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MINOR LABDANE DITERPENOIDS FROM *HALIMIUM VERTICILLATUM*

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Key Word Index—*Halimium verticillatum*, Cistaceae, labdane diterpenoid acids, diol.

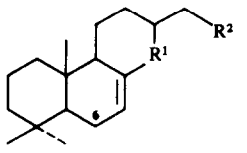
Abstract—Seven novel diterpenes with the labdane skeleton were isolated from the *n*-hexane extract of *Halimium verticillatum* and identified as methyl 15-*Z* cinnamoyloxy-7-labden-17-oate, methyl 15-methoxy-7-labden-17-oate, methyl 7-labden-15,17-dioate, methyl 15-hydroxy-7α-methoxy-8-labden-17-oate, methyl 6β,15-dihydroxy-7-labden-17-oate, methyl 7β-15-diacetoxy-8-labden-17-oate and 15,17-diacetoxy-7-labdene.

INTRODUCTION

Recently, we reported the isolation from *Halimium viscosum* and *H. verticillatum* of several novel diterpenic acids with the labdane skeleton having the C-17 carboxyl group conjugated with the C-7 double bond and the lateral chain saturated [1] or unsaturated [2]. In this article we describe another six new labdane acids with a saturated lateral chain and an unsaturated diol.

RESULTS AND DISCUSSION

From the sodium hydroxide soluble part of the *n*-hexane extract of *Halimium verticillatum* (Corrois, Portugal), three major fractions in the form of methyl esters were separated by column chromatography: I (10%), II (50%) and III (40%). Successive column chromatography and preparative TLC of fraction I afforded three products, compounds **1**, **3** and **6**, together with those already described [1]. From fraction II, besides methyl 15-hydroxy-7-labden-17-oate, a minor product, compound **7**, was isolated by column chromatography. From the most polar fraction III an hydroxyester, compound **9**, and, after acetylation, compound **11**, were isolated.



		R¹	R²
1		COOMe	*Z*—CH_2OCO—CH=CH—C_6H_5
2		COOMe	*E*—CH_2OCO—CH=CH—C_6H_5
3		COOMe	CH_2OMe
4		COOMe	CH_2OAc
5		COOMe	CH_2OH
6		COOMe	COOMe
9	6βOH	COOMe	CH_2OH
10	6βOAc	COOMe	CH_2OAc
14		CH_2OAc	CH_2OAc

Compound **1** is an α,β-unsaturated diester with an aromatic ring (IR 1710, 1620, 1240 and 1160 cm^{-1}). Its ^{13}C NMR spectrum presents 30 carbon signals: five methyls, eight methylenes, 11 methynes (eight olefinic) and six tetrasubstituted carbons. The ^1H NMR spectrum shows signals of the following groups: –CH=C–COOMe (δ6.63, 1H, *m*; 3.68, 3H, *s*), $-CH_2OCO-$(4.13, 2H, *m*), C_6H_5–CH=CH–COO– (6.39, 1H, *d*; 5.95, 1H, *d*), three Me-C and one Me-CH. Both the ^1H and ^{13}C NMR spectra of **1** and **2** are similar, the unique difference being the chemical shifts and coupling constants of the olefinic hydrogens of the cinnamoyl group (C_6H_5–CH=CH–CO, J = 12, 7 Hz) which corresponds in **1** to a *Z*-double bond. Consequently, compound **1** is assigned the structure of methyl 15-*Z* cinnamoyloxy-7-labden-17-oate.

Compound **3**, also an α,β-unsaturated ester (IR ν 1710, 1640 and 1240 cm^{-1}), presents in the ^{13}C NMR spectrum signals of twenty two carbon atoms: six methyls (two of them highly deshielded), eight methylenes, four methynes and four tetrasubstituted carbons. In its ^1H NMR spectrum, besides signals due to four methyl groups (three Me-C and one Me-CH), the following groupings can be observed: –CH=C–COOMe (6.62, 1H, *m*; 3.70, 3H, *s*), $-CH_2-CH_2-O$ (3.39, 2H, *t*) and –OMe (3.32, 3H, *s*). Comparison with the ^1H and ^{13}C NMR spectra of compounds **4** and **5** shows that compound **3** has a C-15 methoxy group indicating the structure of methyl 15-methoxy-7-labden-17-oate.

Compound **6** is an α,β-unsaturated methyl diester (IR ν 1720, 1710, 1640 and 1240 cm^{-1}) whose ^{13}C NMR spectrum presents 22 carbon signals: six methyls, seven methylenes, four methynes and five tetrasubstituted carbons, two of these being carboxylic. Its ^1H NMR spectrum exhibits four methyl signals (three Me–C and one Me–CH) and the groupings: –CH=C–COOMe (δ6.63, 1H, *m*; 3.71, 3H, *s*) and –COOMe (3.66, 3H, *s*). The second

Table 1. ^{13}C NMR data of compounds **1**, **3**, **6**–**12** and **14*** (50, 3 MHz, $CDCl_3$, TMS, as internal standard)

C	1	3	6	7	8	9	10	11	12	14
1	39.73	39.73	39.68	39.92	36.04	39.56	39.41	37.94	38.88	39.18
2	18.63	18.63	18.62	18.82	18.84	18.44	18.33	18.60	18.50	18.82
3	42.12	42.19	42.16	41.33	41.33	43.64	43.31	41.36	40.60	42.61
4	32.84	32.85	32.84	33.12	33.12	32.90	32.97	33.04	33.37	32.99
5	49.66	49.68	49.65	44.99	45.02	51.53	50.76	49.43	50.04	48.86
6	23.97	23.96	23.97	22.47	22.31	68.93	71.17	25.28	35.00	23.82
7	136.64	136.45	136.78	74.70	74.71	139.29	137.39	72.79	196.17	128.77
8	135.65	135.80	135.55	126.72	126.72	135.95	134.58	125.43	132.51	134.29
9	51.20	51.18	51.21	159.73	159.73	57.04	53.24	158.88	167.87	52.84
10	37.03	37.04	37.04	40.79	40.80	36.51	36.50	40.24	41.16	36.94
11	25.57	25.64	25.62	28.00	27.48	25.85	25.63	25.88	27.88	23.89
12	38.23	38.43	38.13	37.86	38.22	38.62	38.53	35.71	35.23	38.86
13	30.87	30.97	31.32	30.85	31.31	30.59	30.84	31.04	31.08	30.71
14	35.31	36.52	41.49	36.00	35.85	39.70	35.34	35.20	35.10	35.37
15	63.00	71.29	173.68	60.68	63.02	61.13	63.03	62.69	62.64	62.94
16	19.50	19.70	19.79	19.55	19.14	19.74	19.49	19.31	19.12	19.58
17	169.77	169.89	169.73	170.16	170.24	169.49	168.95	168.83	170.97	67.71
18	33.19	33.20	33.18	33.11	32.88	32.21	35.69	33.28	32.46	33.08
19	22.00	22.00	21.97	21.82	21.83	22.53	22.68	21.86	21.41	21.83
20	14.46	14.44	14.41	18.32	18.42	15.48	15.49	20.11	18.42	13.67
COOMe	51.21	51.26	51.28 51.33	51.38	51.39	51.06	51.51	51.21	51.96	
OMe		58.48		56.59	58.59					
OOCMe					171.06		171.06 172.00	170.25 170.99	172.01	170.73 171.06
OOCMe					20.98		20.96 21.65	20.93 21.05	20.93	20.94 21.06

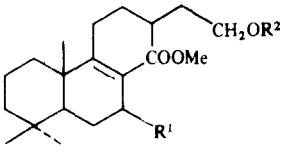
Compound **1**: chemical shifts of cinnamoyl group carbons were 1′ (166.27), 2′ (120.12), 3′ (142.73), 4′ (135.09), 5′ (128.90), 6′ (128.02) 7′ (129.69), 8′ (128.02), 9′ (128.90)

*Assignments based on chemical shift correlations with methyl 15-hydroxy-17-oate and DEDT experiments.

carboxylic group is attached to C-15. From the above data compound **6** was identified as the methyl 7-labden-15, 17-dioate and this assignment was proved by preparing **6** using chromium trioxide oxidation of **5** [3] followed by treatment with diazomethane.

Compound **7**, isolated by column chromatography from the major fraction II, is an α,β-unsaturated hydroxyester (IR ν 3400, 1710 and 1240 cm^{-1}) that shows 22 carbon signals in its ^{13}C NMR spectrum: six methyls, eight methylenes, three methynes and five tetrasubstituted carbons (two of these are olefinic). Its ^{1}H NMR spectrum shows the following groupings: –CH–OMe– (δ4.11, 1H, *t*; 3.31, 3H, *s*), –COOMe (3.73, 3H, *s*) –CH_2OH (3.67, 2H, *m*), three Me-C and one Me-CH. The chemical shift of the hydrogen atom, geminal to the methoxy group (δ4.11) allows its assignment to an allylic position in respect to a tetrasubstituted double bond (126.72, *s* and 159.73, *s* in the ^{13}C NMR) conjugated with the methoxycarbonyl (the UV spectra of the acetyl derivative **8** presents a maximum at 222 nm). The α-orientation of the C-7 methoxy group followed from the coupling constants of its geminal hydrogen. Thus, compound **7** was assigned the structure of the methyl 15-hydroxy-7α-methoxy-8-labden-17-oate.

From fraction III, compounds **9** and **11** were isolated, the latter in the form of a diacetylderivative. Compound **9** is an α,β-unsaturated hydroxyester (IR ν 3400, 1710, 1640 and 1240 cm^{-1}), whose acetyl derivative **10** exhibits a maximum at 213 nm in its UV spectrum. The ^{13}C NMR spectrum of **9** presents 21 carbon signals: five methyls, seven methylenes, five methynes (one olefinic) and four tetrasubstituted carbons. In its ^{1}H NMR spectrum the following groupings are observed: –CH=C–COOMe (6.42, 1H, *t*; 3.71, 3H, *s*), =C–CH–OH (4.36, 1H, *ddd*), –CH_2–OH (3.36, 2H, *m*), three Me–C and one Me–CH. The secondary hydroxyl group is in an allylic position relative to the trisubstituted double bond as shown by the deshielding of its geminal hydrogen atom (δ4.36 in **9** and 5.58 in its acetyl derivative **10**). In a system with a labdane skeleton and a C-17 carboxyl group this hydroxyl group must be situated at C-6. The lateral chain is identical to



	R¹	R²
7	αOMe	H
8	αOMe	Ac
11	βOAc	Ac
12	=O	Ac
13	βOH	Ac

that of **5**. The β-orientation of the hydroxyl group of **9** may be concluded from the coupling constants of its geminal hydrogen atoms, the difficulty in preparing the acetyl derivative **10** and the deshielding of two of the bicyclic methyl singlets (δ 1.13 and 1.08). From the above data compound **9** was identified as methyl 6β,15-dihydroxy-7-labden-17-oate.

Acetylation of the most polar fraction permitted isolation of the α,β-unsaturated diacetoxyester **11** (IR ν 1720, 1230 cm^{-1}), whose ^{13}C NMR spectrum presents 25 carbon signals: seven methyls, eight methylenes, three methynes and seven tetrasubstituted carbons, two of these being olefinic. Its ^1H NMR spectrum exhibits the signals of four methyls of the labdane skeleton (three Me–C and one Me–CH) such as the previously described compounds and the groupings: –CHOAc (δ 5.72, 1H, *m*), $-CH_2OAc$–(4.07, 2H, *m*), –COOMe (3.68, 3H, *s*) and two –OCOMe (2.03 and 1.98, 3H, *s*). The chemical shift of the hydrogen geminal to the secondary acetoxyl group corresponds to an allylic position relative to the tetrasubstituted double bond which must be conjugated with the methoxycarbonyl in a group –CH(OAc)–C(COOMe) = C. Consequently, the acetoxyl group must be located at C-7 and compound **11** is assigned the structure of methyl 7β,15-diacetoxy-8-labden-17-oate. This assignment was confirmed by partial synthesis. Oxidation of compound **4** with sodium dichromate produced the α,β-unsaturated ketone **12**, with a tetra-substituted double bond. Reduction of **12** with sodium borohydride followed by acetylation [4] of the product **13** afforded compound **11**.

The neutral part of the *n*-hexane extract (22%) was dewaxed and saponified with sodium hydroxide–methanol. Column chromatography of the nonsaponifiable products followed by acetylation afforded the diacetyl-derivative of a diol, compound **14**, whose ^1H NMR spectrum presents signals of four methyl groups (three Me-C and one Me-CH) and of the grouping: $-CH{=}C-CH_2OAc$ (δ 4.54, 1H, *d*; 4.40, 1H, *d*), $-CH_2OAc$ (4.07, 2H, *t*) and two –COOMe (2.04, 3H, *s* and 2.02, 3H, *s*). Compound **14** was assigned the structure of 15,17-diacetoxy-7-labdene which was confirmed by the preparation of an authentic sample by lithium aluminium hydride reduction of **5** followed by acetylation.

EXPERIMENTAL

The extraction of the aerial parts of *Halimium verticillatum* (Corroios, Portugal) was previously described [1]. CC (silica gel), CC (silica gel plus 10% $AgNO_3$) and prep. TLC of the methyl ester fractions I–III therein described gave **1** (38 mg), **3** (90 mg), **6** (20 mg), **7** (50 mg), **9** (60 mg) and **11** (70 mg).

Methyl 15-Z *cinnamoyloxy-7-labden-17-oate* (**1**). Colourless oil $[\alpha]_D^{22} - 25.5°$ ($CHCl_3$; *c* 2.10) IR ν_{max}^{film} cm^{-1}: 1710, 1620, 1240, 1160. ^1H NMR (200 MHz): δ 7.58 (2H, *m*), 7.32 (3H, *m*), 6.93 (1H, *d*, *J* = 12.7 Hz, H-3′), 5.95 (1H, *d*, *J* = 12.7 Hz, H-2′), 6.63 (1H, *m*, H-7), 4.13 (2H, *m*, H-15), 3.68 (3H, *s*), 0.90 (3H, *s*, Me-19), 0.85 (3H, *d*, *J* = 6.8 Hz, Me-16), 0.85 (3H, *s*, Me-18) and 0.81 (3H, *s*, Me-20).

Methyl 15-*methoxy-7-labden-17-oate* (**3**). Colourless oil $[\alpha]_D^{22}$ $-21.8°$ ($CHCl_3$, *c* 0.67); IR ν_{max}^{film} cm^{-1}: 1710, 1640, 1240, 1120, 1060. UV λ_{max}^{EtOH} nm: 216 (ε 3800). ^1H NMR (200 MHz): δ 6.62 (1H, *m*, H-7), 3.70 (3H, *s*), 3.39 (2H, *t*, *J* = 6.4 Hz, H-15), 3.32 (3H, *s*, OMe). 0.90 (3H, *s*, Me-19), 0.87 (3H, *d*, *J* = 6.8 Hz, Me-16), 0.86 (3H, *s*, Me-18) and 0.82 (3H, *s*, Me-20).

Methyl 7-*labden*-15,17-*dioate* (**6**). Colourless oil $[\alpha]_D^{22} - 21.8°$ ($CHCl_3$; *c* 0.77); IR ν_{max}^{film} cm^{-1}: 1720, 1710, 1640, 1240, 1060. UV λ_{max}^{EtOH} nm: 215 (ε 4000). ^1H NMR (200 MHz): δ 6.63 (1H, *m*, H-7), 3.71 (3H, *s*), 3.66 (3H, *s*), 0.92 (3H, *d*, *J* = 6.5 Hz, Me-16), 0.90 (3H, *s*, Me-19), 0.87 (3H, *s*, Me-18) and 0.82 (3H, *s*, Me-20).

Oxidation of methyl 15-*hydroxy-7-labden-17-oate* (**5**) *to yield compound* **6**. A soln of 99 mg of **5** in 5 ml of CH_2Cl_2 and 1 ml of AcOH was added to 0.062 g of CrO_3 in 0.5 ml of HOAc. The mixture was mantained at room temp. for 1 hr. After usual work-up of the reaction product an ethereal soln of CH_2N_2 was added; by CC (*n*-hexane–EtOAc, 19:1) 50 mg of **6** were separated.

Methyl 15-*hydroxy-7α-methoxy-8-labden-17-oate* (**7**). Colourless oil. IR ν_{max}^{film} cm^{-1}: 3400, 1710, 1240, 1140, 1060, 1020. ^1H NMR (200 MHz): δ 4.11 (1H, *t*, *J* = 3.4 Hz, H-7), 3.74 (3H, *s*), 3.67 (2H, *m*, H-15), 3.31 (3H, *s*, OMe), 0.91 (3H, *d*, *J* = 6.3 Hz, Me-16), 0.98, 0.92 and 0.87 (3H, *s*, each, Me-19, Me-18 and Me-20, respectively).

Methyl 15-*acetoxy-7α-methoxy-8-labden-17-oate* (**8**). Treatment of **7** with Ac_2O–pyridine produced **8**. Colourless oil, $[\alpha]_D^{22}$ $+21.36°$ ($CHCl_3$; *c* 1.10); IR ν_{max}^{film} cm^{-1}: 1720, 1620, 1230, 1080. UV λ_{max}^{EtOH} nm: 222 (ε 4700). ^1H NMR (200 MHz): δ 4.10 (1H, 2H, *m*, H-7 and H-15), 3.74 (3H, *s*), 3.31 (3H, *s*, OMe), 2.04 (3H, s), 0.90 (3H, *d*, *J* = 6.3 Hz, Me-16), 0.97, 0.91 and 0.87 (3H, *s*, each, Me-19, Me-18 and Me-20, respectively).

Methyl 6β,15-*dihydroxy-7-labden-17-oate* (**9**). Colourless oil IR ν_{max}^{film} cm^{-1}: 3400, 1710, 1640, 1240, 1050. ^1H NMR (200 MHz): δ 6.42 (1H, *t*, *J* = 2.4 Hz, H-7), 4.36 (1H, *ddd*, J_1 = 2.4 Hz, J_2 = 3.4 Hz, J_3 = 10.7 Hz, H-6), 3.71 (3H, *s*), 3.66 (2H, *m*, H-15), 1.13 and 1.06 (3H, *s*, each, Me-19 and Me-20), 0.87 (3H, *d*, *J* = 6.8 Hz, Me-16), 0.85 (3H, *s*, Me-18).

Methyl 6β,15-*diacetoxy-7-labden-17-oate* (**10**). Treatment of **9** (100 mg) with Ac_2O-pyridine, produced 20 mg of **10**. Colourless oil $[\alpha]_D^{22} + 55.0°$ ($CHCl_3$; *c* 1.50); IR ν_{max}^{film} cm^{-1}: 1720, 1660, 1220, 1130, 1020. UV λ_{max}^{EtOH} nm: 213 (ε 4100). ^1H NMR (200 MHz): δ 6.25 (1H, *t*, *J* = 2.5 Hz, H-7), 5.58 (1H, *ddd*, J_1 = 2.5 Hz, J_2 = 3.4 Hz, J_3 = 10.7 Hz, H-6), 4.11 (2H, *m*, H-15), 3.71 (3H, *s*), 2.06 and 2.03 (3H, *s*, each), 0.97, 0.95 and 0.91 (3H, *s*, each, Me-19, Me-18 and Me-20, respectively); 0.88 (3H, *d*, *J* = 6.2 Hz, Me-16).

Methyl 7β,15-*diacetoxy-8-labden-17-oate* (**11**). Acetylation and CC (silica gel) of the product eluted with *n*-hexane–EtOAc (1:1) from CC of fraction III [1] afforded compound **11**. Colourless oil $[\alpha]_D^{22} + 24.0°$ ($CHCl_3$, *c* 1.32); IR ν_{max}^{film} cm^{-1}: 1720, 1230, 1140, 1020. ^1H NMR (200 MHz): δ 5.71 (1H, *m*, H-7), 4.07 (2H, *t*, *J* = 6.8 Hz, H-15), 3.68 (3H, *s*), 2.03 and 1.98 (3H, *s* each), 1.11 (3H, *s*, Me-20), 0.95 (3H, *d*, *J* = 6.1 Hz, Me-16), 0.91 and 0.85 (3H, *s*, each, Me-19 and Me-18, respectively).

Oxidation of compound **4** to yield **12**. To 0.2 g of **4** in 1.1 ml of C_6H_6, 177 mg of Na_2CrO_4, 0.9 ml of HOAc, 1.5 ml of Ac_2O and 136 mg of NaOAc were added. Heating at 45° was maintained for 4 hr. Following the usual extraction procedure 0.258 g of oxidation product was obtained. CC (silica gel, *n*-hexane–EtOAc, 9:1) of this product produced 100 mg of methyl 15-acetoxy-7-oxo-8-labden-17-oate (**12**). Colourless oil $[\alpha]_D^{22}$ $+36.8°$ ($CHCl_3$; *c* 0.76); IR ν_{max}^{film} cm^{-1}: 1740, 1670, 1620, 1340, 1240, 1150, 1030. UV λ_{max}^{EtOH} nm: 242 (ε 98 000). ^1H NMR (200 MHz): δ 4.05 (2H, *t*, *J* = 6.8 Hz, H-15); 3.76 (3H, *s*); 2.00 (3H, *s*); 1.13 and 0.90 (3H, *s*, each, Me-20 and Me-19, respectively); 0.88 (3H, *d*, *J* = 6.7 Hz, Me-16); and 0.86 (3H, *s*, Me-18).

Reduction of **12** *with* $NaBH_4$ *to yield* **13**. To 64 mg of **12** in MeOH with stirring, 14 mg of $NaBH_4$ were added. Stirring was continued for 4 hr at room temp. Usual work-up afforded 80 mg of the reduction product. CC of this product allowed separation of 25 mg of Methyl 15-acetoxy-7-hydroxy-8-labden-17-oate (**13**). Colourless oil, IR ν_{max}^{film} cm^{-1}: 3400, 1740, 1720, 1250, 1120, 1100, 1050. ^1H NMR (200 MHz): δ 5.58 (1H, *dd*, J_1 = 7.3 Hz, J_2 = 10.2 Hz, H-7), 4.10 (2H, *dd*, J_1 = 7.3 Hz, J_2 = 6.8 Hz, H-15),

3.68 (3H, *s*), 2.03 (3H, *s*), 1.11 (3H, *s*, Me-20), 0.95 (3H, *d*, $J = 6.1$ Hz, Me-16), 0.91 and 0.85 (3H, *s*, each, Me-19 and Me-18, respectively). Acetylation of **13** produced **11**.

15,17-*diacetoxy*-7-*labdene* (**14**). The neutral part of the dewaxed *n*-hexane extract of *H. verticillatum* (22%) [1] was dissolved in 5% NaOH–MeOH, and maintained at room temp. for 12 hr. From the unsaponifiable part (43%) by CC with Et_2O–MeOH (19:1), 31% of the mixture of hydroxyderivatives were eluted. Acetylation of this mixture and subsequent CC (silica gel) produced 70 mg of **14**. Colourless oil, $[\alpha]_D^{22} - 9.7°$ ($CHCl_3$; *c* 0.83); IR ν_{max}^{film} cm^{-1}: 1740, 1240. ^1H NMR (200 MHz): δ5.78 (1H, *br s*, H-7); 5.54 and 4.40 (1H, *d*, each , $J_{AB} = 12.2$ Hz, H-17); 4.07 (2H, *t*, $J = 6.8$ Hz, H-15); 2.04 and 2.02 (3H, *s*, each) 0.91 (3H, *d*, $J = 6.5$ Hz, Me-16); 0.86, 0.84 and 0.74 (3H, *s*, each, Me-19, Me-18 and Me-20, respectively).

Treatment of **5** (50 mg) with $LiAlH_4$ (20 mg) and acetylation of the reaction product produced **14**.

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REFERENCES

1. Urones, J. G., Marcos, I. S., Diez Martín, D., Brito Palma, F. M. S. and Rodilla, J. M. (1987) *Phytochemistry* **26**, 3037.
2. De Pascual Teresa, J., Urones, J. G., Marcos, I. S., Diez Martín, D. and Alvarez, V. M. (1986) *Phytochemistry* **25**, 711.
3. Jayme, M., Schaefer, P. C. and Richards, J. H. (1970) *J. Am. Chem. Soc.* **92**, 2059.
4. House, H. O. (ed.) (1972) *Modern Synthetic Reactions*, p. 280. Benjamin Cummings.