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REACTIVITY OF METHYL LABDANOLATE WITH LEAD TETRAACETATE

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Abstract.- The reactivity of the methyl labdanolate, 3 with $Pb(OAc)_4$ and/or $Pb(OAc)_4/I_2$ was studied. The long distance functionalization at C-12 led to compounds 8b and 9b, whose oxidation with RuO_4 produced 16 at a 100% yield. Compounds 14 and 15 were obtained from 16 (3:1). These compounds were also obtained from the O_3 oxidation of 8b and/or 9b at a lower yield, in addition to compound 16 that was obtained at a 57% yield in the same reaction. Also, when 3 was treated with $Pb(OAc)_4$, β -fragmentation products 7c and 7d were obtained; and when the same reaction was carried out with $Pb(OAc)_4/I_2$ the α-iodoketones 20b and 20c were also obtained.

Introduction.- Labdanolic acid 1 and labdanediol 2 are the major components of the resin of the Cistus ladaniferus L.[1]. Previously we have communicated[2] the results about the reactivity of 1, 2 and labdanolamide 4 with $Pb(OAc)_4$ or $Pb(OAc)_4/I_2$. The objetive of these research is the synthesis with a good yield of the α and β -levantanolides 14 and 15 through the intermediate cyclic ethers 8b and 9b. These ethers are precursors of norambreinolide that can easily be transformed into perfume fixers with the "ambergris" smell, such as "ambrox" and "isoambrox".

Moreover , the treatment of 3 with LTA yields β -fragmentation products with one more carbon than the labdane skeleton 7; with rearrangement and successive elimination, 12, and with elimination and later acetoxylation, 19. We also observed a saturation of the free radical of C-9 generated in this process yielding a seco-labdane, 20a, together with side reactions such as the α-iodination of the methyl-ketone resulting from the previous process of β -fragmentation, to give 20b and 20c.

Results and discussion

I.- Reaction of methyl labdanolate with lead tetraacetate[3]: In order to study the reactivity of the hydroxyl group of 3, the reaction with LTA was carried out under two different conditions: photolytic and thermal. Table 1 shows only the most important reactions.

Thermal treatment leads to products of O-acetylation 5, dehydration 6, β -fragmentation 7c and 7d, and oxidative cyclization 8b and 9b; however, in the photolytic reactions, besides the mentioned substances, products of acetoxylation at C-12 were isolated, (11a and 11b), of acetoxylation followed by dehydration, 10a and 10b; of β -fragmentation and rearrangement, 12a and 12b; and of β -fragmentation followed by degradative oxidation, 12c and 12d.

The structure of 5 was confirmed by partial synthesis[4] from 3.

The compounds 6a and 6c have been isolated in several species of Cistus[5] and, on the other hand, 6a, 6b and 6c have been obtained from 1 by dehydration[6] with $POCl_3$/Py.

7c and 7d are two isomeric keto-esters |MS: m|e 352(M^+,3%),$C_{22}H_{40}O_3$| which can only be separated by p.t.l.c. as ethylenedioxy derivatives[7] 7e and 7f, which by acid hydrolysis lead to 7c and 7d respectively. There are two seco-labdanes with an additional methyl at C-9, that are epimeric in this centre and that are describted for the first time.

The R-configuration at C-9 in compounds 7a, 7c and 7e imply the gauche conformation between the Me groups attached to C-9 and C-10 (figure 1), leading to shielding syn 1,2 interaction[8]. Therefore, the corresponding signals appear at a higher field (Table 2). However, since the S configuration at C-12 determines an antiperiplanar conformation between the two methyl groups, the interaction disappears and the signals appear at a lower field in the compounds 7b, 7d and 7f.

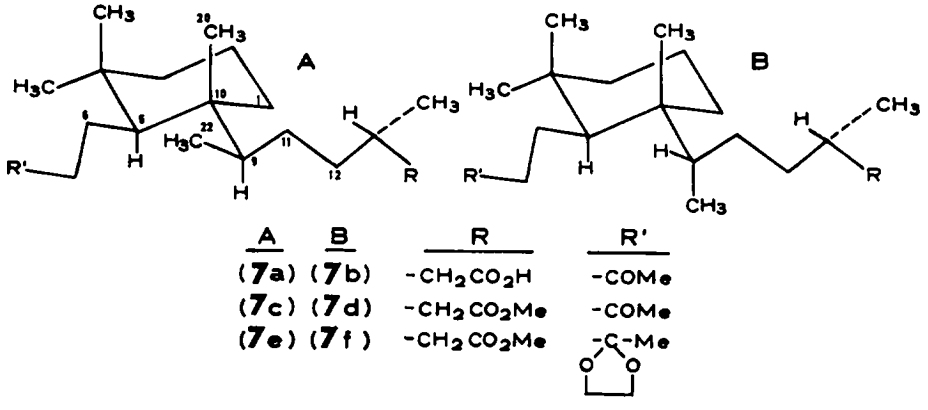
The differences in the ^{13}C chemical shifts of the atoms affected by the configuration change at C-9 (1, 5, 6, 9, 10, 20 and 22; Table 3), are explained by the following interactions: γ gauche, γ trans and δ syn axial[9,10,11] and allow the conformation of the assignments of the established configurations for 7c and 7d.

Table 1.- Conditions and product distribution in the reaction of methyl labdanolate 3 with lead tetraacetate

Treatment	Reaction[a]	Reaction time[i] (in h)	Conversion[k] (%)	Products (Yields in %)[j,l] 5	6[m]	7c,7d[n]	8b,9b[n]	10[n]	11[n]	12a,12b[n]	12c,12d[n]
Thermal[d]	I[b]	120	62	5	10	20	38				
	II	120	73	10	13	24	44				
	III[f]	120	19	13	15	10	30				
Photolytic[e]	IV	3	100		6	34	40	5	5	4	6
	V[c,g]	5	100		13	30	24	15	8	4	6
	VI[h]	15	100		5	16	20	5	4	2	4

[a]General reaction conditions: 8 moles of lead tetraacetate per mol of 3; 2.5 moles of pyridine per mol of LTA; 125 ml of solvent per gram of 3; boiling solvent temperature. [b]The molar ratio LTA/3= = 6:1 is used. [c]Fractionated addition of LTA (2 + 3 + 3 moles). [d]Cyclohexane as solvent and heating as inducer are used. [e]Benzene as solvent and u.v. light as inducer are utilized. [f]500 ml cyclohexane per gram of 3. [g]40 ml of benzene per gram of 3. [h]Reaction temperature is 20°C. [i]At the time indicated, the Pb(IV) test is negative. The excess of LTA on the stoichiometric quantity, decomposes into $Pb(OAc)_2$, CO_2 and methyl radicals. [j]In % respect to the transformed substrate. [k]Calculated according to the recuperated quantity of 3. [l]The other products to complete 100% yield are an unsolvable complex mixture of very polar acetoxylated substances. [m]The ratio 6a: 6b:6c is 1:3:1 in I and VI; 1:2:4 in II and V; 2:2:1 in III; and 2:1:3 in IV. [n]In every substance marked with the supra-index "n" the ratio between the corresponding two epimers is 1:1.

FIGURE 1



A	B	R	R'
(7a)	(7b)	$-CH_2CO_2H$	-COMe
(7c)	(7d)	$-CH_2CO_2Me$	-COMe
(7e)	(7f)	$-CH_2CO_2Me$	-C(O)(O)-Me

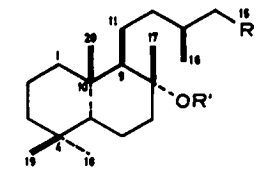
Table 2.- Chemical shift difference induced by the variation in the configuration at C-9 of 7a to 7f

	7c	7d	7e	7f	7a	7b
C(10)Me	0.82	0.88	0.75	0.85	0.80	0.87
C(9) Me	1.04	1.05	0.80	0.88	1.04	1.05

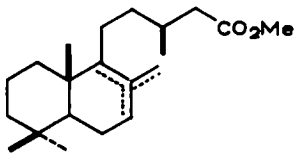
From the product of the reaction of 3 with $Pb(OAc)_4$ a mixture of cyclic ethers, 8b and 9b (1:1), have been isolated. They can only be separated by h.p.l.c. and their structure and stereochemistry have been determined[2].

The treatment of 8b and 9b (scheme 1) with $F_3B.OEt_2/Ac_2O$ yields 10a and 10b, respectively[12]. The alkaline hydrolisis of 10a and 10b leads to the γ-lactones 13a and 13b respectively, which are obtained directly from 8b and 9b by reaction[13] with $MgBr_2/Ac_2O$ or with HCl/MeOH.

If the ethers 8b and/or 9b adsorbed on silicagel are treated with O_3[14], the products obtained are two spiro γ-lactones 14 (12%) and 15 (4%) and a keto-hydroxy-ester 16 (57%). The formation of these products takes place by hydroxylation at C-12 of 8b and/or 9b, giving the corresponding

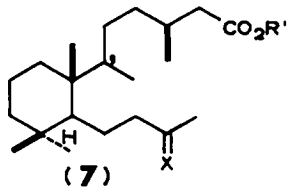


	R	R'
(1)	$-CO_2H$	H
(2)	$-CH_2OH$	H
(3)	$-CO_2Me$	H
(4)	$-CONH_2$	H
(5)	$-CO_2Me$	Ac



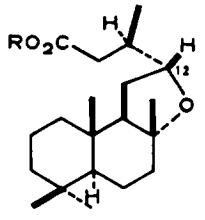
(6)

a	Δ^7
b	Δ^8
c	$\Delta^{8(17)}$



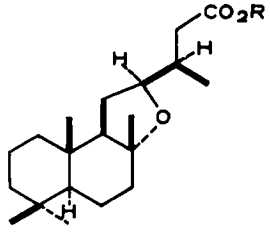
(7)

	X	R	Config. C-9
a	O	H	R
b	O	H	S
c	O	CH_3	R
d	O	CH_3	S
e		CH_3	R
f		CH_3	S



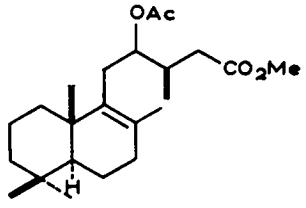
(8)

	R
a	H
b	CH_3



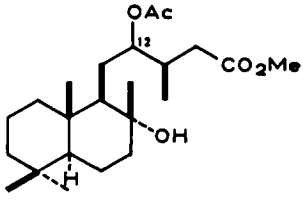
(9)

	R
a	H
b	CH_3



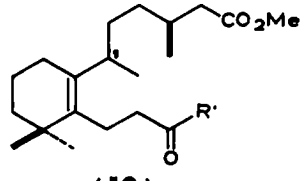
(10)

	Config. C-12
a	R
b	S



(11)

	Config. C-12
a	R
b	S



(12)

	R'	Config. C-9
a	CH_3	R
b	CH_3	S
c	OH	R
d	OH	S
e	OCH_3	R
f	OCH_3	S

hemiketals which are in equilibrium through a ketonic form 16.

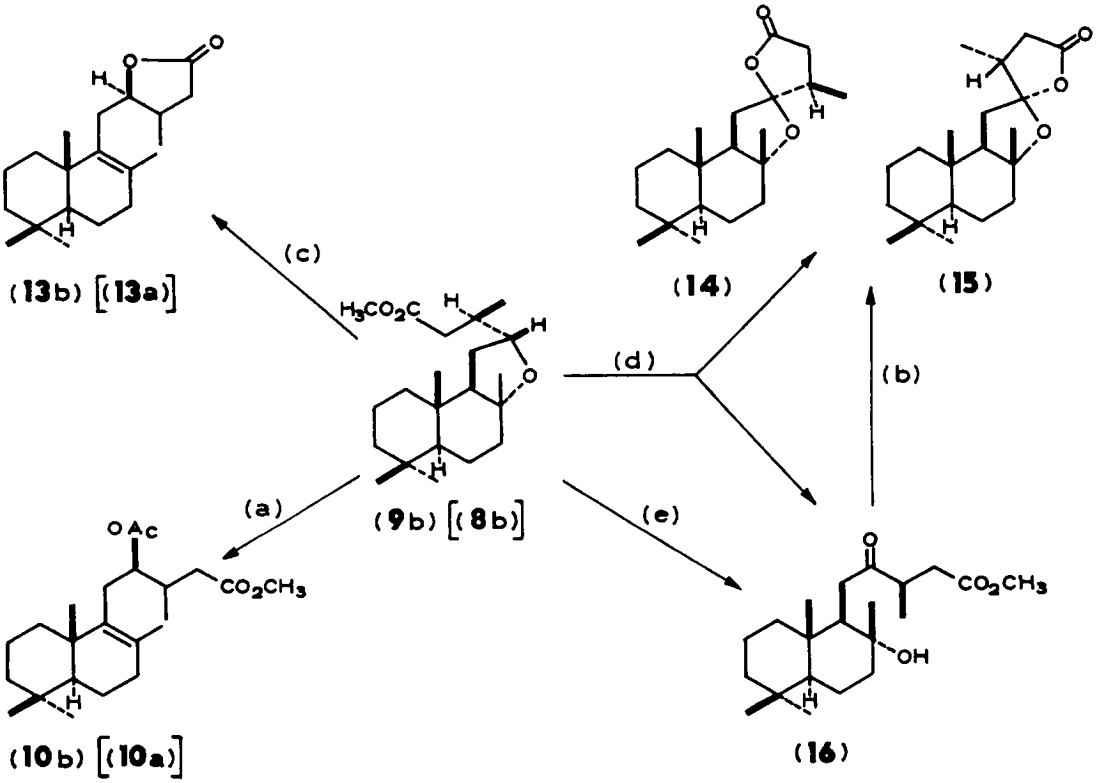
The spirolactones α and β-levantanolides 14 and 15 have been isolated from C. ladaniferus[15] and from turkish tobacco[16] and these have been previously synthesized by us[2].

By oxidation[17] of 8b and/or 9b with RuO_4 16 is obtained with a quantitative yield (scheme 1). The saponification of these leads exclusively to a mixture of 14 and 15 with a 3:1 ratio.

The structure of the products of acetoxylation at C-12, 11a and 11b were determined by alkaline hydrolisis (fig. 2) since they led to the γ-lactones 17 and 18, (labdanolide and 12-epi-labdanolide), respectively, isolated as natural product 15 and previously synthesized[2] by us from 1.

TABLE 3.- ^{13}C Chemical shifts, in ppm, of the pairs of epimers 7c/7d and 8b/9b
Asaigment based on DEPT experiments

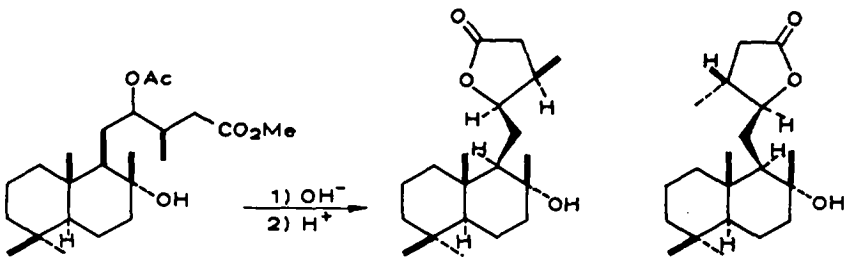
Carbon	C 7c	C 7d	C 8b	C 9b
1	38.58	38.30	39.38	39.71
2	18.93	18.93	18.44	18.48
3	42.73	42.64	42.55	42.60
4	35.12	34.98	33.09	33.14
5	52.07	51.12	57.53	57.21
6	20.59	20.40	20.91	20.62
7	37.85	37.72	40.10	37.49
8	212.85	212.70	82.76	78.74
9	48.93	48.63	61.63	59.92
10	37.32	37.72	36.67	35.13
11	30.02	29.91	28.35	25.34
12	45.09	44.99	80.49	90.73
13	30.52	30.45	36.33	36.39
14	41.74	41.73	40.56	40.11
15	173.60	173.60	173.70	173.56
16	19.85	19.92	16.20	15.39
17	28.37	28.35	24.60	21.29
18	34.23	34.32	33.53	33.58
19	22.27	22.16	21.08	21.21
20	16.76	17.11	17.51	14.81
21	51.23	51.22	51.09	51.23
22	19.78	19.11		



a) BF_3/Ac_2O; b) OH^-, H^+; c) $MgBr_2/Ac_2O$; d) O_3/SiO_2 r-85°C; e) RuO_4.

SCHEME 1

Figure 2



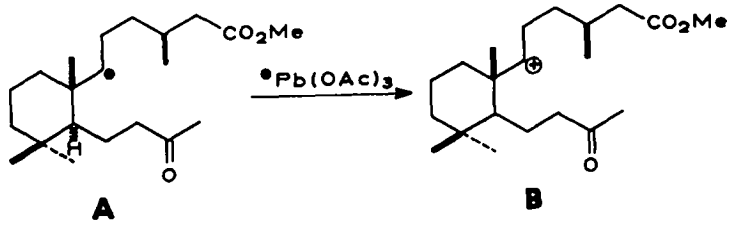
(11)
a 12 R
b 12 S

(18)
(12R)

(17)
(12S)

Keto-esters 12a and 12b are minor products of the β-fragmentation, and are epimers at C-9. In their ^{1}H NMR they show signals of two methyl groups on a quaternary carbon; two on a CH, one CO_2-CH_3, and one $COCH_3$. In the MS, the parent molecular ion M^+ of m/e ratio 336 corresponds to a formula of $C_{21}H_{36}O_3$, and the fragments with m/e ratios 279 (M^+-57) and 129 correspond to an allylic breakage of the side chains. Degradative oxidation performed "in situ" of 12a and 12b lead to acids 12c and 12d of molecular formula $C_{20}H_{34}O_4$ [MS: m/e 338(M^+) ; the base peak of mass 150 is produced by the loss of the two side chains]. The ^{1}H NMR spectrum shows signals corresponding to two CH_3-CH, two CH_3-C and one CO_2CH_3.

The acetate 5 was obtained through a mechanism previously described by Mosher and Kehr[19]. Compounds 7c and 7d are formed by β-fragmentation of the intermediate (A) by the free methyl radicals which are produced in the reaction[20]; 8b, 9b, 10a, 10b, 11a and 11b are formed through the free radical at C-12[18,21], and when A is oxidated to the carbocation (B), 12 (a, b and c) are obtained through a Wagner-Meerweinn rearrangement.



A B

II.- Reactions of methyl labdanolate with LTA and iodine[22].- Several reactions were carried out with 3 and $Pb(OAc)_4$ varying the amount of iodine (Table 4).

Table 4.- Conditions and product distribution in the reaction of lead tetraacetate and iodine with methyl labdanolate

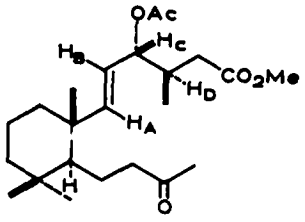
Reaction	I_2[c]	Temperature(°C)	Reaction time(in h)	Products (Yields in %)[d,e] 6	7c,7d[e]	8b,9b[e]	19	20a	20b,20c[e]
VII[b]	0.1	78	48	3	26	38	3		
VIII	1.2	78	1			54		2	20
IX	1.2	40	1.5			58		3	32
X	2.5	78	1			50		2	30
XI	1	20	1.5			64		2	34

[a]General reaction conditions: 6 moles of LTA per mol of 3; 2.5 moles of pyridine per mol of LTA; 80 ml of benzene per gram of 3; lighting with two lamps of 100 watts and heating as inducer. Conversion is 100% in every case. [b]Molar ratio LTA/3 is 8:1. [c]In moles per mol of 3. [d]The other products to complete 100% yield, are a unsolvable complex mixture of acetoxyl-and/or iodine-derivatives. [e]The ratio between the corresponding two epimers is 1:1.

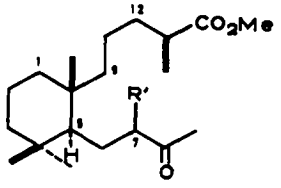
An indirect relationship can be established between the reaction temperature and the yield of 8b and 9b. In the reactions of 3 with LTA/I_2, the oxidative cyclization is favoured with respect to the β-fragmentation, reaching a 64% yield in reaction XI for compounds 8b and 9b[23].

In reaction VII, in addition to 6, 8b, 9b, 7c and 7d, a dehydrogenated and acetoxylated secolabdan, 19, is isolated, whose 1H n.m.r. spectrum shows, among other signals, a doublet of H_A (H_{AB} 15.4Hz) at 5.52 ppm, a dd of H_B (J_{BA} 15.4, J_{BC} 8.2Hz) at 5.15 ppm, and another dd (J_{CB} 8.2, J_{CD} 6.9Hz) at 4.96 ppm of H_C geminal to the acetoxyl group of C-12.

From the analysis of these signals it is undoubtable[24] that the double bond 9(11) has an E configuration and that the absolute configuration at C-12 must be R, since if it were S, the coupling constants would not agree with those observed in the spectrum.



(19)



(20)

	R'	Config. C-7
a	H	
b	I	R
c	I	S

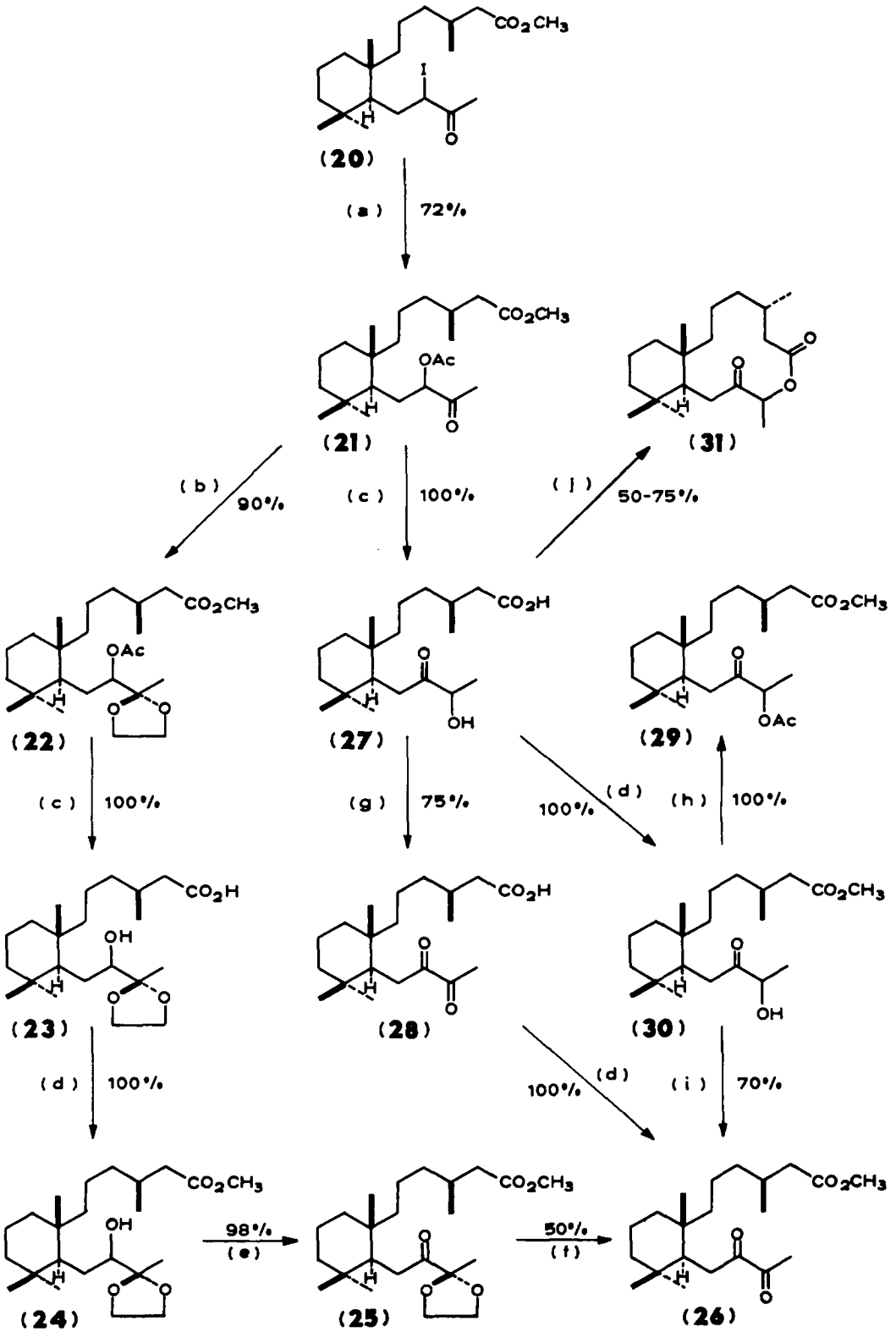
20a is a secolabdan with a molecular formula $C_{21}H_{38}O_3$, it is an isomer of 3 which is formed by β-fragmentation with the formation of a methyl-ketone, and whose structure is clear according to its spectroscopic properties.

Compounds 20b and 20c are two α-iodo-ketones epimeric at C-7 which are formed at a proportion of 1:1 by iodination of 20a in the reaction medium.

The formation of the reaction products of 3 with LTA/I_2 is easily explained[25]. The intermediate (A) is the precursor of 20a, 20b and 20c while (B) is the precursor of 19.

A series of transformations of 20b and 20c was carried out (scheme 2) to obtain a series of derivatives whose structure confirm the structure assigned to the new iodinated secolabdanes, following three parallel sequences of reactions which coincide in a final and unequivocal substance 26; a further aim was to prepare lactonizable secolabdan syntons to obtain macrolides with antibiotic activity, such as 31.

The formation of acyloin 27 from 21 is explained through an unisolated acyloinic intermediate which is rearranged 26 both in acid and basic media to give 27. This tautomeric transformation is shown by blocking the carbonyl in the form of ethylenedioxy derivative and following the sequence (b) $\longrightarrow$ (f) and by carrying out a comparative study of the isomers 21 and 29.



SCHEME 2

a) $AcOK/Me_2CO$; b) $HO-(CH_2)_2-OH/TsOH$; c) 1) KOH/MeOH, 2) HCl (pH 5); d) CH_2N_2; e) CrO_3/Py; f) HCl (0.1 M); g) O_2; h) Ac_2O/Py; i) $Cu(OAc)_2/AcOH$; j) 1) $(CH_2OH)_2/TsOH$, 2) DPDS and $(C_6H_5)_3P$ in xylene and after $AgClO_4$, 3) HCl (0.1 M), step in process of investigation and optimization.

EXPERIMENTAL

The i.r. spectra were determined on a Beckman-33-IR spectrophotometer in the form in each case indicated. The 60 MHz ^1H n.m.r. were performed in a Hitachi-Perkin-Elmer-R-24. The 200 MHz ^1H n.m.r. and 50 MHz ^{13}C n.m.r. spectra were determined on a Bruker WP-200-SY spectrometer using TMS as the internal standard. The mass spectra were obtained on a Hewlett-Packard-5930-A apparatus at 70 eV and at suitable temperature in each case, generally 170°C. The u.v. absorptions were measured on a digital Varian-8-654 spectrophotometer. Optical rotations were performed in a chloroformic solution except where otherwise indicated, with a digital Perkin-Elmer-241 polarimeter. Melting points were determined in a capillary tube in a Büchi apparatus or in a Kofler hotplate apparatus. G.l.c. analysis were carried out on a Varian-R-2740 chromatograph with H_2-flame detector using N_2 or He as the carrier gas. The separation by h.p.l.c. were carried out on a Water-PREP LC/System-500 chromatograph in the conditions specified in each case. Microanalysis were performed using a Carlo-Erba 1106 Elemental Analiser. The raw-material, (3), was isolated from a n-hexane extract of Cistus ladaniferus L., according to the reference 4.

Thermal reaction of 3 with lead tetraacetate.- Compound 3 (2 g, 5.9 mmol) in dry cyclohexane (250 ml) was reacted with LTA (21 g, 47 mmol) in the presence of anhydrous pyridine (117 ml), refluxing for 120 h. Ethyleneglycol (3 ml) is added and the mixture is shaken for 5 min; after this it is cooled, filtered and the solid is washed with hot cyclohexane. The organic solution is washed with water and dried with anhydrous Na_2SO_4. The crude mixture (2.02 g) is chromatographed on silica-gel, to yield five fractions. From fraction A (hexane-ether 95:5) the compound 5 (167 mg) is separated, fraction B (hexane-ether 95:5) is composed of a mixture of three isomers, which is rechromatographed on SiO_2-$AgNO_3$ (20%), giving 6b (63 mg) (hexane-ether 90:10), 6a (28 mg) (hexane-ether 85:15) and 6c (42 mg) (hexane-ether 80:20). Fraction C is homogeneous in t.l.c. but g.l.c. (DEGS 5%, 2m) reveals that it is composed of two substances (1:1) which are separated by h.p.l.c. on silicagel with hexane ether (90:10) (column prep. LC/system-500; solvent flow rate 45 ml/min, solvent pressure 5 atm; chamber pressure 32 atm) giving 324 mg of each epimer 8b and 9b. Fraction D (hexane-ether 85:15) (370 mg) is composed of a mixture (1:1) of two epimers 7c and 7d which are separated as ethylenedioxy-derivatives 7e and 7f, respectively, by p.t.l.c. on SiO_2 eluting twice with benzene-ether (95:5). Finally, fraction E (hexane-ether 70:30) yielded 0.540 g of initial product 3 (conversion 73%).

Photolytic reaction of 3 with lead tetraacetate.- Compound 3 (4 g, 12 mmol) in dry benzene (500 ml) and anhydrous pyridine (2.5 ml) is placed in a quartz flask and LTA (42 g,95 mmol) is added. The mixture under constant stirring is irradiated with a Hannau-PL-368 (80 w) UV lamp. After three hours, conversion is total; the mixture is cooled, filtered and the residue is washed with hot benzene. The solvent is eliminated by distillation under vacuum. The crude extract is dissolved in ether and the ethereal solution is washed with 0.5M HCl and water until a neutral pH. This is dried and concentrated, yielding a crude mixture (4.1 g) that is chromatographed on SiO_2 eluting with hexane-ether to afford in order of elution: 6, 192 mg, (hexane-ether 95:5); 8b and 9b,1.344 g (hexane-ether 90:10); 7c and 7d, 1.197 g (hexane-ether 85:15); 10a and 10b, 181 mg (hexane-ether 60:20); 12a and 12b, 140 mg (hexane-ether 60:20); 11a and 11b, 190 mg, (hexane-ether 70:30) which are separated in the form of the labdanolides 18 and 17, respectively; and finally 12c and 12d, 211 mg, (hexane-ether 50:50).

Methyl 8-Acetoxy-Labdan-15-oate, 5. Crystalline product, m.p. 82-83°C (from n-hexane); $[\alpha]_D$= = -27.3° (c 1.0, $CHCl_3$); ν_{max} (melted) 1740, 1250, 1225, 1205 and 1155 cm^{-1}; δ_H(60 MHz, CCl_4), 0.79(3H, s, 10-Me), 0.83(3H, s, 4-Me axial), 0.88(3H, s, 4-Me equatorial), 0.92(3H, d, J= 7Hz, 13-Me), 1.39(3H, s, 8-Me), 1.85(3H, s, AcO-) and 3.57(3H, s, $-CO_2Me$); m/z 380 [6%, $M^+(C_{23}H_{40}O_4)$], 365(3,M^+-15), 349(5,M^+-31), 337(4,M^+-43), 321(5,M^+-59), 320(10,M^+-AcOH), 306(8,M^+-74), 191(60, $C_{14}H_{23}^+$), 177(20, $C_{13}H_{21}^+$), 137(34,$C_{10}H_{17}^+$), 124(26,$C_9H_{16}^+$), 123(50,$C_9H_{15}^+$), 122(50,$C_9H_{14}^+$), 121 (60,$C_9H_{13}^+$), 109(82,$C_8H_{13}^+$), 95(54,$C_7H_{11}^+$), 69(100,$C_5H_9^+$); (Found: C, 72.5; H, 10.4; $C_{23}H_{40}O_4$ requires C, 72.6; H, 10.6%).

5 is synthesized from 3 in the following way: 3, 134 mg (0.35 mmol) in 0.5 ml of NEt_3 (freshly distilled over KOH) are reacted with 0.2 ml (2 mmol) of Ac_2O and 2 mg of p-(N,N-Dimethyl-amino)-pyridine at 50°C for 120 h. Excess Ac_2O is hydrolyzed with ice water and the product is extracted with ether in the usual way, giving 130 mg of crude mixture which is chromatographed on SiO_2 yielding 23 mg of 3 (conversion 98%) (benzene-ether 1:1) and 94 mg of 5 (benzene-ether 90:10)

Methyl 9(S)-8,8-Ethylendioxy-9-Methyl-8,9-seco-labdan-15-oate or Methyl 3(S),6(R), 1'(R), 2'(S)-3,6-Dimethyl-6-[1,3,3-trimethyl-2-(3,3-ethylen-dioxy-butyl)-1-cyclohexyl]-hexanoate, 7e.- Colourless oil; $[\alpha]_D^{20}$ -26.8° (c 0.6, $CHCl_3$); ν_{max} (film) 1745(C=O), 1165 and 1080 and 1050 cm^{-1}; δ_H(200 MHz, $CDCl_3$), 0.75(3H, s, 10-Me), 0.80(3H, d, J= 7Hz, 9-Me), 0.93(6H, s, 4-Me_2), 1.14(3H, s, 8-Me), 3.54(3H, s, $-CO_2Me$) and 3.78(4H, s, $-O-CH_2-CH_2-O-$); m/z 396[2%, $M^+(C_{24}H_{44}O_4)$], 381(10, M^+-15), 322(15, M^+-74), 309(26, M^+-87), 123(30), 95(32) and 87(100, $C_4H_7O_2^+$); (Found: C, 72.7; H, 11.0; $C_{24}H_{44}O_4$ requires C, 72.7; H, 11.2%).

Methyl 9(S)-8,8-Ethylendioxy-9-Methyl-8,9-seco-labdan-15-oate or Methyl 3(S),6(S),1'(R), 2'(S)-3,6-Dimethyl-6-[1,3,3-trimethyl-2-(3,3-ethylendioxy-butyl)-1-cyclohexyl]-hexanoate, (7f).- Colourless oil; $[\alpha]_D^{20}$ -11.9° (c 0.8, $CHCl_3$); ν_{max} (film) 1745, 1460, 1085 and 1050 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.85(3H, s, 10-Me), 0.88(6H, d, J= 7Hz, 9-Me and 13-Me), 0.90(6H, s, 4-Me_2), 1.15(3H, s, 8-Me), 3.54(3H, s, $-CO_2Me$) and 3.78(4H, s, $-O-(CH_2)_2-O-$); m/z 396[2%, $M^+(C_{24}H_{44}O_4)$], 381(18), 309(15), 137(30), 123(38), 109(30), 98(10), 95(40) and 87(100, $C_4H_7O_2^+$); Found: C, 72.6; H, 11.3; $C_{24}H_{44}O_4$ requires C, 72.7; H, 11.2%).

Methyl 9(R)-9-Methyl-8-oxo-8,9-seco-labdan-15-oate or Methyl 3(S), 6(R), 1'(R), 2'(S)-3,6-Dimethyl-6-[1,3,3-trimethyl-2-(3-oxo-butyl-1-cyclohexyl]-hexanoate, 7c.- 20 mg (0.05 mmol) of 7e dissolved in 2 ml of MeOH are treated with 0.4 ml of water and 0.04 ml (0.5 mmol) of HCl at room temperature for 5h. The product is extracted with ether to yield 19 mg of 7c. $[\alpha]_D^{17}$ -17.4° (0.7, $CHCl_3$);

ν_{max}(film) 1740, 1720, 1210, 1170 and 1100 cm^{-1}; δ_H(200 MHz, $CDCl_3$) 3.67(3H, s, $-CO_2Me$), 2.16(3H, s -COMe), 1.05(3H, d, J=6.9Hz, 9-Me), 0.93(3H, d, J= 6.4Hz, 13-Me), 0.89(3H, s, 4-Me equatorial), 0.82(3H, s, 4-Me axial), 0.80(3H, s, 10-Me), 2.56(1H, m, br $W_{½}$20Hz, 7-H), 2.31(1H, dd, J_1= 5.9 and J_2= 14.6Hz, 14-H), 2.12(1H, dd, J_1= 8:3 and J_2= 14.6Hz, 14-H) and 1.94(1H, m, br $W_{½}$20Hz, 7-H), δ_c(50MHz, $CDCl_3$), see Table 3; m/z 352|3%, $M^+(C_{22}H_{40}O_3)$|, 337(12), 321(23), 309(23), 293(33), 137(41), 123(56), 81(62), 74(41), 69(100) and 43(100); (Found: C, 74.8; H, 11.3; $C_{22}H_{40}O_3$ requires C, 74.9; H, 11.4%).

Methyl 9(S)-9-Methyl-8-oxo-8,9-seco-labdan-15-oate or Methyl 3(S), 6(S), 1'(R), 2'(S)-3,6-Dimethyl-6-[1,3,3-trimethyl-2-(3-oxo-butyl)-1-cyclohexyl]-hexanoate, 7d.- 22 mg of the ketal 7f are hydrolyzed in the same conditions as the previous case, giving 21.4 mf of a methylketone 7d; $|\alpha|_D^{17}$ -2.4° (c 0.8, $CHCl_3$); ν_{max}(film) 1740, 1720, 1205, 1175 and 1090 cm^{-1}; δ_H(200MHz, $CDCl_3$) 3.66(3H, s, $-CO_2Me$), 2.53(1H, m, br $W_{½}$20Hz, 7-H), 2.30(1H, dd, J_1 5.8 and J_2 14.6Hz, 14-H), 2.11(1H, dd, J_1 7.1 and J_2 14.6Hz, 14-H), 1.95(1H, m, br $W_{½}$20Hz, 7-H), 1.09(3H, d, J= 6.9Hz, 9-Me), 0.93(3H, d, J= 6.5Hz, 13-Me), 0.87(3H, s, 4-Me equatorial) and 0.85(6H, s, 10-Me and 4-Me axial), δ_c(50MHz, $CDCl_3$), see Table 3; m/z 352|1%, $M^+(C_{22}H_{40}O_3)$|, 137(14), 123(46), 109(35), 95(42), 81(50), 74(35), 69(100) and 43(100); (Found: C, 74.9; H, 11.2; $C_{22}H_{40}O_3$ requires C, 74.9; H, 11.4%).

9(R)-9-Methyl-8-oxo-8,9-secolabdan-15-oic acid, 7a.- By saponification of 7c, the acid 7a is obtained. $|\alpha|_D^{20}$ -15.6° (c, 0.6, $CHCl_3$); ν_{max}(film) 3600-2500, 1720, 1705, 1200, 1180, 1075 and 950 cm^{-1}; δ_H(200MHz, $CDCl_3$) 0.80(3H, s, 10-Me), 0.85(6H, s, 4-Me_2), 0.91(3H, d, J= 7Hz, 13-Me), 1.04(3H, d, J= 7Hz, 9-Me) and 2.04(3H, s, 8-Me); m/z 338|3%, $M^+(C_{21}H_{38}O_3)$|, 293(15), 278(15), 137 (25), 123(38), 81(65) and 69(100, $C_5H_9^+$), (Found: C, 74.4; H, 11.3; $C_{21}H_{38}O_3$ requires C, 74.5; H, 11.3%).

9(S)-9-Methyl-8-oxo-8,9-seco-labdan-15-oic acid or 3(S), 6(S),1'(R),2'(S)-3,6-Dimethyl-6-[1,3,3-trimethyl-2-(3-oxobutyl)-cyclohexyl]-hexanoic acid, 7b.- By saponification of 7d, the acid 7b is obtained; $|\alpha|_D^{20}$ -1.02° (c 0.7, $CHCl_3$); ν_{max}(film) 3600-2500, 1720, 1705, 1200, 1180, and 1085 cm^{-1}; δ_H(200MHz, $CDCl_3$), 0.89(9H, s, br, 10-Me and 4-Me_2), 0.87(3H, d, J= 7Hz, 10-Me), 1.05(3H, d, J= 7Hz, 9-Me) and 2.06(3H, s, 8-Me); m/z 338|4%, $M^+(C_{21}H_{38}O_3)$|, 323(24), 320(34), 137(15), 123(50), 109(35), 98(20), 95(45), 81(60) and 69(100, $C_5H_9^+$); (Found: C, 74.4; H, 11.2; $C_{21}H_{38}O_3$ requires C, 74.5; H, 11.3%).

Methyl 12(R)-8,12-Epoxy-labdan-15-oate, 8b.- Colourless oil; $|\alpha|_D^{20}$ -6.1° (c 5.5, $CHCl_3$); ν_{max}1735 (ester), 1270, 1170, 1160 and 1020 cm^{-1} (C-O-C); δ_H(200MHz; $CDCl_3$) 0.82(6H, s, 4-Me axial and 10-Me), 0.87(3H, s, 4-Me equatorial), 0.93(3H, d, J= 6.6Hz, 13-Me), 1.12(3H, s, 8-Me), 2.48(2H, dd, J= 13.0 and 3.4Hz, 14-H_2), 3.66(3H, s, $-CO_2Me$) and 3.96(1H, ddd, J= 2.1 8.2 and 4.2Hz, 12-H); δ_c (50 MHz, $CDCl_3$), see Table 3; m/z 336|5%, $M^+(C_{21}H_{36}O_3)$|, 321(25, M^+-15), 305(6, M^+-CH_3O), 235(17, M^+-101), 207(35, $C_{15}H_{25}^+$), 192(21). 191(100, $C_{14}H_{23}^+$), 177(22), 144(90, $C_7H_{12}O_3^+$), 137(46), 123(45), 121(40), 109(76), 101(28, $C_5H_9O_2^+$), 95(75) and 81(77); (Found: C, 75.1; H, 10.9; $C_{21}H_{36}O_3$ requires C, 74.9; H, 10.8%).

12(R)-8,12-Epoxy-labdan-15-oic acid, 8a.- Saponification of 8b in the usual way, afforded 8a, $|\alpha|_D^{20}$ -1.02° (c 1.0, $CHCl_3$); ν_{max} 3600-2400 and 1705(-CO_2H), 1415, 1160 and 1125, 1080, 1020 and 920 cm^{-1} (C-O-C); δ_H(200 MHz; $CDCl_3$) 0.82(6H, s, 4-Me axial and 10-Me), 0.87(3H, s, 4-Me equatorial), 0.96(3H, d, J= 6.5Hz, 13-Me), 1.14(3H, s, 8-Me) and 4.06(1H, m, br $W_{½}$18Hz, 12-H); m/z 322|3%, $M^+(C_{20}H_{34}O_3)$|, 307(20), 235(20), 191(100), 109(65) and 95(80); (found: C, 74.7; H, 10.9; $C_{20}H_{34}O_3$ requires C, 74.5; H, 10.6%).

To 0.25 g (0.78 mmol) of 8a dissolved in 2 ml of hot ethyl acetate, 0.1 ml (0.87 mmol) of cyclohexylamine are added. This is allowed to cool slowly with the subsequent precipitation of cyclohexylammonium 12(R)-8,12-Epoxy-labdan-15-oate, mp. 139-140° (from AcOEt); $|\alpha|_D^{21}$ -5.5° (c, 1.0, MeOH).

Methyl 12(S)-8,12-Epoxy-labdan-15-oate, 9b.- Colourless oil, $|\alpha|_D^{20}$ -12.6° (c 5.6, $CHCl_3$); ν_{max} 1735(C=O), 1265, 1190, 1150 and 1005 cm^{-1} (C-O-C); δ_H(200MHz; $CDCl_3$) 0.82(3H, s, 10-Me), 0.84(3H, s, 4-Me axial), 0.87(3H, s, 4-Me equatorial), 0.87(3H, d, J= 6.2Hz, 13-Me), 1.11(3H, s, 8-Me), 3.60(1H, m, $W_{½}$16Hz, 12-H) and 3.65(3H, s, $-CO_2CH_3$); δ_c(50 MHz; $CDCl_3$), see Table 3; m/z 336|2%, $M^+(C_{21}H_{36}O_3)$|, 321(78, M^+-CH_3), 305(18, M^+-CH_3O), 235(20, M^+-101), 192(20), 191(100, $C_{14}H_{23}^+$), 144 (40, $C_7H_{12}O_3^+$), 137(36), 123(27), 121(33), 109(47), 101(45), 95(65) and 81(60); (Found: C, 74.7; H, 10.8; $C_{21}H_{36}O_3$ requires C, 74.9; H, 10.8%).

12(S)-8,12-Epoxy-labdan-15-oic acid, 9a.- The saponification of 9b yields 9a; $|\alpha|_D^{20}$ -7.3° (c 2.3, $CHCl_3$), ν_{max}3600-2400 and 1705(-CO_2H), 1415, 1160 and 1140, 1050, 1010 and 920 cm^{-1} (C-O-C); δ_H (200MHz, $CDCl_3$) 0.82(3H, s, 10-Me), 0.84(3H, s, 4-Me axial), 0.87(3H, s, 4-Me equatorial), 0.92 (3H, d, J= 6.5Hz), 1.14(3H, s, 8-Me) and 3.62(1H, m, $W_{½}$20Hz, 12-H); m/z 332|4%, $M^+(C_{20}H_{34}O_3)$|, 307 (40), 235(25), 191(100), 137(40), 123(30), 121(40), 109(50), 95(60) and 81(55); (Found: C, 74.3; H, 10.8; $C_{20}H_{34}O_3$ requires C, 74.5; H, 10.6%). Cyclohexylammonium 12(S)-8,12-Epoxy-labdan-15-oate, m.p. 145-146°C; $|\alpha|_D^{21}$ -11.4° (c 1.0, MeOH).

Reaction of 8b and 9b with $Et_2O.BF_3$: Methyl 12(R,S)-12-Acetoxy-labd-8-en-15-oate, 10a and 10b.- To 0.38 g (1.13 mmol) of 8b and 9b (1:1) dissolved in 9.1 ml of dry benzene, 0.34 (2.4 mmol) of freshly distilled Ac_2O are added. The mixture is stirred and kept at 0°C. At this point 0.45 ml (3.46 mmol) of $Et_2O.BF_3$ are added and the reaction is kept under these conditions for 30 min. and then 1 ml of water is added, the mixture is shaken for 5 min and extracted with ether. The ethereal

phase is washed with aqueous 6% $NaHCO_3$ and with water to neutrality, dried and the solvent eliminated under vacuum, yielding a crude mixture (0.37 g) which is chromatographed on Silicagel/$AgNO_3$ (20%) giving 0.20 g (53%) (hexane-ether 90:10) of an oily product composed of 10a and 10b (1:1). ν_{max}(film) 1740, 1660, 1250, 1225, 1205 and 1175 cm^{-1}; δ_H(60 MHz, $CDCl_3$), 4.90(1H, m, br, 12-H), 3.59(3H, s, $-CO_2Me$), 1.90(3H, s, AcO-), 1.57(3H, s, 8-Me), 0.98(3H, d, J= 7Hz, 13-Me), 0.92 (6H, s, 4-Me_2) and 0.83(3H, s, 10-Me); m/z 376|5%, $M^+(C_{23}H_{38}O_4)$|, 347(12), 335(33), 205(24), 191(22) 137(21), 123(47), 121(60), 109(66), 95(66), 95(71), 81(68) and 69(100, $C_5H_9^+$); (Found: C, 72.9; H, 10.1; $C_{23}H_{38}O_4$ requires C, 73.0; H, 10.1%).

12(R,S)-labd-8-en-15(12)-olide, 13a and 13b.- 27 mg (0.07 mmol of 10a and 10b (1:1) are dissolved in 2 ml of MeOH adding 2 ml (4 mmol) of 2M KOH/MeOH, and this is kept at room temperature overnight. After this the usual procedure is followed, giving 21 mg (100%) of the -lactones 13a and 13b (1:1). ν_{max}(film) 1780, 1220, and 1160 cm^{-1}; δ_H(60MHz, $CDCl_3$) 4.01(1H, q, J= 6Hz, 12-H), 1.59(3H, s, 8-Me), 1.14(3H, d, J= 7Hz, 13-Me), 0.99(3H, s, 4-Me equatorial), 0.90(3H, s, 4-Me axial and 0.84(3H, s, 10-Me); m/z 304|5%, $M^+(C_{20}H_{32}O_2)$|, 289(12, M^+-15), 205(15, $C_{15}H_{25}^+$), 191(36), 177(13), 137(33), 123 (70), 121(38), 99(80), 95(70), 81(73) and 69(100, $C_5H_9^+$); (Found: C, 78.8; H, 10.7; $C_{20}H_{32}O_2$ requires C, 78.9; H, 10.6%).

Reaction of 8b and 9b with $MgBr_2/Ac_2O$: 13a and 13b.- 0.06 ml (0.6 mmol) of Ac_2O and 75 mg (0.41 mmol) of freshly prepared $MgBr_2$ are added to 100 mg (0.30 mmol) of 8b and 9b (1:1) dissolved in 0.5 ml of dry acetonitrile. The reaction mixture is kept at room temperature for 48 h and in reflux for 20 h. After, it is filtered and evaporated yielding a crude extract (0.105 g) which is chromatographed on SiO_2 eluting with hexane-ether (90:10) 41 mg of the initial substrate (conversion 51%), and 51 mg (47%) of a product which is purified by p.t.l.c. (hexane-ether 1:1) and whose physical and spectroscopical properties are identical to those of the -lactones 13a and 13b.

Treatment of 8b and 9b with HCl/MeOH: 13a and 13b.- 95 mg (0.28 mmol) of 8b and 9b (1:1) are dissolved in 3 ml of MeOH and 0.5 ml (6 mmol) of HCl are added. This mixture is kept at room temperature for 24 h and in reflux for 87 h. Evaporation of the solvent afforded 90 mg of a crude mixture which is chromatographed on SiO_2 and by elution with hexane-ether 95:5 yields 22 mg of initial substrate (conversion 72%) and 22 mg of the -lactones 13a and 13b (1:1).

Reaction of 8b and/or 9b with O_3 by the method of "Dry-Ozonation": 14, 15, 16.- 0.11 g (0.3 mmol) of 8b and/or 9b are absorbed on 10 g of SiO_2 previously dried in an oven at 300°C for 3 h. This silicagel was placed in a ozonization reactor at -85°C during 30 min under current of dry O_3 until saturation (dark blue colour). The reactor was removed and left to reach room temperature slowly (2 hours). The process was repeated three times (controlled by t.l.c.) The silicagel was placed in a column and extracted with EtOAc, yielding 0.12 g of crude mixture that was chromatographed over SiO_2, with a gradient of hexane/ether as eluent affording 5 mg of the initial substrate. The 96% yield is composed of 16 (57%) and a mixture of 14 and 15 (3:1 ratio, 16%) which were separated later yielding 22.5 mg of 14 (12%) and 7.5 mg of 15 (4%).

Methyl 8-Hydroxy-12-oxo-labdan-15-oate, 16.- Crystalline product, m.p. 53-54°C (from n-hexane); $[\alpha]_D^{22}$ +7.4° (c 1.1, $CHCl_3$); ν_{max}(film) 3600-3400, 1740, 1720, 1200, 1170, 1130, 1085, 1010, 940 and 910 cm^{-1}; δ_H(60MHz, CCl_4) 3.60(3H, s, $-CO_2Me$), 1.11(3H, d, J= 7Hz, 13-Me), 1.07(3H, s, 8-Me), 0.89(3H, s, 4-Me equatorial) and 0.80(6H, s, 10-Me and 4-Me axial); δ_H(C_6D_6) 3.70(3H, s, $-CO_2Me$), 1.47(3H, s, 8-Me), 1.34(3H, d, J= 7Hz, 13-Me), 1.20(3H, s, 4-Me equatorial), 1.12(3H, s, 4-Me axial) and 1.05(3H, s, 10-Me); m/z 352|3%, $M^+(C_{21}H_{36}O_4)$|, 337(6, M^+-15), 334(21, M^+-18), 321(3, M^+-31); 251(10, M^+-101), 205(5, $C_{15}H_{25}^+$), 191(100, $C_{14}H_{23}^+$), 177(30), 150(10, $C_{10}H_{14}O^+$), 143(25, $C_7H_{11}O_3^+$), 137(65), 129(30, $C_6H_9O_3^+$), 125(80), 124(45), 123(85), 121(40), 109(75), 101(25, $C_5H_9O_2^+$) and 95(65); (Found: C, 71.6; H, 10.2; $C_{21}H_{36}O_4$ requires C, 71.5; H, 10.3%).

Oxidation of 8b and/or 9b with RuO_4: 16.- 600 mg (2.8 mmol) of $NaIO_4$ dissolved in 3 ml of water are added to 80 mg (0.6 mmol) of RuO_2 suspended in 10 ml of acetone. To this yellow solution (containing RuO_4) are slowly (1h) added 3 ml of acetone. The reaction mixture is stirred continuously for 10h at room temperature (the RuO_4 is regenerated by addition of a solution of 1.4 g of $NaIO_4$ in 5 ml of acetone/water (3:1) when the black precipitate of RuO_2 begins to appear). After achieving complete conversion of the substrate, 2 ml of isopropylic alcohol are added to consume the excess of oxidant. The mixture is filtered, the solid is washed with acetone and the filtrate is percolated through cellite, dried with anhydrous $MgSO_4$ and concentrated, obtaining a single product 16, 0.167 g (100%).

Alkaline hydrolisis of 16: 14 and 15.- 0.1 g (0.28 mmol) of 16 are saponificated at room temperature with 2 ml (2 mmol) of 1M KOH/MeOH for three hours. The usual procedure is followed, yielding 91 mg (100%) of a product composed exclusively of 14 and 15 (3:1) which are separated as described previously.

Methyl 12(R,S)-12-Acetoxy-8-Hydroxy-labdan-15-oate: 11a, 11b.- Crystalline mixture of epimers in C-12 11a and 11b at a proportion of 1:1, inseparable by chromatography (though they can be separated as -lactone derivatives, 17 and 16, respectively), with the following properties: m.p. 91-94°(from n-hexane); ν_{max}(melting) 3600-3400, 1740, 1735, 1250, 1225, 1200, 1170, 1080, 1010, 940 and 910 cm^{-1}; δ_H(60MHz, CCl_4) 4.75(1H, m, br $W_{½}$ 16Hz, 12-H), 3.59(3H, s, $-CO_2Me$), 1.98(3H, s, AcO-), 1.08 (3H, s, 8-Me), 0.98(3H, d, J= 7Hz, 13-Me), 0.86(3H, s, 4-Me equatorial) and 0.78(6H, s, 4-Me axial and 10-Me); m/z 396|6%, $M^+(C_{23}H_{40}O_5)$|, 381(3, M^+-15), 378(6, M^+-18), 365(3, M^+-31), 353(4, M^+-43). 337(15, M^+-59), 336(20, M^+-AcOH), 191(21), 177(19), 137(18), 123(32), 121(33), 109(66), 95(62) and 69(100, $C_5H_9^+$); (Found: C, 69.7; H, 10.1; $C_{23}H_{40}O_5$ requires C, 69.7; H, 10.2%).

Saponification of 11a and 11b: 17 and 18.- 323 g (0.8 mmol) of 11a and 11b are saponificated at room temperature with 1 ml of 2M KOH/MeOH for 5 h. After this, the usual procedure is followed, obtaining 258 mg (100%) of a mixture of 17 and 18 which is chromatographed on silicagel, eluting with benzene-ether (90:10) a fraction A which when crystallized from hexane yields 0.127 g of 17, with H/E (85:15) fraction B is eluted from which p.t.l.c (benzene-ether 30:70, two developments), yields 0.125 g of 18 which is purified by recrystallization from n-hexane.

Methyl 9(R,S)-9-Methyl-10-nor-8-oxo-8,9-seco-labd-5(10)-oate or Methyl 3(S),6(R,S)-3,6-Dimethyl-6-[3,3-dimethyl-2-(3-oxo-butyl)-1-cyclohexenyl]-hexanoate: 12a, 12b.- Oily product; ν_{max} 1740(ester), 1720(ketone), 1260, 1210, 1160 and 1010 cm^{-1}; δ_H(60MHz; CCl_4) 0.90(6H, d, J= 7Hz, 3-Me and 6-Me), 0.97(6H, s, 3'-Me_2), 2.01(3H, s, -CO-CH_3) and 3.53(3H, s, -CO_2CH_3); m/z 336|2%, M^+ ($C_{21}H_{36}O_3$)|, 321(13, M^+-CH_3), 308(15, M^+-28), 293(31, M^+-CH_3-C≡O$^+$), 262(16, M^+-$C_3H_6O_2^+$), 179(15, $C_{13}H_{22}^+$), 165 (12, $C_{12}H_{20}^+$), 164(36, $C_{12}H_{19}^+$), 151(16, $C_{11}H_{19}^+$), 137(40), 136(30), 123(35), 121(27), 109(27), 95(45), 81(55) and 43(100, $CH_3C{\equiv}O^+$); (Found: C, 74.7; H, 10.7; $C_{21}H_{36}O_3$ requires C, 74.9; H, 10.8%).

3-[6,6-Dimethyl-2-[2(R,S),4(S)-dimethyl-5-methoxycarbonyl-pentyl]-1-cyclohexen-1-yl]-propanoic acid: 12c, 12d.- Colourless oil; ν_{max}(film) 3600-2500, 1740, 1700, 1300, 1280, 1150, 1090 and 1010 cm^{-1}; δ_H(60MHz, $CDCl_3$) 3.49(3H, s, -CO_2Me), 1.22(3H, d, J= 7Hz, 9-Me), 0.90(3H, d, J= 7Hz, 13-Me), 0.83 (3H, s, 4-Me axial) and 0.79(3H, s, 4-Me equatorial); m/z 338|2%, M^+($C_{20}H_{34}O_4$)|, 323(2, M^+-15), 307(5, M^+-31), 293(10, M^+-45), 279(10, M^+-59), 209(52, M^+-129), 150(100, $C_{11}H_{18}^+$), 149(56, $C_{11}H_{17}^+$), 137(40), 136(20), 129(49, $C_7H_{13}O_2^+$), 123(33), 122(70), 121(46), 109(33) and 95(45); (Found: C, 70.9; H, 10.2; $C_{20}H_{34}O_4$ requires C, 71.0; H, 10.1%).

Methyl 3(S),6(R,S)-3,6-Dimethyl-6-[3,3-dimethyl-2-(3-methoxy-carbonyl-ethyl)-1-cyclohexenyl]-hexanoate: 12e, 12f.- 405 mg of 12c and 12d are sterified with a saturated ethereal solution of CH_2N_2 yielding 422 mg of the methyl diesters 12e and 12f respectively, with an oily aspect and with the following properties: ν_{max}(film) 1740, 1300, 1200, 1180 and 1050 cm^{-1}; δ_H(60MHz, CCl_4) 3.53(6H, s, -CO_2Me), 1.20(3H, d, J=7Hz, 9-Me), 0.91(3H, d, J= 7Hz, 13-Me), 0.86(3H, s, 4-Me equatorial) and 0.80(3H, s, 4-Me axial); m/z 352|2%, M^+($C_{21}H_{36}O_4$)|, 337(3, M^+-15), 321(14, M^+-31), 293(15, M^+-59), 279(10, M^+-73), 223(47, M^+-129), 150(100, $C_{11}H_{18}^+$), 149(56), 137(50), 129(49, $C_7H_{13}O_2^+$), 123(33) and 122(70); (Found: C, 71.4; H, 10.1; $C_{21}H_{36}O_4$ requires C, 71.5; H, 10.3%).

Procedure for the lead tetraacetate and iodine reaction with (3), (Reaction XI).- In a 250 ml glass reactor vessel are placed 1 g (3.1 mmol) of 3 dissolved in 50 ml of dry benzene, 6.4 g (19 mmol) of LTA and 47.5 mmol of anhydrous pyridine. 0.8 g (3.1 mmol) of I_2 dissolved in 30 ml of dry benzene are slowly added to this mixture with constant stirring. After this addition, the reaction mixture is irradiated with two 100w lamps, refrigerating the system so that temperature is maintained at 20°C. After 1.5 h, conversion is total and 1 ml of ethyleneglycol is added and the mixture stirred for 5 min. It is then allowed to cool and the benzenic solution is washed with aqueous (5%) $Na_2S_2O_3$, dried with anhydrous Na_2SO_4 and brought to dryness, yielding an oily orange-reddish crude mixture of 1.1 g. This crude mixture is column chromatographed on SiO_2, eluting with H/E (95:5) a fraction A which is rechromatographed with p.t.l.c. on SiO_2 (H/E (80:20), two developments), separating 20a (2%); with H/E (90:10) fraction B is eluted, composed of 20b and 20c (1:1)(34%) and with H/E(80:20) (64%) of 8b and 9b (1:1) is eluted which are separated by h.p.l.c. as described

Methyl (E),12(R)-12-Acetoxy-8-oxo-8,9-seco-labd-9(11)-en-15-oate: 19.- 3% of 19 is separated from the crude mixture of reaction VII by successive c.c. on SiO_2 (hexane-ether 7:3) and p.t.l.c. (benzene-ethyl acetate 8:2). Colourless oil; $|\alpha|_D^{18}$ +11.9° (c 1.1, $CHCl_3$); ν_{max}(film) 3010, 1735, 1720, 1675, 1290, 1250, 1030 and 990 cm^{-1}; δ_H(200MHz, CCl_4) 5.52(1H, d, J= 15.4Hz, 9-H_A), 5.15(1H, dd, J_1= 15.4 and J_2= 8.2Hz, 11-H_B), 4.96(1H, dd, J_1=8.2 and J_2= 6.9Hz, 12-H_C), 3.67(3H, s, -CO_2Me), 2.10(3H, s, AcO-), 1.96(3H, s, MeCO-), 1.01(3H, s, 10-Me), 0.91(3H, d, J= 6.4Hz, 13-Me), 0.89(3H, s, 4-Me equatorial) and 0.86(3H, s, 4-Me axial); m/z 394|2%, M^+($C_{23}H_{38}O_5$)|, 379(2, M^+-15), 335(8, M^+-59), 334(10, M^+-AcOH), 320(14, M^+-74), 293(33, M^+-101), 137(20), 123(40), 109(43), 101(6, $C_5H_9O_2^+$), 95(30), 81(45), 69(54) and 43(100, $C_2H_3O^+$); (Found: C, 70.1; H, 9.8; $C_{23}H_{38}O_5$ requires C, 70.0; H, 9.7%).

Methyl 8-oxo-8,9-seco-labdan-15-oate: 20a.- Oily product, $|\alpha|_D^{26}$ -6.3° (c 1.3, $CHCl_3$); ν_{max}(film) 1740, 1720, 1200, 1160, 1090 and 1010 cm^{-1}; δ_H(200MHz, $CDCl_3$) 3.67(3H, s, -CO_2Me), 2.13(3H, s, COMe), 0.93(3H, d, J= 6.6Hz, 13-Me), 0.89(3H, s, 4-Me equatorial), 0.84(3H, s, 4-Me axial) and 0.82 (3H, s, 10-Me); m/z 338[3%, M^+($C_{21}H_{38}O_3$)], 323(13, M^+-15), 307(9, M^+-31), 295(25, M^+-43), 279(3, M^+-59), 179(45, $C_{13}H_{23}^+$), 151(20, $C_{11}H_{19}^+$), 149(13, $C_{11}H_{15}^+$); 143(8, $C_8H_{15}O_2^+$), 137(55), 123(61), 112(10, $C_7H_{12}O_2^+$), 95(91), 83(81) and 69(100); (Found: C, 74.5; H, 11.1; $C_{21}H_{38}O_3$ requires C, 74.5; H, 11.3%).

Methyl 7(R,S)-8-oxo-8,9-seco-7-iodo-labdan-15-oate: 20b, 20c.- Oily product composed of a mixture (1:1) of two iodinated derivatives epimeric at C-7; ν_{max}(film) 1740, 1720, 1200, 1170, 1090 and 1010 cm^{-1}; δ_H(60MHz, CCl_4) 4.51(1H, t, J= 7Hz, 7-H), 3.56(3H, s, -CO_2Me), 2.34(3H, s, 8-Me), 0.99 (3H, s, 4-Me equatorial), 0.91(3H, d, J= 7Hz, 13-Me), 0.90(3H, s, 4-Me axial) and 0.88(3H, s, 10-Me) m/z(80°C, 70 eV) 464|5%, M^+($C_{21}H_{37}O_3I$)|, 449(12, M^+-15), 421(15, M^+-43), 405(12, M^+-59), 337(10, M^+-127), 336(18, M^+-IH), 305(16, M^+-159), 159(13, CH_4OI^+), 151(30, $C_{11}H_{19}^+$), 143(10, $C_8H_{15}O_2^+$), 137(50), 128(31, IH), 127(30, I^+), 123(33) and 69(100); (Found: C, 54.1; H, 7.9; $C_{21}H_{37}O_3I$ requires C, 54.3; H, 8.0%).

Methyl 7(R,S)-7-Acetoxy-8-oxo-8,9-seco-labdan-15-oate 21.- 0.2 g (2.04 mmol) of KAcO (previously dried at 300°C for several h) are added to 0.106 g (0.23 mmol) of 20b and 20c dissolved in 10 ml of anhydrous acetone, refluxing the mixture for 10 h. This is allowed to cool, the salts are filtered and washed with hot acetone. The mixture is then brought to dryness, ether is added and the mixture is washed with water, dried and concentrated, yielding 90 mg of crude extract which is column chromatographed on SiO_2, eluting with hexane-ether (80:20) 62 mg (72%) of a mixture (1:1) of two acetates epimeric at C-7 (g.l.c. OV-1) which cannot be separated by chromatography. ν_{max}(film) 1740, 1725, 1720, 1250, 1200, 1190, 1085, and 1015 cm^{-1}; δ_H(60MHz, CCl_4) 4.84(1H, m, br, $W_{\frac{1}{2}}$ 15Hz, 7-H), 3.58(3H, s, -CO_2Me), 2.09(6H, s, AcO- and MeCO-), 0.93(3H, s, 4-Me equatorial), 0.91(3H, s, J= 7Hz, 13-Me) and 0.90(6H, s, 10-Me and 4-Me axial); m/z 396|(2%, M^+($C_{23}H_{40}O_5$)|, 353(17), 293(16), 281(30), 143(19), 137(50), 134(22), 123(65), 115(40), 107(30), 95(41), 83(42) and 69(100); (Found: C, 69.8; H, 10.1; $C_{23}H_{40}O_5$ requires C, 69.7; H, 10.2%).

Methyl 7(R,S)-7-Acetoxy-8,8-Ethylendioxy-8,9-seco-labdan-15-oate, (22).- 0.5 ml (8.94 mmol) of ethyleneglycol and 9 mg (0.05 mmol) of TsOH are added to 0.141 g (0.36 mmol) of 21 dissolved in 2 ml of dry benzene. The mixture is maintained under reflux with a water separator for 4 h. After

this the usual procedure is followed, obtaining 0.139 g of 22; ν_{max}(film) 1735, 1245, 1225, 1200, 1170, 1160, 1080 and 1040 cm^{-1}; δ_H(60MHz, CCl_4) 4.85(1H, m, br, $W_{1/2}$ 18Hz, 7-H), 3.88(4H, s, -O-$(CH_2)_2$-O-), 3.60(3H, s, $-CO_2Me$), 1.99(3H, s, AcO-), 1.26(3H, s, 8-Me), 0.92(3H, s, 4-Me equatorial), 0.89(3H, s, J= 7Hz, 13-Me), 0.88(3H, s, 4-Me axial) and 0.80(3H, s, 10-Me); m/z 440|5%, $M^+(C_{25}H_{44}O_6)$|, 409(10), 151(13), 137(25), 123(23), 115(18), 95(30), 87(60), 84(30), 83(22), 74(98), 69(50) and 59(100, $C_2H_3O_2^+$); (Found: C, 68.3; H, 10.2; $C_{25}H_{44}O_6$ requires C, 66.1; H, 10.1%).

7(7R,S)-8,8-Ethylendioxy-7-hydroxy-8,9-seco-labdan-15-oic acid, 23.- 0.122 g (0.28 mmol) of 22 are dissolved in 2 ml of MeOH and this is saponificated with 3 ml of KOH/MeOH at room temperature for 3h. The solvent is eliminated under vacuum, water is added and the mixture is carefully acidulated to pH 5 with 1M HCl. The usual procedure is followed, giving 0.106 g of 23; ν_{max}(film) 3650-3200, 3600-2500, 1700, 1155, 1075 and 1050 cm^{-1}; δ_H(60MHz, CCl_4) 6.98(1H, s br, $W_{1/2}$ 20Hz, -OH), 3.86(4H, s, -O-$(CH_2)_2$-O-), 3.37(1H, m br, $W_{1/2}$ 18Hz, 7-H), 1.25(3H, s, 8-Me), 0.92(3H, d, J= 7Hz, 13-Me), 0.89(3H, s, 4-Me_2) and 0.78(3H, s, 10-Me); m/z(80°C, 70 eV) 384|3%, $M^+(C_{22}H_{40}O_5)$|, 137(25), 123(34), 109(15), 95(30) and 87(100, $C_4H_7O_2^+$); (Found: C, 68.6; H, 10.4; $C_{22}H_{40}O_5$ requires C, 68.7; H, 10.5%).

Methyl 7(R,S)-8,8-Ethylendioxy-7-hydroxy-8,9-seco-labdan-15-oate, 24.- ν_{max}(film) 3600-3300, 1740, 1200, 1175, 1160, 1080, 1050 and 1040 cm^{-1}; δ_H(60MHz, CCl_4) 3.88(4H, s, -O-$(CH_2)_2$-O-), 3.57(3H, s, $-CO_2Me$), 3.35(1H, m br, $W_{1/2}$ 24Hz, 7-H), 1.24(3H, s, 8-Me), 0.89(9H, s, $W_{1/2}$ 8Hz, 4-Me_2 and 13-Me) and 0.78(3H, s, 10-Me); m/z(80°C, 70 eV) 398|2%, $M^+(C_{23}H_{42}O_5)$|, 143(12), 137(10), 123(24), 121(45), 117 (18), 109(16), 95(24) and 87(100, $C_4H_7O_2^+$); (Found: C, 69.1; H, 10.5; $C_{23}H_{42}O_5$ requires C, 69.3; H, 10.6%).

Methyl 8,8-Ethylendioxy-7-oxo-8,9-seco-labdan-15-oate, 25.- 1.5 ml of pyridine are placed in a 50 cc Erlenmeyer flask externally cooled with ice. 0.252 g (2.52 mmol) of CrO_3 in small portions are added with stirring until a thick yellow paste is obtained. This is allowed to reach room temperature and is maintained with stirring for 15 min. The reagent thus prepared is poured onto 92 mg (0.23 mmol) of 24 dissolved in 0.5 ml of pyridine. The reaction mixture is stirred continuously at room temperature for 40 h. AcOEt is added and the mixture is stirred overnight. It is then percolated on cellite/neutral alumina (1:1) and the solvent is eliminated under vacuum obtaining 83 mg (98%) of a ketone 25; $|\alpha|_D^{26}$ -7.7° (c 1.3, $CHCl_3$); ν_{max}(film) 1735, 1725, 1170, 1115, 1080, 1040 and 1010 cm^{-1} δ_H(60MHz, CCl_4) 3.93(4H, s, -O-$(CH_2)_2$-O-), 3.56(3H, s, $-CO_2Me$), 2.37(2H, d, J= 7Hz, 6-H_2), 1.37(3H, s, 8-Me), 0.88(3H, d, J= 7Hz, 13-Me), 0.87(3H, s, 10-Me), 0.81(3H, s, 4-Me axial) and 0.68(3H, s, 4-Me equatorial shielding by the ketonic carbonyl); m/z(80°C, 70 eV), 396|3%, $M^+(C_{23}H_{40}O_5)$|, 151(25) 143(12), 137(25), 123(27), 109(30), 95(40) and 87(100); (Found: C, 69:9; H, 10.2; $C_{23}H_{40}O_5$ requires C, 69.7; H, 10.2%).

Methyl-7,8-Dioxo-8,9-seco-labdan-15-oate, 26.- 0.15 ml of 2M HCl are added to a solution of 40 mg (0.1 mmol) of 25 in 0.5 ml of MeOH; this is kept at room temperature for 5 h. The MeOH is eliminated under vacuum, water is added and the product is extracted with ether. The ethereal solution is dried and concentrated to dryness, yielding 36 mg of a product which is chromatographed on SiO_2, eluting with hexane-ether 80:20, 18 mg (50%) of an α -diketone 26; $|\alpha|_D^{16}$ +1.7° (c 0.6, $CHCl_3$); λ_{max} (EtOH) 265 nm (ε 7400 $dm^3.mol^{-1}.cm^{-1}$); ν_{max}(film) 3400, 1735, 1720, 1665, 1640, 1235, 1140, 1080 and 1010 cm^{-1}; δ_H(60MHz, CCl_4) 5.51(1H, d, J= 11.5Hz, 6-H), 3.56(3H, s, $-CO_2Me$), 2.40(1H, d, J= 11.5Hz, 5-H), 2.30(3H, s, 8-Me), 0.92(6H, s, 10-Me and 4-Me axial), 0.89(3H, d, J= 7Hz, 13-Me) and 0.79(3H, s, 4-Me equatorial); m/z(60°C, 70 eV), 352|5%, $M^+(C_{21}H_{36}O_4)$|, 165(20), 137(50), 124 (22), 123(55), 122(30), 121(25), 109(37), 95(50), 85(18), 83(36), 81(50) and 69(100); (Found: C, 71.4; H, 10.2; $C_{21}H_{36}O_4$ requires C, 71.5; H, 10.3%).

8(R,S)-8-Hydroxy-7-oxo-8,9-seco-labdan-15-oic acid, 27.- 0.174 g (0.44 mmol) of 21 dissolved in 1 ml of MeOH are saponificated with 2 ml of KOH/MeOH at room temperature. This is concentrated under vacuum, H_2O is added, the mixture is carefully acidulated with 2M HCl to pH 5 and then the usual procedure is followed, obtaining 0.149 g of 27; ν_{max}(film) 3600-3100, 3600-2500, 1720, 1700, 1210, 1175, 1100, 1115 and 1020 cm^{-1}; δ_H(60MHz, CCl_4) 7.01(1H, s br, -OH), 4.20(1H, q, J= 7Hz, 8-H). 1.29(3H, d, J= 7Hz, 8-Me), 0.91(3H, d, J= 7Hz, 13-Me), 0.88(3H, s, 4-Me axial), 0.82(3H, s, 10-Me) and 0.66(3H, s, 4-Me equatorial); m/z(100°C, 70 eV) 340|2%, $M^+(C_{20}H_{36}O_4)$|, 152(30), 150(15), 137(47) 123(51), 121(38), 85(63), 83(85), 81(83), 73(31) and 69(100); (Found: C, 70.7; H, 10.6; $C_{20}H_{36}O_4$ requires C, 70.5; H, 10.7%).

Methyl 6(R,S)-8-Hydroxy-7-oxo8,9-secolabdan-15-oate, 30.- ν_{max}(film) 3600-3200, 1740, 1720, 1200, 1170, 1115, 1100 and 1010 cm^{-1}; δ_H(60MHz, CCl_4) 4.15(1H, q, J= 7Hz, 8-H), 3.59(3H, s, CO_2Me), 3.30(1H, m br, $W_{1/2}$ 12Hz, -OH), 2.32(2H, d, J= 4Hz, 6-H_2), 1.32(3H, d, J= 7Hz, 8-Me), 0.88(3H, d, J= 7Hz, 13-Me), 0.86(3H, s, 4-Me axial), 0.81(3H, s, 20-Me) and 0.66(3H, s, 4-Me equatorial, shielding by the ketonic carbonyl); m/z (60°C, 70 eV), 354|2%, $M^+(C_{21}H_{38}O_4)$| , 152(13), 150(23), 137(45), 123(51), 95(63), 83(85), 81(83) and 69(100); (Found: C, 71.0; H, 10.9; $C_{21}H_{38}O_4$ requires C, 71.1; H, 10.8%).

Methyl 8(R,S)-8-Acetoxy-7-oxo-8,9-seco-labdan-15-oate, 29.- 80 mg (0.22 mmol) of 30 dissolved in 2 ml of anhydrous pyridine are acetylated with 3 ml (31.8 mmol) of Ac_2O at room temperature for 12 h. Ice is added and after one hour the product is recovered in the usual way, yielding 87 mg of 29; $|\alpha|_D^{20}$ -4.2° (c 4.3, $CHCl_3$); ν_{max}(film) 1740, 1725, 1250, 1200, 1190, 1085 and 1015 cm^{-1}; δ_H(60MHz, CCl_4) 4.99(1H, q, J= 7Hz, 8-H), 3.57(3H, s, $-CO_2Me$), 1.35(3H, d, J= 7Hz, 8-Me), 0.86(3H, d, J= 7Hz, 13-Me), 0.85(6H, s, 10-Me and 4-Me axial), and 0.68(3H, s, 4-Me equatorial, shielding by the ketonic carbonyl); m/z (80°C, 70 eV), 396|3%, $M^+(C_{23}H_{40}O_5)$|, 152(27), 151(18), 143(25), 137(35), 123(55), 115(20), 112(25), 95(35), 87(30), 81(25) and 69(100); (Found: C, 69.8; H, 10.1; $C_{23}H_{40}O_5$ requires C, 69.7; H, 10.2%).

7,8-Dioxo-8,9-seco-labdan-15-oic acid, 28.- O_2 is bubbled through a solution of 0.1 g (0.29 mmol) of 27 in 10 ml of benzene for 12 h. The solvent is eliminated under vacuum, yielding a crude mixture which is chromatographed by p.t.l.c. on silicagel (C_6H_6/AcOH/H_2O, 1:2:2, two elutions), yielding 75 mg (75%) of 28; $|\alpha|_D^{20}$ -0.35° (c 0.6, $CHCl_3$); ν_{max}(film) 3600-2500, 3400, 1720, 1710,

1670, 1645, 1235, 1140, 1080 and 970 cm^{-1}; δ_H(60MHz, CCl_4) 5.53(1H, d, J= 11.5Hz, 6-H), 2.41(1H, d, J= 11.5Hz, 5-H), 2.34(3H, s, 8-Me), 0.94(6H, s, 10-Me and 4-Me axial), 0.90(3H, d, J= 7Hz, 13-Me) and 0.80(3H, s, 4-Me equatorial); m/z (80°C, 70 eV), 338|2%, $M^+(C_{20}H_{34}O_4)$|, 320(11), 295(15), 293 (11), 165(10), 149(15), 137(15), 129(20), 123(60), 121(25), 109(50), 95(65), 85(20), 83(40), 81(70) and 69(100); (Found: C, 70.9; H, 10.2; $C_{20}H_{34}O_4$ requires C, 71.0; H, 10.1%).

Oxidation of 30 with $Cu(OAc)_2$:26.- 40 mg (0.22 mmol) of $Cu(OAc)_2$ dissolved in 0.5 ml of AcOH/H_2O (1:1) are added to a solution of 35 mg (0.10 mmol) of 30 in 0.5 ml of MeOH and the mixture kept at room temperature with constant stirring for 30 min. The red Cu_2O precipitate is filtered through cellite, the solvent is eliminated, water is added and the product is extracted with ether. The ethereal solution is washed with aqueous $NaHCO_3$ and water, dried and concentrated, which following silicagel c.c. yields 70% of the α-diketone 26.

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