Tetrahedron Vol. 41, No. 4, pp. 671 to 680, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00
Pergamon Press Ltd.

FURTHER NEO-CLERODANE DITERPENES FROM LINARIA SAXATILIS (L.) CHAZ.

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(*Received in UK 26 September* 1984)

Abstract - Eleven neo-clerodane diterpenoids were isolated from the aerial parts of Linaria saxatilis. Their structures were determined by spectroscopic and chemical methods including the transformation of one of them into the known solidagolactone.

Linaria saxatilis (L.) Chaz. var. saxatilis is an autochtonous plant growing in the western Iberian Peninsula. In previous reports on its chemical composition[1,2] we have described the study of a methanol defatted extract where some methylated diterpenes which could be artefacts were found. In this paper we describe the study of an acetone defatted n-hexane extract of the same plant in which no methylated diterpenoid was detected. Futhermore, some new neo-clerodane diterpenoids were isolated.

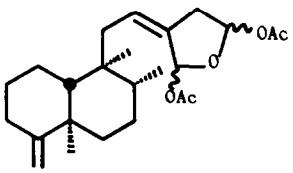
RESULTS AND DISCUSSION

The acetone defatted n-hexane extract (6.3% of dry material) after DCC, CC and TLC yielded compounds **1** - **11**.

The less polar product is a mixture of isomers **1** (major) and **2** which are unstable and on standing or during chromatographic separations are transformed into the previously described isolinadial **3** [1]. The IR spectrum of **1** + **2** contains absorptions of hemiacetalic acetates (1760,1230 cm^{-1}) and the ^1H NMR spectrum (Table 1), apart from the signals belonging to the bicyclic unsaturated system which are close to those of **3**, shows a doublet (J=5.5 Hz) at 6.40 ppm and a singlet at 6.71 ppm for **1**, and a doublet of doublets (J_1=5.9 Hz, J_2=2.0 Hz) at 6.36 ppm and a singlet at 6.73 ppm for **2**, which are respectively assigned to H_{15} and H_{16}. LAH reduction of **1** + **2** yields isolinaridiol **3a** as the only product which could be isolated; thus both **1** and **2** have the same configuration at the Δ^{12} double bond which is established as **Z** through the observation of a NOE on H_{14} upon $\{H_{12}\}$ irradiation. The ^{13}C NMR spectrum of **1** + **2** shows duplicate peaks for almost all carbons and the larger shifts occur between signals assignable to C_{13}, C_{15} and C_{16} for each compound (Table 2). The multiplicity of H_{15} signals and the conformational study on molecular models permitted us to propose that **1** and **2** were epimers at C_{15} and **1** had a relative trans disposition between the acetoxyl groups.

Compound **4** is an oil of $[\alpha]_D$= -50.6°. In its EIMS the molecular ion was not observed but the fragment at m/z = 270 (M^+-2AcOH) was in agreement with the formula $C_{24}H_{38}O_4$. Its IR spectrum showed absorptions due to acetoxyl groups (1745, 1240, 1030 cm^{-1}) and unsaturations (3090, 1640, 890 cm^{-1}).

The ^{1}H NMR spectrum showed the presence of two acetates (1.91, 1.97 ppm), on terminal methylene groups which absorb at 4.04 ppm (t, J=6 Hz) and 4.47 ppm (s). All these data allowed us to propose structure 4, which was confirmed through its saponification to 3a.



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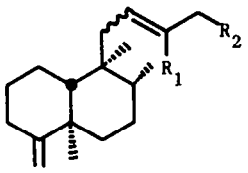
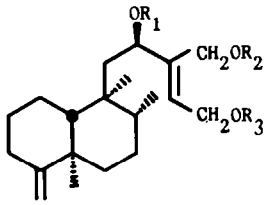
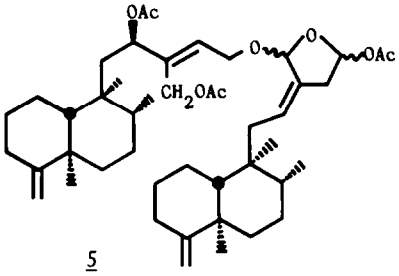


	R_1	R_2	12
3	CHO	CHO	Z
12	CHO	CHO	E
3a	CH_2OH	CH_2OH	Z
4	CH_2OAc	CH_2OAc	Z



	R_1	R_2	R_3
6	Ac	Ac	Ac
6a	H	H	H
9	H	Ac	Ac
10	Ac	H	Ac
11	Ac	Ac	H



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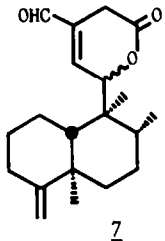

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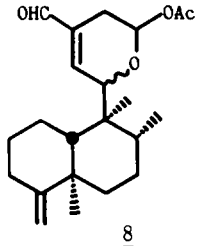

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Compound 5 is an oil of $[\alpha]_D$= -14.2° whose IR spectrum shows absortions of acetoxyl group (1760-1745, 1235, 1030 cm^{-1}) and unsaturations (3090, 1640, 890 cm^{-1}). Its ^{1}H NMR contains absorptions of two -C=CH- (5.5-5.9 ppm), two -CH-OAc (6.34 ppm, d, J=5 Hz and 5.22 ppm, dd, J_1=9 Hz, J_2=4 Hz), $-CH_2$-OAc (4.61 ppm, s). This number of functions needs a molecule larger than a diterpene for them to be placed and it was deduced that the compound had a bis-clerodane moiety. 5 by LAH reduction yielded 3a and 6a, and after AcOH/ether treatment gave E-isolinaridial 12, triacetate 6 and diacetates 9 , 10 and 11. The spectroscopic data and the results of these reactions permitted us to propose structure 5 for this substance. Although 12 has E configuration at Δ^{12} double bond, configuration in the clerodane part containing the acetalic function was proposed to be Z because in the conditions used for the AcOH/ether treatment of 5, Z-isolinaridial 3 isomerizes to E-isolinaridial 12.[2]

Compound 6 is an oil of $[\alpha]_D$= +17.3°. Its EIMS showed no molecular ion, but a fragment at m/z= 328 (M^+-2AcOH) with an apparent formula of $C_{26}H_{40}O_6$ was observed. Its IR spectrum is similar to that of compound 4. Its ^{1}H NMR spectrum showed three AcO- singlets, an AB system (4.63 ppm , J=12.7 Hz) of a terminal $-CH_2$-OAc, a doublet (4.67 ppm, 2H, J=6.6 Hz) of =CH-CH_2OAc, a broadened doublet (5.25 ppm, 1H, J=6.4 Hz) of -CH-OAc and a triplet (5.64 ppm, J=6.6 Hz) of an olefinic proton. These data clearly support the existence of a 12,15,16 triacetoxy derivative. E configuration of the Δ^{13} double bond was established through the NOEs on H_{14}(6.5%) and H_{16}(6.1%) upon {H_{12}} irradiation and those on H_{12}(5.7%) and H_{15}(7.8%) when irradiating {H_{15}}.The 12R configuraton of 6 was determined by application of Horeau's method [3] to the hydroxyfuran derivative 26, which was obtained from 6 via the triol 6a through MnO_2 oxidation.(Scheme 2).

Following 6 in the CC, a mixture of two substances was eluted which after acetylation and CC was resolved into 7 and 8. Compound 7 is an oil of $[\alpha]_D$=-5.3° whose IR spectrum showed absorptions of unsaturated aldehyde (2710, 1705 cm^{-1}), δ-lactone (1730, 1220, 1010 cm^{-1}) and unsaturations (3080, 1640, 895 cm^{-1}). In its ^{1}H NMR spectrum, apart from the absorptions due to the bicyclic unsaturated system, the following signals were observed: a singlet of an aldehyde group (9.41 ppm),

Table 1. ^{1}H NMR spectral data of 1 and 2
(200 MHz, $CDCl_3$ solution, Chem. shifts are in δ-values from TMS, J in Hz)

Compound	H-20	H-17	H-19	H-11	H-14	H-18	H-12	H-15	H-16
1	0.75 s	0.81 bd	1.02 s	~2.03 m	~3.07 m	4.49 bs	5.64 t	6.40 d (J=5.5)	6.73 s
2	0.74 s	0.78 bd	1.04 s				5.55 t	6.36 dd (J_1=5.9, J_2=2.0)	6.73 s

Table 2. ^{13}C NMR spectral data of 1, 2, 3a, 6, 6a, 7, 8, 18 and 26[Ξ].
(50.3 MHz, $CDCl_3$ solution, Chem. shifts are δ-values from TMS)

Carbon atom	1[†]	2[†]	3a	6	6a[§]	7	8	18	26
1	22.3	22.2	22.1	22.1	21.6	23.5	23.6	18.4	22.2
2	28.4	28.2	28.7	28.2	27.8	28.1	28.2	22.3	28.3
3	33.0	32.8	33.1	32.9	32.6	32.7	32.8	120.3	33.0
4	160.1	159.3	160.4	159.6	159.7	159.1	159.1	144.3	-
5	40.4 ¶	40.1 ¶	40.5 ¶	40.1	40.3 ¶	40.3	40.4	38.7 ¶	40.3¶
6	37.5	37.3	37.2	37.2	36.9	36.7	36.5	35.4	37.3
7	27.4	27.5	27.6	27.5	27.2	27.9 ¶	28.0 ¶	27.5	27.7
8	37.1	37.1	37.1	37.8	36.7	36.4	36.7	36.4	37.9
9	40.1 ¶	40.0 ¶	40.2 ¶	40.1	39.3 ¶	46.4	46.4	38.2 ¶	40.0¶
10	49.8	49.3	49.4	49.0	48.2	49.4	49.5	46.5	49.0
11	36.8	36.8	36.0	41.6	43.7	84.3	84.4	26.8	45.8
12	125.3	124.8	127.2	72.5	69.9	142.8	142.9	36.7	63.6
13	133.2	134.1	137.5	138.9	144.3	135.0	135,1	171.2	131.2
14	37.0	37.0	39.8	126.4	126.4	27.0 ¶	27.1¶	115.0	108.5
15	97.0	97.8	63.0	59.3	56.9	167.2	96.0	174.0	138.4
16	93.9	94.7	60.3	60.2	57.2	189.6	189.7	73.0	143.4
17	16.0	16.2	16.3	16.2	16.3	13.1	13.2	16.0	16.5
18	102.7	103.1	102.7	103.1	102.6	103.5	103.6	19.9	102.7
19	20.6	20.6	20.7	21.1	20.4	20.6	20.7	18.1	17.9
20	17.3	17.3	17.7	17.7	17.9	17.3	17.4	17.9	
$\underline{C}H_3$-COO-	21.0	20.8		20.8			20.7		
CH_3-$\underline{C}$OO-	169.6	169.6		169.8 170.3 170.4			167.4		

Ξ ^{13}C assignments have been performed on the basis of DEPT experiments and particularly on C/H (HCCORR) and H/H (COSY) two dimensional correlations for isolinaridiol 3a.
† Assigned from the spectrum of 1+2 mixture.
¶ Assignments may be interchanged.
§ DMSO solution.

a broad singlet of an olefinic proton (7.07 ppm) which became sharper upon irradiation of another multiplet of a -CH(I)-OCO- group absorbing at 5,21 ppm, and finally a complex multiplet of an AB system (3.25 ppm, J=22 Hz) which is split into sixteen peaks by small coupling with protons absorbing at 5.25 ppm and 7.07 ppm. The ^{13}C NMR of 7 (Table 2) confirms the presence of aldehyde (189.6 ppm) and lactone (167.2 ppm) functions. All these data allowed us to propose structure 7 for this compound.

Compound 8 is also an oil of $[\alpha]_D$=-14.7°. Its EIMS show a fragment (M^+-AcOH) at m/z = 300 which agrees with the formula $C_{22}H_{34}O_4$. From the comparison of IR and ^{1}H NMR spectra with those of compound 7 it is deduced that the difference between both substances occurs at C_{15}, changing from the

carbonyl group in 7 to an acetoxyl group in 8, as shown by the 1750, 1220 and 970 cm^{-1} IR absorptions, and the AcO-CH-O in its ^1H and ^{13}C NMR (Table 2) spectra. Since $J_{11,12} \simeq 0$ Hz, H_{11} should be pseudo-axial and as H_{15} shows a coupling of 9.3 Hz with H_{14b}, H_{15} should be axial, assuming that the dihydropyrane ring has a half-chair conformation, a cis relationship between the OAc at C_{15} and the decalin system at C_{11} was deduced.

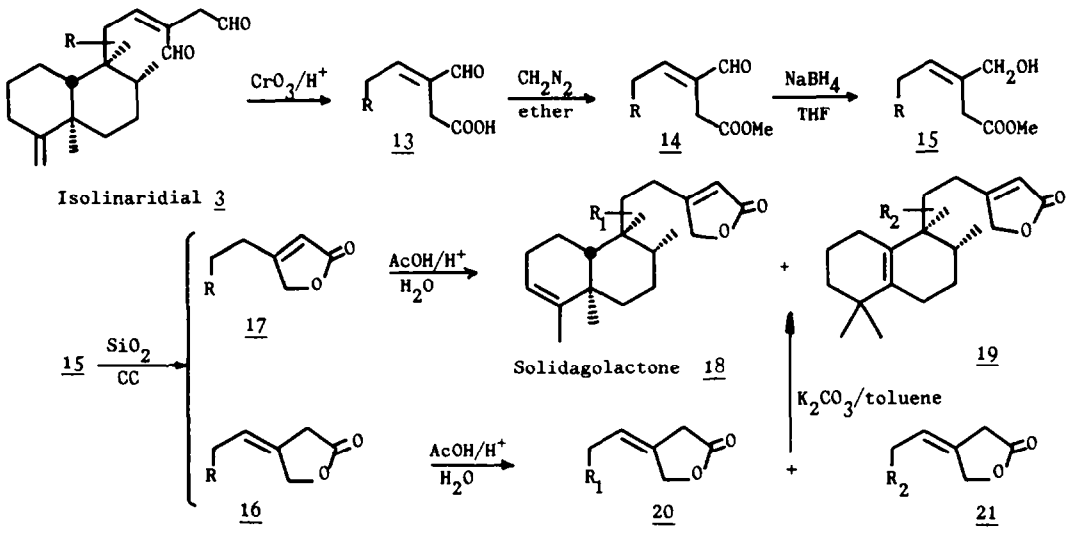
Compounds 9, 10 and 11 were oily products with very similar IR and ^1H NMR spectra. They have two acetate groups and one free hydroxyl group and upon acetylation the three substances are transformed into triacetate 6. By partial hydrolysis of 6 with K_2CO_3 in ethanol we were able to obtain these three compounds. From ^1H NMR data shown in Tabla 3, 9 has a hydroxyl at C_{12} and two acetates at C_{15} and C_{16}, while 10 has the free hydroxyl at C_{16} and 11 has it at C_{15}. The 12 R configuration of C_{12} was determined by application of Horeau's method[3] to 9.

Table 3. ^1H NMR spectral data of 9, 10 and 11.
(60 MHz, $CDCl_3$ solution, Chem. shifts are in δ-values from TMS, J in Hz)

Compound	H-12	H-14	H-15	H-16
9	4.19 dd (J_1=5.5,J_2=4.5)	5.59 t (J=7.0)	4.61 d (J=7.0)	4.59 s
10	5.15 dd (J_1=5.5,J_2=4.5)	5.58 t (J=7.0)	4.63 d (J=7.0)	4.12 s
11	5.25 dd (J_1=6.0,J_2=4.0)	5.88 t (J=7.0)	4.19 d (J=7.0)	4.59,4.67 AB(J=12.0)

The absolute stereochemistry of the trans-clerodane skeleton was established by the study of the CD spectrum of ketone 23 which was prepared from triacetate 6 through epoxydation and periodic acid oxidation (Scheme 2). 23 showed a negative Cotton effect $\Delta\varepsilon_{297}$=-0.19 which agreed with the 5R, 8R, 9S, 10R configuration.

To confirm the proposals concerning the clerodane structure of the above described compounds, the transformation of isolinaridial 3 into the known solidagolactone 18 was carried out (Scheme 1). Through Jones oxidation of isolinaridial 3 followed by CH_2N_2 methylation of the resulting oxoacid 13 and $NaBH_4$ reduction of the oxoester 14, crude hydroxyester 15 was obtained which during chromatographic separation through SiO_2 was transformed into exocyclic and endocyclic unsaturated γ-lactones (16 and 17) at a relative ratio of 2:3. Isomerization of lactone 17 by H_2SO_4 in acetic-aqueous solution yielded as major products the expected solidagolactone 18 and a new compound with



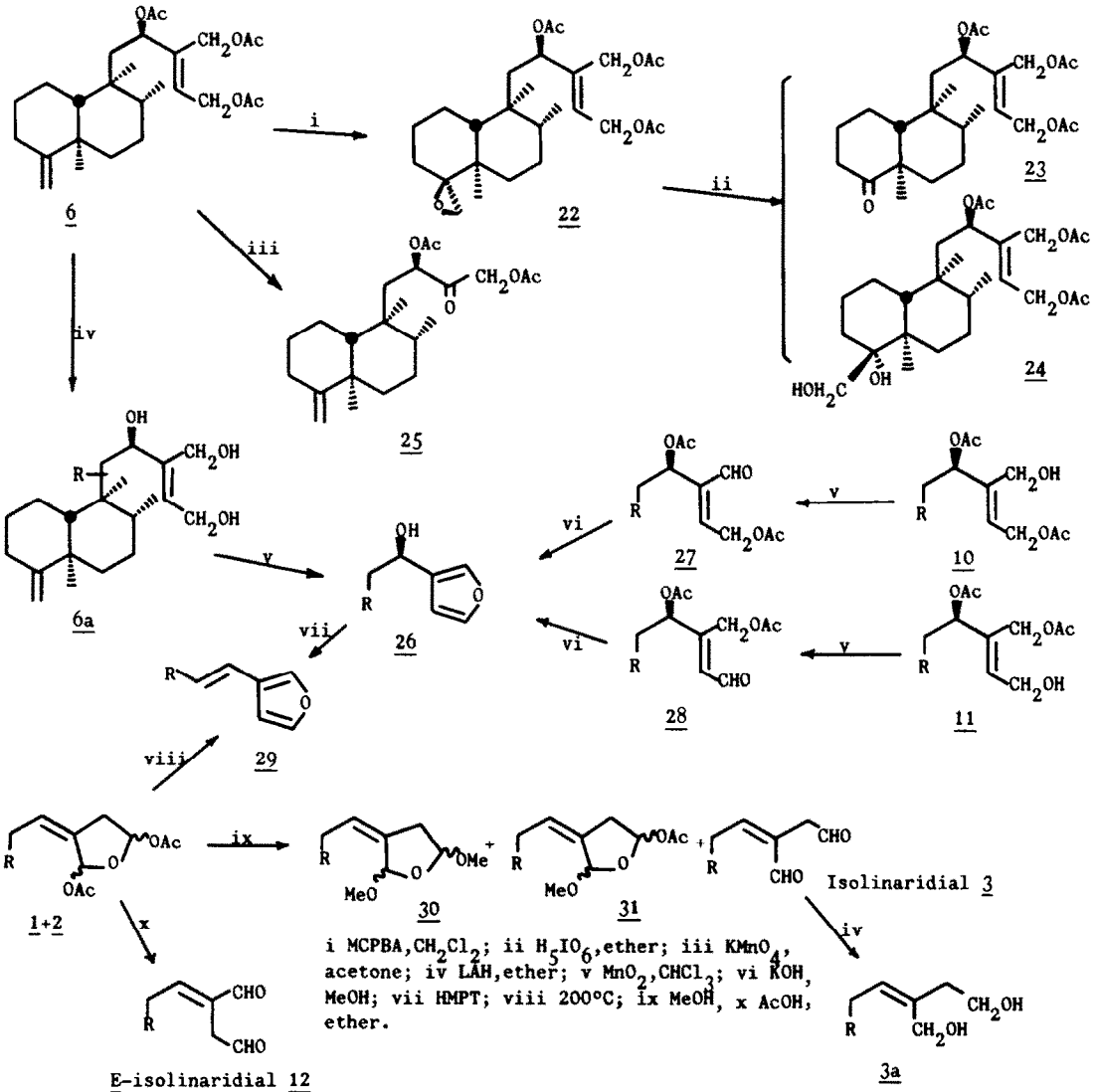
-Scheme 1-

the following spectral properties: a fragment at m/z 191 (100) in its MS, together with the absence of olefinic proton absorptions (other than those corresponding to H_{14}) in the IR and ^1H NMR spectra and the existence of three methyl singlets (0.87, 1.01 and 1.01 ppm) in the ^1H NMR spectrum. This clearly support structure 19 for this substance. Likewise the H_2SO_4 isomerization of lactone 16 gave a mixture of lactones 20 and 21 which without putification were isomerized to 18 and 19 by treatment with K_2CO_3 in toluene. Compound 18 shows m.p. 70°C (n-hexane) and $[\alpha]_D$=-48° (c 0.6,$CHCl_3$) (Lit[4] oil, $[\alpha]_D$= -73.4°). Its IR and ^1H NMR spectra were identical to those of solidagolactone submitted to us by Okazaki.

To complete the relationships between these new natural compounds some other chemical transformations were performed (Scheme 2). Triacetate 6 by LAH reduction gave triol 6a which on MnO_2 oxidation led to hydroxyfuran 26. Diacetate 10 was oxydized at C_{16} to the corresponding aldehyde 27 by MnO_2 in absolute $CHCl_3$ and 27 through KOH in MeOH treatment was transformed into hydroxyfuran 26. Likewise diacetate 11 was also transformed into 26.

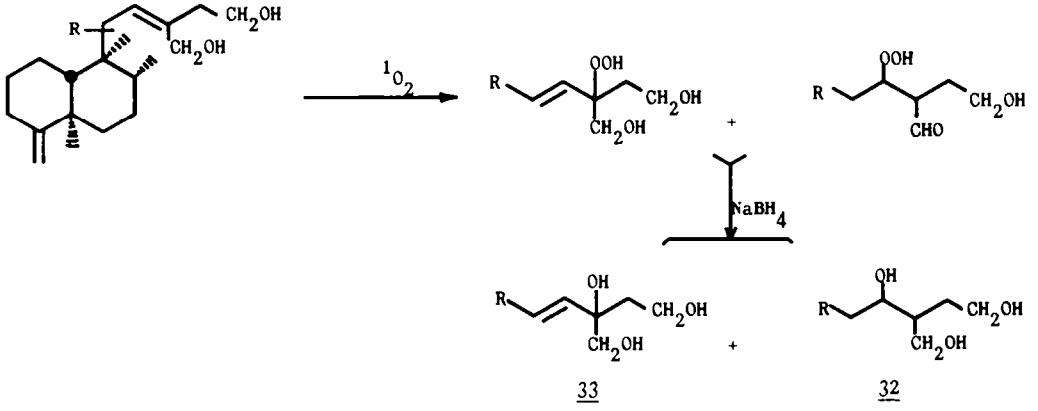
Reflux heating of 26 in HMPT gave a substance which lacks hydroxyl groups in the IR spectrum and shows an AB system of olefinic protons (5.60 and 6.06 ppm, J=16 Hz) of a trans double bond which led us to propose structure 29 for this compound. 29 was also obtained through direct heating of a mixture of diacetates 1 and 2 at 200°C under N_2 atmosphere.

Previously described [2] methylated compounds 30 and 31, now shown to be artefacts, as well as isolinaridial 3, were formed by heating natural diacetates 1 + 2 in refluxing MeOH.



-Scheme 2-

Sensitized photoxidation of isolinaridiol 3a followed by $NaBH_4$ reduction yielded triols 32 and 33, though no Δ^{13} product, as expected from the prefered sin abstraction pathway [5]. A suggested explanation for the formation of triols in these reactions is included in Scheme 3.



-Scheme 3-

EXPERIMENTAL

Mps are uncorrected and were determined in capillaries. Optical rotations were measured with a Perkin-Elmer mod. 241 digital polarimeter in $CHCl_3$. UV spectra were recorded in EtOH on a Hitachi mod. 100-60 spectrometer. IR spectra were measured on Beckman (AcuLab VIII) spectrophotometer in film or $CHCl_3$ solution. ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer R-24B (60 MHz) or on Bruker WP200SY (200 MHz) spectrometers using $CDCl_3$ solution and TMS as int. standard. ^{13}C NMR were recorded at 50.3 MHz. EIMS were obtained on a Hewlett-Packard 5930 A. 70 eV. CD curves were measured on a Jovin-Yvon Dichrograph III in n-hexane. Eluents for all CC separations were mixtures n-hexane-AcOEt. Their proportions are shown in parenthesis for each substance.

Collection of plants. Linaria saxatilis (L.) Chaz. var. saxatilis was collected in July at the municipal district of Fresnoalhandiga (Salamanca, Western Spain) The plant was identified by Prof. M. Ladero, from Department of Botany of Salamanca University.

Extraction and isolation. Dry aerial part (4.58 Kg) was extracted in a Soxhlet with n-hexane. After cooling for 20 hr at 4°C , the hexane soluble fraction on evaporation of the solvent, gave an oily residue (6.3% of vegetal material). This residue was defatted with acetone yielding 208.38 g (72% of crude hexane extract) of acetone soluble product. 33.90 g of this residue were chromatographed on 500 g of Si gel (dry column) developing with n-hexane-AcOEt 4:1 to give:

Fr	g	%	Composition
1	10.92	32.21	1 , 2 , 3
2	1.66	4.80	1 , 2 , 3 , 4 , 5
3	4.93	14.54	β-sitosterol, 6, 7 , 8
4	7.27	22.18	9 , 10 , 11

and different components were purified by repeated prep. CC or TLC.

15,16-acetoxy-15,16-epoxy-ent-cleroda-4(18),12Z-dieno 1 and 2. (95:5)

$$[\alpha]^{\lambda}= \frac{589 \quad 578 \quad 546 \quad 436}{-55.2° \quad -58.3° \quad -66.8° \quad -116.6°} \quad (c\ 0.9)$$

IR ν_{max} cm^{-1}: 3080, 2940, 2870, 1760, 1640, 1450, 1380, 1230, 1005, 980, 930, 890. ^1H NMR (200 MHz) Table 1. ^{13}C NMR Table 2. MS, M/z (%): 284(1), 191(13), 135(12), 121(18), 112(10), 107(18),95(100), 91(25), 79(31).

Conversion of 1 + 2 to 30, 31 and 3. A solution of 1+2 (301 mg) in MeOH (15 ml) was kept refluxing for 3 hr. The reaction mixture after Si gel CC gave 70 mg of 30, 124 mg of 31 and 33 mg of isolinaridial 3.

Pyrolysis of 1 + 2. 270 mg of net 1+2 mixture were kept at 200°C under N_2 atmosphere for 10 min. After percolation of Si gel gave 16 mg of 29, oil of:

$$[\alpha]^{\lambda}= \frac{589 \quad 578 \quad 546 \quad 436 \quad 365}{-22.5° \quad -25.0° \quad -30.0° \quad -68.7° \quad -152.9°} \quad (c\ 0.8)$$

IR ν_{max} cm^{-1}: 3090, 1640, 1580, 1510, 1460, 1380, 1160, 1070, 1030, 970, 890, 870. UV λ_{max} nm: 203 (ε 4502), 206 (ε 4502), 212 (ε 3886), 224 (ε 3744), 228 (ε 3696). ^{1}H NMR (60 MHz) (δ ppm):0.84(3H, bd,H-17), 0.90(3H,s,H-20), 1.05(3H,s,H-19), 4.50(2H,bs,H-18), 5.60,6.06(2H,AB,J=16 Hz,H-11 and H-12), 6.52(1H,bs,H-14), 7.36(1H,d,H-15), 7.37(1H,s,H-16).

E-isolinaridial 12. 7 ml of AcOH were added to a solution of 1 + 2 (260 mg) in ether (7 ml), and the mixture was refluxed for 2.5 hr. Then poured into ice-water, neutralized with aq.saturated $NaHCO_3$ and extracted with AcOEt, gave 190 mg of E-isolinaridial 12.

Isolinaridiol 3a. Reduction of 3 (35 mg) with LAH (50 mg) in dry ether for 3 hr followed by usual work up yielded 27 mg of isolinaridiol 3a, m.p. 87-88° ($CHCl_3$),

$$[\alpha]^{\lambda} = \frac{589}{+19.8°} \quad \frac{578}{+36.1°} \quad \frac{546}{+31.9°} \quad \frac{436}{+48.0°} \quad (c\ 1.2)$$

IR ν_{max} cm^{-1} ($CHCl_3$): 3640, 3425, 3090, 2940, 1730, 1635, 1390, 1210, 1050, 1010, 890, 670. ^{1}H NMR (200 MHz) (δ ppm): 0.75(3H,s,H-20), 0.82(3H,d,J=6Hz,H-17), 1.04(3H,s,H-19), 2.10(2H,m,H-11),2.34(2H, t,J=5.7 Hz,H-14), 3.68(2H,t,J=5.7 Hz,H-15), 4.49(2H,d,J=1.4 Hz,H-18), 5.32(1H,t,J=7.5 Hz, H-12). ^{13}C NMR Table 2. MS, m/z (%): 306(0.2), 288(1), 250(2), 235(3), 191(11), 175(11), 109(23), 95(100), 79(40).

Photooxygenation of 3a. A solution of 360 mg of isolinaridiol 3a in 33 ml of isopropanol reacted with oxygen, in presence of rose bengal (6.5 mg) as sensitizer, for 6 hr. After reduction with 335 mg of $NaBH_4$, extraction and chromatography on Si gel, yielded 30 mg of 32 (7:3) and 107 mg of 33 (1:1). 32 shows IR ν_{max} cm^{-1}: 3350, 3080, 1640, 1090, 1045, 890. ^{1}H NMR (60 MHz) (δ ppm): 0.75 (3H,s,H-20), 0.83(3H,bd,H-17), 1.05(3H,s,H-19), 3.55-4.03(5H,m,H-12,H-15 and H-16), 4.50(2H,bs,H-18). 33 shows m.p. 73-75° (AcOEt),

$$[\alpha]^{\lambda} = \frac{589}{+4.3°} \quad \frac{578}{+5.0°} \quad \frac{546}{+5.3°} \quad (c\ 0.6)$$

IR ν_{max} cm^{-1} ($CHCl_3$): 3620, 3260, 3080, 1640, 1450, 1380, 1115, 1050, 990, 890. ^{1}H NMR (60 MHz) (δ ppm): 0.80(3H,bd,H-17), 0.85(3H,s,H-20), 1.06(3H,s,H-19), 2.15(2H,m,H-14), 3.45(2H,s,H-16), 3.80 (2H,t,J=5 Hz,H-15), 4.51(2H,bs,H-18), 5.20,5.40(2H,AB,J=15 Hz,H-11 and H-12). MS, m/z (%): 291(25), 191(18), 121(23), 115(77), 109(53), 101(100), 95(9), 91(36).

Oxidation of isolinaridial 3. To a solution of 3 (1.97 g) in acetone (33 ml) 4 ml of Jones reagent were added and the solution stirred at 0°C for 30 min. After dilution on ice-water and extraction with $CHCl_3$ gave 2.08 g of 13, oil,

$$[\alpha]^{\lambda} = \frac{589}{-0.1°} \quad \frac{578}{-0.2°} \quad \frac{546}{-0.8°} \quad (c\ 0.65)$$

IR ν_{max} cm^{-1}: 3090, 3600-2400, 1720, 1690, 1640, 1450, 1330, 890. UV λ_{max} nm: 235 (ε 9554). ^{1}H NMR (60 MHz) (δ ppm): 0.86(3H,s,H-20), 0.88(3H,bd,H-17), 1.05(3H,s,H-19), 2.35(2H,d,J=8 Hz,H-11), 3.30 (2H,s,H-14), 4.48(2H,s,H-18), 6.68(1H,t,J=8 Hz,H-12), 9.31(1H,s,H-16). Crude 13 (1.86 g) treated with excess ethereal CH_2N_2 afforded 1.66 g of ester-aldehyde 14, oil,

$$[\alpha]^{\lambda} = \frac{589}{+4.8°} \quad \frac{578}{+5.4°} \quad \frac{546}{+5.5°} \quad (c\ 1.1)$$

IR ν_{max} cm^{-1}: 3090, 2715, 1740, 1690, 1640, 1170, 1120, 890. UV λ_{max} nm: 232 (ε 8140). ^{1}H NMR (60 MHz) (δ ppm): 0.86(3H,s,H-20), 0.90(3H,bd,H-17), 1.04(3H,s,H-19), 2.35(2H,d,J=8 Hz,H-11) , 3.30(2H,s,H-14), 3.64(3H,s,MeO-15), 4.50(2H,s,H-18), 6.67(1H,t,J=8 Hz,H-12), 9.37(1H,s,H-16).

Reduction of 14 with $NaBH_4$. To a ice-cooled solution of 14 (1.54 g) in dry THF (40 ml), $NaBH_4$ (746 mg) was added, the mixture was kept stirring at 0°C for 2 hr, then poured into ice-water . After usual work up, the residue (1.48 g) chromatographed on Si gel CC afforded 228 mg of lactone 16 ((95:5) and 340 mg of lactone 17 (95:5). 16 shows:

$$[\alpha]^{\lambda} = \frac{589}{+10.1°} \quad \frac{578}{+24.7°} \quad \frac{546}{+27.7°} \quad \frac{436}{+43.6°} \quad \frac{365}{+58.8°} \quad (c\ 1.2)$$

IR ν_{max} cm^{-1}: 3090, 1790, 1680, 1645, 1180, 1165, 1030, 890. ^{1}H NMR (60 MHz) (δ ppm): 0.77 (3H, s , H-20), 0.82(3H,bd,H-17), 1.04 (3H,s,H-19), 2.10(2H,m,H-11), 3.10(2H,m,H-14), 4.49(2H,bs,H-18), 4.80 (2H,bs,H-16), 5.39(1H,m,H-12). Lactone 17 shows:

$$[\alpha]^{\lambda} = \frac{589}{+12.08°} \quad \frac{578}{+13.4°} \quad \frac{546}{+15.1°} \quad \frac{436}{+22.8°} \quad \frac{365}{+26.4°} \quad (c\ 0.9)$$

IR ν_{max} cm^{-1}: 3090, 1790, 1760, 1640, 1175, 1030, 890. UV λ_{max} nm: 212 (ε 19920). ^{1}H NMR (60 MHz) (δ ppm): 0.77(3H,s,H-20), 0.80(3H,bd,H-17), 1.04(3H,s,H-19), 4.48(2H,bd,H-18), 4.67(2H,bs,H-16) , 5.60(1H,m,H-14).

Isomerization of 17. 17 (340 mg) was added to a mixture of AcOH(18 ml), H_2SO_4(1.2 ml) and water (4.8 ml). After keeping 2 hr 15 min at room temperature with stirring, the reaction mixture was purified through Si gel-$AgNO_3$(20%) CC to give 66 mg of lactone 19 (95:5) and 95 mg of solidagolactone 18 (95:5). 18 shows m.p. 70°(n-hexane),

$$[\alpha]^{\lambda} = \frac{589}{-48.0°} \quad \frac{578}{-49.8°} \quad \frac{546}{-57.0°} \quad \frac{436}{-98.0°} \quad \frac{365}{-155.8°} \quad (c\ 0.6)$$

(Lit.[4] oil,$[\alpha]_D$=-73.4°, b.p. 160-170°C/0.007 mm Hg)

IR ν_{max} cm^{-1} ($CHCl_3$): 3015, 1785, 1755, 1640, 1175, 1130, 1030, 890, 855, 800. UV λ_{max} nm : 215 (ε 11600). ^{1}H NMR (200 MHz) (δ ppm): 0.77(3H,s,H-20), 0.81(3H,d,H-17), 1.00(3H,s,H-19), 1.58(3H,s, H-18), 4.47(2H,s,H-16), 5.18(1H,m,H-3), 5.82(1H,s,H-14). ^{13}C NMR Table 2. MS, m/z (%): 302 (15), 288(14), 260(10), 228(9), 191(61), 178(41), 150(27), 136(34), 124(50), 108(94), 96(100). Lactone

19 shows m.p. 40° (n-hexane),

$$[\alpha]^{\lambda} = \frac{589}{+25.7°} \quad \frac{578}{+27.0°} \quad \frac{546}{+30.4°} \quad \frac{436}{+52.1°} \quad \frac{365}{+77.7°} \text{ (c 0.7)}$$

IR ν_{max} cm^{-1}: 1875, 1840, 1710, 1630, 1450, 1170, 1100, 890, 840. UV λ_{max} nm: 222 (ϵ 9240). ^{1}H NMR (60 MHz) (δ ppm): 0.87(3H,s,H-20), 0.92(3H,d,H-17), 1.01(6H,s,H-18 and H-19), 4.74(2H,bs , H-16), 5.84(1H,m,H-14). MS m/z (%): 302(5), 191(100), 150(18), 136(27), 122(21), 110(20), 108(20), 96(27), 93(22).

Isomerization of 16. To a solution of 16 (53 mg) in AcOH (7.5 ml), 2 ml of H_2O and 0.5 ml of conc. H_2SO_4 were added. After keeping 2 hr 30 min at room temperature with stirring, the reaction mixture was poured into water and extracted with ether to give 42 mg of mixture lactones 20 and 21. Lactone 20 , oil, IR ν_{max} cm^{-1}: 3030, 1790, 1170, 1030. ^{1}H NMR (60 MHz) (δ ppm) (Cl_4C): 0.73 (3H,s,H-20), 0.80(3H,bd,H-17), 0.97(3H,s,H-19), 1.54(3H,s,H-18), 3.01(2H,m,H-14), 3.37(2H,m,H-16), 5.10(1H,m,H-3), 5.37(1H,m,H-12). To a solution of mixture lactones 20 and 21 (42 mg) in 4.5 ml of dry toluene, 114 mg of K_2CO_3 were added and the mixture refluxed for 5 hr under N_2 and with stirring. The residue obtained after filtration, evaporation of solvent and Si gel CC furnished solidagolactone 18 (24 mg) and lactone 19 (traces).

Isolinaridiol diacetate 4 (95:5), $[\alpha]_D$= -50.6° (c 1.8). IR ν_{max} cm^{-1}: 3090, 1745, 1675, 1640, 1240, 1030, 970, 890. ^{1}H NMR (50 MHz) (δ ppm): 0.75(3H,s,H-20), 0.81(3H,bd,H-17), 1.03(3H,s,H-19), 1.91(3H,s,AcO-15), 1.97(3H,s,AcO-16), 2.38(2H,d,J=6 Hz,H-14), 4.04(2H,t,J=6 Hz,H-15), 4.43(2H,bs, H-18), 4.47(2H,s,H-16), 5.45(1H,m,H-12). MS m/z (%): 345(1), 318(2), 286(2), 284(2),270(2),241(2), 191(24), 175(10), 154(10), 135(21), 126(67), 109(29), 96(100), 93(27), 81(27).

Hydrolysis of 4. To 43 mg of 4 2 ml of methanolic KOH 10% were added. After 10 min at room temperature the reaction mixture was successively neutralized with 2N HCl, evaporated , diluted with water and extracted with ether to give 32 mg of isolinaridiol 3a.

Bis-clerodane 5 (9:1), oil,

$$[\alpha]^{\lambda} = \frac{589}{-14.2°} \quad \frac{578}{-15.3°} \quad \frac{546}{-17.5°} \quad \frac{436}{-31.7°} \text{ (c 1.5)}$$

IR ν_{max} cm^{-1}: 3090, 2920, 1760, 1640, 1450, 1375, 1235, 1170, 980, 890. ^{1}H NMR (60 MHz) (δ ppm): 0.72(3H,s,H-20), 0.76(3H,s,H-20´), 0.85(6H,bd,H-17 and H-17´), 1.03(6H,s,H-19 and H-19´) , 1.97 (6H,s) and 2.02(3H,s) (3xOAc), 4.23(2H,m,H-15) 4.52(4H,s,H-19 and H-19´), 4.61(2H,s,H-16), 5.22 (1H,dd,J_1=9 Hz, J_2=4 Hz,H-12), 5.50-5.90(2H,m,H-14 and H-12´), 5.60(1H,s,H-16´), 6.34(1H,d,J=5 Hz, H-15´).

Reduction of 5. Treatment of 5 (94 mg) with LAH (202 mg) in dry ether for 20 hr gave 56 mg of reaction product, wich after Si gel CC afforded 17 mg of isolinaridiol 3a and 24 mg of isolinaritriol 6a.

Acetolysis of 5. To a solution of 5 (275 mg) in ether (7 ml) 7 ml of AcOH were added ; the mixture was refluxed for 50 min and then poured into ice-water. The mixture was neutralized with aq. saturated $NaHCO_3$ and extracted with AcOEt, after CC 23 mg of E-isolinaridial 12, 20 mg of triacetate 6, 15 mg of diacetate 9, 14 mg of diacetate 10 and 21 mg of diacetate 11 were obtained.

Isolinaritriol triacetate 6 (9:1), oil, $[\alpha]_D$= +17.3° (c 1.1). IR ν_{max} cm^{-1}: 3090, 3030, 1745 , 1675, 1645, 1240, 1030, 970, 890. ^{1}H NMR (200 MHz) (δ ppm): 0.72(3H,s,H-20), 0.86(3H,d,J=5.8 Hz, H-17), 1.04(3H,s,H-19), 2.00, 2.04 and 2.05 (9H, 3xOAc), 4.52(2H,bs,H-18), 4.62,4.65 (2H , AB , J=12.7 Hz,H-16), 4.67 (2H,d,J=6.6 Hz,H-15), 5.23(1H,bd,J=6.4 Hz,H-12), 5.64(1H,t,J=6.6 Hz,H-14). ^{13}C NMR Table 2. MS m/z (%): 328(2), 313(1), 268(7), 253(13), 215(4), 191(27), 189(30), 175(29), 121(37), 107(35), 95(100), 81(49).

Isolinaritriol 6a. Treatment of 6 (99 mg) with LAH (214 mg) in dry ether for 22 hr, followed by CC of the reaction product gave 81 mg (1:1) of isolinaritriol 6a , m.p. 160-161° (AcOEt),

$$[\alpha]^{\lambda} = \frac{589}{+44.2°} \quad \frac{578}{+35.8°} \quad \frac{546}{+40.6°} \quad \frac{436}{+68.3°} \text{ (c 1)}$$

IR ν_{max} cm^{-1}(nujol): 3230, 3040, 1645, 1460, 1380, 1320, 1050, 1000, 890. ^{1}H NMR (200 MHz)(δ ppm) (DMSO): 0.64(3H,s,H-20), 0.81(3H,d,J=4 Hz,H-17), 1.00(3H,s,H-19), 4.04(2H,t,J=5.5 Hz, H-16), 4.35 (2H,d,J=6 Hz,H-15), 4.48(2H,s,H-18), 4.51(1H,t,J=5.5 Hz,H-12), 5.45(1H,t,J=6 Hz,H-14). ^{13}C NMR (DMSO) Table 2. MS m/z (%): 286(1), 270(2), 255(2), 253(2), 206(4), 191(22), 175(33), 161 (10) , 136(23), 121(29), 95(100).

Oxidation of 6a. 6a (253 mg) in $CHCl_3$ (12 ml) was treated with active MnO_2 (1.8 g) for 5 hr at room temperature and with stirring. After filtration and crystallization 61 mg of 26 were obtained. 26 shows m.p. 81° (n-hexane),

$$[\alpha]^{\lambda} = \frac{589}{+35.2°} \quad \frac{578}{+37.0°} \quad \frac{546}{+42.2°} \quad \frac{436}{+72.2°} \quad \frac{365}{+114.4°} \text{ (c 1.1)}$$

IR ν_{max} cm^{-1}: 3450, 3090, 1640, 1570, 1510, 1470, 1380, 1030, 890, 870, 800. UV λ_{max} nm : 203 (ϵ16950). ^{1}H NMR (200 MHz) (δ ppm): 0.73(3H,s,H-20), 0.91(3H,d,J=6 Hz,H-17), 1.04(3H,s,H-19), 4.51(2H,bd,H-18), 4.73(1H,dd,J_1=7.2 Hz,J_2=4 Hz,H-12), 6.37(1H,sa,H-14),7.34(1H,bs,H-16), 7.37(1H, bs,H-15). ^{13}C NMR Table 2. MS m/z (%): 302(9), 301(7), 286(7), 204(7), 191(33), 176(23), 150(20), 136(29), 110(41), 98(100), 96(91), 84(56).

Dehydration of 26. A solution of 26 (99 mg) in HMPT (5 ml) was refluxed for 5 hr to gave after AcOEt extraction 98 mg of furane 29, identical to that obtained from 1+2 .

Epoxidation of 6. 188 mg of mCPBA were added to a solution of 6 (191 mg) in CH_2Cl_2 (4 ml). The mixture was kept at room temperature for 1 hr 15 min. The excess of oxidizing agent was eliminated with aq. $NaHSO_3$ and by CH_2Cl_2 extraction were obtained 183 mg of 22, oil,

$$[\alpha]^{\lambda} = \frac{589}{+21.9°} \quad \frac{578}{+22.7°} \quad \frac{546}{+25.7°} \quad \frac{436}{+43.3°} \quad \frac{365}{+65.8°} \text{ (c 1.5)}$$

IR ν_{max} cm^{-1}: 3030, 1745, 1235, 1030, 970, 930. ^1H NMR (60 MHz) (δ ppm): 0.70(3H,s,H-20), 0.85 (3H,bd,H-17), 1.11(3H,s,H-19), 2.01,2.03 and 2.05(9H, 3xOAc), 2.30,2.75(2H,AB,J=5 Hz,H-18), 4.63 (2H,s,H-16), 4.65(2H,d,J=7 Hz,H-15), 5.24(1H,dd,J_1=7 Hz,J_2=4 Hz,H-12), 5.72(1H,t,J=7Hz,H-14) . Treatment of 22 (183 mg) with H_5IO_6 (90 mg) in dry ether for 5 min.yielded 127 mg of reaction product, which by Si gel CC afforded 16 mg of ketone 23 (9:1) and 20.5 mg of diol 24 (8:2). 23 shows:

$$[\alpha]^{\lambda}= \frac{589}{+1.0^\circ} \quad \frac{578}{+1.1^\circ} \quad \frac{546}{+1.3^\circ} \quad \frac{436}{+1.6^\circ} \text{ (c 1.2)}$$

IR ν_{max} cm^{-1}: 3030, 1745, 1710, 1230, 1030. ^1H NMR (60 MHz) (δ ppm): 0.77(3H,s,H-20), 0.85(3H, bd,H-17), 1.11(3H,s,H-19), 1.96(3H,s,1xOAc) and 2.01(6H,s,2xOAc),4.61(2H,s,H-16), 4.63(2H,d,J=6 Hz, H-15), 5.59(1H,dd,J_1=5 Hz,J_2=3 Hz,H-12), 5.70(1H,t,J=6 Hz,H-14). CD (n-hexane): $\Delta\varepsilon_{297}$= -0.19. The diol 24 shows $[\alpha]_D$= +31.8° (c 0.4). IR ν_{max} cm^{-1}: 3500, 3020, 1750, 1230, 1030. ^1H NMR (60 MHz) (δ ppm): 0.87(3H,s,H-20), 0.95(3H,bd,H-17), 0.98(3H,s,H-19), 1.98(3H,s,OAc) and 2.06(6H,s,2xOAc) , 3.10,3.66(2H,AB,J=11 Hz,H-18), 4.60(2H,s,H-16), 4.61(2H,d,J=6 Hz,H-15), 5.21(1H,dd,H-12), 5.75(1H, t,J=6 Hz,H-14).

Oxidation of 6 by $KMnO_4$. To 110 mg of 6 a solution of $KMnO_4$ (312 mg) in acetone (25 ml) was added and the mixture kept for 49 hr at room temperature. After AcOEt extraction and percolation on Si gel, 13 mg of ketone 25 were obtained (95:5), $[\alpha]_D$= +17.2° (c o.6). IR ν_{max} cm^{-1}: 3090, 1750, 1645, 1230, 1080, 1030, 890. ^1H NMR (60 MHz)(δ ppm): 0.78(3H,s,H-20), 0.85(3H,bd,H-17), 1.05(3H,s, H-19), 2.05 and 2.09(6H,s,2xOAc), 4.48(2H,bs,H-18), 4.55(2H,s,H-16), 4.85(1H,dd,J_1=8 Hz,J_2=4 Hz , H-12).

Partial hydrolysis of 6. To 1.16 g of 6 1M K_2CO_3 in ethanol were added and the mixture kept at room temperature for 2 hr. After neutralization with 2N HCl, ether extraction and CC, 99 mg of diacetate 9, 65 mg of diacetate 10 and 114 mg of diacetate 11, as well as their mixtures and unreacted 6, were obtained.

16-Oxo-ent-cleroda-4(18),12-dien-15,11-lactone 7 (9:1)

$$[\alpha]^{\lambda}= \frac{589}{-5.3^\circ} \quad \frac{578}{-5.4^\circ} \quad \frac{546}{-6.5^\circ} \quad \frac{436}{-11.9^\circ} \text{ (c 1.7)}$$

IR ν_{max} cm^{-1}: 3060, 2710, 1730, 1705, 1660, 1640, 1240, 1020, 1000, 895. UV λ_{max} nm:235 (ε 2556). ^1H NMR (200 MHz) (δ ppm): 0.88(3H,bd,H-17), 1.08(3H,s,H-19), 1.25(3H,s,H-20), 3.25(2H,AB,J=22 Hz, H-14), 4.53(2H,bs,H-18), 5.21(1H,m,H-11), 7.07(1H,bs,H-12), 9.41(1H,bs,H-16). ^{13}C NMR Table 2.

15-Acetoxy-11,15-epoxy-ent-cleroda-4(18),12-dien-16-al 8 (9:1).

$$[\alpha]^{\lambda}= \frac{589}{-14.7^\circ} \quad \frac{578}{-15.5^\circ} \quad \frac{546}{-17.9^\circ} \quad \frac{436}{-33.4^\circ} \text{ (c 0.25)}$$

IR ν_{max} cm^{-1}: 3070, 2700, 1750, 1690, 1640, 1220, 970, 895. UV λ_{max} nm: 234 (ε 20545). ^1H NMR (200 MHz) (δ ppm): 0.97(3H,bd,H-17), 0.98(3H,s,H-20), 1.03(3H,s,H-19), 2.14(3H,s,AcO-15), 2.85(1H, qq,J_1=15 Hz,J_2=9.3 Hz,J_3=3.8 Hz,J_4=2.4 Hz,H-14b), 3.30(1H,dd,J_1=15 Hz,J_2=5.5 Hz,H-14a), 4.51(2H,s, H-18), 5.08(1H,dd,J_1=3.8 Hz,J_2=2.2 Hz,H-11), 6.34(1H,dd,J_1=9.3 Hz,J_2=5.5 Hz,H-15), 6.71(1H,bs,H-12), 9.46(1H,s,H-16). ^{13}C NMR Table 2. MS m/z (%): 300(1), 284(1), 271(2), 257(2), 233(2) , 202 (2) , 191(19), 136(15), 96(65), 84(75), 60(76), 32(100).

15,16-Diacetate of isolinaritriol 9 (8:2).

$$[\alpha]^{\lambda}= \frac{589}{+21.8^\circ} \quad \frac{578}{+22.5^\circ} \quad \frac{546}{+25.5^\circ} \quad \frac{436}{+42.7^\circ} \quad \frac{365}{+63.7^\circ} \text{ (c 1.2)}$$

IR ν_{max} cm^{-1}: 3480, 3090, 3030, 1745, 1675, 1240, 1030, 970, 890. ^1H NMR (60 MHz)(δ ppm): 0.72 (3H.s.H-20), 0.85(3H,bd,H-17), 1.05(3H,s,H-19), 2.04(6H,s,2xOAc), 4.19(1H,dd,J_1=5.5 Hz,J_2=4.5 Hz, H-12), 4.46(2H,bs,H-18), 4.59(2H,s,H-16), 4.61(2H,d,J=7 Hz,H-15), 5.59(1H,t,J=7 Hz,H-14).

12,15-Diacetate of isolinaritriol 10 (8:2), $[\alpha]_D$= +10.8° (c 2.4). IR ν_{max} cm^{-1}: 3480, 3090 , 3030, 1745, 1675, 1240, 1030, 970, 890. ^1H NMR (60 MHz)(δ ppm): 0.71(3H,s,H-20), 0.81(3H,bd,H-17), 1.03(3H,s,H-19), 2.02 and 2.08(6H,s,2xOAc), 4.12 (2H,s,H-16), 4.45(2H,bs,H-18), 4.63(2H,d,J=7 Hz, H-15), 5.15(1H,dd,J_1=5.5 Hz,$J_2$4.5 Hz,H-12), 5.58(1H,t,J=7 Hz,H-14).

Oxidation of 10. A mixture of 10 (880 mg) and active MnO_2 (6.4 g) in absolute $CHCl_3$ (16.4 ml) was stirred at room temperature for 5 days. The oxidation product was chromatographed by Si gel CC to afford 159 mg of aldehyde 27 (9:1), oil, IR ν_{max} cm^{-1}: 3090, 2750, 1750, 1690, 1640, 1450 , 1375, 1240, 1030, 890. UV λ_{max} nm: 230 (ε 15100). ^1H NMR (60 MHz)(δ ppm): 0.71(3H,s,H-20), 0.81 (3H,bd,H-17), 1.05(3H,s,H-19), 2.03 and 2.08(6H,s,2xOAc), 4.51(2H,bs,H-18), 4.98(2H,d,J=6 Hz,H-15), 5.48(1H,dd,H-12), 6.41(1H,t,J=6 Hz,H-14), 9.87(1H,s,H-16). Hydrolysis of 27 (54 mg) with methanolic KOH 10% (2 ml) for 3 hr, after neutralization, ether extraction and CC gave 6 mg of hydroxyfuran 26.

12,16-Diacetate of isolinaritriol 11 (8:2), $[\alpha]_D$= +32.3° (c 1). IR ν_{max} cm^{-1}: 3480, 3090, 1745, 1640, 1240, 1030, 970, 890. ^1H NMR (60 MHz)(δ ppm): 0.71(3H,s,H-20), 0.81(3H,bd,H-17), 1.04(3H,s, H-19), 2.00 and 2.03(6H,s,2xOAc), 4.19(2H,d,J=7 Hz,H-15), 4.50(2H,bs,H-18), 4.59,4.67(2H,AB,J=12Hz, H-16), 5.25(1H,dd,J_1=6 Hz,J_2=4 Hz,H-12), 5.88(1H,t,J=7 Hz,H-14).

Oxidation of 11. A mixture of 11 (350 mg) and active MnO_2 (2.5 g) in absolute $CHCl_3$ (6.5 ml) was stirred at room temperature for 28 hr. The oxidation product was chromatographed by Si gel to afford 109 mg of aldehyde 28 (9:1), oil IR ν_{max} cm^{-1}: 3090, 2750, 1685, 1640, 1450, 1370, 1240, 1030, 890. UV λ_{max} nm: 229 (ε 10380). ^1H NMR (60 MHz) (δ ppm): 0.75(3H,s,H-20), 0.86(3H,bd,H-17), 1.05(3H,s,H-19), 2.03 and 2.08(6H,s,2xOAc), 4.51(2H,bs,H-18), 4.98(2H,d,J=5 Hz,H-16), 5.25(1H,dd, H-12), 6.04(1H,d,J=8 Hz,H-14), 10.2(1H,d,J=8 Hz,H-15). Hydrolysis of 28 (46 mg) with methanolic KOH 10% (2 ml) for 3 hr, after neutralization, ether extraction and CC, gave 13 mg of hydroxyfurane 26.

Acknowledgments. We thank professor J. de Pascual for facilities obtained from his laboratory, Dr. J.M. Hernandez for mass spectral measurements (Faculty of Chemistry, Salamanca) and Profs. B. Casaseca and M. Ladero (Botany Department, Salamanca) for identification of vegetal material. This work has been financed by Spanish C.A.I.C.Y.T.

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