acetylenes [2-4]. As a part of a further investigation on the constituents of this species, we examined a specimen of *Laurencia obtusa* collected at La Graciosa (Canary Islands) in September 1985. In this paper we wish to report the structures, including the absolute configurations, of two new bromo ethers possessing a bromo propargylic and bromo allenic moieties, respectively.

RESULTS AND DISCUSSION

Graciosin (**1**) $[\alpha]_D^{25} = -14.5^\circ$ (CHCl_3 , c 0.62) was previously reported as **2** [4], without absolute configuration. However, by using 2D NMR techniques, the structure was modified to **1** and the chemical shifts were reassigned (Table 1) In addition, the absolute configuration was determined on the alcohol **3** as follows. Alkaline hydrolysis at room temperature of graciosin (**1**) with potassium carbonate in acetone gave a compound containing a 2,6-dioxabicyclo[3.3.0]octane ring system [4], but when potassium carbonate–methanol at -25° was used, the alcohol **3** was obtained. This compound yielded a crystal suitable for X-ray analysis by crystallization from *n*-hexane and the crystallographic study was carried out. Crystals were orthorhombic, space group $P2_12_12_1$, $a = 7\ 309(1)$, $b = 8\ 880(1)$, $c = 27\ 196(3)$ Å, $D_c = 1\ 54\text{ g/cm}^3$, $z = 4$. The intensity of 1080 unique reflexions was measured using graphite-monochromated Cu-K α radiation ($\lambda = 1.5418$ Å) and $\omega\ \theta$ scan in Siemens AED4 four circle computer controlled diffractometer 1057 reflexions with $I > 3\sigma(I)$ were judged observed after correction for Lorentz and polarization. The structure was solved by MULTAN 80 [5]. Full-matrix ls refinement anisotropic temperature factors for bromine and oxygen, isotropic for carbon and fixed isotropic contribution for hydrogens atoms converged at $R = 0.094$. The absolute configuration was fixed by using the 10 more relevant Bijvoet

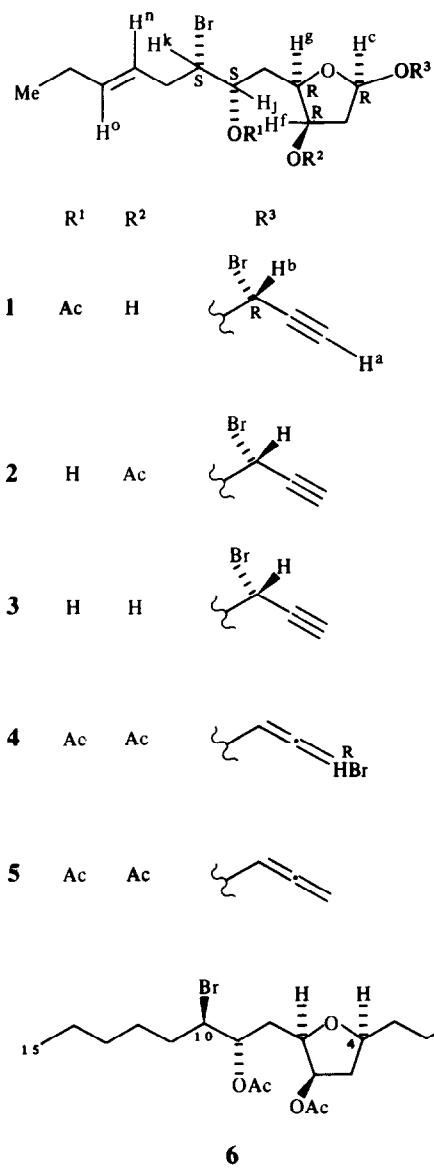


Table 1 ^1H NMR spectra of graciosin (**1**) and graciosallene (**4**) showing chemical shifts and multiplicities*†

		1	4
H-1	H ^a	2.69	<i>d</i> , $J_{ab} = 2.2$
H-2	-	--	—
H-3	H ^b	4.58	<i>dd</i> , $J_{ba} = 2.2$, $J_{bc} = 6.1$
H-4	H ^c	4.17	<i>ddd</i> , $J_{cb} = 6.1$, $J_{cd} = 4.4$, $J_{ce} = 9$
H ₂ -5	H ^d	2.45	<i>m</i>
	H ^e	2.05	<i>m</i>
H-6	H ^f	3.75	<i>ddd</i> , $J_{fc} = 3.4$, $J_{fd} = 7.4$, $J_{fg} = 3.4$
H-7	H ^g	4.27	<i>ddd</i> , $J_{gf} = 3.4$, $J_{gh} = 1.4$, $J_{gi} = 4.5$
H ₂ -8	H ^h	2.00	<i>m</i>
	H ⁱ	2.00	<i>m</i>
H-9	H ^j	5.15	<i>ddd</i> , $J_{jk} = 3.8$, $J_{ji} = 1.2$, $J_{jh} = 10.2$
H-10	H ^k	4.10	<i>ddd</i> , $J_{kj} = 3.8$, $J_{km} = 5.5$, $J_{ki} = 6.1$
H ₂ -11	H ^l	2.5	<i>m</i>
	H ^m	2.5	<i>m</i>
H-12	H ⁿ	5.42	<i>ddd</i> , $J_{nl} = 5.4$, $J_{no} = 15.5$, $J_{nm} = 5.4$
H-13	H ^o	5.54	<i>ddd</i> , $J_{on} = 15.5$, $J_{op} = 7.1$, $J_{oq} = 6.2$
H ₂ -14	H ^p	2.02	<i>m</i>
	H ^q	2.02	<i>m</i>
H ₃ -15	H ^r	0.96	<i>t</i> , $J_{rp} = 7.5$, $J_{rq} = 7.5$
	-OC(O)Me	2.09	s(3H)
			6.06
			<i>dd</i> , $J_{ab} = 5.7$; $J_{ac} = 1.6$
			5.47
			<i>dd</i> , $J_{ba} = 5.7$, $J_{bc} = 7$
			4.48
			<i>ddd</i> , $J_{ca} = 1.6$, $J_{cb} = 7$, $J_{cd} = 3.8$, $J_{ce} = 15.8$
			2.03
			2.50
			<i>m</i>
			5.27
			<i>ddd</i> , $J_{fg} = 4.2$, $J_{fd} = 2$, $J_{fe} = 8$
			3.86
			<i>ddd</i> , $J_{gl} = 4.2$, $J_{gh} = 3$, $J_{gi} = 9$
			2.1
			<i>m</i>
			2.1
			<i>m</i>
			5.12
			<i>ddd</i> , $J_{jk} = 3.2$, $J_{jh} = 4.5$, $J_{ji} = 8$
			4.02
			<i>ddd</i> , $J_{kj} = 3.2$, $J_{kl} = 5.2$, $J_{km} = 8.5$
			2.06
			<i>m</i>
			2.53
			<i>m</i>
			5.38
			<i>ddd</i> , $J_{no} = 15.2$, $J_{nm} = 6$, $J_{nl} = 6$
			5.55
			<i>ddd</i> , $J_{on} = 15.2$, $J_{op} = 7$, $J_{oq} = 7$
			2.05
			<i>m</i>
			2.05
			<i>t</i> , $J_{rq} = 7.4$, $J_{rp} = 7.4$
			s(6H)
			2.07

* The spectra were recorded at 200 MHz in CDCl_3 solution

Chemical shifts are reported in ppm relative to TMS (0)

† COSY 2D NMR data support the proton assignments

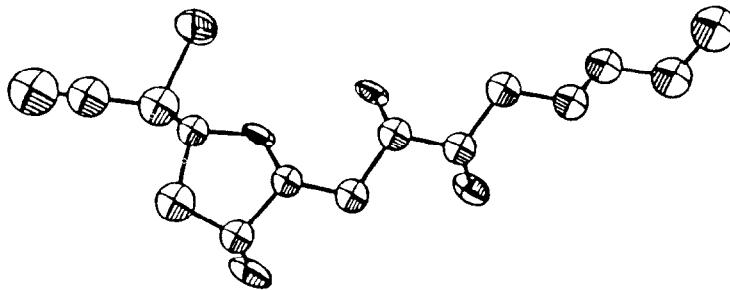


Fig. 1 ORTEP drawing of graciosin (**1**) showing the right enantiomer

pairs with $\Delta F_c > 1.3$ which are in the ranges of: $0.2 \leq \sin \theta / \lambda \leq 0.5$, 15 F_o 60 and $F_o = 10\sigma(F_o)$. The averaged Bijvoet differences are 0.62 for the right enantiomer vs 0.54 for the wrong one [6]. Figure 1 shows the structure with the right enantiomer. Atomic co-ordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

Graciosallene (**4**) was isolated in small amount as an oil, $[\alpha]_D^{25} = -83.3^\circ$ (CHCl_3 , $c = 0.018$) In the IR spectrum a band at 1950 cm^{-1} first suggested the presence of an allene function. The ^1H NMR spectrum (CDCl_3) δ 5.47 (*dd*, $J = 7.08$ and 5.76 Hz), 6.06 (*dd*, $J = 1.65$ and 5.76 Hz) (Table 1) and the fragment ions in the mass spectrum at m/z 375, 377 [$\text{M} - \text{C}_3\text{H}_2\text{Br}$]⁺ showed the presence of a bromo allenic side chain. The structure and absolute configuration of **4** were established by the following chemical method. Treatment of **3** with zinc-acetic acid in ethanol at 0° yielded compound **5**. This compound was treated with acetic anhydride-pyridine at room temp

and hydrogenated over PtO_2 in diethyl ether to give **6**. These results indicated that the stereochemistry at C-4, C-6, C-7, C-9 and C-10 in **4** should be *R*, *R*, *R*, *S* and *S*-configurations, respectively. Finally, in view of the strong negative rotation of graciosallene, the absolute configuration of the bromo allene moiety in **4** could be assigned as *R* by the application of Lowe's rule [7].

EXPERIMENTAL

Mps uncorr ^1H and ^{13}C NMR spectra were recorded at 200 MHz

Collection, extraction and chromatographic separation *Laurencia obtusa* was collected in Sept 1985 using SCUBA (-3 to -10 m) in Graciosa Island. A voucher specimen was deposited in the Departamento de Biología Vegetal (Universidad de La Laguna, Tenerife, Spain). The alga was air-dried and ground in a Wiley mill to a 1 mm particle size. The dried alga (4 kg) was extracted with Et_2O (2 l) and EtOAc (2 l). The combined extracts were evapd and the crude extract chromatographed on a silica

gel column using a mixture of *n*-hexane-EtOAc of increasing polarity as eluent. The *n*-hexane-EtOAc (3:2) eluate yielded a dark green oil which was chromatographed on a Sephadex LH-20 column using *n*-hexane-CHCl₃-MeOH (2:1:1) as eluent, yielding a colourless oil which contained a mixture of graciosin (1) and graciosallene (4). Prep. TLC (*n*-hexane-EtOAc, 4:1) gave 350 mg of pure 1 and 30 mg of pure 4.

Graciosin (1) Oil, $[\alpha]_D^{25} = -14.5^\circ$ (CHCl₃, *c* 0.62). The physical and spectroscopic data (TLC, GLC, IR, NMR, MS) were identical with those reported previously [4].

Compound 3 To a soln of 30 mg of graciosin (1) in 10 ml of MeOH cooled at -25° was added excess of K₂CO₃ (15 mg) and the mixture stirred for 6 hr. The mixture was filtered off, the solvent evapd and the residue crystallized from *n*-hexane to give 24 mg of 3, colourless crystals, mp 96°, IR ν_{max} cm⁻¹ 3500, 3300, 2950, 2100, 1435, 1370, 1240 and 1100. ¹H NMR (CDCl₃): δ 0.91 (3H, *t*, *J* = 7.3 Hz), 2.63 (1H, *d*, *J* = 2.4 Hz); 3.8-4.03 (3H, *m*); 4.19 (2H, *m*), 4.57 (1H, *dd*, *J* = 2.4 and 6.4 Hz), 5.36 (1H, *ddd*, *J* = 5.4, 5.4 and 15 Hz), 5.53 (1H, *ddd*, *J* = 6.2, 7 and 15 Hz). MS *m/z* (rel int.) 329, 331 [M-Br]⁺ (4), 311, 313 [M-Br-H₂O]⁺ (15); 273, 275 [M-C₃H₂Br-H₂O]⁺ (3).

Graciosallene (4) Oil, $[\alpha]_D^{25} = -83.3^\circ$ (CHCl₃, *c* 0.018) IR ν_{max} cm⁻¹ 3000, 1950, 1735, 1730 and 1370. ¹H NMR (See Table 1), MS *m/z* (rel. int.) 375, 377 [M-C₃H₂Br]⁺ (2), 353, 355 [M-HOAc-Br]⁺ (1), 255, 257 [M-C₃H₂Br-2HOAc]⁺ (7).

Compound 5 To a soln of 10 mg of 3 in 1 ml of EtOH at 0°, was added 10 mg of Zn powder and 50 μ l of HOAc. The mixture was stirred for 1 hr, filtered off and the solvent evapd to give 6 mg of 5; oil, $[\alpha]_D^{25} = -5.5^\circ$ (CHCl₃, *c* 0.4). IR ν_{max} cm⁻¹ 3660, 3565, 1950, 1600, 1570 and 1260. ¹H NMR (CDCl₃): δ 0.98 (3H, *t*, *J* = 7.4 Hz); 4.3 (1H, *m*); 4.5 (1H, *m*), 4.8 (1H, *ddd*, *J* = 1.6, 2.7 and 6.6 Hz), 5.3 (1H, *ddd*, *J* = 6.55, 6.57 and 12.3 Hz); 5.42 (1H, *ddd*, *J* = 5.4, 5.4 and 15.5 Hz); 5.54 (1H, *ddd*, *J* = 6.2, 7 and 15.5 Hz); MS at *m/z* (rel. int.) 273, 275 [M-C₃H₃]⁺, 255, 257 [M-C₃H₃-H₂O]⁺.

Compound 6 Compound 5 (5 mg) was treated with

Ac₂O-pyridine at room temp to give the diacetate. The resulting crude compound was dissolved in 1 ml of dry Et₂O and a catalytic amount of PtO₂ was added. The mixture was stirred under H₂ for 2 hr, the soln filtered and the Et₂O evapd to give, after chromatography on silica gel, the pure compound 6, oil, $[\alpha]_D^{25} = -18.6^\circ$ (CHCl₃, *c* 0.5). IR ν_{max} 1735, 1730 cm⁻¹. ¹H NMR (CDCl₃): δ 0.89 (3H, *t*, *J* = 6.7 Hz), 0.92 (3H, *t*, *J* = 7.1 Hz), 2.03 (3H, *s*), 2.05 (3H, *s*), 3.73 (2H, *m*), 4.07 (1H, *ddd*, *J* = 4.3, 3.4 and 8.7 Hz), 5.15 (1H, *m*), 5.21 (1H, *m*). MS *m/z* (rel int.) 341 [M-Br]⁺ (2), 300, 302 [M-2HOAc]⁺ (7), 257, 259 [M-2HOAc-C₃H₃]⁺ (7), 221 [M-2HOAc-Br]⁺ (100).

Catalytic hydrogenation of graciosallene (4) Hydrogenation of graciosallene 4 in the same manner as described above for 5 gave in 90% yield a compound which was identified as 6 by comparison of the $[\alpha]_D$ and spectroscopic data with those of an authentic sample.

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REFERENCES

- 1 Erickson, K. L. (1983) in *Marine Natural Products* (Scheuer, P. J., ed) Vol V, pp. 132-257. Academic Press, New York
- 2 González, A. G., Martín, J. D., Norte, M., Martín, V. S., Pérez, R. and Ruano, J. Z. (1982) *Tetrahedron* **38**, 1009
- 3 González, A. G., Martín, J. D., Norte, M., Pérez, R., Rivera, P., Ruano, J. Z., Rodríguez, M. L., Perales, A. and Fayos, J. (1983) *Tetrahedron Letters*, **24**, 4143
- 4 González, A. G., Martín, J. D., Norte, M., Rivera, P. and Ruano, J. Z. (1984) *Tetrahedron* **40**, 3443
- 5 Main, P., Hull, S. E., Lessinger, L., Germain, G., Declerq, J. P. and Woolfson, M. M. (1980) University of York, England
- 6 Fayos, J., Martínez-Ripoll, M. (1980), CONFAB, Instituto Rocasolano, CSIC Madrid (Spain)
- 7 Lowe, G. (1965) *Chem Commun* 411