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Ambergris Compounds from Labdanolic Acid

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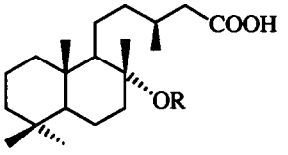
Abstract: Labdanolic acid (*Cistus ladaniferus)* is transformed into derivatives with amber odor. The strategy used allowed a process in which the oxidative decarboxylation reaction was carried out with the hydroxyl group protected.

INTRODUCTION

Following our studies[1,2,3] on the transformation of the main components of *Cistus ladaniferus* to obtain derivatives with amber odor, we now wish to report the conversion of labdanolic acid into oxides **8** and **9**, ambroxdiol **13** and 12–*nor*ambreinolide, **17**.

Labdanolic acid **1a** is the main component of the acid fraction of *Cistus ladaniferus* obtained from a hexane extract of the plant. *C. ladaniferus* is a widely distributed plant of the uncultivated areas of the West Iberian Peninsula, thus the starting material is readily accessible. Our interest is to make possible the use of labdanolic acid as a source for products of economical interest like ambroxdiol **13** and 12–*nor*–ambreinolide **17**.

In previous papers[1,2], Methyl labdanolate had been used as the starting material. In this case, the same acid has been used with the hydroxyl group protected as the acetate instead of protecting the carboxyl group. In this way, we got a process for the obtention of 12-*nor*-ambreinolide, ambrox® precursor, where the amount of Lead tetracetate (LTA) used in the first step of the synthesis (an oxidative decarboxylation reaction) is decreased.

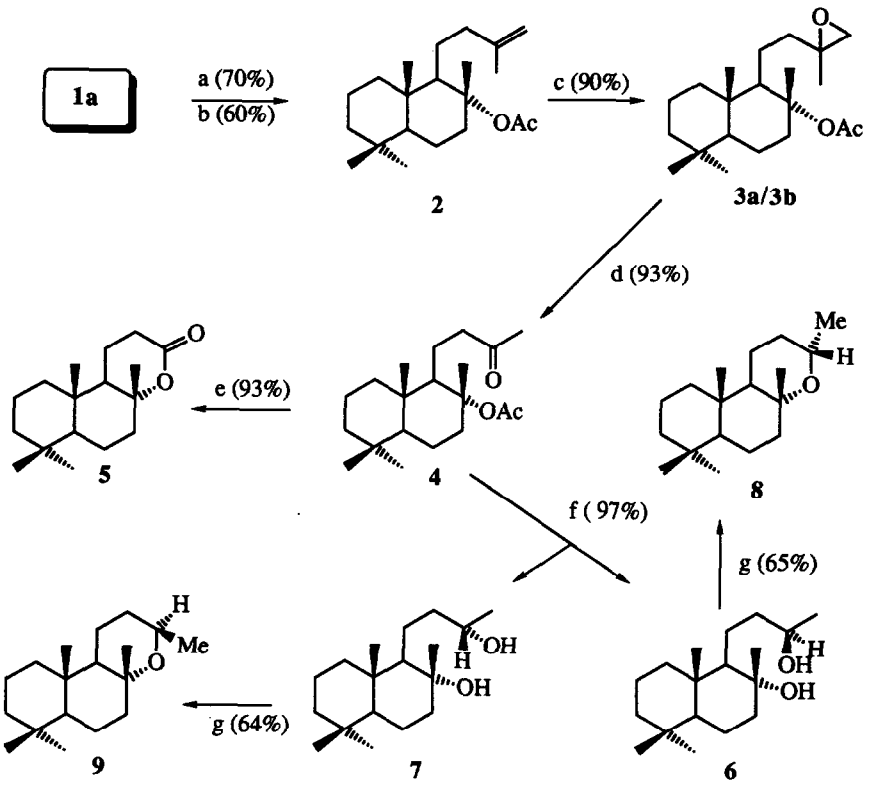


	R
1a	**H**
1b	**Ac**

RESULTS AND DISCUSSION

Treatment of labdanolic acid, **1a**, with Ac_2O/Et_3N/DMAP at 35–40° C produced the acetyl derivative **1b** in 75% yield(Scheme 1). Decarboxylation[4] of the acetate with LTA/$(Cu(OAc)_2$ produced the alkene **2** in 60% yield. Upon treatment of **2** with *m*CPBA, the mixture of epoxides (**3a/3b**) was obtained. The mixture of epoxides was treated with periodic acid giving a crystalline product **4**,with a pleasant amber odor, which shows in its ^1H NMR spectrum the characteristic signals of a methyl ketone (2.12, 3H, s) and acetoxyl (1.91, 3H, s) groups. In the ^{13}C NMR spectrum (Table **1**)the signals corresponding to 20 carbon atoms are observed, two of them are carbonyl carbons at δ 170.0 and 208.9 ppm.

Ketone **4** is the starting material for the oxides **8** and **9** as well as for ambreinolide **5**. Treatment of **4** with Br_2 in basic medium led to lactone **5**, ambreinolide, that is the precursor of the corresponding oxide with amber odor. When **4** is reduced with Lithium Aluminum hydride (LAH) a mixture of diols, **6** and **7**, that can be separated by column chromatography, is obtained.

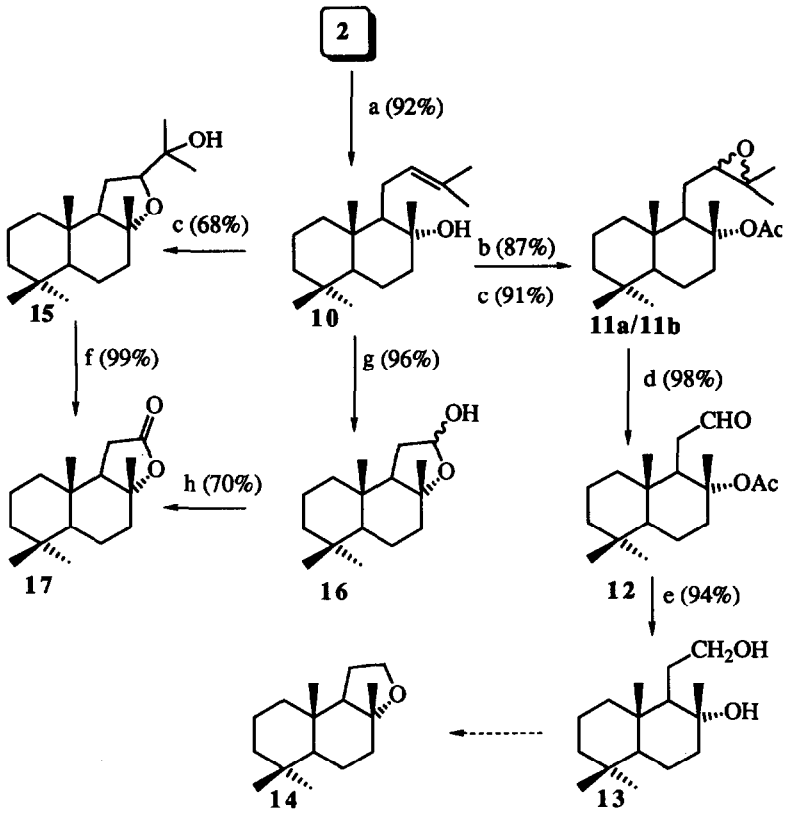


Scheme 1. [a]Ac_2O/Py/DMAP; [b]LTA/C_6H_6/$Cu(OAc)_2$; [c]*m*CPBA; [d]HIO_4/Me_2CO; [e]Br_2/OH^-; [f]LAH; [g]MsCl, Py

Oxides **8** and **9** are reported in the literature[5] and the stereochemistry at C-13 for both compounds determined by ^1H NMR Induced–Shift experiments by the addition of $Eu(Fod)_3$ complex. By comparison and correlation of these data, the stereochemistry at C-13 for each diol (**6** and **7**) can be determined, due to the fact that cyclation with MsCl /Py, proceeds through an S_N2 mechanism, leading to oxides **8** and **9**, respectively.

The 12-*nor*-ambreinolide **17** and ambroxdiol **13** (Scheme 2) are obtained from a common intermediate, **10**, that is obtained from **2** after isomerization of the double bond with Lithium/ethylenediamine.[6] When **10** was subjected to epoxidation with *m*CPBA, the tetrahydrofuran derivative **15** was obtained, due to the effect caused by the hydroxyl group that induces epoxide–ring opening, in 68% yield. Oxidation of **15** with Na_2CrO_4 led to 12-*nor*-ambreinolide in 99% yield.

Another route to **17** is accomplished by transformation of **10** in an acetalic intermediate **16** by ozonolysis; oxidation of the latter with Jones reagent gave **17.**



Scheme 2. [a]Li/Ethylenediamine; [b]MeCOCl/N,N–Dimethylaniline; [c]*m*CPBA; [d]HIO_4; [e]LAH; [f]Na_2CrO_4; [g]O_3; [h]Jones reagent

10 was transformed to ambroxdiol, **13**, according to the following sequence of reactions: acetylation of **10** with Acetyl chloride and N,N–Dimethylaniline led to the monoacetate that with *m*CPBA led to a mixture of epoxides **11a/11b**. Treatment of this mixture with periodic acid led to aldehyde **12** that, after reduction with LAH, gave diol **13**, that could be transformed into ambrox®, **14**.[7]

The mixture of epoxides (**11a/11b**) could be separated by careful column chromatography. The stereochemistry of the epoxide ring for each one of them has been determined by comparison of ^{13}C NMR spectra. The main difference corresponds to the chemical shift observed for C9 57.1 ppm for the less polar epoxide (**11a**) and 55.9 ppm for the most polar (**11b**). The variation in the chemical shift can be used to assign the stereochemistry due to the fact that a homoallylic carbon (γ from the oxygen), bearing an axial hydrogen, is strongly affected by the configuration of the epoxide ring. If the epoxide oxygen and the axial hydrogen in the γ position are *cis*, the carbon bearing the hydrogen is shielded.[8] According to this fact and considering that the side chain in **11a** and **11b** has a very low mobility, only the epoxide with R configuration at C12 can adopt a preferred conformation leading to a *cis* relationship between the oxiranic oxygen and H9. In the case of a *trans* relationship, S configuration at C12, there are any not hindered conformations with the relative atom arrangement leading to a shielding of the homoallylic carbon. Thus, the stereochemistry at C12 is assigned as S for **11a** and R for **11b**, respectively.

Table 1. ^{13}C NMR data (CDCl3, 50.3 MHz)

C	1a	1b[a]	2	4	5	6	7	8	9	10	11a	11b	12	13	15	16	17
1	39.8	38.9	38.9	39.8	39.3	39.9	39.8	39.3	39.3	40.1	39.0	38.7	39.1	39.5	39.9	39.9	38.9
2	18.5	18.4	18.4	18.4	18.5	18.5	18.5	18.7	18.6	18.7	18.4	18.5	18.3	18.5	18.4	18.4	18.2
3	42.1	41.6	41.1	41.9	41.9	42.1	42.3	42.3	42.2	43.9	41.9	41.8	41.7	44.3	42.6	42.5	42.3
4	33.3	33.1	33.2	33.2	33.3	33.2	33.3	33.4	33.3	33.4	33.2	33.2	33.3	33.3	33.1	32.8	33.2
5	56.1	55.7	55.8	55.8	56.0	56.2	56.1	56.6	56.6	58.3	55.7	55.5	55.7	56.1	57.5	57.1/57.2	56.6
6	20.5	20.1	20.1	20.0	19.7	20.1	20.6	20.0	20.2	20.3	20.0	20.0	19.9	20.5	20.6	20.6/20.8	20.6
7	40.6	39.7	39.7	38.9	29.1	40.9	42.1	42.3	43.3	42.0	40.0	40.1	40.3	42.0	40.0	40.1/40.5	39.6
8	75.0	88.1	88.0	88.1	84.5	74.4	74.7	74.7	74.8	74.3	87.7	86.9	86.1	73.0	81.2	81.6/83.1	86.3
9	62.1	59.1	58.8	58.2	53.8	58.7	61.6	57.5	53.1	61.6	57.1	56.0	53.6	59.4	60.4	60.9	59.2
10	39.2	39.5	39.5	39.6	38.6	39.3	39.3	36.9	37.3	38.9	39.1	39.2	38.8	39.5	36.4	36.1/36.2	36.2
11	23.9	23.2	24.6	19.7	16.0	20.6	22.1	18.7	15.5	23.8	25.1	25.0	40.0	28.0	24.4	31.7/31.8	28.7
12	43.9	42.0	42.0	46.6	41.4	44.3	44.4	35.5	30.4	127.4	66.2	65.6	201.8	64.0	82.6	97.3/99.0	176.1
13	31.3	31.0	146.8	208.9	171.5	65.5	69.8	65.4	66.2	130.5	59.3	58.9			72.1		
14	41.6	39.8	109.4							21.8	19.1	19.1			26.6		
15	177.7	179.1															
16	20.0	19.8	22.4	29.8		24.6	24.4	20.8	26.3	17.9	22.9	23.0			24.5		
17	23.1	22.8	22.8	20.6	22.9	23.2	23.8	22.7	23.5	24.6	25.0	25.0	22.4	24.6	21.5	22.9/24.1	21.6
18	33.4	33.3	33.4	33.4	33.4	33.4	33.4	33.4	33.5	33.6	33.4	33.4	33.2	33.5	33.6	33.5	33.2
19	21.5	21.5	21.5	21.5	21.5	21.5	21.5	21.8	21.5	21.6	21.5	21.5	21.4	21.5	21.3	21.1	21.0
20	15.5	15.7	15.7	15.6	15.1	15.3	15.2	15.6	15.2	15.4	15.2	15.8	15.9	15.9	14.8	15.3	15.1
$MeCO_2$		170.3	169.9	170.0							169.9	170.2	169.4				
$MeCO_2$		20.5	20.6	22.9							20.6	21.1	20.3				

[a] The assignment of 1b has been done by 2D heteronuclear ($^1H/^{13}C$) correlation spectroscopy.

EXPERIMENTAL SECTION

Spectral analysis. NMR spectra were obtained on a 200 MHz spectrometer, operating at 200 MHz for ^1H and 50.3 MHz for ^{13}C, respectively. 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. Melting points were determined in a Kofler type hot–stage apparatus and are uncorrected. IR spectra were recorded in a BOMEM MB–100 FT–IR spectrometer. Mass Spectra were obtained in a VG TS 250 Mass Spectrometer by Electron ionization with a potential of 70eV.

Isolation. Labdanolic acid, **1a**, was isolated from a hexane extract of *C. ladaniferus*, L. according to the procedure described.[9]

8–acetoxy-labdanolic acid: **1b**. To **1a** (15.4 g, 48 mmol) were added 38 ml of Et_3N, freshly distilled, 19 ml of Ac_2O and 468 mg DMAP The reaction was maintained between 35–40°C for 96 hours; then, ice was added and the mixture extracted with ether. The organic phase was then washed with 2N HCl and water, dried over Na_2SO_4 and evaporated to dryness. The crude product was chromatographed on a column of silica gel to afford **1b** (13.2 g, 75% yield). mp 127–129°C. $[\alpha]_D$ –25.6 ($CHCl_3$, c 1.1). IR ν_{max} cm^{-1} 3380, 1730, 1710, 1460, 1390, 1365, 1260, 1210, 1080. MS: 366 [M^+, 6], 306 (53), 291 (39), 191 (60), 177 (42), 168 (16), 137 (30), 109 (51), 95 (63), 81 (73), 69 (100). ^1H NMR δ 1.90 (3H, s, OAc), 1.43 (3H, s, Me-17), 0.96 (3H,d, J=6.7 Hz, Me-16), 0.84 (3H, s), 0.81 (3H, s), 0.76 (3H, s). ^{13}C NMR (see Table 1).

15–nor–8–acetoxy–13–labdene: **2**. To a solution of **1b** (9.8 g, 27 mmol) dissolved in 475 ml of dry benzene, were added pyridine (2.1 ml) and $Cu(OAc)_2$ (1.26 g). LTA (22.3 g, 70.2 mmol) was added to this solution in fractions over a six hour period, maintaining the mixture at 80°C under a N_2 atmosphere. The benzene is evaporated and the crude product was dissolved in ether, washed with 10% Na_2CO_3 giving a neutral fraction (8.3 g) and an acid fraction (715 mg), starting material. The neutral fraction was chromatographed on a column of silica gel to afford, on elution with Hexane/ Ether (4:1), **2** (5.2 g, 60 % yield). mp 65-69°C. $[\alpha]_D$ –12.8 ($CHCl_3$, c 1.9). IR ν_{max} cm^{-1} 3100, 1740, 1660, 1465, 1400, 1370, 1255, 1130, 1020, 890. MS: 320 [M^+, 3], 277 (33), 260 (20), 233 (35), 205 (29), 177 (38), 167 (52), 137 (32), 109 (65), 95 (54), 81 (61), 69 (100). ^1H NMR δ 4.66 (2H, s, $=CH_2$), 1.91 (3H, s, OAc), 1.72 (3H, s, Me-16), 1.45 (3H, s, Me-17), 0.85 (3H, s), 0.82 (3H, s), 0.77 (3H, s). ^{13}C NMR (see Table 1).

Epoxidation of **2**: **3a/3b**. To a solution of **2** (2.48 g, 7.8 mmol) dissolved in 7.5 ml of CH_2Cl_2, was added *m*CPBA (1.37 g) dissolved in 12 ml of CH_2Cl_2 and the reaction being monitored by TLC. After 5 hours the reaction was judged complete. The reaction mixture was filtered and washed with 10% Na_2SO_3, $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated to dryness to afford 2.50 g of **3a** and **3b**, that are not separated by CC over silica gel.

14,15–dinor–8–acetoxy–labdan–13–one: **4**. To a solution of **3a/3b** (1.5 g, 4.5 mmol) dissolved in 7.5 ml of THF was added 1.5 g of periodic acid dissolved in water(11 ml) and /THF (18 ml). The reaction was stirred at room temperature for 2 hours, after that time the reaction was extracted with hexane, washed with water, 5% $Na_2S_2O_3$ and water, dried over Na_2SO_4 and evaporated to dryness to afford 1.3 g of **4** (93 % yield). mp 118-121°C. $[\alpha]_D$ –22.2 ($CHCl_3$, c 1.2). IR ν_{max} cm^{-1} 1725, 1240. MS: 322 [M^+, 4], 280 (14), 262 (16), 229 (24), 204 (75), 191 (46), 177 (30), 137 (58), 123 (56), 109 (76), 95 (94), 81 (80), 69 (100). ^1H NMR δ 2.12 (3H, s, MeCO), 1.91 (3H, s, OAc), 1.46 (3H, s, Me-17), 0.86 (3H, s), 0.83 (3H, s), 0.77 (3H, s). ^{13}C NMR (see Table 1).

Ambreinolide: **5**. NaOH (1.85 g) was dissolved in 8 ml of water. The alkaline solution was chilled in an ice bath and Br_2 (1.85 g, 0.6 ml) was added and the solution stirred for 1 hour at room temperature. 0.8 ml of this solution was added to a solution of **4** (83 mg, 0.25 mmol) dissolved in 1 ml of dioxane and stirring is maintained

for 5 hours at room temperature. The excess of hypobromite was destroyed with 40% $NaHSO_3$. The alkaline solution is acidulated and extracted with ether affording after the usual work-up **5** (59 mg, 88% yield). mp 140–143°C. $[\alpha]_D$ +29.1 ($CHCl_3$, c 0.6). IR ν_{max} cm^{-1} 1730, 1450, 1390, 1310, 1290, 1270. MS: 264 [M^+, 2], 249 (15), 192 (63), 191 (38), 177 (60), 137 (34), 136 (31), 123 (23), 121 (35), 95 (66), 81 (70), 67 (100), 43 (39). ^1H NMR δ 2.69 (1H, ddd, J=3.9, 8.3, 18.6 Hz, H-12a), 2.51 (1H, dt, J=18.6 , 8.3 Hz, H-12b), 1.38 (3H, s, Me-17), 0.89 (3H, s), 0.84 (3H, s), 0.82 (3H, s). ^{13}C NMR (see Table 1).

Reduction of **4**: **6** and **7**. To a stirred solution of **4** (660 mg, 2.04 mmol) dissolved in dry ether (32 ml) was added 120 mg of $LiAlH_4$ and the stirring maintained for 1 hour at room temperature, after that time a few drops of wet ether were added and the mixture saturated with Na_2SO_4, filtered and evaporated. The crude product was chromatographed on a column of silica gel affording **6** (320 mg, 57%, Hexane/EtOAc, 7:3) and **7** (240 mg, 42% yield, Hexane/EtOAc, 1:1).

14,15–dinor–8,13(R)labdanediol: **6** mp 102–103°C. $[\alpha]_D$ –38.6 ($CHCl_3$, c 2.5). IR ν_{max} cm^{-1} 3340 (broad), 1120, 1080, 940, 910. ^1H NMR δ 3.90 (1H, m), 1.15 (3H, d, J=6.4 Hz), 1.13 (3H, s, Me-17), 0.85 (3H, s), 0.78 (3H, s), 0.77 (3H, s). ^{13}C NMR (see Table 1).

14,15–dinor–8,13(S)labdanediol: **7**. mp 112–113°C. $[\alpha]_D$ +6.4 ($CHCl_3$, c 2.8). IR ν_{max} cm^{-1} 3350 (broad), 1110, 1070, 940, 910. ^1H NMR δ 3.78 (1H, m), 1.16 (3H, d, J=6.4 Hz), 1.15 (3H, s, Me–17), 0.85 (3H, s), 0.77 (6H, s). ^{13}C NMR (see Table 1).

Cyclation of **6** *and* **7**: **8** and **9**. To a stirred solution of **6** (120 mg, 0.42 mmol) dissolved in 0.4 ml of pyridine and 2ml of benzene under Argon was added 0.04 ml of Mesyl chloride. The mixture was heated at 40°C during 24 h. The reaction was cooled, water was added and extracted with ether. The ether extract was washed with 2N HCl and water until neutrality, dried over Na_2SO_4 and evaporated to dryness. The crude product was chromatographed on a column of silica gel eluted with Hexane/Ethyl acetate 9:1, to afford **8** (72 mg, 65% yield). **7** (105 mg, 0.37 mmol), was treated in a similar manner and after chromatography afforded **9** (63 mg, 64% yield).

14,15–dinor–8,13(S)–epoxy–labdane: **8**.$[\alpha]_D$ –9.5 ($CHCl_3$, c 0.7). ^1H NMR δ 3.72 (1H, m), 1.24 (3H, s), 1.09 (3H, d, J=6.5 Hz), 0.86 (3H, s), 0.79 (3H, s), 0.74 (3H, s). ^{13}C NMR (see Table 1).

14,15–dinor–8,13(R)–epoxy–labdane: **9**. $[\alpha]_D$ +18.0 ($CHCl_3$, c 0.7). ^1H NMR δ 3.97 (1H, m), 1.22 (3H, s), 1.14 (3H, d, J=6.5 Hz), 0.86 (3H, s), 0.80 (6H, s). ^{13}C NMR (see Table 1).

Isomerization of **2**: *15–nor–8–hydroxy–12–labdene*: **10**. To 50 ml of freshly distilled ethylene diamine was added Lithium (1.5 g) in portions over a two hours period. The mixture was heated under Argon at 100°C during the addition and for two more hours. After that time the reaction was cooled to room temperature and a solution of **2** (5g, 15.6 mmol) dissolved in 5 ml of dry benzene was added. The mixture was stirred at room temperature for 2.5 hours. The solution was then cooled with ice. Water was added and the reaction mixture extracted with ether. After the usual work–up **10** (4 g, 92%) was obtained. Colourless oil. $[\alpha]_D$ +18.8 ($CHCl_3$, c 3.3). IR(film) ν_{max} cm^{-1} 3400, 1670, 1460, 1390, 1130, 1090, 940. ^1H NMR δ 5.24 (1H, t, J=6.8 Hz, H-12), 1.67 (6H, s), 1.19 (3H, s, Me-17), 0.87 (3H, s), 0.82 (3H, s), 0.80 (3H, s). ^{13}C NMR (see Table 1).

Acetylation and Oxidation of **10**: **11a/11b**. To a solution of **10** (4 g, 14.7 mmol) dissolved in 1 ml of CH_2Cl_2 were added N,N–dimethylaniline (9.8 ml) and acetyl chloride (4 ml). The reaction mixture was stirred at room temperature for 10 hours, after that time, ice was added and the mixture extracted with ether. The ether extract was washed with 2N HCl and water until neutrality, dried over Na_2SO_4 and evaporated to afford 4.1 g (87 % yield)of 15–nor–8–acetoxy–12–labdene. Colourless oil. $[\alpha]_D$ +4.0 ($CHCl_3$, c 0.5). IR(film) ν_{max} cm^{-1} 1730, 1660, 1460, 1390, 1250, 1130, 1020. ^1H NMR δ 5.12 (1H, t, J=6.8 Hz, H-12), 2.47 (1H, dd, J_1=12.2 Hz, J_2=3.4 Hz, H-7b), 1.85 (3H, s, OAc), 1.64 and 1.59 (3H, s, ea., Me–14 and Me–16), 1.42 (3H, s, Me-17), 0.83 (6H, s), 0.76 (3H, s).

To a solution of the acetyl derivative (15–nor–8-acetoxy–12–labdene, 2.2 g, 9.7 mmol) dissolved in 2.7 ml of CH_2Cl_2 was added a suspension of *m*CPBA in 25 ml of CH_2Cl_2. Stirring was maintained for 2 hours at room temperature, then, the mixture was filtered and the filtrate was washed with 10% Na_2SO_3, 10% $NaHCO_3$ and brine. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to afford a mixture of epoxides that is carefully chromatographed on a column of silica gel to afford **11a** (200 mg, Hexane/Ether, 9:1) **11a + 11b** (1.9 g, Hexane/Ether, 9:1) and **11b** (840 mg, Hexane/Ether, 9:1).

15–nor–8-acetoxy–12S,13–epoxy–labdane: **11a**. mp 62–66°C. $[\alpha]_D$ –7.3 ($CHCl_3$, c 0.4). IR ν_{max} cm^{-1} 1730, 1460, 1390, 1370, 1250, 1125, 1080, 1020. ^1H NMR δ 2.85 (1H, dd, J_1=4.4 Hz, J_2=6.3 Hz, H-12), 2.74 (1H, dt, J_1=12.2 Hz, J_2=3.4 Hz, H-7b), 1.93 (3H, s, OAc), 1.50 (3H, s, Me-17), 1.30 (6H, s, Me-14 and Me-16), 0.87 (3H, s), 0.83 (3H, s), 0.79 (3H, s). ^{13}C NMR (see Table 1).

15–nor–8-acetoxy–12R,13–epoxy–labdane: **11b**. Colourless oil. $[\alpha]_D$ –18.4 ($CHCl_3$, c 1.5). IR (film) ν_{max} cm^{-1} 1730, 1460, 1390, 1250, 1125, 1080, 1020. ^1H NMR δ 2.84 (1H, t, J=5.9 Hz, H-12), 2.56 (1H, dt, J_1=12.2 Hz, J_2=3.4 Hz, H-7b), 1.93 (3H, s, OAc), 1.45 (3H, s, Me-17), 1.28 (6H, s, Me-14 and Me-16), 0.87 (3H, s), 0.84 (3H, s), 0.78 (3H, s). ^{13}C NMR (see Table 1).

13,14,15,16–tetranor–8-acetoxy–12–labdanal : **12**. To a solution of the mixture of epoxides **11a** and **11b** (520 mg, 1.5 mmol) dissolved in 2.4 ml of THF was added periodic acid (480 mg) dissolved in 5.7 ml of THF and 3.7 ml of water. The mixture was stirred at room temperature for 2 hours. After that time, the mixture was extracted with hexane and the organic phase washed with 5% $Na_2S_2O_3$ and water, dried over anhydrous Na_2SO_4 to afford 440 mg of **12** (98% yield). mp 54–57°C. $[\alpha]_D$ –53.5 ($CHCl_3$, c 0.2). IR ν_{max} cm^{-1} 2730, 1730, 1460, 1390, 1365, 1250, 1130, 1020. MS: 294 [M^+, 10], 276 (8), 252 (21), 234 (100), 219 (45), 192 (94), 177 (69), 163 (28), 137 (58), 124 (69), 109 (68), 95 (54), 81 (67), 69 (82).^1H NMR δ 9.60 (1H, dd, J_1=2.9 Hz, J_2=1.9 Hz, CHO), 2.72 (1H, dt, J_1=12.2 Hz, J_2=2.9 Hz, H-7b), 2.36 (2H, m, H-11 and H-7a), 2.18 (1H, dd, J_1=4.9 Hz, J_2=7.3 Hz, H-11a), 1.81 (3H, s, OAc), 1.44 (3H, s, Me-17), 0.84 (3H, s), 0.80 (3H, s), 0.75 (3H, s). ^{13}C NMR (see Table 1).

Reduction of **12**: *Ambroxdiol*: **13**. To a solution of **12** (131 mg, 0.45 mmol) dissolved in 3 ml of dry ether was added $LiAlH_4$ (17 mg) and the stirring maintained for 2 hours at room temperature, after that time a few drops of wet ether were added and the mixture saturated with Na_2SO_4, filtered and evaporated affording **13** (107 mg, 94%). mp 189–90°C. $[\alpha]_D$ +36.4 ($CHCl_3$, c 0.4). IR ν_{max} cm^{-1} 3300, 1460, 1390, 1370, 1250, 1130, 1020. MS: 254 [M^+, 5], 236 (9), 221 (14), 195 (62), 177 (42), 165 (18), 151 (40), 137 (17), 123 (28), 109 (65), 95 (68), 83 (61), 69 (100).^1H NMR δ 3.75(1H, ddd, J=3.9, 4.0 and 10.2 Hz, H-12b), 3.42 (1H, ddd, J=6.8, 6.8 and 10.2 Hz, H-12a), 1.9 (2H, m, H-11), 1.17 (3H, s, Me-17), 0.86 (3H, s), 0.78 (6H, s). ^{13}C NMR (see Table 1).

15–nor–13–hydroxy–8,12–epoxy–labdane: **15**. To a solution of **10** (112 mg, 0.4 mmol) dissolved in 1 ml of CH_2Cl_2 was added a suspension of *m*CPBA (90 mg) in 1.5 ml of CH_2Cl_2. The solution was stirred for 12 hours at room temperature, after which time, the mixture was filtered and washed with 10% Na_2SO_3, 10% $NaHCO_3$ and brine. The crude product (103 mg) was chromatographed over silica gel to afford **15** (80 mg, 68%, Hexane/Ether, 9:1). Colourless oil. IR(film) ν_{max} cm^{-1} 3370, 1470, 1460, 1390, 1380, 1110. ^1H NMR δ 3.84 (1H, dd, J_1=8.8 Hz, J_2=3.9 Hz, H-12), 1.17 (3H, s), 1.13 (6H, s), 0.86 (3H, s), 0.81 (6H, s). ^{13}C NMR (see Table 1).

Oxidation of **15**: *12–nor–ambreinolide* : **17**. To a solution of **15** (37 mg, 0.13 mmol) dissolved in 1.4 ml of benzene were added 1.3 ml of acetic acid, 1.3 ml of Ac_2O, 27 mg of NaOAc and 74 mg of Na_2CrO_4. The mixture was heated to 40° C during 5 hours. After that time, ice was added and after a few minutes, the reaction mixture was extracted with ether. After the usual work–up, **17** (31 mg, 99% yield) was obtained. mp 118–119°C. $[\alpha]_D$ +49.8 ($CHCl_3$, c 0.9). IR ν_{max} cm^{-1} 1775, 1470, 1400, 1300, 1245, 1210, 1100. MS: 250 [M^+,

5], 235 (50), 206 (69), 191 (18), 169 (14), 150 (23), 137 (42), 123 (100), 109 (60), 95 (80), 83 (30), 69 (86). ^{1}H NMR δ 2.42 (1H, dd, J_1=14.7 Hz, J_2=16.1 Hz, H-11b), 2.23 (1H, dd, J_1=6.5 Hz, J_2=16.1 Hz, H-11a), 1.31 (3H, s, Me-17), 0.90 (3H, s), 0.86 (3H, s), 0.82 (3H, s). ^{13}C NMR (see Table 1).

Ozonolysis of **10**: **16**. To a solution of **10** (147 mg, 0.53 mmol) dissolved in 21 ml of CH_2Cl_2 and cooled to –78°C was passed through a stream of ozone until the mixture had a blue color (5 minutes). Then, the solution was poured over 2 ml of acetic acid and 1g of Zn, cooled at –78°C. After 5 minutes, the bath is taken off and the mixture was warmed to room temperature and maintained for about 30 minutes. The mixture is then extracted with CH_2Cl_2 and the organic layer worked up in the usual manner affording the mixture of epimers **16** (128 mg). 13,14,15,16–tetranor–12–hydroxy–8,12-epoxy–labdane. Colourless oil. IR(film) ν_{max} cm^{-1} 3320, 1460, 1380, 1180, 970. ^{1}H NMR δ 5.50 (1H, m); 5.41 (1H, m) and the methyl groups for both epimers at 1.24, 1.14, 0.86, and 0.81 (3H, 3H, 12H, 6H, s, ea.).

Oxidation of **16**: *12–nor–ambreinolide*: **17**. To 35 mg (0.1 mmol) of **16** dissolved in 10 ml of acetone freshly distilled from $KMnO_4$, were added a few drops of Jones reagent, until the reagent color persist. Inmediately isopropyl alcohol and water were added and the organic solvents evaporated. The mixture was extracted with ether and after the usual work up afforded 31 mg of a crude product that was further purified by column chromatography over silica gel, affording **17** (25 mg , Hexane/Ether, 9:1).

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