Tetrahedron Vol. 48, No. 47, pp. 10389-10398, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Chemistry of Labdanediol from *Cistus ladaniferus*, L. Synthesis of 12–*Nor*–ambreinolide and α and β–Levantenolides

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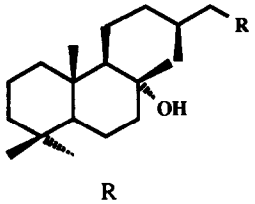
(*Received in UK* 21 *September* 1992)

Abstract: Labdanediol, **2**, the major component of the neutral part of *Cistus ladaniferus* L, was transformed into 12–*nor*–ambreinolide, precursor of ambrox®, in three steps with an overall yield of 70%. Molecular modelling techniques have been used to determine the stereochemistry of the byproducts of these reactions. The selenylation and elimination reactions of α and β levantanolides, obtained from labdanediol, **2**, were used to synthetise α and β–levantenolides.

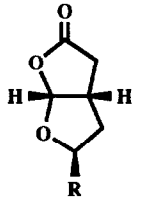
INTRODUCTION

The two main components from the hexane extract of *Cistus ladaniferus*, are the labdanolic acid **1** (40 % of the acid fraction) and labdanediol **2** (70 % of the unsaponificable neutral fraction).



R

1 COOH
2 CH_2OH



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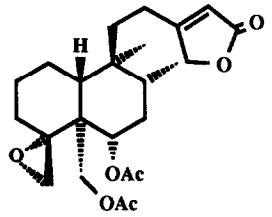

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In our previous work,[1,2] we described the transformation of methyl labdanolate into 12–*nor*–ambreinolide **5**, precursor of ambrox®. In this work, we describe the transformation of labdanediol, **2**, to 12–*nor*–ambreinolide, **5**, using iodine and lead tetracetate. We also discuss the byproducts **9a** and **9b**, (Scheme 1) arising from the oxidative cleavage of the B ring; the stereochemistry of these compounds was assigned by the use of molecular modelling techniques.

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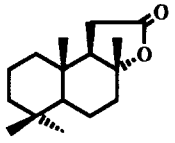
We also report the synthesis of α and β–levantenolides **6a** and **6b** from labdanediol, **2**. These compounds have been isolated from the turkish tobacco[3] in small quantities. The functionality of these compounds is reminiscent not only of the furofuranic ring of some clerodanes,[4] **3**, with biological activity,[5,6] but also of the γ–butenolide ring of Ajugarin I,[7] **4**, which has antifeedant activity.[8] This feature is also found in the levantanolides whose synthesis we have previously reported. In order to have a good source of these compounds for biological screening we decided upon their synthesis.



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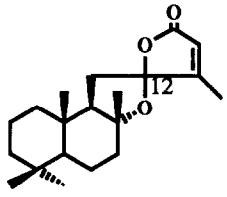


6a: α-levantenolide (12*S*)
6b: β-levantenolide (12*R*)

RESULTS AND DISCUSSION

The labdanediol **2** was isolated from the neutral part of the hexane extract of *Cistus ladaniferus*, where it is found both free or esterified.

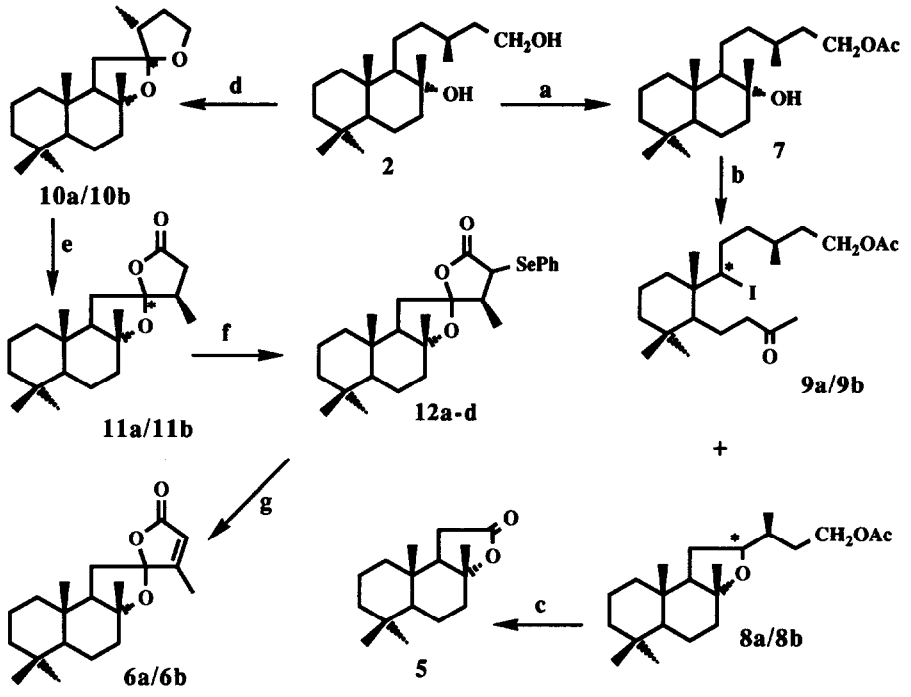
The functionalization of C–12 is achieved with the hydroxyl group of C–15 either free or as its acetyl derivative, which is readily obtained from **2** by treatment with Ac_2O/Py at room temperature in quantitative yield.

The treatment of the acetyl derivative **7** (Scheme 1) with LTA/I_2[9] gave four main components. Two of them are cyclic compounds **8a** / **8b** (71 %) and the other two **11a** / **11b** (23 %) are compounds resulting from β–fragmentation.

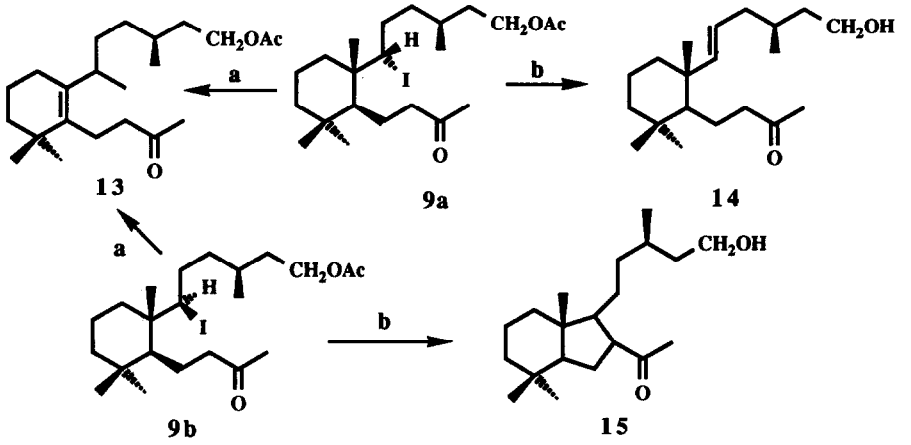
8a and **8b** were separated by P.T.L.C. and the absolute configuration at C–12 assigned by comparison of their spectroscopic properties. In fact, when comparing the ^1H NMR spectra, the signal of the hydrogen on C–12 in **8a** is deshielded respect to the same signal in **8b**, suggesting that the Me–17 and H–12 have a *cis*–relationship and that a 1,3–diaxial interaction exists causing a deshielding effect on H–12. Moreover, the difference between the chemical shifts for that hydrogen between **8a** and **8b** ($\Delta\delta$=0.38 ppm) could be explained by the shielding effect caused by the oxiranic oxygen on C–12, which is more pronounced when Me–17 and the hydrogen at C–12 are trans as they are in **8b**. Hence the absolute configuration of C–12 in **8a** is *R* and in **8b** is *S*.

Oxidation with Na_2CrO_4 of the mixture **8a** / **8b** gives **5** with an excellent 97% yield, a considerable improvement on the yield of **5** using CrO_3.[1] The other two compounds formed in the reaction of **7** with LTA/I_2 are the iododerivatives **9a** and **9b**. The cleavage of ring B was detected by analysis of their spectroscopic properties (IR, ^1H and ^{13}C NMR (Table 1), and MS) of the products as well as the presence of iodine in these molecules.

By comparison of spectroscopic data for **9a** and **9b** it could be deduced that both were epimers at C–9. In order to confirm the structures of these compounds some chemical transformations were performed (Scheme 2). Treatment of **9a** and **9b** with NaOAc and AcOH for 7 hours under reflux yields the same compound **13**. This compound is the product of a Wagner–Meerwein type rearrangement. However, when treated with KOH/MeOH their behaviour is quite different: **9a** gives only the olefin **14**, whereas **9b** gives the cyclisation product **15**.

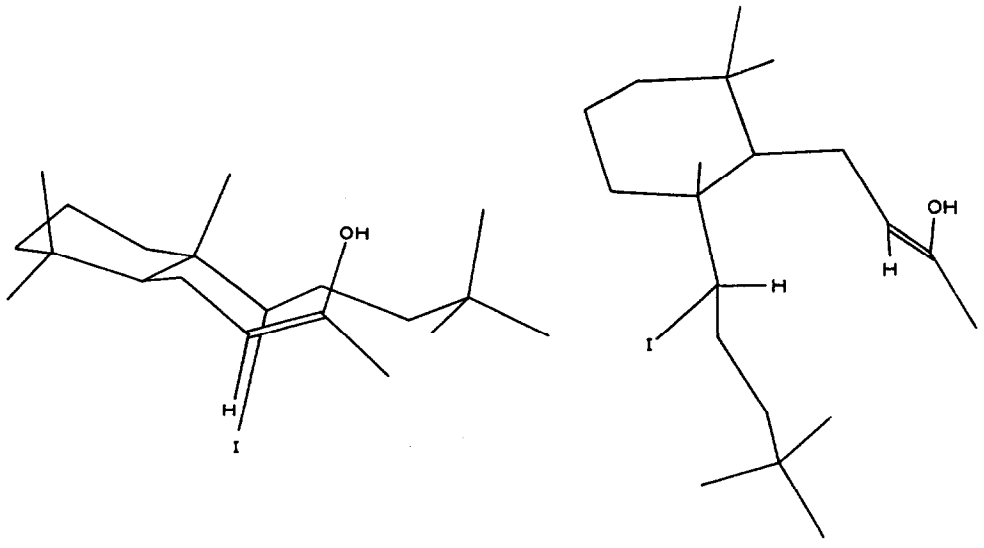


Scheme 1. [a]Ac_2O/ Py; [b]LTA/I_2, $CaCO_3$, 81°C; [c]Na_2CrO_4, AcOH, Ac_2O, NaOAc;[d]LTA/I_2, $CaCO_3$, 25°C; [e]RuO_2 / $NaIO_4$, Me_2CO / H_2O; [f]LDA,C_6H_5SeCl,HMPA; [g]AcOH / H_2O_2



Scheme 2. [a]NaOAc / AcOH; [b]KOH / MeOH

In order to explain the difference in reactivity between **9a** and **9b**, a molecular modelling study was performed, from which we have deduced the stereochemistry of both iododerivatives. This study[10] was done with the Macromodel Program MM2 forcefield, final minimization with FMNR option, and the most stable conformations found are shown **Ia** and **IIa** (Fig.1). Geometric data are given in table 2, for the three most stable conformations.



Ia IIa

Figure 1

I and II are the enols of models of **9a / 9b** in which the sidechain was modelled by a t–butylgroup for simplicity.

Although the distance in these ground states between the nucleophile and the C–9 atom, that bears the halogen , is very similar in all conformations, the dihedral angles are quite different. In I a–c the angle varies between 86.6 and 95.0°, so an intramolecular SN2 displacement would require substantial changes from the ground–state to the transition state geometry and thus a large activation energy. By contrast, in II a–c that angle is nearly 180° and so the cyclization may be expected to take place with a low free energy of activation and hence a high rate to give **9b** (9R). In both cases I and II the iodine atom has an antiperiplanar hydrogen with angles between 158.7 and 170.3° so an E2 elimination is possible for both compounds, and could thus be expected to be more quicker for **9a** than the disfavoured intramolecular SN2 reaction. The streochemical assignment for C–5 in compounds **9a** and **9b** is confirmed on the basis of the ^{13}C NMR chemical shifts observed for that carbon atom in C–9 oxygenated seco–labdanes[11] (Table 1).

The reaction between labdanediol **2** and LTA/I_2 gives two epimeric spiranes at C–12, **10a** and **10b**[1,12] that are easily interchangeable in $CDCl_3$; for this reason the NMR spectra were recorded in C_6D_6. Oxidation of **10a / 10b** with $RuO_2/NaIO_4$ gives α and β–levantanolides **11a** and **11b**.

Treatment of **11a / 11b** with LDA/THF followed by quenching with PhSeCl[13] gives a mixture of four selenoderivatives. Whether the selenylation is done with **11a** or **11b**, the same derivatives are obtained. The oxidation/elimination reaction of these selenides gives a mixture of α and β–levantenolides **6a** and **6b** that were separated by P.T.L.C. and tested biologically.[14]

Table 1. ^{13}C NMR Data (50.3 MHz)

C	2[a]	5	6a[b]	6b[b]	7	8a	8b	9a[a]	9b[a]	10a[b]	10b[b]	11a[b]	11b[b]	13	14	15
1	39.91	39.59	40.05	40.33	39.93	39.81	40.17	35.20	36.29	40.33	40.04	40.10	40.30	40.71	23.76	35.03
2	18.53	18.15	18.60	18.60	18.53	18.48	18.51	18.49	18.63	18.76	18.73	18.60	18.55	18.33	19.57	19.87
3	42.11	42.26	42.60	42.36	42.12	42.59	42.60	41.47	42.10	42.78	42.66	42.66	42.36	42.35	40.13	41.46
4	33.27	33.20	33.11	33.07	33.29	33.14	33.16	35.88	36.00	33.20	33.15	33.10	33.03	34.64	35.50	33.11
5	56.22	58.75	57.37	56.39	56.27	57.49	57.27	53.77	48.43	57.46	56.83	57.31	56.26	53.59	136.05	51.51
6	20.57	20.82	20.73	21.42	20.63	20.82	20.98	19.69	20.22	20.73	21.17	20.73	21.06	21.33	21.91	27.52
7	40.94	38.81	40.05	39.33	41.04	40.11	40.73	46.77	46.33	40.57	41.20	39.81	39.70	47.34	45.57	56.75
8	74.41	86.31	84.78	85.44	74.20	80.59	80.38	208.89	207.70	81.43	81.68	84.08	84.18	208.75	208.48	210.67
9	62.48	59.19	62.65	58.09	62.54	59.96	61.03	62.18	62.45	62.06	58.95	62.08	57.76	145.06	35.18	53.67
10	39.19	36.14	36.60	36.50	39.24	36.38	36.38	42.66	42.77	36.36	36.27	36.33	36.10	40.92	135.61	43.54
11	23.09	28.73	32.48	33.07	22.89	25.81	28.31	32.33	33.33	32.67	30.24	34.02	30.38	124.49	32.06	29.85
12	44.31	176.74	113.74	113.64	44.85	79.17	83.51	38.44	38.82	114.32	116.21	115.67	117.01	40.93	35.18	35.28
13	30.65		164.87	164.34	30.90	35.12	38.23	29.41	29.76	43.00	42.47	41.09	40.08	30.18	30.28	29.67
14	39.80		117.48	119.33	35.62	31.47	33.39	35.53	35.44	32.86	32.37	36.60	37.22	39.50	35.66	40.24
15	60.52		169.72	169.00	62.99	63.20	63.33	62.87	62.83	65.61	64.90	174.22	174.30	61.13	63.04	61.09
16	20.03		11.71	12.15	19.54	15.04	15.93	19.22	20.05	13.75	16.86	13.08	15.97	19.83	19.56	19.77
17	24.01	21.60	22.53	23.69	24.07	21.31	24.81	29.93	30.06	23.48	23.35	21.11	23.09	29.83	29.75	28.71
18	33.47	33.20	33.53	33.07	33.45	33.57	33.58	34.18	33.67	33.55	33.52	33.48	33.35	33.82	28.98	33.73
19	21.53	20.96	21.10	21.07	21.53	21.15	21.10	21.52	22.18	21.23	21.17	22.77	21.06	22.02	28.60	21.44
20	15.52	15.09	14.91	15.74	15.50	14.79	15.58	16.44	24.72	15.06	15.54	14.91	15.54	18.05	19.55	23.21
OCOMe					171.08	171.10	171.07	171.08	171.02						171.08	
COMe					20.98	20.98	20.98	20.99	20.97						20.96	

[a] The assignment has been done by 2D Heteronuclear ($^1H/^{13}C$) Correlation Spectroscopy. [b] Chemical Shifts in C_6D_6.

Table 2. Geometric Data

compound	energy KJ/mol	diedral angle C7–C9 –I	diedral angle Me–C10–C9 –I	diedral angle H–C11–C9 –I	distance (Å) C7–C9 –I
Ia	132.38	89.7°	171.6°	169.0°	3,16
Ib	134.94	95.0°	174.3°	169.4°	3.18
Ic	138.80	86.6°	173.4°	166.7°	3.18
IIa	130.08	144.6°	51.8°	170.3°	3.15
IIb	134.14	139.3°	49.4°	167.0°	3.21
IIc	141.17	148.7°	65.1°	158.7°	3.19

EXPERIMENTAL SECTION

The IR spectra were determined on a Bomem–100FT spectrophotometer in the form in each case indicated. The 200 MHz ^1H NMR and 50 MHz ^{13}C NMR spectra were determined on a Bruker WP–200–SY spectrometer. Chemical shifts are referenced in $CDCl_3$ to the residual $CHCl_3$, 7.26 ppm for ^1H and 77.0 ppm for ^{13}C, respectively and in C_6D_6 to the residual C_6H_6, 7.15 ppm for ^1H and 129.0 ppm for ^{13}C, respectively. Mass spectra were obtained on a VG 7070B instrument. Optical rotations were performed in a chloroformic solution unless otherwise stated, with a digital Perkin–Elmer–241 polarimeter. Melting points were determined in a Kofler hot plate apparatus and are uncorrected. Molecular modelling calculations were carried out using Macromodel V. 2.5 running on a MicroVax II.

Isolation of labdanediol **2.** Labdanediol, **2**.(48 g), was isolated from the unsaponificable part of the hexane extract of *Cistus ladaniferus* by chromatography on silica gel (800g) eluting with mixtures Hexane/EtOAc of increasing polarity. The fraction eluted with Hexane/EtOAc 7:3 (33.6 g), 70% of the unsaponificable neutral part is labdanediol, **2**.

8,15–dihydroxy–labdane (labdanediol) **2.** Mp 82–83°C (Hexane). $[\alpha]_D$ –5.2° ($CHCl_3$, c 1.3). IR ν_{max} cm^{-1}: 3350, 1150, 1130, 1080, 1050, 940 and 910. ^1H NMR δ: 3.62 (2H, m, H–15), 1.12 (3H, s, Me–17), 0.90 (3H, d, J=6.5 Hz, Me–16), 0.85 (3H, s, Me–19), 0.77 (6H, s, Me–18 and Me–20). MS, m/z 310 (M^+, 5), 293 (10), 195 (15), 157 (45), 128 (60), 84 (95), 69 (100). ^{13}C NMR (See table 1).

Acetylation of **2.** Labdanediol, **2**, (5.0 g, 16.1 mmol) was dissolved in 4.3 ml of pyridine and acetic anhydride (6.5 ml) was added. The reaction mixture was left at room temperature over 15 hours. Ice was added and after one hour, the product was extracted with ether. The ethereal phase was washed with 2M HCl, 6% $NaHCO_3$ and water; dried over Na_2SO_4, and then the solvent was evaporated to give labdanediol acetate (5.2 g) in quantitative yield..

15–acetoxy–8–hydroxylabdanol **7**. $[\alpha]_D$ –6.5° ($CHCl_3$, c 1.0). IR ν_{max} cm^{-1} 3400, 1750, 1460, 1400, 1380, 1250, 940 and 910. ^1H NMR δ: 4.08 (2H, m, H–15), 2.00 (3H, s, –OAc), 1.09 (3H, s, Me–17), 0.89 (3H, d, J=6.5 Hz, Me–16), 0.82 (3H, s), 0.75 (6H, s). ^{13}C NMR (See table 1).

Reaction of 3 with $Pb(OAC)_4/I_2$. To labdanediol **2** (2.32, 6.59 mmol) dissolved in cyclohexane (100 ml) were added $Pb(OAc)_4$ (17.59g, 39.6 mmol) and $CaCO_3$ (4.95 g, 49.5 mmol). I_2 (1.67 g, 6.5 mmol), dissolved in 86 ml of cyclohexane, was added dropwise. After the addition of Iodine, the reaction mixture was irradiated with two 100W lamps, refrigerating the system so that temperature is maintained at 25°C. The reaction was monitored by T.L.C. After 3 hours the lighting was stopped and ethyleneglycol (3 ml) was added. The solution

was filtered, washed with 5% $Na_2S_2O_3$ and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by chromatography on silica gel to give **8a/8b** (1.3 g, 71%) and **9a/9b** (0.65 g, 23%) eluting with Hexane/EtOAc 8:2 (0.15 g, 5.5%) and labdanediol **2** (0.15 g, 5.5%) eluting with Hexane/EtOAc 1:1. The mixture of oxides **8a/8b** were separated by P.T.L.C. eluting three times with Hexane/EtOAc 9:1.

12(R)–15–acetoxy–8,12 epoxy–labdane **8a.** $[\alpha]_D$ –5.7°($CHCl_3$, c 1.1). IR ν_{max} cm^{-1} 1740, 1250, 1170, 1150 and 1120. ^1H NMR δ: 4.05 (2H, m, H–15), 3.98 (1H, ddd, J_1=2.1 Hz, J_2=8.2 Hz and J_3=4.2 Hz, H–12), 2.04 (3H, s, –OAc), 1.12 (3H, s, Me–17), 0.93 (3H, d, J=6.6 Hz, Me–16), 0.87 (3H, s), 0.82 (6H, s). ^{13}C NMR. (See table 1).

12(S)–15–acetoxy–8,12 epoxy–labdane **8b.** $[\alpha]_D$ –3.3° ($CHCl_3$, c 1.1). IR ν_{max} cm^{-1} 1740, 1250, 1170, 1150 and 1120. ^1H NMR δ: 4.15 (2H, t, J=7 Hz, H–15), 3.60 (1H, m, J =16 Hz, H–12), 2.03 (3H, s, –OAc), 1.10 (3H, s, Me–17), 0.87 (3H, s, Me–19), 0.84 (6H, s, Me–18 and Me–20). ^{13}C NMR (See table 1).

9(S)–15–acetoxy–8–oxo–8,9 seco– 9–iodo–labdane: **9a.** $[\alpha]_D$ –3.3° ($CHCl_3$, c 1.1). IR ν_{max} cm^{-1} 1740, 1720, 1250, 1170 and 1150. ^1H NMR δ: 4.20 (3H, m, H–15 and H–9), 2.14 (3H, s, $-COCH_3$), 2.04 (3H, s, –OAc), 1.04 (3H, s, Me–19), 0.93 (3H, s, Me–18), 0.91 (3H, d, J=7 Hz, Me–16) and 0.89 (3H, s, Me–20). MS, m/z 478 (M^+, 4), 419 (1), 401 (3), 351 (7), 333 (90), 291 (9), 273 (11), 195 (15), 177 (36), 163 (42), 149 (38), 128 (71), 121 (59), 109 (100), 95 (93). ^{13}C NMR. (See table 1).

9(R)–15–acetoxy–8–oxo– 8,9 seco–9–iodo–labdane **9b.** IR ν_{max} cm^{-1} 1740, 1720, 1250, 1170 and 1150; ^1H NMR δ : 4.15 (3H, m, H–15, H–9), 2.13 (3H, s, –CO–CH_3), 2.05 (3H, s, –OAc), 1.08 (3H, s, Me–19), 0.97 (3H, d, J=7.0 Hz, Me–16), 0.92 (3H, s, Me–18) and 0.91 (3H, s, Me–20). MS, m/z 478 (M^+, 2), 351 (10), 333 (100), 291 (11), 273 (22), 177 (49), 163 (47), 149 (46), 135 (42), 128 (72), 121 (48), 109 (75), 95 (91). ^{13}C NMR. (See table 1).

Treatment of **9a** *with AcONa/AcOH* **13**. A mixture of **9a** (82 mg, 0.17 mmol) and NaOAc (26 mg, 0.32 mmol) and acetic glacial acid (44 mg, 0.73 mmol) were refluxed over 7 hours. Then the mixture was cooled, water was added and extracted with ether. The ethereal phase was washed with water to neutrality, dried and after evaporation of the solvent and chromatography on silica gel eluting with Hexane/EtOAc 8:2, gave **13** (22 mg, 37%) as an oil: IR ν_{max} cm^{-1} 1735, 1720, 1250, 1170, 1090 and 1010. ^1H NMR δ: 4.15 (2H, t, J=7 Hz, H–15), 2.13 (3H, s, $COCH_3$), 2.04 (3H, s, OAc), 0.98 (3H, s, Me–19), 0.97 (3H, s, Me–18), 0.90 (3H, d, J=6.7 Hz, Me–C–9), 0.97 (3H, d, J=6.1 Hz, Me–16). ^{13}C NMR. (See table 1).

Treatment of **9b** *with AcONa/AcOH*. A mixture of **9b** (48 mg, 0.10 mmol) and NaOAc (15 mg, 0.18 mmol) and acetic glacial acid (258 mg, 0.43 mmol) were refluxed over 29 hours. Then the mixture was cooled, water was added. After the usual work–up, chromatography on silica gel eluting with Hexane/EtOAc 8:2, gave **13** (22 mg, 63%).

Treatment of **9a** *with KOH/MeOH* **14**. 50 mg of **9a** dissolved in 4 ml of MeOH were saponificated with 4 ml of 2M KOH/MeOH, at room temperature overnight. The reaction mixture is concentrated under vacuum, H_2O is added, the mixture is carefully acidulated with 2N HCl to pH 5 and extracted with ether affording, after the usal work up, **14** (30 mg, 92%) as an oil: IR ν_{max} cm^{-1} 3400, 1700, 1650, 1450, 1050 and 970. ^1H NMR δ: 5.2 (2H, m, H–9 and H–11), 3.58 (2H, t, J=6.5 Hz, H–15), 2.53 (1H, m, H–7), 2.07 (3H, s, $COCH_3$), 0.98 (3H, s, Me–19), 0.89 (3H, d, J=7 Hz, Me–16), 0.88 (6H, s, Me–18 and Me–20). ^{13}C NMR (See table 1).

Treatment of **9b** *with KOH/MeOH* **15**. To a solution of **9b** (48 mg) in MeOH were added 4ml of a solution of 2M KOH/MeOH, the mixture was kept at room temperature during 7 hours. After working in the usual way **15** (34 mg, 96%) was obtained as an oil: IR ν_{max} cm^{-1} 1740, 1710, 1380, 1360 and 1250. ^1H NMR

δ: 4.12 (2H, t , J=7 Hz, H–15), 2.18 (3H, s, $COCH_3$), 2.03 (3H, s, OAc), 0.89 (3H, s, Me–19), 0.88 (3H, d, J=6 Hz, Me–16), 0.86(3H, s, Me–18) and 0.83 (3H, s, Me–20). ^{13}C NMR. (See table 1).

Oxidation of **8a/8b** *with* Na_2CrO_4 *:* **5**. To **8a/8b** (210 mg, 0.6 mmol) dissolved in benzene (8 ml), were added 8 ml of AcOH, 8 ml of Ac_2O and 174 mg of NaAcO. Later Na_2CrO_4 (445 mg, 2.74 mmol) was added and the temperature kept between 30–40°C. After 12 hours, ice was added and extracted with ether and the organic layer was washed with $NaHCO_3$ and H_2O, dried over Na_2SO_4. Filtration and evaporation of the solvent afforded **5** (146 mg, 97%) .

12–nor–ambreinolide **5**. mp 118–119°C (hexane). $[\alpha]_D$ +49.7° ($CHCl_3$, c 1.0). IR ν_{max} cm^{-1} 1775, 1285, 1270, 1220, 1170, 1120 and 1110. ^1H NMR δ : 2.42 (1H, dd, J_1=16.1 Hz, J_2=14.7 Hz, H_a–11), 2.23 (1H, dd, J_1=16.1 Hz, J_2=6.5 Hz, H_b–11), 1.31 (3H, s, Me–17), 0.90 (3H, s, Me–19), 0.86 (3H, s, Me–18), 0.82 (3H, s, Me–20). ^{13}C NMR. (See table 1).

Reaction of, **2** *with* $Pb(OAc)_4/I_2$. 20 g of $Pb(OAc)_4$ (45 mmol) and 8 g of $CaCO_3$ were dissolved in dry cyclohexane (450 ml). To the solution labdanediol, **2** (2.2 g, 7 mmol), dissolved in 50 ml of cyclohexane and 4.8 g of I_2 (18.9 mmol) dissolved in 100 ml of cyclohexane, were added The reaction mixture was stirred and lighted with two 100W lamps and monitored by T.L.C.. After 1 hour 4 ml of ethylenglycol was added. The solution was washed with, 5% $Na_2S_2O_3$, dried over Na_2SO_4 and evaporated. Column chromatography of the residue on silica gel, Hexane/EtOAc 95:5 afforded the mixture of spiranes **10a/10b** (1.56 g, 72%). The spiranes **10a/10b** were separated by P.T.L.C (Benzene/EtOAc)

12(R)–8(12),12(15)–diepoxy–labdane **10a**. mp 93–94°C (acetone). $[\alpha]_D$ +42.2° ($CHCl_3$, c 0.9). IR ν_{max} cm^{-1} 2840, 1510, 1400, 1290, 1270, 1230, 1120, 1010, 970 and 940. ^1H NMR δ (C_6D_6): 3.97 (1H, m, H_a–15), 3.74 (1H, m, H_b–15), 1.44 (3H, s, Me–17), 1.05 (3H, d, J=7.3 Hz, Me–16), 0.78 (3H, s), 0.75 (6H, s). ^{13}C NMR. (See table 1).

12(S)–8(12), 12(15)–diepoxy–labdane **10b**. $[\alpha]_D$ –63.7° ($CHCl_3$, c 0.9). IR ν_{max} cm^{-1}: 2970, 2960, 1570, 1500, 1450, 960 and 850. ^1H NMR δ (C_6D_6): 4.00 (1H, m, H_a–15), 3.79 (1H, m, H_b–15), 1.04 (3H, s, Me–17), 0.85 (3H, d, J=6.8 Hz, Me–16), 0.75 (6H, s) and 0.71 (3H, s). ^{13}C NMR. (See table 1).

Oxidation of spiranes, **10a/10b** *with* RuO_4 */ Acetone* . To 266 mg of RuO_2 in 33 ml of acetone, $NaIO_4$ (2 g, 9.3 mmol) dissolved in H_2O (10 ml) was added. To the yellow solution (**10a/10b**) (666 mg, 2.17 mmol) dissolved in acetone (33 ml) were added. A solution of 4.6 g of $NaIO_4$ in 13 ml of water and 13 ml of acetone was used to keep the colour of the solution yellow. The reaction was monitored by T.L.C. After 47 hours EtOH (2 ml) was added . The solution was filtered and pass through a pad of celite and the acetone evaporated. Water was added to the residue and extracted with ether. The ethereal phase was dried over Na_2SO_4, filtered and evaporated under vacuum. Column chromatography of the residue (627 mg) on silica gel Hexane/EtOAc gave 29 mg of starting material (**10a/10b**, 4.35%; Hexane/EtOAc 95:5) and lactones **11a/11b** (471 mg, 67.5%). These lactones were separated by flash chromatography on silica gel eluting with Hexane/EtOAc 9:1.

12(S)–8,12–epoxy–labdan–15(12)–olide (α–levantanolide) **11a**. mp 145–146°C (Hexane). $[\alpha]_D$ +19.5 ° ($CHCl_3$, c 1.0). IR ν_{max} cm^{-1}: 2290, 1780, 1460, 1590, 1280, 1220 and 910. ^1H NMR δ (C_6D_6): 1.23 (3H, s, Me–17), 0.76 (3H, s), 0.75 (3H, d, J=6.4 Hz, Me–16), 0.71 (3H, s) and 0.63 (3H, s), MS, m/z 320 (M^+, 8), 319 (15), 305 (57), 304 (7), 276 (5), 191 (53), 167 (34), 125 (40), 109 (59), 69 (100). ^{13}C NMR. (See table 1).

12(R)–8,12–epoxy–labdan–15(12)–olide (β–levantanolide) **11b**. $[\alpha]_D$ –42 °($CHCl_3$, c 0.6). IR ν_{max} cm^{-1}: 2950, 1780, 1460, 1380, 1285, 1280, 1140 and 1000. ^1H NMR δ (C_6D_6) 2.69 (1H, dd, J_1=7.3 Hz and J_2=16.6 Hz, Ha–15), 0.88 (3H, s, Me–17), 0.76 (3H, s), 0.72 (3H, s), 0.60 (3H, s), MS, m/z 320 (M^+, 4), 319 (2), 305 (80), 276 (5), 191 (60), 167 (34), 125 (40), 109 (59), 69 (50), 43 (100). ^{13}C NMR. (See table 1).

α–Selenylation of **11a/11b**. *n*–BuLi , (0.75 ml of a 1.6M solution in hexane) was added dropwise to a stirred solution of diisopropylamine (0.17 ml, 1.2 mmol) in dry tetrahydrofurane (4 ml) at –78°C. A solution of **11a/11b** (174 mg, 0.54 mmol) dissolved in dry THF (0.5ml) was added dropwise. The mixture was kept at –78°C for 30 minutes, then warmed to 0°C. After 45 minutes at 0°C was cool down to –78°C and a solution of C_6H_5SeCl (229 mg, 1.2 mmol), was added in dry THF (1.2 ml) and HMPA (0.2ml). After one hour at –78°C The temperature was warmed slowly to –30°C. Stirring was continued for another 2.5 hours, then saturated aqueous ammonium chloride solution (3ml) was added and the mixture allowed to warm to room temperature. Water (5ml) was added and the aqueous layer extracted with ether . The combined organic layers were washed with $NaHCO_3$, brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and chromatography of the residue (306mg, Hexane/EtOAc 95:5) gave 140 mg of a mixture of selenides **12** (55%).

Oxidation/Elimination of **12 6a/6b**. To the mixture of selenides **12** (34 mg, 0.07 mmol) dissolved in THF (0.15 ml) at 0°C with some AcOH (0.15ml), was added 30% H_2O_2 (0.2 ml). After 30 minutes at 0°C, saturated sodium hydrogencarbonate solution (5ml) was added. The aqueous layer was then extracted with ether and the combined organic layers washed with brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and chromatography of the residue (Hexane/EtOAc 8:2) afforded a mixture of levantenolides **6a/6b** (18mg, 79%). These two compounds were separated by P.T.L.C. on silica gel eluting with Hexane/EtOAc 8:2.

α–levantenolide **6a**. mp 210 °C (hexane), $[\alpha]_D$ +60.0°($CHCl_3$, c 0.7). IR ν_{max} cm^{-1}: 3100, 1770, 1630, 1265, 1215, 1114, 1075, 1015, 900, 860 and 780. ^1H NMR δ (C_6D_6): 5.33 (1H, q, J=1.5 Hz, H–14), 1.39 (3H, d, J=1.5 Hz, Me–16), 1.28 (3H, s, Me–17), 0.75 (3H, s), 0.70 (3H, s), 0.61 (3H, s). ^{13}C NMR. (See table 1).

β–levantenolide **6b**. $[\alpha]_D$ –59.0°($CHCl_3$, c 0.8). IR ν_{max} cm^{-1}: 3100, 1770, 1650, 1280, 1135, 1090, 1010, 940, 880 and 780. ^1H NMR δ (C_6D_6): 5.47 (1H, q, J=1.5 Hz, H–14), 1.47 (3H, d, J=1.5 Hz, Me–16), 0.98 (3H, s, Me–17), 0.82 (3H, s), 0.78 (3H, s), 0.67 (3H, s). ^{13}C NMR (See table 1).

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10. Structure I was built using the template and sketching options of the general ORGANIC mode of Macromodel. II was generated from I by inversion at C–9. Both structures were minimised MM2 forcefield option: 100 iterations of stepest descent (SD) minimisation followed by further minimisation, using the block diagonal Newton–Raphson method (BDNR), until default convergence criteria were met) and then set up for a conformational search. The six–membered ring was treated as rigid as was the t–butyl group used as a model for the sidechain of 8a and 8b. The remaining carbon–carbon bonds were defined as rotatable with an increment of 30º, except the enol

carbon carbon double bond which was allowed to adopt torsions of only 0 or 180°. All conformers generated were subjected to 100 iterations of SD, 100 iterations of BDNR and final minimisation to the default convergence criteria using the full matrix Newton–Raphson method. The three lowest energy conformers Ia–c and IIa–c of each model were subjected to geometric analysis as discussed in the text.

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14. The biological data will be published elsewhere.