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TRICYCLIC DITERPENES FROM *HALIMIUM VISCOSUM*

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Key Word Index—*Halimium viscosum*; Cistaceae; tricyclic diterpenes; valparanes.

Abstract—Several tricyclic diterpenes with a valparane skeleton have been isolated from the aerial parts of *Halimium viscosum* collected at Celorico da Beira, Portugal. Two new compounds have been identified as valpara-2,15-diene-1,4-dione and 3α,4α-epoxyvalpar-15-en-2-one, besides the previously known compounds: valpara-2,13-diene; valpara-2,15-diene; valpara-3,15-dien-2-one; 2β,3β-epoxyvalpar-14-ene and 1β-metoxy-valpara-2,15-diene. Their structures have been established by means of 2D NMR experiments (^{1}H-^{13}C, and HMQC) and X-ray studies. This plant sample may represent a new chemotype. © 1998 Elsevier Science Ltd. All rights reserved

INTRODUCTION

The acid part of the hexane extract of *Halimium viscosum* collected at Celorico da Beira (Portugal), only contains acids with an *ent*-halimane skeleton with the side chain saturated [1], similar to those isolated from the chemotype of *Halimium viscosum* collected at La Fregeneda, Spain [2]. However, from the neutral part of *Halimium viscosum* (from Celorico da Beira, Portugal), some tricyclic diterpenes, with a valparane skeleton, have been isolated and characterized, which were only isolated from another chemotype of *Halimium viscosum* from the Iberian Peninsula (Valparaiso, Spain) [3, 4]. Consequently it is probable that we have found a new chemotype of *Halimium viscosum* (Celorico da Beira, Portugal).

RESULTS AND DISCUSSION

The hexane extract of *Halimium viscosum* (collected at Celorico da Beira, Portugal), was dewaxed with methanol and fractionated into neutral and acid parts, as described previously [1]. The neutral fraction was saponified and from the non-saponificable material labd-7-ene-3β,15-diol [5] was isolated by crystalization.

The remaining material was separated into seven fractions by CC (see Experimental part).

After several CC (on silica-gel and/or silicagel–$AgNO_3$, 10%) of the less polar fractions the following compounds were isolated: valpara-2,13-diene (**1**) [3]; valpara-2,15-diene (**2**) [4]; **3**; valpara-3,15-dien-2-one (**4**) [6]; 2β,3β-epoxyvalpar-15-ene (**5**) [4]; 1β-methoxy-valpara-2,15-diene (**6**) [6] and **7**.

Compound **3** was an unsaturated ketone (IR cm^{-1}; 3008, 1706, 1668, 752) which showed in its ^{1}H NMR spectrum signals corresponding to an isopropenyl group Me—C(=CH_2) (δ 1.76, 3H, *s*; 4.84 and 4.81 1H, *s* each), two methyl groups (δ 1.24 and 0.83, 3H, *s* each) and the following groups: CO—CH=CMe (δ 6.36, 1H, *d*, J = 1.8 Hz; 1.98, 3H, *d*, J = 1.8 Hz) and CO—CH_2—CH (δ 2.88, 1H, *dd*, J_1 = 17.7 Hz, J_2 = 11.0 Hz; 2.65, 1H, *dd*, J_1 = 17.7 Hz, J_2 = 2.4 Hz; 2.15, 1H, *dd*, J_1 = 11.0 Hz, J_2 = 2.4 Hz). The ^{13}C NMR spectrum possessed signals from four methyls, six methylenes (one of them olefinic) four methines (one olefinic) and six quaternary carbon atoms, two of them sp^3, two olefinic and two carbonyl groups (δ 208.5 and 202.8). An isopropenyl group and three methyls (two quaternary and another one on a double bond) together with the other groupings can be located on a valparane skeleton with carbonyl groups at C-1 and C-4.

Table 1 shows the results of 2D correlation experiments (one bond and long-range), those indicated with a continuos line correspond to the groups clearly observed in structure **A**.

Only two methylenes showed no clear correlations. Thus, compound **3** was assigned the structure of valpara-2,15-diene-1,4-dione.

Compound **7**, was an unsaturated ketone (IR cm^{-1}: 3078, 1731, 1642, 893) whose 1H NMR spectrum exhibited the signal of an isopropenyl group (δ 1.73, 3H,

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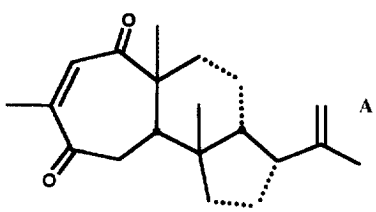
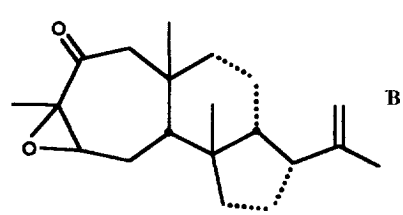
Table 1. NMR data for compound **3** ($CDCl_3$) and correlations observed in a 2D experiment

Position	C	H		HMBC
1	208.5			
2	134.5	6.36	1H, *d*, J = 1.8 Hz	4, 11, 19
3	143.5			
4	202.8			
5	42.8	2.88	1H, *dd*, J_1 = 17.7,	4, 6, 11
		2.65	J_2 = 11.0	
6	48.6	2.15	1H, *dd*, J_1 = 11.0, J_2 = 2.4	1, 4, 5, 7, 11, 18, 20
7	45.5			
8	54.5	1.59	1H, *sb*	10, 15
9	21.2			
10	39.5			
11	50.7			
12	41.2			
13	26.8			
14	46.0	2.74	1H, *m*	
15	147.5			
16	110.7	4.84;	1H, *s* each	14, 17
17	25.0	1.76	3H, *s*	14, 15, 16
18	16.6	0.83	3H, *s*	6, 7, 8, 12
19	19.9	1.98	3H, *d*, J = 1.8	2, 3, 4
20	19.0	1.24	3H, *s*	1, 6, 10, 11



A



B

s; 4.81 and 4.77, 1H, *s* each), three methyl singlets, one of them deshielded due to location on a carbon bonded to oxygen, one oxiranic proton (δ 3.31, 1H, *dd*, J_1 = 7.3 Hz, J_2 = 3.3 Hz) and the grouping CO—CH_2—C (δ 2.68 and 1.96, 1H, *d*, J_{AB} = 11.2 Hz each). The ^{13}C NMR spectrum presented signals of four methyls groups, seven methylenes (one olefinic), four methines (one bonded to oxygen δ 63.9) and five quaternary carbons, one carbonyl (δ 208.8), one olefinic and another one bonded to oxygen (δ 64.8).

The EI mass spectrum showed a molecular ion at m/z 302 in agreement with the molecular formula $C_{20}H_{30}O_2$, and corresponding to a tricyclic diterpene with a double bond, a carbonyl group and an oxiranic ring.

Table 2 shows the results of 2D correlation experiments ($^1H/^{13}C$) using $CDCl_3$ and C_6D_6 as solvents, one bond (HMQC) and long-range (HMBC).

These correlations revealed the partial structure **B**. The multiplicity of the oxiranic hydrogen (*dd*, J_1 = 7.3 Hz, J_2 = 3.3 Hz) indicated the proposed structure for **7** as 3α,4α-epoxyvalpar-15-en-2-one, which was confirmed by X-ray studies (Figure 1).

EXPERIMENTAL

Spectral analysis

NMR: 400 or 250 MHz for ^1H and 100.1 or 62.9 MHz for ^{13}C. Chemical shifts are given in δ (ppm) and are referenced to the residual $CHCl_3$, 7.26 ppm for the ^1H and 77.0 ppm for ^{13}C.

Extraction and isolation

Aerial parts of *Halimium viscosum* (1.3 kg) collected in Celorico da Beira (Guarda, Portugal) were dried and extracted with *n*-hexane in a Soxhlet apparatus for 24 h. The extract (124.8 g) was dewaxed with MeOH (9.5 g) and then extracted with 4% NaOH (91.4 g). The neutral fraction weighed 23.8 g. A part of the neutral fraction (18.0 g) was saponified with 10% KOH in MeOH and the neutral part (12.1 g) was crystallized giving as major component the 3 β, 15-dihidroxy-7-labdene (5.9 g). The remaining part (7.2 g) was chromatographed on a silica gel column with *n*-hexane–EtOAc mixtures giving seven factions (I–VII). CC of faction I on silica gel-10% $AgNO_3$ gave **1**

Table 2. NMR data for compound **7** and correlations in a 2D experiment

	$CDCl_3$				C_6D_6			
Position	C	H		HMBC	C	H		HMBC
1	51.3	2.68 ; 1.96	1H, *d*, $J = 11.2$	2, 3, 6, 10, 11, 20	50.3	2.80 ; 1.74	1H, *d*, $J = 11.3$ each	2, 3, 6, 10, 11,
2	208.8				207.8			
3	64.8				64.8			
4	63.9	3.31	1H, *dd*, $J_1 = 7.3$ $J_2 = 3.3$	3, 5, 6, 19	64.2	2.91	1H, *t*, $J = 4.3$	3, 5, 6, 19
5	27.0	2.12	2H, *dd*, $J_1 = 15.3$ $J_2 = 7.3$	3, 4, 6, 7, 11	26.8			
6	56.1				56.7			
7	46.3				46.4			
8	54.6				54.4			
9	21.7				22.0			
10	41.5				41.3			
11	36.0				35.6			
12	41.7				41.5			
13	26.6				26.8			
14	46.2	2.68	1H, *m*		46.3	2.38	1H, *m*	8, 17
15	147.8				147.7			
16	110.5	4.81 ; 4.77	1H, *s* each	14, 17	110.7	4.88 ; 4.81	1H, *s* each	14, 17
17	25.0	1.73	3H, *s*	14, 15, 16	25.1	1.64	3H, *s*	14, 15, 16
18	16.6	0.71	3H, *s*	6, 7, 8, 12	16.8	0.52	3H, *s*	6, 7, 8, 12
19	17.1	1.43	3H, *s*	2, 3, 4	17.2	1.36	3H, *s*	2, 3, 4
20	22.5	0.92	3H, *s*	1, 6, 10, 11	22.9	0.66	3H, *s*	1, 6, 10, 11

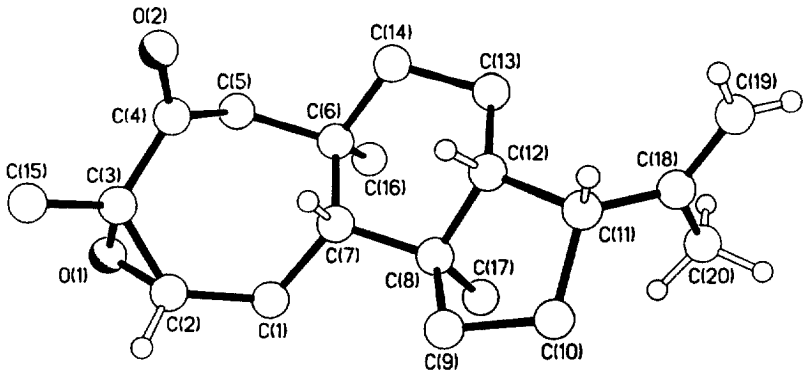
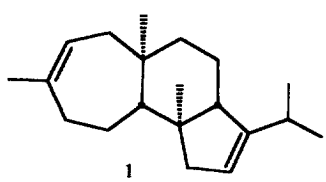


Fig. 1.



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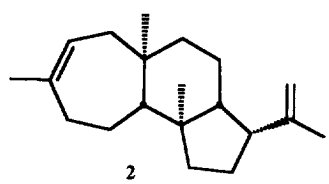

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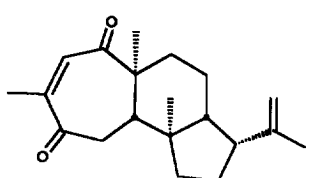

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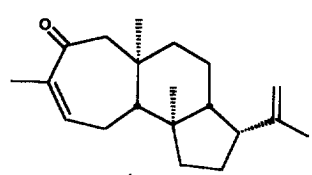

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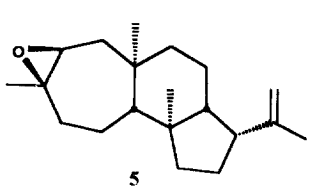

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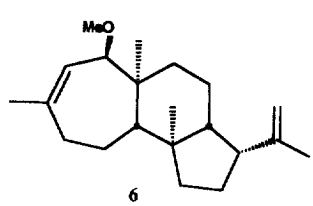

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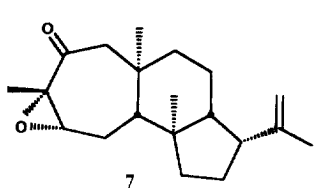

7

(50 mg) and **2** (60 mg). CC of fraction II afforded **3** (60 mg) and fraction III **4** (80 mg), **5** (95 mg) and **6** (13 mg), fraction IV gave **7** (93 mg).

Valpara-2,15-*diene*-1,4-*dione* (**3**). Colourless oil. IR ν_{max}^{film} cm^{-1}: 3441, 1706, 1668, 1445, 1382, 1223, 752. λ_{max}^{EtOH} nm(log ε): 235 (3.52), 216 (3.48), 205 (3.50). ^1H and ^{13}C NMR see Table 1.

3α,4α-*Epoxyvalpar*-15-*en*-2-*one* (**7**). Colourless crystals, IR ν_{max}^{film} cm^{-1}: 3377, 3072, 1731, 1452, 1375, 1172, 1115, 1071, 893. ^1H and ^{13}C NMR see Table 2. GC-MS, 70 eV, *m/z* (rel. int.): 302 $[M]^+$ (2), 260 (25), 217(19), 191 (21), 189 (26), 187 (15), 178 (18), 175 (21), 173 (25), 163 (47), 161 (36), 160 (17), 159 (35), 149 (36), 147 (100), 146 (22), 145 (47), 135 (33), 134 (27), 133 (69), 131 (28), 123 (21), 122 (18), 121 (54), 120 (18), 119 (51), 109 (78), 108 (25), 107 (67), 106 (17), 105 (66), 99 (29), 98 (23), 95 (63), 94 (18), 93 (72), 92 (15), 91 (82), 85 (15), 83 (21), 82 (62), 81 (69), 80 (15), 79 (86), 77 (53), 71 (17), 69 (38), 68 (72), 67 (63), 65 (16), 55 (59).

X-ray analysis of 3α,4β-*epoxyvalpar*-15-*en*-2-*one*

Crystals: monoclinic, $a = 6.216(1)$, $b = 12.428$ (2). $c = 10.967(1)$ Å, $U = 845.6(2)$ $Å^3$. Cu–K_α radiation ($\lambda = 1.54178$ Å) using ω-scans. The structure was solved by direct method and refined anisotropically to give $R = 0.0412$, $R\omega = 0.1172$ for 1575 independently observed reflections [$|F_o| > 4\sigma(|F_o|)$, $\theta > 63°$]. Atomic coordinates, bond lengths and angles, and thermal parameters are deposited in the Cambridge Crystallographic Data Centre.

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