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TETRAHEDRON

Novel marine polyethers

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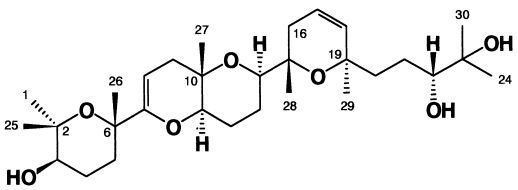
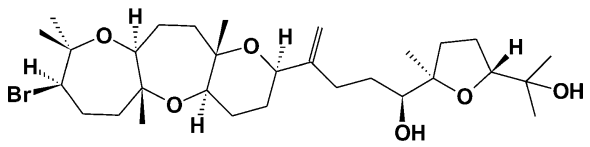
Abstract—The red seaweed *Laurencia viridis* is a rich source of secondary metabolites derived from squalene. Novel polyethers, clavidol **4**, 3-*epi*-1111-dehydrothyrsiferol **5**, and lactodehydrothyrsiferol **6**, have been isolated and their structures established by spectroscopical methods. The relative stereochemistry proposed for these compounds is based on ROESY and NOEDIFF data. Possible biogenetic pathways are also discussed.

Research into secondary metabolites from marine organisms has produced a host of compounds with unique structural features and promising biological activities.[1] Compounds with a polyether moiety, particularly polyether squalene-derived triterpenes, are prime examples of such marine natural products. These metabolites have been found mainly in red algae of the genus *Laurencia* and in sponges of the *Axinellidae* family.[2] Analysis of the biological activity of these compounds has been focused principally on their potent cytotoxic effects,[3] although other antiviral and inhibitory activities on protein phosphatase type 2A have also been reported.[4,5]

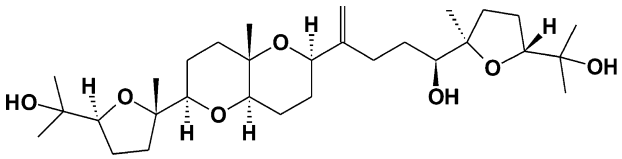
This type of cytotoxic compounds have been studied in the course of our research into the secondary metabolites of *Laurencia* species[6–8] and recently we reported the identification of several new examples such as martiriol **1**, dioxepandehydrothyrsiferol **2** and pseudodehydrothyrsiferol **3**, isolated from specimens of *Laurencia viridis* collected around the Canary Islands.[9]



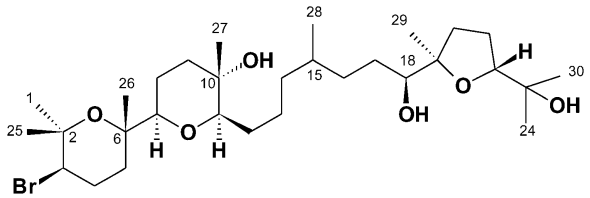
1 Martiriol



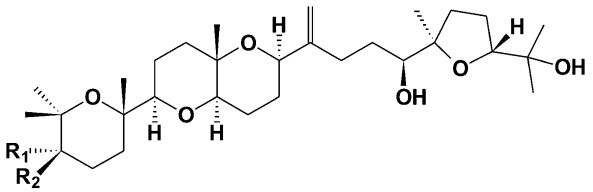
2 Dioxepandehydrothyrsiferol



3 Pseudodehydrothyrsiferol



4 Clavidol



5 3-*epi*-Dehydrothyrsiferol; R_1=Br; R_2=H
9 Dehydrothyrsiferol; R_1= H; R_2=Br

Keywords: polyethers; terpenoids; squalene; marine metabolites.

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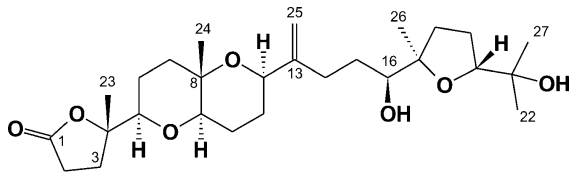
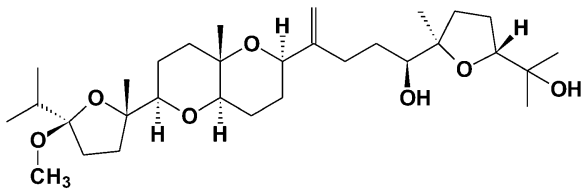
PII: S0040-4020(02)00912-2

Table 1. ^{13}C NMR data for compounds **3**–**5** and **7**–**9**

Carbon	3	4	5	7	8	9
1	24.0	31.6	27.9	17.8	20.9	31.0
2	70.6	75.1	74.4	29.5	76.6	74.9
3	86.7	59.2	59.4	112.8	84.9	59.0
4	26.3	28.3	26.5	34.4	27.5	28.2
5	35.2	37.0	30.8	32.6	31.7	37.1
6	84.0	74.9	73.2	84.9	84.2	74.4
7	84.0	85.9	82.9	79.0	83.9	86.7
8	24.5	23.2	22.7	24.7	24.7	22.9
9	38.7	38.7	38.2	38.9	38.8	38.7
10	72.8	70.1	73.0	72.8	72.8	72.9
11	78.9	75.5	78.8	78.6	78.7	78.9
12	21.8	20.0	21.3	21.7	21.9	21.8
13	26.4	27.7	26.1	26.3	26.3	26.6
14	72.5	28.9	72.0	72.6	72.6	72.5
15	151.3	38.7	150.8	151.3	151.3	151.3
16	29.7	27.3	29.1	29.9	29.7	29.9
17	29.9	27.0	29.4	30.1	30.0	30.3
18	76.2	74.5	75.8	76.5	76.2	76.2
19	86.1	84.9	86.3	86.1	86.1	86.0
20	31.6	32.8	31.2	31.7	34.4	31.7
21	26.5	26.6	26.0	26.6	26.6	26.3
22	87.6	87.0	87.0	87.6	87.6	87.6
23	70.4	71.9	70.7	70.5	70.4	70.5
24	23.9	24.3	23.2	24.0	24.0	24.0
25	27.5	23.6	28.9	17.8	20.9	23.6
26	22.7	20.1	19.9	23.8	22.8	20.1
27	19.4	30.9	19.1	19.6	19.5	19.4
28	109.9	16.9	109.4	109.9	109.9	109.8
29	23.7	24.3	22.5	23.8	23.8	23.7
30	27.7	29.3	27.2	27.7	21.7	27.7
CH_3O–				47.2	49.8	



6 Lactodehydrothyrsiferol



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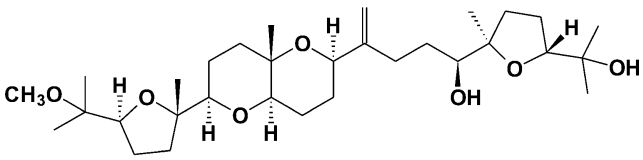

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Table 2. ^{1}H NMR data for compounds **4**, **5**, **7** and **8**

Carbon	Clavidol **4**			3-*epi*-Dehydrothyrsiferol **5**			**7**			**8**		
1	1.23	s		1.31	s		0.88	d	6.9	1.09	s	
2							2.20					
3	3.83	dd	4.0; 12.3	4.09	dd	3.3; 7.6				3.91	dd	6.1; 8.8
4	2.08/2.22			2.12/2.20			1.65/2.20			1.70/1.85		
5	1.47/1.75			1.52/2.12			1.80/2.07			1.58/2.10		
6												
7	3.04	dd	2.5; 11.5	3.43	dd	1.8; 10.8	3.50	d	10.0	3.36	dd	2.7; 11.5
8	1.45/1.75			1.56/1.79			1.57/1.65			1.48/1.66		
9	1.57/1.77			1.55/1.80			1.58/1.83			1.56/1.80		
10												
11	3.95	dd	8.0; 9.8	3.46	dd	5.9; 10.0	3.45	dd	5.4; 11.4	3.46	dd	5.5; 11.3
12	1.36/1.88			1.62/1.83			1.64/1.84			1.63/1.84		
13	1.55/2.14			1.84/2.08			1.84/2.09			1.85/2.09		
14	1.25 (2H)			4.27	dd	4.2; 7.6	4.29	dd	3.9; 7.6	4.28	dd	3.4; 7.1
15	1.35											
16	1.39/1.53			2.19/2.45			2.18/2.46			2.18/2.46		
17	1.20/1.54			1.46/1.63			1.46/1.64			1.46/1.65		
18	3.76	dd	2.2; 13.0	3.51	dd	1.5; 10.6	3.53	dd	1.5; 9.5	3.52	dd	1.2; 10.3
19												
20	1.50/2.11			1.56/2.12			1.58/2.10			1.59/2.05		
21	1.79 (2H)			1.85 (2H)			1.85 (2H)			1.85 (2H)		
22	3.73	dd	6.0; 10.0	3.74	dd	5.7; 10.2	3.76	dd	6.0; 10.0	3.76	dd	6.0; 10.0
23												
24	1.10	s		1.11	s		1.13	s		1.12	s	
25	1.37	s		1.33	s		0.92	d	6.9	1.14	s	
26	1.17	s		1.12	s		1.24	s		1.15	s	
27	1.24	s		1.22	s		1.25	s		1.25	s	
28	0.82	d	6.4	4.86/5.03	bs/bs		4.88/5.05	bs/bs		4.88/5.05	bs/bs	
29	1.10	s		1.12	s		1.14	s		1.13	s	
30	1.24	s		1.20	s		1.21	s		1.21	s	
CH_3O–							3.19	s		3.25	s	
OH-18										2.38	s	

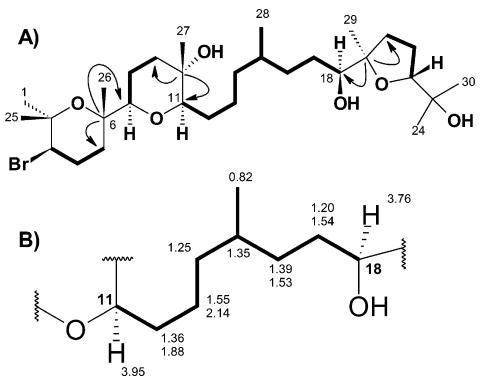


Figure 1. (A) Selected HMBC correlations and partial structures in clavidol **4** obtained from COSY and TOCSY spectra. (B) ^{1}H NMR assignment for fragment C-11→C-18.

Complementing this work, we now report the isolation of three more new compounds, clavidol **4**, 3-*epi*-dehydrothyrsiferol **5** and lactodehydrothyrsiferol **6**, together with probably artefacts, compounds **7** and **8**. The structures were established from their spectral data, and the relative stereochemistries were proposed on the basis of ROESY, NOEDIFF data and biogenetic considerations.

Clavidol **4** was isolated as an amorphous white solid, $[\alpha]_D^{25}$=+1.1 (*c* 0.18, $CHCl_3$) and its molecular formula was established as $C_{30}H_{55}O_6Br$ by FAB-HRMS. ^{13}C and DEPT NMR spectra of **4** revealed the presence of eight methyl, 11 methylene and six methine groups, as well as five oxygenated quaternary carbon centres (Table 1). Comparison of the ^{1}H NMR spectral data of compound **4** with those reported for the derivatives of this series, enabled the methine signals at δ_H 3.95, 3.83, 3.76, 3.73 and 3.04 in the low field region (Table 2)[6–9] to be assigned to H-11, H-3, H-18, H-22 and H-7, respectively. COSY and TOCSY correlation experiments showed the presence of four substructures of clavidol **4**, located at fragments C-3→C-5, C-7→C-9, C-11→C-18 and C-20→C-22 (Fig. 1(A)).

The fragment C-11→C-18 presented unusual modifications, the most important being the absence of olefinic protons and the presence of a signal corresponding to a secondary methyl group at δ_H 0.82 (H_3-28, d, *J*=6.4 Hz). This fragment was constructed from the methine H-11 (δ_H 3.95, dd, *J*=8.0 and 9.8 Hz) which is coupled to the methylene H_2-12 (δ_H 1.36 and 1.88) and these protons proved to be connected with H_2-13 (δ_H 1.55 and 2.14). H_2-13 in its turn was connected with H_2-14 (δ_H 1.25); the methine H-15 (δ_H 1.35) with H_2-14, H_2-16 (δ_H 1.39 and 1.53) and H_3-28 (δ_H 0.82); H_2-16 with H_2-17 (δ_H 1.20 and 1.54); and finally H_2-17 with H-18 (δ_H 3.76, dd, *J*=2.2 and 13.0 Hz) (Fig. 1(B)). Compared with dehydrothyrsiferol **9**,[10] in accordance with these data, this fragment is characterized by the absence of one of the tetrahydropyran rings, hitherto always present in this series of compounds. The correlations observed in the HMBC experiment between the quaternary carbon C-6 (δ_C 74.9) and H_2-5 (δ_H 1.47 and 1.75), H-7 (δ_H 3.04, dd, *J*=2.5 and 11.5 Hz) and H_3-26 (δ_H 1.17); between C-10 (δ_C 70.1) and H-11, H_2-9 (δ_H 1.57 and 1.77) and H_3-27 (δ_H 1.24); and between C-19 (δ_C 84.9) and H-18, H_2-20 (δ_H 1.50 and 2.11) and H_3-29 (δ_H 1.10) made it possible to connect the partial structures supporting the planar structure shown in Fig. 1(A). The relative configurations of the stereocentres of the carbons C-3, C-6, C-7, C-10, C-11, C-18, C-19 and C-22 were established as identical to those found in the thyrsiferol series on the basis of correlations observed in the ROESY experiment as well as through interpretation of NMR coupling constant data (Fig. 2).[6–8] This compound is the first example in this series without the trans-fused oxane system.

The next compound, 3-*epi*-dehydrothyrsiferol **5**, was an isomer of dehydrothyrsiferol **9**, as shown by its molecular formula, $C_{30}H_{51}O_6Br$. Interpretation of the 2D NMR spectra (Tables 1 and 2) readily demonstrated that the sole difference between the two was the stereochemistry of the bromine atom at carbon C-3. Comparison of the coupling constants of proton H-3 in compound **5** (δ_H 4.09, dd, *J*=3.3

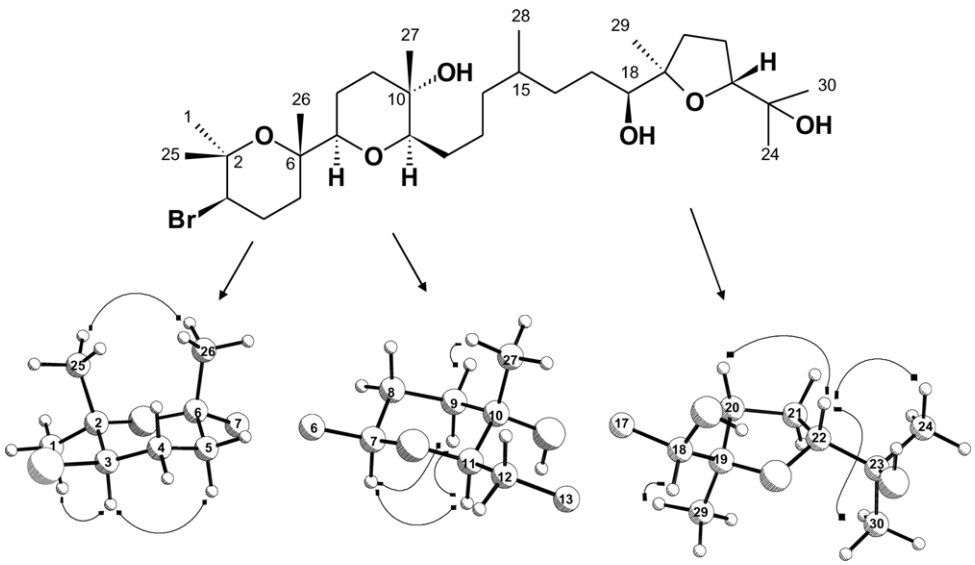


Figure 2. Spatial disposition and most significant NOE correlations in clavidol **4**.

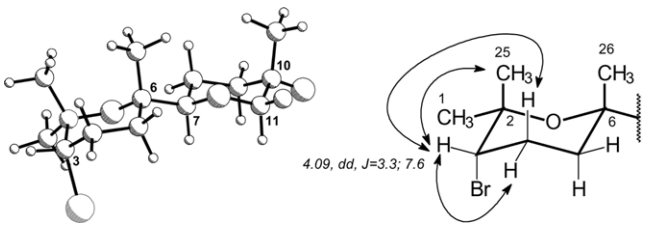


Figure 3. Lowest energy conformation and significant NOE correlations for ring A in compound **5**.

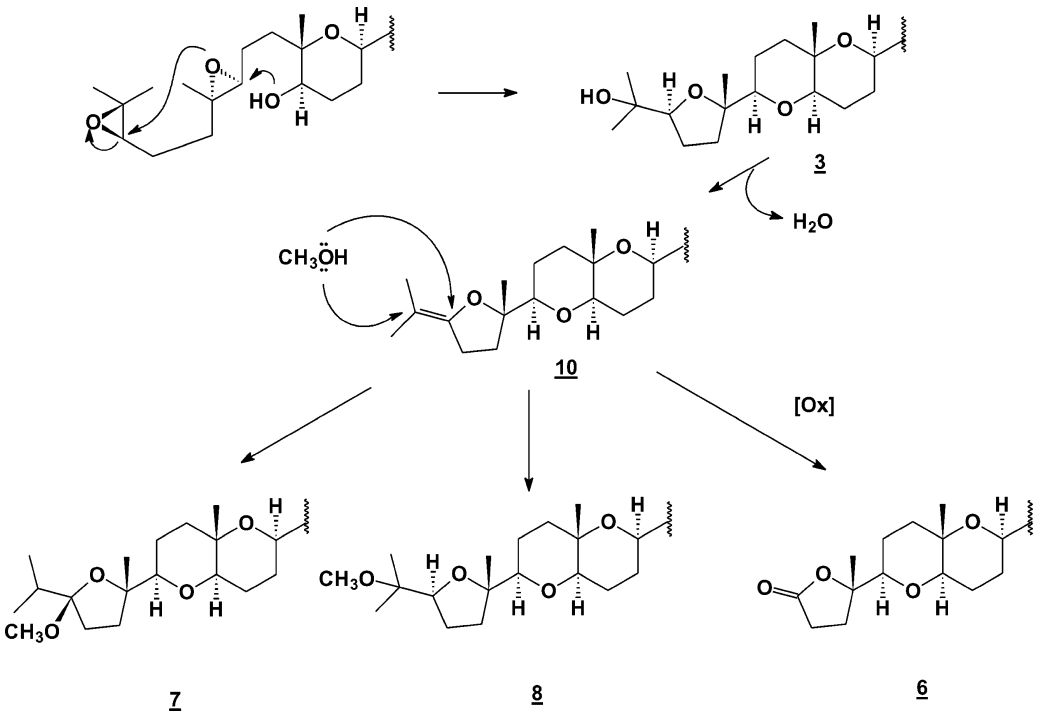
Table 3. ^{13}C and ^{1}H NMR data for compound **6**

Carbon		Lactodehydrothyrsiferol **6**		
1	177.4			
2	29.7	2.50/2.68		
3	29.1	1.75/2.46		
4	87.1			
5	82.7	3.53	dd	1.7; 11.8
6	24.3	1.49/1.67		
7	38.3	1.63/1.87		
8	72.2			
9	78.8	3.46	dd	5.6; 11.7
10	21.6	1.60/1.88		
11	26.2	1.85/2.06		
12	72.7	4.28		
13	151.1			
14	29.3	2.18/2.47		
15	29.8	1.50/1.65		
16	76.2	3.53	dd	1.5; 11.7
17	86.1			
18	31.6	1.60/2.13		
19	26.6	1.87 (2H)		
20	87.7	3.76	dd	6.6; 10.6
21	70.5			
22	24.0	1.13	s	
23	23.3	1.34	s	
24	19.5	1.26	s	
25	110.0	4.89/5.05	bs/bs	
26	23.8	1.14	s	
27	27.7	1.22	s	

and 7.6 Hz) and **9** (δ_H 3.89, dd, J=4.1 and 12.6 Hz) supported this conclusion, indicating the axial disposition of the bromine atom shown in Fig. 3 and, therefore, that the relative stereochemistry at carbon C-3 would be S^* for 3-*epi*-dehydrothyrsiferol **5**.

Lactodehydrothyrsiferol **6**, was also isolated as a white solid $[\alpha]_D^{25}$=+4.3 (*c* 0.21, $CHCl_3$). The absorption at ν_{max} 1771 cm^{-1} in the IR spectrum suggested the presence of a γ-lactone moiety. This fact, in conjunction with the analysis of the NMR spectra and the quasi-molecular ion observed in its HRMS at *m/z* 1111 481.3178 (Calcd 481.3165, $C_{27}H_{45}O_7$ [MH^+]), pointed to this lactone having been formed by oxidative degradation of the original squalene skeleton (Table 3). Comparison of the ^{1}H and ^{13}C NMR spectral data of this compound with those of the other metabolites of the series showed no signals for the protons H_3-1, H_3-25 and H-3 and the carbons C-1, C-2 and C-25, as well as a signal for a carbonyl C atom of a ester carbonyl at δ_C 177.4. The COSY experimental results showed the presence of a system formed by two diastereotopic methylenes centred at δ_H 2.50 and 2.68, and at δ_H 1.75 and 2.46, which were correlated in the HSQC experiment with the carbons at δ_C 29.7 and 29.1, respectively. These methylenes were identified as C-2 and C-3 on the basis of the correlations observed in the HMBC experiment. Thus, the carbon C-1 (δ_C 177.4) showed a correlation with H_2-2 and H_2-3; the correlations between the carbon C-4 (δ_C 87.1) and the protons H_2-2, H_2-3, H-5 (δ_H 3.53, dd, J=1.7 and 11.8 Hz) and H_3-23 (δ_H 1.34) confirmed the γ-lactone moiety on ring A. The proposed structure for this compound, including the same relative configuration as that found in the thyrsiferol series, was consistent with the correlations observed in the ROESY experiment.

From a biogenetic point of view, this lactone could be



Scheme 1. Plausible biogenetic pathway for compounds **3**, **6**–**8**, which involves the common intermediate **10**.

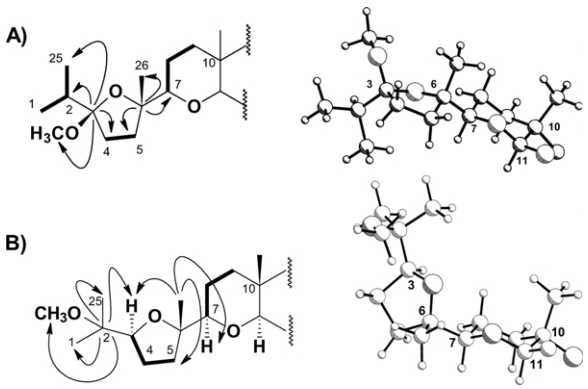
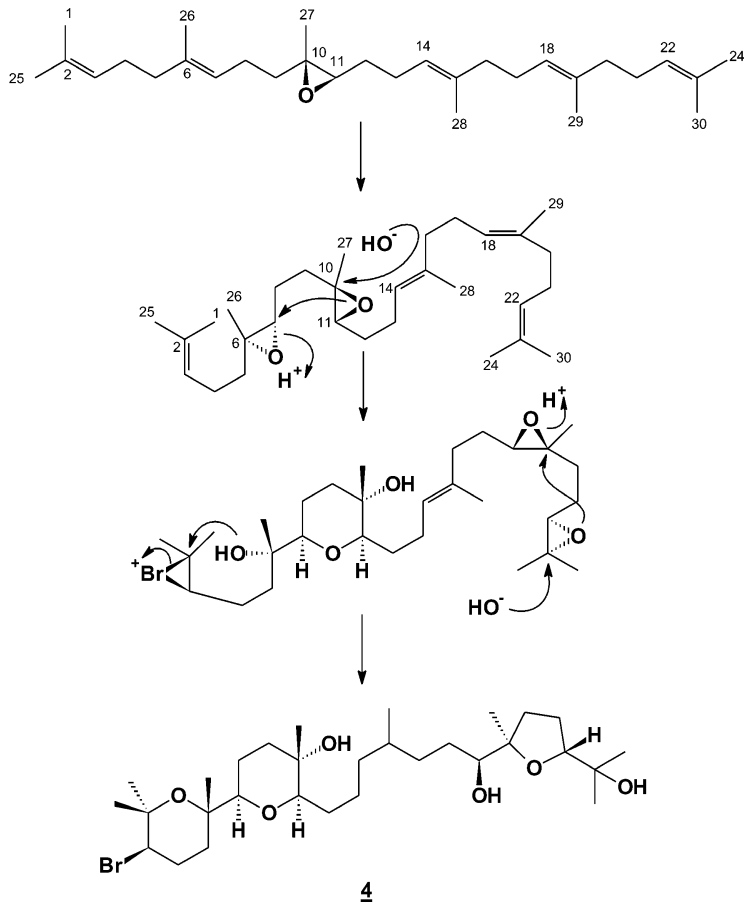


Figure 4. Partial structures and HMBC correlations for fragment C-1⟶C-7 for compounds **7** (A) and **8** (B).

considered as a derivative of pseudodehydrothyrsiferol **3** after dehydration and oxidative fragmentation of the double bond (Scheme 1). The isolation of compounds **7** and **8** reinforces this hypothesis as they can be attributed to the same biogenetic pathway. Compound **7** was isolated as an amorphous white solid, $[\alpha]_D^{25}=+3.6$ (c 0.03, $CHCl_3$), and analysed as $C_{31}H_{54}O_7$ by HRMS. The NMR data showed that **7** was almost identical with **3** except for the presence of an isopropyl (H_3-1, δ_H 0.88, d, J=6.9 Hz; H_3-25, δ_H 0.92, d, J=6.9 Hz; H-2, δ_H 2.20, m) and a methoxy (CH_3O-, δ_H 3.19, s) moiety, instead of an isopropyl alcohol and the methine H-3, respectively. Taking these data into account, it may be concluded that these compounds must be differentiated around ring A (Tables 1 and 2). The connectivities observed in COSY and HSQC experiments made it possible to assign the carbons of this fragment as follows: δ_C 17.8 (C-1), 17.8 (C-25), 29.5 (C-2), 34.4 (C-4), 32.6 (C-5), 23.8 (C-26) and 47.2 (CH_3O-). The quaternary centres C-3 and C-6 were identified at δ_C 112.8 and 84.9, respectively, based on their numerous HMBC correlations such as those from H_3-1, H_3-25, H-2, H_2-4 (δ_H 1.65 and 2.20) and the methoxy group to C-3; and from H_2-5 (δ_H 1.80 and 2.07), H-7 (δ_H 3.50) and H_3-26 (δ_H 1.24) to C-6. The relative configurations of the stereocentres in **7** were also assigned on the basis of correlations observed in the ROESY spectrum. In particular, H_3-26 showed a ROE correlation with the methoxy group, consistent with the proposed relative configuration as R^* at carbon C-3 (Fig. 4(A)).

A similar situation was observed on the basis of its mass spectrum and its NMR spectral data for compound **8**, which proved to be an isomer of compound **7** (Tables 1 and 2). The only significant variations between the two compounds were the downfield shift of H-3 (δ_H 3.91, dd, J=6.1 and 8.8 Hz) and the presence of the signal at δ_H 3.25 (CH_3O-, s), suggestive of the presence of a methoxyl group at carbon C-2. This assignment was confirmed by the HMBC correlations to the carbon C-2 (δ_C 76.6) from its neighbouring protons at H_3-1 (δ_H 1.09, s), H_3-25 (δ_H 1.14, s), H-3 and from those of the methoxy group (Fig. 4(B)). The relative stereochemistry at carbon C-3 in this compound was established as S^* in agreement with the cross peak observed in the ROESY experiment between protons H-3



Scheme 2. Probable biogenetic pathway for compound **4**.

and H-5α (δ_H 2.10) and the absence of ROE correlation with the protons H_3-26.

Biogenetic considerations suggest that polyoxygenated squalene-derived ethers isolated from *Laurencia* species may have (10*R*,11*R*)-squalene 10,11-epoxide as a common precursor, evolving through the main intermediate (6*S*,7*S*,10*R*,11*R*,14*R*,15*R*,18*S*,19*S*)-squalene tetraepoxide.[2,9] We have argued elsewhere against the classic biogenetic proposal that the process should occur through a sequential rather than a concomitant cyclisation of the polyepoxy-derivative and had proposed the primary formation of the B–C ring system starting with enzymatic protonation to (6*S*,7*S*)-epoxide followed by cyclisation and hydroxylation at C-15 for compound **3**, pseudodehydrothyrsiferol. Ring A should be formed by protonation to (2,3*R*)-epoxide and reaction with the hydroxy group at C-6 on the C-3 position which, after dehydration, evolves to **10** as a common precursor for **6**–**8**. Thus, compounds **7** and **8** could be generated in the extraction process with methanol/chloroform, whereas the metabolite **6**, lactodehydrothyrsiferol, could be formed by an oxidative degradation process from **10** (Scheme 1).

The most interesting compound in the present report, from a biogenetic viewpoint, is clavidol **4**. The biosynthetic proposal for this metabolite starts from (6*S*,7*S*,10*R*,11*R*)-squalene diepoxide instead of the squalene-tetraepoxide. The formation of ring B could be rationalised by enzymatic protonation to (6*S*,7*S*)-epoxide followed by formation of ring A, as shown in the pathway in Scheme 2. Finally, the remaining tetrahydrofuran ring, common for the thyrsiferol series, is possibly biosynthesised from the diepoxide fragment 18*S*, 19*S*, 22*R*, by protonation to (18*S*, 19*S*)-epoxide followed by hydroxylation at C-23.[2,9]

1. Experimental

1.1. General methods

Optical rotations were determined on a Perkin–Elmer 241 polarimeter. IR spectra were measured on a Bruker IFS55 spectrometer. The NMR spectra were obtained with a Bruker 400 Advance instrument. Chemical shifts are reported relative to TMS and coupling constants are given in Hz. HRMS were performed on a VG AutoSpec FISON spectrometer. HPLC was carried out with a LKB 2248 system equipped with a differential diffractometer detector. Silica gel CC and TLC were performed on Silica gel Merck 60 G. TLC plates were visualised by spraying with H_2SO_4/H_2O/AcOH (1:4:20) and heating.

1.2. Plant material

Seeds of *L. viridis* were collected in April 1999 in the intertidal zone at Callao Salvaje, Paraiso Floral, El Palmar (Tenerife, Canary Islands). Dried material from the sterile plants, sporophytes and gametophytes was filed at TFC Phyc. (Herbario de la Universidad de La Laguna, Departamento de Biología Vegetal, Botánica, Tenerife).

1.3. Extraction

The dried alga (3 kg) was extracted with $CHCl_3$/MeOH (1:1) at room temperature. The combined extracts were evaporated in vacuo to leave a dark-green viscous oil (39.0 g, 1.3% dry weight).

1.4. Chromatographic separation

The crude extract was chromatographed on a silica gel column eluted with increasing concentrations of EtOAc in *n*-hexane. Fractions with polarity EtOAc/*n*-hexane 2:3 and 3:2 were collected and those exhibiting similar TLC profiles were combined to give different fractions in order of increasing polarity. Each was rechromatographed on a Sephadex LH-20 column using *n*-hexane/$CHCl_3$/MeOH (2:1:1) and LiChropred RP-18, with MeOH/H_2O (17:3) $CHCl_3$, as the respective eluents. Final purification was carried out by HPLC reverse phase chromatography on μ-Bondapak C-18 column using MeOH/H_2O in different proportions affording the pure new compounds clavidol **4** (2.3 mg), *epi*-dehydrothyrsiferol **5** (1.8 mg), lactodehydrothyrsiferol **6** (2.1 mg), **7** (1.5 mg), and **8** (1.4 mg).

1.4.1. Compound 4. Amorphous white solid; $[\alpha]_D^{25}$=+1.1 (*c* 0.18, $CHCl_3$); IR ν_{max} ($CHCl_3$): 2955, 2922, 2752, 1736 and 1654 cm^{-1}; FAB-HRMS: 615.3126 (Calcd 615.3059, $C_{30}H_{55}O_6{}^{81}Br$ Na $[M^+ + Na]$), 592.3167 (Calcd 592.3161, $C_{30}H_{55}O_6{}^{81}Br$ $[M^+]$); FAB-MS (NBA) *m/z*: 615, 613, 592, 590, 533, 531; ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) See Tables 1 and 2.

1.4.2. Compound 5. Amorphous white solid; $[\alpha]_D^{25}$=+3.9 (*c* 0.18, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3438, 2978, 1644, 1455, 1374 and 1320 cm^{-1}; FAB-HRMS: 588.2869 (Calcd 588.2848, $C_{30}H_{51}O_6$ ^{81}Br $[M^+]$); MS *m/z*: 588, 586, 529, 329, 279, 176, 143; ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) See Tables 1 and 2.

1.4.3. Compound 6. Amorphous white solid; $[\alpha]_D^{25}$=+4.3 (*c* 0.21, $CHCl_3$); IR ν_{max} ($CHCl_3$): 2924, 2852, 2776, 2712, 1771, 1457 and 1376 cm^{-1}; FAB-HRMS: 503.2997 (Calcd 503.2984, $C_{27}H_{44}O_7$ Na $[M^+ + Na]$), 481.3178 (Calcd 481.3165, $C_{27}H_{45}O_7$ $[MH^+]$); FAB-MS (NBA) *m/z*: 503, 481, 479, 463; ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) See Table 3.

1.4.4. Compound 7. Amorphous white solid; $[\alpha]_D^{25}$=+3.6 (*c* 0.03, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3400, 2960, 2926, 2854, 1731, 1671 and 1461 cm^{-1}; HRMS: 506.3610 (Calcd 506.3607, $C_{30}H_{50}O_6$ $[M^+ - CH_3O]$), 488.3557 (Calcd 488.3501, $C_{30}H_{48}O_5$ $[M^+ - CH_3O - H_2O]$); MS *m/z*: 506, 488, 470, 363, 319, 143; ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) See Tables 1 and 2.

1.4.5. Compound 8. Amorphous white solid; $[\alpha]_D^{25}$=+44.7 (*c* 0.07, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3434, 2926, 1461, 1376 and 1095 cm^{-1}; HRMS: 506.3580 (Calcd 506.3607, $C_{30}H_{50}O_6$ $[M^+ - CH_3O]$), 488.3520 (Calcd 488.3501, $C_{30}H_{48}H_5$ $[M^+ - CH_3O - H_2O]$), 447.3127 (Calcd 447.3110, $C_{27}H_{43}O_5$ $[M^+ - CH_3O - C_3H_7O]$); MS *m/z*: 506, 488, 470, 447, 429, 363, 143; ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) See Tables 1 and 2.

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