Pergamon

Phytochemistry, Vol. 35, No. 3, pp. 713-719, 1994

0031 9422/94 $6.00+0.00

COMPOUNDS WITH THE LABDANE SKELETON FROM *HALIMIUM VISCOSUM*

JULIO G. URONES,* ISIDRO S. MARCOS, PILAR BASABE, DAVID DIEZ, NARCISO M. GARRIDO, CONCEPCIÓN ALONSO, ISABEL M. OLIVA, ANNA M. LITHGOW, ROSALINA F. MORO, M^a JOSE SEXMERO and CARLOS LOPEZ

Departamento de Química Orgánica, Universidad de Salamanca, Plaza de los Caídos 1-5, 37008 Salamanca, Spain

(*Received* 8 *June* 1993)

Key Word Index—*Halimium viscosum*; Cistaceae; labdanes; diterpenes.

Abstract—The study of the chemical components of the neutral part of the extract of *Halimium viscosum*, chemotype Valparaíso, has been completed. Twelve labdanes have been isolated, nine are new natural compounds (two of them are *tetranor*-derivatives). Their structures were determined by spectroscopic methods and by chemical transformations from the major components present in this extract.

INTRODUCTION

The isolation and characterization of bicyclic diterpenes containing a C-17 carboxyl group [1] from the acid part of *Halimium viscosum* (Valparaíso), as well as a large group of tricyclic diterpenes belonging to the valparane or valparolane class [2–6] from its unsaponifiable part have been reported. Now, we report 12 bicyclic diterpenes also isolated from the unsaponifiable part that differ in the functionality at C-17: **1** and **3** have a methyl group, **8** a methylene and the rest possess an oxygenated function (acetoxymethylene in **5–7**, **9** and **10**, methoxycarbonyl in **11** and **12**, formyl in **4** and a lactonic carboxyl in **2**), but they mainly differ in the size and functionalization of the side chain. Compounds **2–5**, **7** and **9–12** are new natural products.

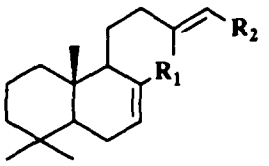
RESULTS AND DISCUSSION

The unsaponifiable part of the hexane extract of *H. viscosum* (Valparaíso) was chromatographed over silica gel, the less polar fraction afforded tricyclic diterpenes with the valparane or valparolane skeleton [2–6]. Twelve bicyclic diterpenes with a labdane skeleton were isolated from the polar fractions by column chromatography, either as hydroxy derivatives or as their acetates: **1–12**, **1**: (7,13*E*-labdadien-15-ol) [1, 7, 8], **2**: (13,14,15,16-*tetranor*-7-labden-17,12-olide), **3–5**: (12,16-diacetoxy-13,14,15,16-*tetranor*-7-labdene), **6**: (15,17-diacetoxy-7-labdene) [9], **7**, **8**: (7α,15-diacetoxy-8(17),13*E*-labdadiene) [10], **9–11**: (methyl 13*R*-hydroxy-14*S*,15-diacetoxy-7-labden-17-oate) and **12**: (methyl 13*S*-hydroxy-14*R*,15-diacetoxy-7-labden-17-oate).

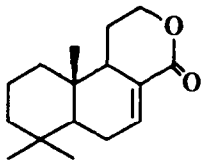
Compound **2** is an unsaturated lactone (IR: 1720, 1660, 1260 cm^{-1}) that shows in the ^{1}H NMR spectrum, in addition to the signals corresponding to three methyl groups (δ0.88, 0.85 and 0.73, 3H, *s*, ea), the signals corresponding to the grouping –CH=C–COOCH$_2$–CH$_2$ [δ7.26, 1H, *m*; 4.42, 1H, *ddd* (J_1 = 11.2, J_2 = 4.4 and J_3 = 2.5 Hz); and 4.18, 1H, *ddd* (J_1 = 11.2, J_2 = 2.5 and J_3 = 2.5 Hz)]. The ^{13}C NMR spectrum shows peaks corresponding to 16 carbon atoms: three methyl groups, six methylenes, three methines (one olefinic) and four quaternary carbon atoms (one olefinic and one carbonyl group). The physical data for **2** ([α]$_D$ −17.0°) are identical to the physical data of 13,14,15,16-*tetranor*-7-labden-17,12-olide which was obtained as an intermediate in the synthesis of drimanes from **14**, the major component of the acid fraction of *H. viscosum* (Valparaíso) [11].

Compound **3** is an unsaturated acetate (IR: 3090, 1750, 1650, 1240 cm^{-1}) and its ^{1}H NMR spectrum shows signals of the following groupings: –C(=CH$_2$)–CHOAc–CH$_2$OAc (δ5.10, 1H, *s*; 5.01, 1H, *s*; 5.41, 1H, *m*; 4.27, 1H, *m*; 4.11, 1H, *m*); –CMe=CH (δ1.69, 3H, *s*; 5.41, 1H, *m*) and signals of three methyl groups (δ0.87, 0.84 and 0.74, 3H, *s*, ea). The ^{13}C NMR spectrum shows peaks corresponding to 24 carbon atoms: six methyl groups, eight methylenes (one olefinic), four methines (one olefinic) and six quaternary carbon atoms (four are sp^2: two olefinic and two carbonyls). When comparing ^{13}C NMR data of **3** with those of **1**, a close relationship between both compounds is observed due to the signals of the bicyclic system that are almost identical [7]. So the grouping with the two acetoxyl groups and the terminal double bond must be located on the side chain. Some of the signals in the ^{1}H and ^{13}C NMR spectra are duplicated, meaning that a mixture of two stereoisomers is present. The structure of **3** can be assigned as the mixture of 14*S* and 14*R*,14,15-diacetoxy-7,13(16)labdadiene, taking into account the similarity of the chemical shift and multiplicity of the signal in the ^{1}H and

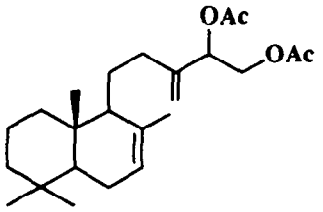
*Author to whom correspondence should be addressed.



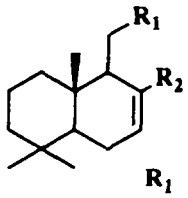
	R_1	R_2
1	Me	CH_2OH
4	CHO	CH_2OAc
7	CH_2OAc	CH_2OAc
13	CH_2OH	CH_2OH
14	COOMe	CH_2OH



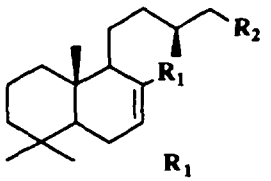
2



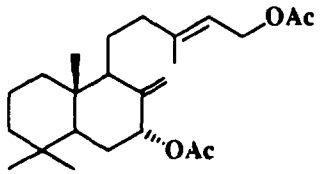
3



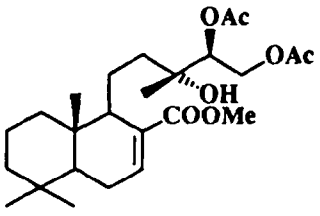
	R_1	R_2
5	CH_2OAc	CH_2OAc
15	CH_2OH	CH_2OH



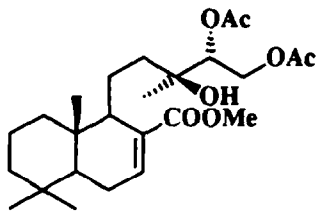
	R_1	R_2
6	CH_2OAc	CH_2OAc
16	CH_2OH	CH_2OH



8



11



12

^{13}C NMR spectra of previously described compounds [12, 13].

Compound **4** is an unsaturated carbonyl with an acetyl function (IR: 1750, 1690, 1640, 1240 cm^{-1}) that shows in the ^1H NMR spectrum, in addition to the signal corresponding to three methyl singlets (δ0.77, 0.86, 0.90, 3H, *s*, ea), the signals corresponding to the following groupings: -CH=C-CHO (δ6.81, 1H, *m*; 9.15, 1H, *s*) and C(Me)=CH-CH_2OAc (δ1.69, 3H, *s*; 5.42, 1H, *t*, J = 6.8 Hz; 4.61, 2H, *d*, J = 6.8 Hz; 2.01, 3H, *s*). The ^{13}C NMR spectrum shows the signals of 22 carbon atoms: five methyl groups, seven methylenes, five methines (two olefinic and one carbonyl) and five quaternary carbons (two olefinic and one acetoxyl). For a labdane diterpene with a primary allylic acetoxyl group on the side chain, the α,β-unsaturated formyl group could only

be located at C-17 with the double bond at C-7. The stereochemistry of the double bond on the side chain is established as *E* because of the chemical shift (δ^1H 1.64, δ^{13}C 16.4) of the methyl group [1]. The structure and absolute stereochemistry for **4** as 15-acetoxy-7,13*E*-labdadien-17-al is confirmed upon reduction with $LiAlH_4$ that afforded the diol **13**, the same diol obtained from **14** after reduction with $LiAlH_4$ [1].

Compound **5** is a diacetoxy-*tetranor*-labdene (IR: 1740, 1640, 1240 cm^{-1}). The ^{1}H NMR spectrum shows signals of three methyl singlets and also the following groupings: $-CH_2-CH_2OAc$ (δ4.37, 2H, *m*; 2.07, 3H, *s*) and $-CH=C-CH_2OAc$ (δ5.86, 1H, *m*; 4.56, 1H, *d*, J = 12.2 Hz; 4.48, 1H, *d*, J = 12.2 Hz; 2.05, 3H, s). Compound **5** yielded, upon alkaline hydrolysis, diol **15** (13,14,15,16-*tetranor*-7-labden-12,17-diol) that was also obtained by synthesis from **14** [11].

Compound **6** was hydrolysed under alkaline conditions to give diol **16**, that has been previously isolated from *H. verticilatum* [9].

The structure of **7** was established as 15,17-diacetoxy-7,13*E*-labdadiene when it was hydrolysed under alkaline conditions to give diol **13** that was previously obtained by reduction of **14** with $LiAlH_4$ [1].

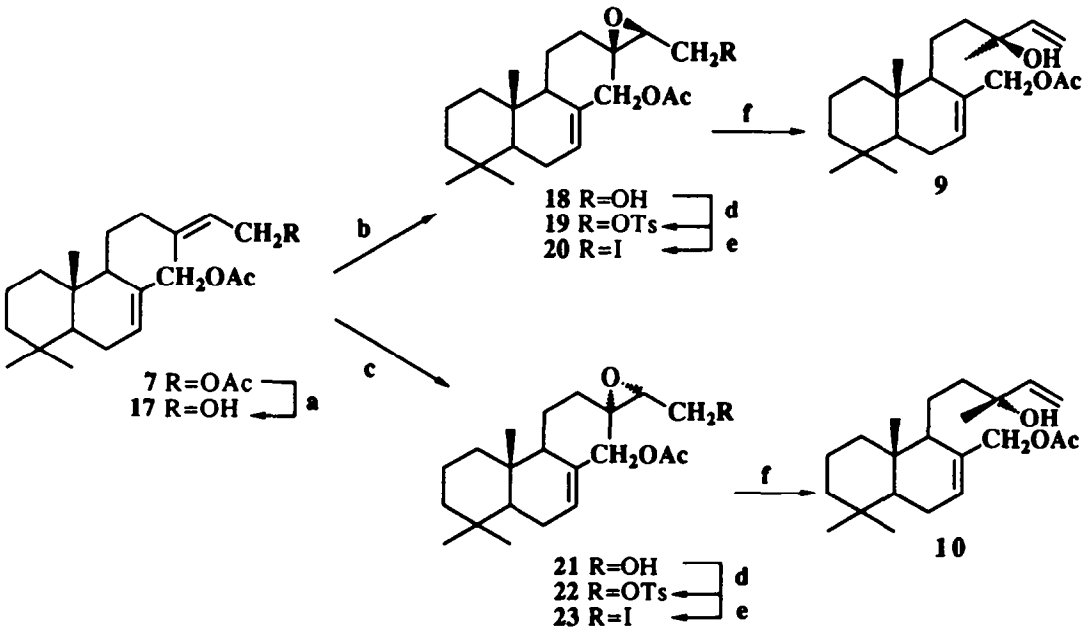
Compounds **9** and **10** (Scheme 1) show in the IR spectra the absorption bands of hydroxyl and acetoxyl groups and a terminal double bond (3400, 3080, 1740, 1640, 1240, 890 cm^{-1}). The ^{1}H NMR spectra show signals of three methyl singlets and of the following groupings: $-CH=C-CH_2OAc$ (5.79, 1H, *m*; 4.63, 1H, *d*, J = 12.2 Hz; 4.34, 1H, *d*, J = 12.2 Hz for **9**, and 5.80, 1H, *m*; 4.64, 1H, *d*, J = 12.2; 4.37, 1H, *d*, J = 12.2 Hz for **10**) and $C(Me)OH-CH=CH_2$ (δ1.26, 3H, *s*; 5.89, 1H, *dd*, J = 10.7, 17.6 Hz; 5.19, 1H, *dd*, J = 17.6, 1.5 Hz; 5.05, 1H, *dd*, J = 10.7, 1.5 Hz for **9**, and 1.26, 3H, *s*; 5.89, 1H, *dd*, J = 10.7, 17.1 Hz; 5.20, 1H, *dd*, J = 17.1, 1.5 Hz; 5.05, 1H, *dd*, J = 10.7, 1.5 Hz for **10**). The ^{13}C NMR spectra show peaks corresponding to 22 carbon atoms, each one: five methyl groups, eight methylenes (one olefinic), four methines (two olefinic) and five quaternary carbon atoms (two sp^2), and one with an oxygen function (δ73.4).

The mass spectra of **9** and **10** are very similar, except for the ratio of the peak fragments; in both cases, instead of the molecular parent ion, the $[M-18]^+$ fragment appears at *m/z* 330. The α,β-unsaturated acetoxymethylene group is similar to the already established functionality in **5**, **7** and **8**, that is located in the B ring of the labdane skeleton, and with the acetoxymethylene at C-17. Accordingly, the tertiary hydroxyl and the vinyl group must be on the side chain.

The structure and stereochemistry of 17-acetoxy-7,14-labdadien-13*R*- or 13*S*-ol for **9** and **10** is confirmed by enantioselective synthesis (Scheme 1).

When **7** was partially hydrolysed (K_2CO_3, MeOH, 30 min, 60%) the monoacetyl derivative **17** was obtained and, after epoxidation by Sharpless methodology [L(+) DET] afforded epoxide **18**. Treatment of the latter with TsCl provided the tosyl derivative **19** that by reaction with NaI in acetone gave the iodo derivative **20**. Upon reduction of **20** with zinc dust in HOAc, **9** was obtained ($[\alpha]_D$ −3.1°). Sharpless asymmetric epoxidation of **17** led to 13*S*,14*S* stereochemistry in the epoxy derivative obtained, **18** [14]. So, the configuration is 13*S* for **9**, as in the reduction with Zn, the stereochemistry of the centre is maintained [15].

In a similar way, Sharpless oxidation of **17** using D(−) DET gave the epoxide **21** (13*R*,14*R*) from which tosylation afforded the tosyl derivative **22**. Treatment of the



Scheme 1. (a) K_2CO_3/MeOH/60 min; (b) L(+)DET/Ti(iPrO)$_4$/^{t}BuOOH/CH_2Cl_2; (c) D(−)DET/Ti(iPrO)$_4$/^{t}BuOOH/CH_2Cl_2; (d) TsCl/pyridine; (e) NaI/acetone; (f) Zn/AcOH.

Table 1. ^{13}C NMR data of **1**, **4**, **6**, **13**, **15**–**18**, **20**, **21** and **23** (50.3 MHz, $CDCl_3$)

C	1	2	3	4	6	7	8	9	10	11	12	13	15	16	17	18	20	21	23
1	39.9	38.9	35.3	39.0	39.2	39.1	39.5	39.2	39.2	39.3	39.4	39.3	39.2	39.8	39.1	39.1	39.2	39.2	39.2
2	18.9	18.6	18.9	18.5	18.8	18.8	19.4	18.8	18.8	18.6	18.6	18.8	18.7	18.9	18.8	18.8	18.8	18.8	18.8
3	42.4	42.0	42.4	42.1	42.3	42.3	42.2	42.3	42.3	42.1	42.1	42.4	42.3	42.5	42.3	42.2	42.2	42.3	42.3
4	33.0	34.8	33.2	32.9	33.0	33.0	33.3	33.0	33.0	33.1	32.8	33.0	33.0	33.0	33.0	33.0	33.0	33.0	33.0
5	50.3	49.0	50.3	49.6	48.9	49.8	48.9	49.9	49.9	49.5	49.6	50.1	48.7	50.3	49.8	49.8	49.8	49.8	49.8
6	23.9	22.8	23.8	25.3	23.8	23.9	21.1	23.9	23.9	24.2	24.2	23.8	23.8	23.8	23.9	23.9	23.9	23.9	23.9
7	122.4	142.8	122.7	152.1	128.7	129.2	76.4	129.0	129.2	138.9	138.3	125.6	138.7	125.4	129.0	129.4	129.4	129.5	129.5
8	135.3	126.6	134.9	144.6	134.3	134.1	142.5	134.3	134.3	134.7	134.9	139.8	126.6	138.4	134.1	133.8	133.8	133.8	133.3
9	54.7	49.8	55.0	50.3	52.8	51.9	51.3	52.7	52.6	51.5	51.4	51.9	50.0	53.1	52.1	52.4	52.4	52.4	52.4
10	36.9	42.0	37.0	36.8	36.9	36.6	37.8	37.1	37.1	37.1	37.2	36.7	36.8	37.0	36.9	37.0	37.0	37.0	37.0
11	25.7	25.2	25.9	25.4	23.8	25.0	29.1	20.6	20.5	21.3	21.4	25.2	28.4	24.3	25.1	21.7	21.9	21.1	21.8
12	42.1	68.5	35.4	41.4	38.9	41.4	38.8	44.2	44.0	40.4	40.7	41.2	64.3	39.3	41.2	40.3	40.2	40.1	40.2
13	140.3		145.4	143.2	30.7	142.5	145.2	73.4	73.4	73.1	73.2	140.3		30.9	139.7	61.2	64.0	61.4	64.0
14	123.6		73.9	118.1	35.4	118.8	118.6	145.0	145.2	76.6	75.5	123.7		39.0	123.9	62.9	62.5	62.7	62.5
15	59.5		64.7	61.5	62.9	61.3	61.4	111.9	111.7	63.3	63.2	59.2		61.2	59.3	61.2	2.4	61.4	2.3
16	16.4		112.4	16.4	19.6	16.5	16.6	27.8	27.7	22.5	23.8	16.4		19.9	16.3	16.9	15.7	16.9	15.8
17	22.1	165.6	22.6	194.8	67.7	67.8	112.1	67.8	67.8	169.5	169.5	66.0	66.4	66.0	67.7	67.9	67.6	67.7	67.7
18	33.2	32.9	33.2	33.1	33.1	33.0	33.1	33.1	33.0	32.8	32.8	33.1	33.1	33.1	33.0	33.0	33.0	33.0	33.0
19	21.9	21.5	21.9	21.9	21.8	21.8	21.4	21.8	21.8	21.8	21.9	21.9	21.8	21.8	21.8	21.8	21.8	21.8	21.8
20	13.6	13.4	13.7	14.2	13.6	13.7	13.7	13.7	13.7	14.2	14.3	13.7	13.6	13.7	13.8	13.8	13.7	13.7	13.7
OCOMe			170.5	171.1	171.1	171.1	170.1	170.9	170.9	170.7	170.7				170.8	170.9	170.6	170.8	170.8
OCOMe			21.7	21.0	21.1	21.1	21.2	21.1	21.1	21.0	20.9				21.1	21.1	21.2	21.1	21.1
OCOMe			169.9		170.7	170.7	170.4			170.5	170.2								
OCOMe			21.0		20.9	21.0	21.0			20.8	20.8								
COOMe										51.5	51.4								

latter with NaI yielded **23**, that by reduction with Zn–HOAc gave **10** ($[\alpha]_D$ −15.9°).

Compounds **11** and **12** are two natural methyl esters that are identified as methyl 13*R*-hydroxy-14*S*,15-diacetoxy-7-labden-17-oate and methyl 13*S*-hydroxy-14*R*,15-diacetoxy-7-labden-17-oate by comparison with authentic samples [12].

EXPERIMENTAL

Spectral analysis. NMR spectra were obtained on a Bruker SP 200 MHz spectrometer, operating at 200 MHz for ^{1}H and 50.3 MHz for ^{13}C, respectively. Chemical shifts are given in ppm and are referenced in $CDCl_3$ to the residual $CHCl_3$, 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C, respectively, unless otherwise stated. Coupling constants are given in Hz. ^{13}C NMR data are given in Table 1. Mps were determined in a Kofler type hot-stage apparatus and are uncorr. IR spectra were recorded in a BOMEM MB-100 FTIR spectrometer. Mass spectra were obtained in a VG TS 250 mass spectrometer by electron ionization with a potential of 70 eV.

Extraction and isolation. The extraction of the aerial parts of *H. viscosum* (Valparaiso) and fractioning of the neutral part was previously described [1, 5]. The more polar frs F (29.7%) and G (3.5%) [5] are the ones studied now.

Fr. F was chromatographed on a silica gel column and eluted with *n*-hexane–EtOAc mixt. of increasing polarity affording 3 main frs: I (hexane–EtOAc 9:1), II (hexane–EtOAc 4:1) and III (hexane–EtOAc 1:1).

From fr. I by CC over silica gel were isolated squalene, phytol and **1** (90 mg).

From fr. II were isolated sitosterol (3.1 g) by crystallization in MeOH and from the mother liquor by CC on silica gel/$AgNO_3$ (10%) eluting with hexane–EtOAc 85:15, **2** (250 mg).

From fr. III (previously acetylated with Ac_2O–pyridine) by CC were isolated: **3** (hexane–EtOAc 98:2, 150 mg), **4** (hexane–EtOAc 9:1, 612 mg), **5** (hexane–EtOAc 4:1, 42 mg), **6** and **7** (hexane–EtOAc 7:3, 964 mg), **8** (hexane–EtOAc 1:1, 189 mg), **9** and **10** (hexane–EtOAc 1:1, 165 mg).

Compounds **6** and **7** were isolated by CC on silica gel/$AgNO_3$ (10%) eluting with hexane–EtOAc 95:5 gave **6** (248 mg) and with hexane–EtOAc 9:1, **7** (520 mg).

Compounds **9** and **10** were isolated by PTLC eluting with benzene–EtOAc 7:3 (× 3) giving **9** (15 mg) and **10** (28 mg).

Fr. G was acetylated with Ac_2O–pyridine and then by PTLC of the acetyl derivatives eluting with hexane–EtOAc 3:2, gave **11** (24 mg) and **12** (18 mg).

15-*Hydroxy*-7,13E-*labdadiene* (**1**). Oil. $[\alpha]_D$ +5.0° ($CHCl_3$; *c* 1.0). IR ν_{max}^{film} cm^{-1}: 3340 (broad), 1640, 1060, 1020, 1000 and 810. ^{1}H: δ5.42 (1H, *t*, *J* = 6.8 Hz, H-14), 5.40 (1H, *m*, H-7), 4.15 (2H, *d*, *J* = 6.82 Hz, H-15), 1.69 (3H, *s*, H-17), 1.68 (3H, *s*, H-16), 0.87 (3H, *s*, H-19), 0.84 (3H, *s*, H-18), 0.74 (3H, *s*, H-20). ^{13}C: δ Table 1.

13,14,15,16-tetranor-7-*Labden*-17,12-*olide* (**2**). Oil. $[\alpha]_D$ −17.0° ($CHCl_3$; *c* 1.1). IR ν_{max}^{film} cm^{-1}: 1720, 1640, 1400, 1270, 1250, 1230, 1120, 930, 740. ^{1}H: δ7.26 (1H, *m*, H-7), 4.42 (1H, *ddd*, *J* = 11.2, 4.4, 2.5 Hz, H_a-12), 4.18 (1H, *ddd*, *J* = 11.2, 2.4, 2.4 Hz, H_b-12), 0.88, 0.85, 0.73 (3H, *s*, each). ^{13}C: δ Table 1.

14,15-*Diacetoxy*-7,13(16)-*labdadiene* (**3**). Oil. IR ν_{max}^{film} cm^{-1}: 3090, 1750, 1650, 1240, 1050 and 910. ^{1}H: δ5.41 (2H, *m*, H-7, H-14), 5.10 (1H, *s*, H_a-16), 5.01 (1H, *s*, H_b-16), 4.27 (1H, *m*, H_a-15), 4.11 (1H, *m*, H_b-15), 2.09 (3H, *s*, OOC-Me), 2.05 (3H, *s*, OOC-Me), 1.69 (3H, *s*, H-17), 0.88 (3H, *s*, H-19), 0.85 (3H, *s*, H-18), 0.76 (3H, *s*, H-20). ^{13}C: δ Table 1.

15-*Acetoxy*-7,13E-*labdadien*-17-*al* (**4**). Oil. $[\alpha]_D$ −17.2° ($CHCl_3$; *c* 2.4). IR ν_{max}^{film} cm^{-1}: 1750, 1690, 1640, 1460, 1370, 1240, 1030. ^{1}H: δ9.15 (1H, *s*, H-17), 6.8 (1H, *m*, H-7), 5.42 (1H, *t*, *J* = 6.8 Hz, H-14), 4.61 (2H, *d*, *J* = 6.8 Hz, H-15), 2.01 (3H, *s*, OOC-Me), 1.69 (3H, *s*, H-16), 0.90 (3H, *s*, H-19), 0.86 (3H, *s*, H-18), 0.77 (3H, *s*, H-20). ^{13}C: δ Table 1.

13,14,15,16-tetranor-12,17-*Diacetoxy*-7-*labdene* (**5**). Mp 135–136°. $[\alpha]_D$ −35.6° ($CHCl_3$; *c* 1.1). IR ν_{max}^{film} cm^{-1}: 1740, 1240 and 1040. ^{1}H: δ5.86 (1H, *m*, H-7), 4.56 and 4.48 (1H, *d*, each, J_{AB} = 12.2 Hz, H-17), 4.07 (2H, *m*, H-12), 2.07 and 2.05 (3H, *s*, each, OOC-Me), 0.89, 0.87 and 0.77 (3H, *s*, each, H-19, H-18 and H-20).

15,17-*Diacetoxy*-7-*labdene* (**6**). Oil. $[\alpha]_D$ −9.7° ($CHCl_3$; *c* 0.8). IR ν_{max}^{film} cm^{-1}: 1740, 1470, 1380, 1240, 1030. ^{1}H: δ5.78 (1H, *m*, H-7), 4.54 and 4.40 (1H, *d*, each, *J* = 12.2 Hz, H-17), 4.07 (2H, *t*, *J* = 6.8 Hz, H-15), 2.04 (3H, *s*, OOC-Me), 2.02 (3H, *s*, OOC-Me), 0.90 (3H, *d*, *J* = 6.1 Hz, H-16), 0.86 (3H, *s*, H-19), 0.84 (3H, *s*, H-18) and 0.74 (3H, *s*, H-20). ^{13}C: δ Table 1.

15,17-*Diacetoxy*-7,13E-*labdadiene* (**7**). Oil. $[\alpha]_D$ −12.6° ($CHCl_3$; *c* 1.1). IR ν_{max}^{film} cm^{-1}: 1740, 1680, 1450, 1370, 1240, 1030 and 960. ^{1}H: δ5.81 (1H, *m*, H-7), 5.33 (1H, *t*, *J* = 7.3 Hz, H-14), 4.57 (2H, *d*, *J* = 7.3 Hz, H-15), 4.55 and 4.46 (1H, *d*, each, J_{AB} = 12.2 Hz, H-17), 2.06 (3H, *s*, OOC-Me), 2.05 (3H, *s*, OOC-Me), 1.69 (3H, *s*, H-16), 0.88 (3H, *s*, H-19), 0.86 (3H, *s*, H-18) and 0.75 (3H, *s*, H-20). ^{13}C: δ Table 1.

7α,16-*Diacetoxy*-8(17),13E-*labdadiene* (**8**). Oil. $[\alpha]_D$ −30.9° ($CHCl_3$; *c* 1.1). IR ν_{max}^{film} cm^{-1}: 1740, 1640, 1440, 1310, 1240. ^{1}H: δ5.40 (1H, *m*, H-7), 5.29 (1H, *t*, *J* = 7.4 Hz, H-14), 5.18 (1H, *s*, H_a-17), 4.76 (1H, *s*, H_b-17), 4.59 (2H, *d*, *J* = 7.3 Hz, H-15), 2.05 (3H, *s*, OOC-Me), 2.04 (3H, *s*, OOC-Me), 1.69 (3H, *s*, H-16), 0.83 (3H, *s*, H-19), 0.79 (3H, *s*, H-18) and 0.68 (3H, *s*, H-20). ^{13}C: δ Table 1.

13(S)-*Hydroxy*-17-*acetoxy*-7,14-*labdadiene* (**9**). Oil. $[\alpha]_D$ −3.1° ($CHCl_3$; *c* 0.5). IR ν_{max}^{film} cm^{-1}: 3400, 3060, 1740, 1680, 1460, 1380, 1240, 1030, 910, 820. ^{1}H: δ5.89 (1H, *dd*, *J* = 10.7 and 17.6 Hz, H-14), 5.79 (1H, *m*, H-7), 5.19 (1H, *dd*, *J* = 1.5 and 7.6 Hz, H_a-15), 5.05 (1H, *dd*, *J* = 1.5 and 10.7 Hz, H_b-15), 4.63 and 4.39 (1H, *d*, each, J_{AB} = 12.2 Hz, H-17), 2.06 (3H, *s*, OOC-Me), 1.26 (3H, *s*, H-16), 0.88, 0.86 and 0.76 (3H, *s*, each, Me-19, Me-18 and Me-20). ^{13}C: δ Table 1. EIMS *m/z* (rel. int.): 330 (15), 288 (20), 270 (60), 243 (15), 203 (100), 187 (80), 124 (70), 109 (99), 82 (95), 69 (55), 55 (53).

17-*Acetoxy*-13(R)-*hydroxy*-7,14-*labdadiene* (**10**). Oil. $[\alpha]_D$ −15.9° ($CHCl_3$; *c* 0.7). IR ν_{max}^{film} cm^{-1}: 3420, 1730,

1230, 1110, 910. ^{1}H: δ5.89 (1H, *dd*, J = 10.7 and 17.1 Hz, H-14), 5.80 (1H, *m*, H-7), 5.20 (1H, *dd*, J = 17.1 and 1.5 Hz, H-15), 5.05 (1H, *dd*, J = 10.7 and 1.5 Hz, H-15), 4.64 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 4.37 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 2.06 (3H, *s*, Me-COO), 1.26 (3H, *s*, Me-16), 0.88, 0.86 and 0.76 (3H, *s*, each, Me-19, Me-18 and Me-20). ^{13}C: δ Table 1. EIMS *m/z* (rel. int.): 330 (10), 288 (25), 270 (65), 243 (10), 203 (100), 187 (80), 124 (60), 109 (95), 82 (90), 69 (65), 55 (50).

Methyl 13R-*hydroxy*-14S,15-*diacetoxy*-7-*labden*-17-*oate* (**11**). Oil. $[\alpha]_D$ −41.5° ($CHCl_3$; *c* 0.8). IR ν_{max}^{film} cm^{-1}: 1750, 1720. 1650, 1470, 1380, 1250, 870. ^{1}H: δ6.7 (1H, *m*, H-7), 5.0 (1H, *dd*, J_{BX} = 8.3, J_{AX} = 2.4 Hz, H-14), 4.5 (1H, *dd*, J_{AB} = 12.2, J_{AX} = 2.4 Hz, H_a-15), 4.16 (1H, *dd*, J_{AB} = 12.2, J_{BX} = 8.3 Hz, H_b-15), 3.69 (3H, *s*, –COOMe), 2.17 and 2.03 (3H, *s*, each, Me–COO–), 1.14 (3H, *s*, H-16), 0.90, 0.86 and 0.82 (3H, *s*, each, Me-19, Me-18 and Me-20). ^{13}C: δ Table 1.

Methyl 13S-*hydroxy*-14R,15-*diacetoxy*-7-*labden*-17-*oate* (**12**). Oil. $[\alpha]_D$ −21.3° ($CHCl_3$; *c* 2.7). IR ν_{max}^{film} cm^{-1}: 1750, 1720, 1650, 1470, 1250, 870. ^{1}H: δ6.72 (1H, *m*, H-7), 5.06 (1H, *dd*, J_{BX} = 8.3, J_{AX} = 2.4 Hz, H-14), 4.52 (1H, *dd*, J_{AB} = 12.2, J_{AX} = 2.4 Hz, H_a-15), 4.17 (1H, *dd*, J_{AB} = 12.2, J_{BX} = 8.3 Hz, H_b-15), 3.66 (3H, *s*, –COOMe), 2.09 and 2.01 (3H, *s*, each, OCOMe), 1.19 (3H, *s*, Me-16), 0.89, 0.85 and 0.81 (3H, *s*, each, Me-19, Me-18 and Me-20). ^{13}C: δ Table 1.

Reduction of **4**. $LiAlH_4$ (12 mg) was added to a stirred, ice-cooled soln of **4** (40 mg) in dry Et_2O (5 ml) and the mixt. was stirred for 30 min at room temp. under N_2. Then Et_2O (30 ml), some drops of H_2O and Na_2SO_4 (200 mg) were added, the mixt. was kept for 15 min. Following this, it was filtered and the solvent evapd off to give **13** (32 mg). Oil. $[\alpha]_D$ +1.8° ($CHCl_3$; *c* 0.9). IR ν_{max}^{film} cm^{-1}: 3330 (broad), 1650, 1090 and 990. ^{1}H: δ5.76 (1H, *m*, H-7), 5.44 (1H, *t*, J = 7.3 Hz, H-14), 4.17 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 4.15 (2H, *d*, J = 7.3 Hz, H-15), 3.99 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 1.69 (3H, *s*, Me-16), 0.88, 0.86 and 0.74 (3H, *s*, each, Me-19, Me-18 and Me-20). ^{13}C: δ Table 1.

Alkaline hydrolysis of **5**. Compound **5** (15 mg) was treated with 2 ml NaOH in MeOH (10%) for 24 hr at room temp. Usual work-up gave **15** (13 mg). Mp 90° ($CHCl_3$). $[\alpha]_D$ −20.9° ($CHCl_3$; *c* 2.0). IR ν_{max}^{film} cm^{-1}: 3380, 1640, 1470, 1400, 1380, 1060, 1010. ^{1}H: δ5.71 (1H, *m*, H-7), 4.28 and 3.84 (1H, *d*, each, J_{AB} = 12.2 Hz, H-17), 3.77 (1H, *ddd*, J = 10.3, 10.3, 5.4 Hz, H_a-12), 3.66 (1H, *ddd*, J = 10.3, 8.4 and 5.8 Hz, H_b-12), 0.88 (3H, *s*, Me-19), 0.86 (3H, *s*, Me-18) and 0.76 (3H, *s*, Me-20). ^{13}C: δ Table 1.

Alkaline hydrolysis of **6**. Upon subjecting 50 mg of **6** to the above treatment, 46 mg of **16** was obtained. Oil, $[\alpha]_D$ −8.4° ($CHCl_3$; *c* 0.4). IR ν_{max}^{film} cm^{-1}: 3340 (broad), 1640, 1440, 1360, 1090, 810. ^{1}H: δ5.75 (1H, *m*, H-7), 4.14 (1H, *d*, J = 12.2 Hz, H_a-17), 3.98 (1H, *d*, J = 12.2 Hz, H_b-17), 3.69 (2H, *m*, H-15), 0.92 (3H, *d*, J = 6.4 Hz, H-16), 0.88 (3H, *s*, Me-19), 0.86 (3H, *s*, Me-18), 0.75 (3H, *s*, Me-20). ^{13}C: δ Table 1.

Reduction of **14** *with* $LiAlH_4$. Upon subjecting 90 mg of **14** to the above treatment, 82 mg of **13** was obtained.

Partial hydrolysis of **7**. Compound **7** (500 mg) was treated with 5 ml K_2CO_3 in MeOH (5%) and the mixt. was stirred for 30 min at room temp., then H_2O was added and the mixt. was extracted with ether. Usual work-up gave 478 mg of crude that was chromatographed over silica gel giving **7** (76 mg, *n*-hexane–EtOAc, 7:3), **17** (264 mg, *n*-hexane–EtOAc, 3:2) and **13** (128 mg, *n*-hexane–EtOAc, 1:1). Compound **17**, oil. IR ν_{max}^{film} cm^{-1}: 3380, 1740, 1240, 1020. ^{1}H: δ5.80 (1H, *m*, H-7), 5.40 (1H, *t*, J = 6.8 Hz, H-14), 4.58 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 4.44 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 4.14 (2H, *d*, J = 6.8 Hz, H-15), 2.08 (3H, *s*, Me–COO–), 1.67 (3H, *s*, Me-16), 0.88, 0.86 and 0.75 (3H, *s*, each, Me-19, Me-18 and Me-20). ^{13}C: δ Table 1.

Sharpless epoxidation of **17**. A 100-ml flask equipped with a Teflon-coated magnetic stirring bar was oven-dried, then flushed with N_2. The flask was charged with dry CH_2Cl_2 (8 ml) and cooled by stirring in a −23° bath. The following liquids were then added sequentially via syringe while stirring in the cooling bath: titanium tetra-isopropoxide (0.15 ml, 0.5 mmol), L-(+)-diethyl tartrate [L-(+)-DET, 0.09 ml, 0.5 mmol]; the mixt. was stirred for 20 min before the next addition, **17** (180 mg) in dry CH_2Cl_2 (10 ml), the mixt. was kept for 20 min and, finally, *t*-butyl hydroperoxide (0.34 ml) was added. The resulting homogeneous soln was then stored (18 hr) in the freezer at −20° in a sealed reaction vessel. The flask was then placed in a −23° bath and 10% aq. tartaric acid soln (6 ml) was added while stirring; the aq. layer solidified. After 30 min, the cooling bath was removed and stirring was continued at room temp. until the aq. layer became clear. After sepn of the aq. layer, the organic layer was washed once with H_2O, dried with Na_2SO_4 and concd to give a yellow oil (178 mg); this was chromatographed on silica gel eluting with *n*-hexane–EtOAc (3:2) to afford **18** (140 mg). Oil, IR ν_{max}^{film} cm^{-1}: 3420, 1740, 1240, 1020. ^{1}H: δ5.81 (1H, *m*, H-7), 4.55 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 4.44 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 3.80 (1H, *dd*, J = 12.2, 4.9 Hz, H-15), 3.68 (1H, *dd*, J = 12.2, 6.4 Hz, H-15), 2.93 (1H, *dd*, J = 6.4 and 4.9 Hz, H-14), 2.05 (3H, *s*, Me–COO–), 1.28 (3H, *s*, Me-16), 0.87, 0.85 and 0.76 (3H, *s*, each, Me-19, Me-18 and Me-20). ^{13}C: δ Table 1.

Esterification of **18** *with* TsCl. TsCl (74 mg) was added portion-wise to a stirred and ice-cooled soln of **18** (140 mg) in dry pyridine (3 ml). The mixt. was left to stand overnight at 0–5°, then poured into ice-H_2O and extracted with Et_2O. The ether extract was washed with H_2O, $CuSO_4$ aq., $NaHCO_3$ aq. and brine, dried (Na_2SO_4) and concd *in vacuo* to give **19** (143 mg). Oil, IR ν_{max}^{film} cm^{-1}: 1740, 1610, 1500, 1240, 1180, 980. ^{1}H: δ7.80 (2H, *d*, J = 8.3 Hz), 7.35 (2H, *d*, J = 8.3 Hz), 5.80 (1H, *m*, H-7), 4.49 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 4.39 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 4.13 (1H, *dd*, J = 12.2 and 2.9 Hz, H-15), 4.07 (1H, *dd*, J = 12.2 and 2.9 Hz, H-15), 2.95 (1H, *t*, J = 2.9 Hz, H-14), 2.44 (3H, *s*, Me-Ar), 2.03 (3H, *s*, Me–COO–), 1.19 (3H, *s*, Me-16), 0.86, 0.84 and 0.74 (3H, *s*, each, Me-19, Me-18 and Me-20).

Reaction of **19** *with* NaI. NaI (136 mg) was added to a soln of **19** (142 mg) in Me_2CO (7 ml) and the mixt. was stirred and heated under reflux for 7 hr. Then it was concd *in vacuo*, diluted with H_2O and extracted with Et_2O. The

ether soln was washed with H_2O, Na_2SO_3 aq., $NaHCO_3$ aq. and brine, dried (Na_2SO_4) and concd in *vacuo* to give **20** (112 mg). Oil, IR ν_{max}^{film} cm^{-1}: 1740, 1240, 1170, 950, 850. ^1H: δ5.80 (1H, *m*, H-7), 4.53 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 4.42 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 3.33 (1H, *dd*, J = 4.9 and 8.8 Hz, H-14), 2.99 (2H, *m*, H-15), 2.04 (3H, *s*, Me–COO–), 1.25 (3H, *s*, Me-16), 0.86, 0.83 and 0.75 (3H, *s*, each, Me-19, Me-18 and Me-20). ^{13}C: δ Table 1.

Reduction of **20** *with* Zn–AcOH. Zn dust (62 mg) was added portion-wise to a stirred and ice-cooled soln of **20** (112 mg) in AcOH (3 ml). The mixt. was stirred for 30 min after the addition at room temp. Then it was diluted with Et_2O and filtered through Celite, the Et_2O soln was washed with H_2O, $Na_2S_2O_3$ aq., $NaHCO_3$ aq. and brine, dried (Na_2SO_4) and concd *in vacuo* to give 109 mg of crude. PTLC of the crude eluting (×2) with *n*-hexane–EtOAc (4:1) gave **9** (54 mg).

Sharpless reaction of **17**. In the same manner as described above, **17** (80 mg) using D(−)DET (0.04 ml) yielded **21** (60 mg). Oil, IR ν_{max}^{film} cm^{-1}: 3420, 1740, 1240, 1030. ^1H: δ5.82 (1H, *m*, H-7), 4.56 (1H, *d*, J_{AB} = 12.2 Hz, H_a-17), 4.42 (1H, *d*, J_{AB} = 12.2 Hz, H_b-17), 3.75 (2H, *m*, H-15), 2.95 (1H, *dd*, J = 6.4 and 4.9 Hz, H-14), 2.06 (3H, *s*, $MeCO_2$–), 1.24 (3H, *s*, Me-16), 0.88 and 0.76 (3H, *s*, each, Me-19 and Me-20). ^{13}C: δ Table 1.

Esterification of **21** *with* TsCl. Upon subjecting **21** (60 mg) to the above treatment **22** (61 mg) was obtained. IR ν_{max}^{film} cm^{-1}: 1740, 1610, 1505, 1240, 1180, 980. ^1H: δ7.80 (2H, *d*, J = 8.3 Hz), 7.36 (2H, *d*, J = 8.3 Hz), 5.82 (1H, *m*, H-7), 4.50 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 4.40 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 4.14 (1H, *dd*, J = 12.2 and 3.0 Hz, H-15), 4.08 (1H, *dd*, J = 12.2 and 3.0 Hz, H-15), 2.98 (1H, *t*, J = 3.0 Hz, H-14), 2.45 (3H, *s*, Me-Ar), 2.04 (3H, *s*, Me–COO–), 1.15 (3H, *s*, Me-16), 0.87, 0.85 and 0.75 (3H, *s*, each, Me-19, Me-18 and Me-20). ^{13}C: δ Table 1.

Reaction of **22** with NaI. Upon subjecting **22** (61 mg) to the above treatment **23** (49 mg) was obtained. IR ν_{max}^{film} cm^{-1}: 1740, 1240, 1010, 950. ^1H: δ5.83 (1H, *m*, H-7), 4.55 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 4.43 (1H, *d*, J_{AB} = 12.2 Hz, H-17), 3.38 (1H, *dd*, J = 4.9 and 8.8 Hz, H-14), 3.02 (2H, *m*, H-15), 2.07 (3H, *s*, Me–COO–), 1.28 (3H, *s*, Me-16), 0.89, 0.87 and 0.77 (3H, *s*, each, Me-19, Me-18 and Me-20). ^{13}C: δ Table 1.

Reduction of **23** *with* Zn–AcOH. Upon subjecting **23** (49 mg) to the above treatment **10** (19 mg) was obtained.

Acknowledgement—The authors thank the CICYT for financial support (PB 88-0369).

REFERENCES

1. Pascual Teresa, J. de, Urones, J. G., Marcos, I. S., Díez Martín, D. and Alvarez, V. (1986) *Phytochemistry* **25**, 711.
2. Urones, J. G., Marcos, I. S., Basabe, P., Alonso, C. A., Díez, D., Garrido, N. M., Oliva, I. M., Rodilla, J. S., Slawin, A. M. Z. and Williams, D. J. (1990) *Tetrahedron Letters* **31**, 4501.
3. Urones, J. G., Marcos, I. S., Basabe, P., Alonso, C. A., Díez, D., Garrido, N. M. and Oliva, I. M. (1990) *Tetrahedron Letters* **31**, 5665.
4. Urones, J. G., Basabe, P., Marcos, I. S., Alonso, C., Oliva, I. M., Garrido, N. M., Díez, D. and Lithgow, A. M. (1992) *Tetrahedron Letters* **33**, 5269.
5. Urones, J. G., Basabe, P., Marcos, I. S., Alonso, C., Oliva, I. M., Garrido, N. M., Díez, D. and Lithgow, A. M. (1993) *Tetrahedron* **49**, 4051.
6. Urones, J. G., Basabe, P., Marcos, I. S., Alonso, C., Oliva, I. M., Garrido, N. M., Díez, D. and Lithgow, A. M. (1993) *Phytochemistry* (1993) **34**, 747.
7. Urones, J. G., Marcos, I. S., Cubillo, L., Monje, V. A., Hernandez, J. M. and Basabe, P. (1989) *Phytochemistry* **28**, 651.
8. Suziki, H., Noma, M. and Kawashima, N. (1983) *Phytochemistry* **22**, 1294.
9. Urones, J. G., Marcos, I. S., Martin, D. D., Alonso, C. A., Brito Palma, F. and Rodilla, J. M. L. (1989) *Phytochemistry* **28**, 557.
10. Urones, J. G., Marcos, I. S., Cubillo, L., Garrido, N. M. and Basabe, P. (1990) *Phytochemistry* **29**, 2223.
11. Urones, J. G., Marcos, I. S. and Díez, D. (1988) *Tetrahedron* **44**, 4547.
12. Urones, J. G., Marcos, I. S., Basabe, P., Sexmero, M. J., Díez, D., Garrido, N. M. and Prieto, J. E. S. (1990) *Tetrahedron* **46**, 2495.
13. Urones, J. G., Marcos, I. S., Sexmero, M. J., Basabe, P. and Lithgow, A. (1990) *Phytochemistry* **29**, 1247.
14. Pfenninger, A. (1986) *Synthesis* 89.
15. Mori, K. and Ueda, H. (1981) *Tetrahedron* **37**, 2581.