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FORMATION OF ORTHOESTERS IN THE SHARPLESS ASYMMETRIC EPOXIDATION : HEMISYNTHESIS OF LABDANES.

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Summary: The orthoesters, **4a** and **4b** were obtained from treatment of methyl-7,13E-labdadien-17-oate, **3**, under Sharpless asymmetric epoxidation conditions . The hydrolysis followed by dehydration of the orthoesters led to the synthesis of two new diterpenic acids isolated from *Halimium viscosum* : 14R,15-dihydroxy-7,13(16)-labdadien-17-oic and 14S,15-dihydroxy-7,13(16)-labdadien-17-oic .

Introduction

Several acidic diterpenes have been isolated as their methyl esters from the acid fraction of an extract of *Halimium viscosum* (Valparaiso)[1,2,3], together with the two unsaturated diols **1** and **2**, the two epimers at C-14 of methyl 14,15-dihydroxy-7,13(16)labdadien-17-oate.

The stereochemistry at C-14 was determined by asymmetric hemisynthesis of **1** and **2** from methyl 15-hydroxy-7,13 E-labdadien-17-oate **3**, the major product isolated from the plant.

Treatment of **3** under Sharpless asymmetric epoxidation conditions[4] afforded orthoesters instead of epoxides. Hydrolysis and acetylation of **5a** and **5b** gave the two lactones **6a** and **6b** and the compounds **7a** and **7b** respectively, as predicted by Deslongchamps[5,6,7].

Dehydration of **7a** and **7b** led to the natural products **1** and **2**, the C-14 stereochemistry of which was further corroborated by circular dichroism.

Results and discussion

The most polar components of the acidic fraction were the epimeric unsaturated dihydroxy compounds **1** and **2** (IR 3480, 1730, 1650 cm^{-1}).

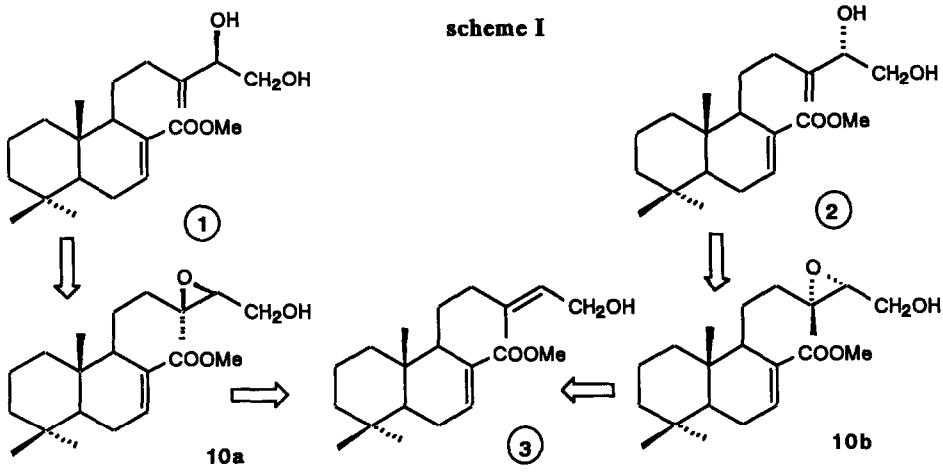
In the ^1H NMR spectrum signals corresponding to the -CH=C-COOMe group were observed (6.7 ppm, 1H, m; 3.7 ppm, 3H,s) together with three methyl singlets (0.91, 0.87 and 0.82 ppm) which were similar to those observed for the rest of the components of the acidic fraction.

The difference between **1** and **2** was manifested only in slight variations in the signals due to the CH_2=C-CHOH-CH_2OH group of the side chain, from which it was deduced that these compounds were the C-14 epimers of methyl 14(R/S), 15-dihydroxy-7,13(16)-labdadien-17-oate.

1 and **2** were synthesised from the major component of the acidic fraction of the extract of *H. viscosum* (Valparaiso) **3**[1].

The retrohemisynthetic plan for **1** and **2** is shown in scheme I.

scheme I



Enantioselective epoxidation following the procedure of Sharpless[4] should lead to **10a** and **10b**. Transformation of these to give **1** and **2**, respectively, could then be accomplished by direct ring opening of the oxirane with a base[8] or alternatively by dehydration of the triols arising from acid hydrolysis using $HClO_4$/DMF[9].

Synthesis of 1.

Reaction of **3** under Sharpless asymmetric epoxidation conditions using L(+) diethyl tartrate gave **4a** (scheme II).

The conclusion that **4a** was not the desired oxirane product of the Sharpless reaction could be drawn immediately on examination of its spectroscopic properties (there were no signals due to protons on an oxirane ring in the ^1H NMR spectum).

The ^1H NMR spectum of a mixture of epoxides **10a** and **10b**, obtained by reaction of **3** with mCPBA, showed a signal due to the oxirane protons at 2.9 ppm (1H, m).

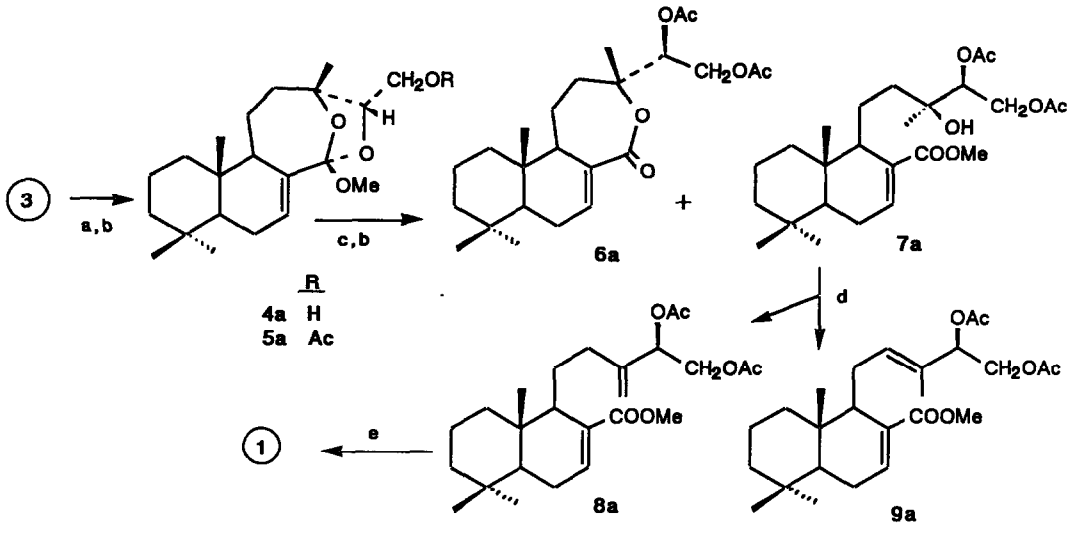
In the ^1H NMR spectum of **4a** signals were observed at : 6.43 ppm (1H, m, H-7); 3.98 (1H,dd), 3.88 (1H, dd) and 3.68 ppm (1H, dd) due to the ABX system of a -O$\underline{H}_2$C-C$\underline{H}$-O- group; 3.42 ppm (3H,s)due to a methoxy group (not a methyl ester) and four methyl singlets, one of which at 1.43 ppm was deshielded by a neighboring oxygenated function.

In the ^{13}C-NMR signals due to 21 carbons were observed, one of which, a quaternary carbon at 117.91 ppm, suggested the presence of an orthoester.

The position of the free hydroxyl group was determined by acetylation of **4a** to give **5a**, which showed a signal at 4.19 ppm (2H, m) in its ^1H NMR spectrum, due to H-15.

The orthoester structures of **4a** and **5a** depicted in the figures were deduced from all these data.

A general procedure for the preparation of orthoesters consists of reaction of an ester with an epoxide under Lewis acid conditions[10].



a) $Ti(iPrO)_4$, L(+)DET, tBuOOH,CH_2Cl_2; b) Ac_2O/Py.; c) HCl, Me_2CO; d) $POCl_3$, Py.; e) NaOH/MeOH (10%).

scheme II

In this work it is clear that, due to the presence of the Lewis acid $Ti(iPrO)_4$ in the reaction mixture, the epoxide initially formed in the Sharpless epoxidation undergoes further intramolecular reaction with the C-17 methoxycarbonyl group[11].

The hydrolysis of geranyl acetate 2,3 epoxide[9] with $HClO_4$/DMF gives, after hydrolysis of the formates, a diol in which the configuration at C-3 has been inverted. This reaction goes via a cyclic ortho amide.

In the reaction described here the opening of the oxirane ring occurs in the same way, but under these conditions the orthoester formed is stable and appears as a reaction product. Inversion takes place at C-13 because, as will be shown later, C-14 retains the stereochemistry predicted by Sharpless.

Hydrolysis of **5a** with hydrochloric acid in acetone at pH 3 followed by acetylation of the crude mixture gave, after chromatography, the lactone **6a** (IR 1710 cm^{-1}) and the acetoxy ester **7a** (IR 3500, 1720 cm^{-1}; ^{1}H-NMR 3.69 ppm, 3H, s). The result of this hydrolysis is in accordance with the work of Deslongchamps[5,6,7].

Stereoelectronic effects in **5a** determine that the initial bond breaking process occur at either the C_{17}-O-C_{13} bond or at the C_{17}-O-C_{14} bond, but not at the C_{17}-O-Me bond; this results in the formation of a hemiorthoester, a tetrahedral intermediate, which may adopt various conformations from which, after acetylation, either the lactone **6a** or the acetoxy-ester **7a** are obtained.

The disubstituted olefin **8a** (IR: 3080, 1640 and 890 cm^{-1}; ^{1}H-NMR 5.07 ppm (1H,s), 4.97 ppm (1H,s); ^{13}C-NMR 122.45 ppm C-16) and trisubstituted olefin **9a** (^{1}H-NMR 5.49 ppm (1H,t), 1.63 ppm (3H,s)) were obtained from the reaction of **7a** with phosphorus oxychloride.

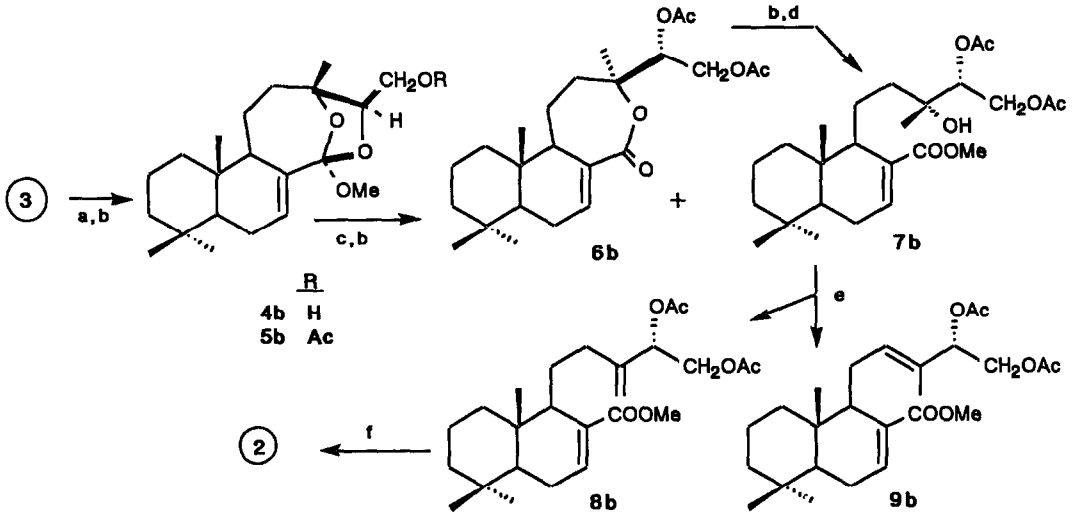
Basic hydrolysis (NaOH/MeOH 10%, 6 h, r.t.) of **8a** deprotected the hydroxyl group to give the dihydroxy compound **1** directly.

The absolute configuration at C-14 of **1** was confirmed by circular dichroism. Thus, when **1** was dissolved in hexane and $Pr(dpm)_3$ added, a positive Cotton effect ($\Delta\varepsilon_{313} = +1.2$) was observed in the C.D. curve, confirming that the configuration at C-14 was (R)[12], the desired stereochemistry.

Therefore **1** is Methyl 14 R, 15-dihydroxy-7,13(16)-labdadien-17-oate.

Synthesis of 2.

2 was obtained following a parallel synthesis to that of **1**. In this instance, the use of D(-) DET in the Sharpless epoxidation led to the orthoester **4b**, which gave **5b** on acetylation, (scheme III).



a) $Ti(iPrO)_4$, D(-)DET, $tBuOOH,CH_2Cl_2$; b) Ac_2O/Py.; c) HCl, $MeOH/H_2O$;d)K_2CO_3, ICH_3; e) $POCl_3$,Py.; f) NaOH/MeOH (10%)

scheme III

Treatment of **5b** under the same conditions as previously applied to **5a** (acid hydrolysis using HCl/acetone at pH 3 followed by acetylation) led only to a poor yield of the lactone **6b** and trace quantities of the ester **7b**. When **5b** was subjected to hydrolysis with $HCl/MeOH/H_2O$ at pH 1, the ratio of ester to lactone products was inverted, but once again high yields were not obtained.

The acetoxy ester **7b** was obtained in good yield by K_2CO_3/MeOH hydrolysis of the ε-lactone **6b**, followed by heating under reflux with methyl iodide[13] and acetylation.

Dehydration of **7b** with $POCl_3$ produced a mixture of olefins **8b** and **9b**, the spectra of which were very similar to those of the corresponding epimers **8a** and **9a**, respectively.

Alkaline hydrolysis of **8b** (10% NaOH/MeOH, 7 h, r.t.) gave **2**.

The circular dichrosim of **2**, determined as before in hexane in the presence of $Pr(dpm)_3$, showed a negative Cotton effect ($\Delta\varepsilon_{313} = -0.3$) in the CD curve, confirming that the C-14 stereochemistry of **2** was S[12].

Thus, **2** is Methyl 14S,15-dihydroxy-7,13(16)-labdadien-17-oate.

TABLE.- ^{13}C Chemical shifts, in ppm. Assignment based on DEPT experiments.

C	1	2	4a	4b	5b	6a	6b	7a	7b	8a	8b	9b
1	39.59	39.50	39.51	39.18	39.20	39.01	38.47	39.32	39.42	39.55	39.48	40.15
2	18.59	18.58	18.97	18.92	18.92	18.66	18.72	18.56	18.60	18.58	18.58	18.61
3	42.12	42.13	42.16	42.21	42.22	41.94	42.04	42.11	42.14	42.16	42.14	42.04
4	32.84	32.84	32.96	32.90	32.89	32.90	33.18	33.06	32.83	32.84	32.84	32.85
5	49.57	49.56	49.64	49.41	49.42	49.00	49.85	49.51	49.56	49.61	49.58	49.51
6	24.11	24.09	23.14	23.19	23.50	24.61	25.42	24.23	24.19	24.04	24.04	25.47
7	137.93	137.71	125.26	125.29	125.62	142.65	144.31	138.86	138.29	137.36	137.39	137.91
8	135.08	135.12	135.61	137.29	136.64	135.08	133.16	134.71	134.85	135.20	135.17	134.22
9	51.01	51.04	52.18	51.62	51.67	50.80	50.51	51.54	51.42	51.02	51.04	50.02
10	37.06	37.01	36.63	36.45	36.46	36.55	36.58	37.07	37.16	37.07	37.01	36.94
11	27.54	27.60	22.21	23.56	23.19	22.41	21.61	21.27	21.44	27.15	27.26	23.84
12	34.53	34.44	34.33	37.84	37.78	37.70	35.53	40.41	40.72	34.44	34.60	129.97
13	149.57	149.56	81.38	83.62	83.73	82.55	81.18	73.11	80.68	145.58	145.49	129.10
14	74.91	75.03	85.71	85.35	81.32	75.24	76.55	76.58	75.54	73.99	73.81	75.97
15	65.78	65.80	62.13	60.85	62.18	62.83	62.80	63.27	63.23	64.69	64.63	64.48
16	110.88	110.73	25.93	23.56	23.44	20.87	24.20	22.47	23.75	112.45	112.50	14.73
17	169.63	169.64	119.71	119.27	119.57	162.52	168.68	169.52	169.51	169.95	169.48	169.03
18	33.12	33.12	33.21	33.30	33.29	33.11	33.12	32.82	32.83	33.14	33.14	33.33
19	21.91	21.92	22.16	22.09	22.07	21.97	21.18	21.81	21.85	21.94	21.93	22.16
20	14.34	14.31	13.99	13.65	13.63	13.76	13.28	14.22	14.32	14.32	14.31	13.14
COO-Me	51.45	51.41						51.54	51.42	51.28	51.31	51.30
O-Me			48.61	48.73	48.73							
OOC-Me					170.65	171.51	170.77	170.85	170.72	171.22	170.58	170.68
OOC-Me					20.83	20.72	20.72	21.00	20.89	21.01	21.03	20.99
OOC-Me						170.52	170.18	170.45	170.23	168.53	169.90	169.90
OOC-Me						20.72	20.72	20.81	20.76	20.71	20.74	20.76

Experimental part

I.R. spectra were measured as films for oils on a Beckman-33-IR spectrophotometer. The 200 MHz ^1H NMR and 50 MHz ^{13}C NMR spectra were determined on a Bruker WP-200-SY spectrometer usually in $CDCl_3$, except where otherwise indicated. Chemical shifts in ppm are reported as relative to TMS in the ^1H NMR and to $CDCl_3$ at 77.0 ppm in the ^{13}C NMR. Mass spectra were recorded on a VG-TS 250 instrument at 70 ev. *m/z* followed by relative abundance (%) are stated. Optical rotations were performed in a chloroformic solution, except where otherwise indicated, with a digital Perkin-Elmer-241 polarimeter. Microanalysis were performed by the Instituto de Quimica organica de CSIC (Madrid, Spain).

The raw-material 3 was isolated from a n-hexane extract of *Halimium viscosum*, as reported in reference[1].

Sharpless reaction of 3 : 4a .-A 100 ml, flask equiped with a Teflon-coated magnetic stirring bar is oven-dried, then flushed with nitrogen .The flask is charged with dry dichloromethane (10 ml) and cooled by stirring in a -23º C bath. Then the following liquids are added sequentially via syringe while stirring in the cooling bath : titanium tetraisopropoxide (0.88 ml , 3 mmol), L-(+)-diethyl tartrate [L-(+)-DET, 0.55 ml, 3 mmol]; the mixture is stirred 5 min. before the next addition, 3 (1 g, 3 mmol) in dry CH_2Cl_2 (5 ml) and, finally, t-butyl hydroperoxide (2 ml , 6 mmol). The resulting homogeneous solution is then stored overnight (18 hours) in the freezer at

-20º C in the sealed reaction vessel. Then the flask is placed in a -23º C bath and 10% aqueous tartaric acid solution (10 ml) is added while stirring; the aqueous layer solidifies. After 30 min., the cooling bath is removed and stirring is continued at room temperature until the aqueous layer becomes clear. After separation of the aqueous layer, the organic layer is washed once with water, dried with Na_2SO_4 and concentrated to give a yellow oil (1.2 g); this is chromatographed on SiO_2 eluting with hexane : AcOEt (80:20) to afford **4a**.- (740 mg, 74 %) Colourless oil ; ν_{max} (film) 3440, 3060, 1625, 1450, 1250, 1180, 1100, 960 ; δ_H ($CDCl_3$) 6.34 (1H , m, 7-H), 3.98 (1H, dd, J= 7.3, 3.4 Hz, 14-H), 3.88 (1H, dd, J =11.2, 7.3, 15-H_A), 3.68 (1H, dd, J =11.2, 3.4 Hz, 15-H_B), 3.42 (3H, s, -COOMe), 1.43 (3H, s, 16-Me), 0.89 (3H, s, 19-Me), 0.86 (3H, s, 18-Me), 0.79 (3H, s, 20-Me) ; δ_C ($CDCl_3$) See table; Anal. Calcd for $C_{21}H_{34}O_4$: C,71.96; H, 9.78; Found C, 71.89; H, 9.74.

Acetylation of **4a** : **5a** - 474 mg of **4a** dissolved in 1.5 ml of anhydrous pyridine were acetylated with 2 ml of Ac_2O at room temperature overnight. Ice was added and after one hour the product was recovered in the usual way, yielding **5a** (438 mg). Colourless oil ; ν_{max} (film) 1740, 1320, 1240, 1110, 960, 850 ; δ_H ($CDCl_3$), 6.32 (1H, m, 7-H), 4.19 (2H, m, 15-H), 4.02 (1H, m, 14-H), 3.30 (3H, s, -COOMe), 2.08 (3H, s, -AcO), 1.43 (3H, s, 16-Me), 0.88 (3H, s, 19-Me), 0.84 (3H, s, 18-Me), 0.78 (3H, s, 20-Me).

Hydrolysis of **5a** : **6a**, **7a**.-HCl (1N , 8 ml) was added to a solution of **5a** (438 mg) in acetone (22 ml). The mixure was stirred at room temperature for 2 days, and was then heated to 40º C for a further 3 hours. Following this, water was added and the solvent was eliminated under vacuum. The crude mixture was extracted with ether. The ethereal solution was washed with Na_2CO_3 and water, dried (Na_2SO_4) and concentrated in vacuo. The residue (364 mg) was dissolved in dry pyridine (1 ml) and acetylated with Ac_2O (1 ml) at room temperature for 16 hours. The excess of Ac_2O was hydrolyzed with ice-water and the product was extracted with ether in the usual way, giving 368 mg of a mixture of acetylderivatives that were separated by column chromatography on SiO_2 and eluting with hexane ; AcOET (95:5, gradient) to afford : 112 mg of the initial sustrate, 150 mg (41%) of **6a** and 90 mg (24.5%) of **7a** .

14 S,15-diacetoxy-7-labden-13 R,17-olide : **6a**.-Colourless oil ; ν_{max} (film) 1750, 1710, 1630, 1240 ; δ_H ($CDCl_3$) 7.02 (1H, m, 7-H), 5.24 (1H, dd, J = 8.3, 2.4 Hz, 14-H), 4.60 (1H, dd, J = 11.7, 8.3 Hz, 15-H_A), 4.19 (1H, dd, J =11.7, 2.4 Hz, 15-H_B), 2.12 (3H, s, AcO-), 2.03 (3H, s, AcO-), 1.34 (3H, s, 16-Me), 0.91 (3H, s, 19-Me), 0.89 (3H, s, 18-Me), 0.77 (3H, s, 20-Me); δ_C ($CDCl_3$) See table; Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.53; H, 8.63; Found C, 68.48; H, 8.60.

Methyl-14 S,15-diacetoxy-13 R-hydroxy-7-labden-17-oate : **7a** .-Colourless oil ; $[\alpha]_D$ -41.9º (c o.78 , $CHCl_3$); ν_{max} (film) 1750, 1720, 1650, 1470, 1380, 1250, 870 ; δ_H ($CDCl_3$), 6.76 (1H , m , 7-H), 5.03 (1H, dd, J = 8.3, 2.4 Hz, 14-H), 4.53 (1H, dd, J =12.2, 8.3 Hz, 15-H_A), 4.16 (1H, dd, J = 12.2, 2.4 Hz, 15-H_B), 3.69 (3H, s, -COOMe), 2.17 (3H, s, AcO-), 2.03 (3H, s, AcO-), 1.14 (3H, s, 16-Me), 0.90 (3H, s, 19-Me), 0.86 (3H, s, 18-Me), 0.82 (3H, s, 20-Me) ; δ_C ($CDCl_3$) See table .

Dehydration of **7a** with $POCl_3$ / Py : **8a** , **9a** .-$POCl_3$ (freshly distilled , 0.75 ml) was added to a solution of **7a** (86.8 mg) in anhydrous pyridine (8 ml) cooled to 0º C. Having completed the addition, the mixture was stirred at room temperature for 18 hours. Then ice and ether were added. The ethereal solution was washed with 2N HCl, aqueous 5% $NaHCO_3$ and water and dried over Na_2SO_4. The solvent was eliminated under vacuum, yielding a crude mixture (80 mg) which by p.t.l.c. on SiO_2 eluting twice with hexane : ether (50:50) afforded : **8a** (31 mg) and **9a** (29 mg).

Methyl-14 R,15-diacetoxy-7,13(16)-labdadien-17-oate ; **8a** .-Colourless oil ; ν_{max} (film) 3080, 1740, 1720, 1640, 1240 890; δ_H ($CDCl_3$) 6.68 (1H, m, 7-H), 5.38 (1H, dd, J = 7.8, 3.4 Hz, 14-H), 5.07 (1H, s, 16-H), 4.97 (1H, s, 16-H), 4.26 (1H, dd , J= 11.7 ,3.4 Hz, 15-H_A), 4.11 (1H, dd, J=11.7, 7.8 Hz, 15-H_B), 3.71 (3H, s, -COOMe), 2.10 (3H, s, AcO-), 2.06 (3H, s, AcO-), 0.91 (3H, s, 19-Me), 0.88 (3H, s, 18-Me), 0.84 (3H, s, 20-Me); δ_C ($CDCl_3$) See table .

Methyl-14 R,15-diacetoxy-7,12-labdadien-17-oate : **9a**.-Colourless oil; ν_{max} (film) 1740, 1720, 1640, 1240 ; δ_H ($CDCl_3$) 6.71 (1H, m, 7-H), 5.49 (1H, t, J=5.8 Hz, 12-H), 5.29 (1H, dd, J=4.3, 4.3 Hz, 14-H), 4.17 (1H, dd, J=11.7, 8.3 Hz, 15-H_A), 4.06 (1H, dd, J=11.7, 8.3 Hz, 15-H_B), 3.67 (3H, s, -COOMe), 2.07 (3H, s, AcO-), 2.05 (3H, s, AcO-), 1.63 (3H, s, 16-Me), 0.91 (3H, s, 19-Me), 0.88 (3H, s, 18-Me), 0.80 (3H, s, 20-Me).

Alkaline hydrolysis of **8a**: **1**.-26 mg of **8a** are saponificated at room temperature with 3 ml of 1M NaOH/MeOH for 6 hours. The usual procedure is followed, yielding 23 mg of **1**.

Methyl-14 R,15-dihydoxy-7,13(16)-labdadien-17-oate : 1.- Colourless oil; $[\alpha]_D$ -47.4º (c 0.4, $CHCl_3$); CD $\Delta\varepsilon_{313}$ +1.2 (n-hexane); ν_{max} (film) 3440, 1730, 1650 ; δ_H ($CDCl_3$) 6.71 (1H, m, 7-H), 5.08 (1H , s, 16-H), 4.94 (1H, s, 16-H), 4.18 (1H, dd, J=7.3, 3.9 Hz, 14-H), 3.73 (1H, dd, J=11.2, 3.9 Hz, 15-H_A), 3.71 (3H, s, COOMe), 3.56 (1H, dd, J=11.2, 7.3 Hz, 15-H_B), 0.91 (3H, s, 16-Me), 0.87 (3H, s, 18-Me), 0.83 (3H, s, 20-Me). δ_C ($CDCl_3$) See table; EIMS 70 ev, *m/z* (rel. int.):350[M^+](5), 332(15), 319(18), 287(30), 248(70), 190(30), 149(60), 109(100); Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78; Found C, 71.87; H, 9.72.

Sharpless reaction of 3 : **4b**.-A 100 ml, flask equipped with a Teflon-coated magnetic stirring bar is over-dried, then flushed with nitrogen. The flask is charged with dry dichloromethane (35 ml) and cooled by stirring in a -23º C bath. The following liquids are then added sequentially via syringe while stirring in the cooling bath : Ti ($iPrO)_4$ (1.6 ml, 5.5 mmol,); D-(-)-DET (1.0 ml, 5.5 mmol), the mixture is stirred 5 min. before the next addition, 3 (1.84 g, 5.5 mmol) in dry CH_2Cl_2 (5 ml) and, finally, t-butyl hydroperoxide (3.7 ml, 11 mmol). The homogeneous solution is then stored overnight (18 hours) in the freezer at -20º C in the sealed reaction vessel. In the same manner as described for the previous Sharpless reaction, a crude mixture was obtained that was chromatographed on SiO_2, to afford **4b** (1,2 g, 65%). Colourless oil ; ν_{max} (film) 3450, 3050, 1645, 1270, 1250, 1190, 975, 850 ; δ_H ($CDCl_3$) 6.22 (1H, m, 7-H), 4.04 (1H, dd, J=7.8, 3.4 Hz, 14-H), 3.94 (1H, dd, J=11.2, 7.8 Hz, 15-H_A), 3.62 (1H, dd, J=11.2, 3.4 Hz, 15-H_B), 3.38 (3H, s, COOMe), 1.36 (3H, s, 16-Me), 0.88 (3H, s, 19-Me) 0.84 (3H, s, 18-Me), 0,74 (3H, s, 20-Me). δ_C ($CDCl_3$) See table; Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78; Found C, 71.94; H, 9.80.

Acetylation of **4b** : **5b**.-1.20 g of **4b** dissolved in 2 ml of anhydrous pyridine were acetylated with 2 ml (20.6 mmol) of Ac_2O at room temperature overnight. Ice was added and after 1 hour product was recovered in the usual way, yielding **5b** (1.20 g). Colourless oil ; ν_{max} (film) 1740, 1650, 1320, 1240, 1110, 960, 850.; δ_H ($CDCl_3$) 6.23 (1H, m, 7-H), 4.29 (1H, dd, J=11.7, 7.8 Hz, 15-H_A), 4.18 (1H, dd, J=11.7, 3.9 Hz, 15-H_B), 4.07 (1H, dd, J=7.8, 3.9 Hz, 14-H) 3.37 (3H, s, -COOMe), 2.08 (3H, s, AcO-), 1.37 (3H, s, 16-Me), 0.87 (3H, s, 19-Me), 0.83 (3H, s, 18-Me), 0.73 (3H, s, 20-Me). δ_C ($CDCl_3$) See table .

Hydrolysis of **5b** : **6b**, **7b**.- 250 mg of **5b** were dissolved in MeOH / H_2O (80:20). pH was adjusted to 1 by addition of 2M HCl. The mixture was stirred for 36 hours at 45º C. Following this, water was added and the solvent was eliminated under vacuum. The crude mixture was extracted with ether and the usual procedure was followed, a crude mixture was obtained that was dissolved in dry pyridine (2 ml) and then acetylated with Ac_2O (2 ml) at room temperature overnight. Ice was added and after one hour the product was recovered in the usual way, yielding after chromatography on SiO_2 and elution with hexane:AcOEt (90 :10, gradient): **5b** (108 mg, 43.4%), **6b** (443 mg, 17.3%) and **7b** (46 mg, 18,7%).

14 R,15-diacetoxy-7-labden-13S,17-olide :**6b** .-Colourless oil; ν_{max} (film); 1760, 1710, 1640, 1465, 1375, 980, 860; δ_H ($CDCl_3$) 7.12 (1H, m, 7-H), 5.11 (1H, dd, J=8.3, 2.4 Hz, 14-H), 4.55 (1H, dd, J=12.2, 2.4 Hz, 15-H_A), 4.18 (1H, dd, J=12.2, 8.3 Hz, 15-H_B), 2.09 (3H, s, AcO-), 2.02 (3H, s, AcO-), 1.48 (3H, s, 16-Me), 0.88 (6H, s, 19-Me, 18-Me), 0.71 (3H, s, 20-Me). δ_C ($CDCl_3$) See table, Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.53; H, 8.63; Found C, 68.56; H, 8.58.

Methyl-14 R,15-diacetoxy-13 S-hydroxy-7-labden-17-oate: **7b**.-Colourless oil; $[\alpha]_D$ -21.8º (c 2.7, $CHCl_3$); ν_{max} (film) 1750, 1720, 1650, 1470, 1250, 870; δ_H ($CDCl_3$) 6.72 (1H, m, 7-H), 5.06 (1H, dd, J=8.3, 2.4 Hz, 14-H), 4.52 (1H, dd, J=12.2, 2.4 Hz, 15-H_A), 4.17 (1H, dd, J=12.2, 8.3 Hz, 15-H_B), 3.66 (3H, s, -COOMe), 2.09 (3H, s, Aco-), 2.01 (3H, s, AcO-), 1.19 (3H, s, 16-Me), 0.89 (3H, s, 19-Me), 0.85 (3H, s, 18-Me), 0.81 (3H, s, 20-Me); δ_C ($CDCl_3$) See table.

Hydrolysis of **6b**; **7b**.-85 mg of **6b** were saponificated with 10 ml of 10% K_2CO_3/MeOH with a few drops of water. The mixture was kept refluxing overnight. Following this, ICH_3 was added and refluxing again for 18 hours. The solvent was eliminated and CH_2Cl_2 was added. The organic solution was washed with Na_2CO_3 and water, dried (Na_2SO_4) and concentrated. The residue (64 mg) was dissolved in dry pyridine (1 ml) and was acetylated with Ac_2O (1 ml) at room temperature overnight. The excess of Ac_2O was hydrolyzed with ice-water and the product was extracted with ether in the usual way, giving **7b**.

Dehydration of **7b** with $POCl_3$/Py .-$POCl_3$ (freshly distilled, 0.75 ml) was added to a solution of **7b** (86 mg) in anhydrous pyridine (7 ml), cooled to 0º C under N_2. Having completed the addition, the mixture was stirred at room temperature for 24 hours. In the same manner as described for the previous dehydration, a crude mixture (70 mg) was obtained that by p.t.l.c. on SiO_2, eluting twice with hexane:AcOEt (60:40) afforded: 30 mg of **8b** and 30 mg of **9b**.

Methyl-14 S,15-diacetoxy-7,13(16)-labdadien-17-oate : **8b**.-Colourless oil ; ν_{max} (film) 3080, 1750, 1720, 1650, 1460, 1440, 1370, 1240, 1050, 950, 890; δ_H ($CDCl_3$) 6.68 (1H, m, 7-H), 5.38 (1H, dd, J=7.8, 3.4 Hz, 14-H), 5.06 (1H, s, 16-H), 4.96 (1H, s, 16-H), 4.24 (1H, dd, J=12.2, 3.4 Hz, 15-H_A), 4.12 (1H, dd, J=12.2, 7.8 Hz, 15-H_B), 3.70 (3H, s, -COOMe), 2.09 (3H, s, AcO-), 2.05 (3H, s, AcO-), 0.90 (3H, s, 19-Me), 0.87 (3H, s, 18-Me), 0.82 (3H, s, 20-Me). δ_C ($CDCl_3$) See table.

Methyl-14 S,15-diacetoxy-7,12-labdadien-17-oate :**9b**.-Colourless oil; ν_{max} (film) 1750, 1715, 1650, 1440, 1370, 1220, 960; δ_H ($CDCl_3$) 6.72 (1H, m, 7-H) 5.49 (1H, t, J=6.3 Hz, 12-H), 5.29 (1H, dd, J=7.8, 4.4 Hz, 14-H), 4.15 (1H, dd, J=11.2, 4.4 Hz, 15-H_A), 4.07 (1H, dd, J=11.2, 7.8 Hz, 15-H_B), 3.65 (3H, s, -COOMe), 2.06 (3H, s, AcO-), 2.04 (3H, s, AcO-), 1.62 (3H, s, 16-Me), 0.91 (3H, s, 19-Me), 0.87 (3H, s, 18-Me), 0.81 (3H, s, 20-Me).δ_C ($CDCl_3$) See table.

Alkaline hydrolysis of **8b**:**2**.-20 mg of **8b** were saponificated at room temperature with 3 ml of 1M NaOH/MeOH for 7 hours. Following this, the solvent was eliminated under vacuum and the product was extracted with ether, in the usual way, giving 15 mg of **2**.

Methyl-14 S,15-dihydroxy-7,13(16)-labdadien-17-oate : **2**.- Colourless oil; $[\alpha]_D$ -37.1° (c 0.3 $CHCl_3$); CD $\Delta\varepsilon_{313}$ - 0.3 (n-hexane); ν_{max} (film) 3400, 1720, 1650, 1450, 1240, 900; δ_H ($CDCl_3$) 6.70 (1H, m 7-H), 5.09 (1H, s, 16-H), 4.94 (1H, s, 16-H), 4.20 (1H, dd, J=8.9, 7.3 Hz, 14-H), 3.70 (3H, s, -COOMe), 3.69 (1H, dd, J=11.2, 8.9 Hz, 15-H_A), 3.57 (1H, dd, J= 11.2, 7.3 Hz, 15-H_B), 0.91 (3H, s, 19-Me), 0.87 (3H, s, 18-Me), 0.82 (3H, s, 20-Me). δ_C ($CDCl_3$) See table; EIMS 70 ev, *m/z* (rel. int.):350[M^+](3), 332(12), 319(120, 287(28), 248(65), 190(45), 149(74), 109(100); Anal. Calcd for $C_{21}H_{34}O_4$: C,71.96; H, 9.78; Found C, 71.92; H, 9.73.

Reaction of **3** with m-CPBA : **10a/10b**.-Compound **3** (70 mg, 0.21 mmol) was dissolved in dry CH_2Cl_2 (5 ml) and m-CPBA (41 mg, o.24 mmol) was added. The mixture was stirred at room temperature for 4 hours. The solvent was eliminated and ether was added. The ethereal solution was washed with Na_2CO_3 and brine, dried (Na_2SO_4) and concentrated in vacuo, to obtain 68 mg of **10a/10b**.- Colourless oil; ν_{max} (film) 3450, 1730, 1655, 1470, 1440, 1280, 1250, 1150, 1070, 790; δ_H ($CDCl_3$) 6.68 (1H, m), 3.74 (2H, m), 3.71 (3H, s, -COOMe), 2.95 (1H, m, 14-H), 1.27 (3H, s), 0.90 (3H, s), 0.86 (3H, s), 0.82 (3H, s).

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