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TERPENOID COMPOUNDS FROM *PARENTUCELLIA LATIFOLIA*

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Key Word Index—*Parentucellia latifolia*; Scrophulareaceae; diterpenes; labdanes; *ent*-clerodanes; malonates.

Abstract—Together with phytol, sitosterol acetate, α-tocopherylquinone and sitosterol, the neutral part of *Parentucellia latifolia* afforded seven esters of diterpene alcohols: 7,13*E*-labdadien-15-ol acetate; *ent*-3,13*E*-clerodadien-15-ol acetate: di-[7,13*E*-labdadien-15-yl]malonate; 7,13*E*-labdadien-15-yl and *ent*-3,13*E*-clerodadien-15-yl malonic acid diester; di-[*ent*-3,13*E*-clerodadien-15-yl] malonate; 7,13*E*-labdadien-15-yl-methyl malonic acid diester; *ent*-3,13*E*-clerodadien-15-yl-methyl malonic acid diester. Three nor diterpenes: 14,15-dinor-7-labden-13-one; 14,15-dinor-*ent*-3-cleroden-13-one; 14,15-dinor-*ent*-2,4(18)clerodadien-13-one; and seven diterpene alcohols, five of them isolated as acetyl derivatives: 7,13*E*-labdadien-15-ol; *ent*-3,13*E*-clerodadien-15-ol; diacetate of 8, (17),13*E*-labdadien-7α,15-diol; 15-acetoxy-8,13*E*-labdadien-7-one; 15-acetoxy-13*E*-labden-8β-ol; 15-acetoxy-13*E*-labden-8-ol and 15-acetoxy-*ent*-3,13*E*-clerodadien-2-one.

INTRODUCTION

We have recently reported on the isolation from *Parentucellia latifolia* of four new monoesters of malonic acid with diterpene alcohols [1] and of iridoidal compounds [2]. In the present work, we describe the isolation and structural determination of the components of the neutral part of this semiparasitic plant that grows in the Euromediterranean region. The work lies within a programme directed towards the study of the chemical components of toxic or endemic plants affecting the grasslands of the Iberian Peninsula.

RESULTS AND DISCUSSION

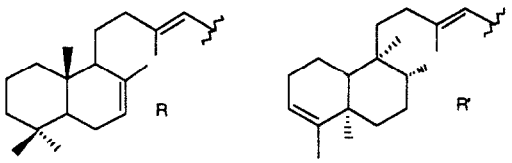
The neutral part of the hexane extract of *Parentucellia latifolia* was fractionated by column chromatography (CC) into three fractions after elution with hexane–acetate: I, II, and III. Rechromatography of fraction I gave four fractions: I_1, I_2, I_3 and I_4. After acid hydrolysis of fraction I_1 phytol (**1**) was isolated in the neutral fraction. The CC on silica gel ($AgNO_3$) of fraction I_2 yielded sitosterol acetate (**2**), 7,13*E*-labdadien-15-ol acetate (**3**) [1] and *ent*-3,13*E*-clerodadien-15-ol acetate (**4**) [1]. The CC of fraction I_3 in the same system gave compounds **5**–**10** and α-tocopherylquinone (**11**) [3]. From fraction I_4, 7,13*E*-labdadien-15-yl-methyl malonic acid diester (**12**) and *ent*-3,13*E*-clerodadien-15-yl-methyl malonic acid diester (**13**) were isolated [1]. Fraction II yielded 7,13*E*-labdadien-15-ol (**14**) [1], *ent*-3,13*E*-clerodadien-15-ol (**15**) [1] and sitosterol (**16**) while alkaline hydrolysis of fraction III followed by acetylation and CC of the neutral part afforded compounds **17**–**19**, 15-acetoxy-13*E*-labden-8-ol (**20**) [1] and 15-acetoxy-*ent*-3,13*E*-clerodadien-2-one (**21**) [1].

Compound **5** is an unsaturated ketone (IR: 1710, 1660, 850 cm^{-1}) whose ^1H NMR spectrum shows signals of the following groupings: CH=C–Me (δ5.35, 1H, *s*; 1.65, 3H, *s*), –CO–Me (δ2.12, 3H, *s*) and three methyl groups (δ 0.87, 3H, *s*; 0.84, 3H, *s*; 0.77, 3H, *s*). The ^{13}C NMR spectrum shows signals of 18 carbon atoms: five methyls, six methylenes, three methines (one of them sp^2) and four tetrasubstituted carbon atoms (two sp^2, one olefinic and another carbonyl at δ208.6). The compound must therefore have a labdane skeleton with a degraded side chain. Its structure as 14,15-dinor-7-labden-13-one, was secured by hemisynthesis (Scheme I).

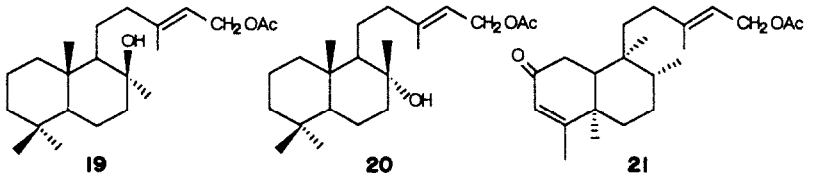
Alkaline hydrolysis of **3** yielded **14**, which by Sharpless enantioselective epoxidation [L(+) DET, Ti(*i*PrO)$_4$, *t*BuOOH] [4] afforded **22**, whose ^1H NMR spectrum shows a singlet (3H) at δ 1.23 of the Me-16 and signals of an ABX system (δ3.80, 1H, *dd*, $J_1=12.1$ Hz, $J_2=3.6$ Hz; 3.65, 1H, *dd*, $J_1=12.1$ Hz, $J_2=4.3$ Hz; 2.91, 1H, *dd*, $J_1=4.3$ Hz, $J_2=3.6$ Hz) formed of two hydrogen atoms at C-15 and one hydrogen at C-14. Treatment of **22** with H_5IO_6 [5, 6] afforded **5**.

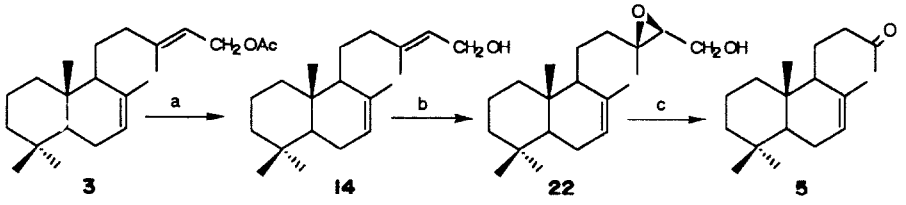
Compound **6** was also an unsaturated ketone (IR: 1710, 1670, 850 cm^{-1}), whose ^1H NMR spectrum showed signals of the following groupings: –CO–Me (δ2.15, 3H, *s*), –CH=CMe– (δ5.18, 1H, *br s*; 1.70, 3H, *s*) and of three methyl groups, two of them singlets and one a doublet (δ1.00, 3H, *s*; 0.70, 3H, *s*; 0.80, 3H, *d*, $J=5.9$ Hz). The ^{13}C NMR spectrum showed signals of 18 carbon atoms of which five were methyls, six methylenes, four methines (one of them sp^2) and four tetrasubstituted carbon atoms (two of them sp^2, one olefinic and the other carbonyl). The assigned structure of 14,15-dinor-*ent*-3-cleroden-13-one was confirmed by hemisynthesis (Scheme 2) using a procedure similar to that outlined above. Alkaline hydrolysis of **4** afforded the hydroxyderivative **15**, which by Sharpless epoxidation [L(+) DET, Ti(*i*PrO)$_4$, *t*BuOOH] yielded the epoxide **23** [^{13}C NMR spectrum (Table 1)] whose cleavage yielded **6**.

Compound **7** was an unsaturated ester (IR: 1750, 1660, 845 cm^{-1}) whose ^1H NMR spectrum showed signals of the groupings: CH=C–Me (δ5.39, 1H, *br s*, 1.69, 3H, *s*), Me–C=CH–CH_2–OCOR (δ5.35, 1H, *t*, $J=6.8$ Hz:



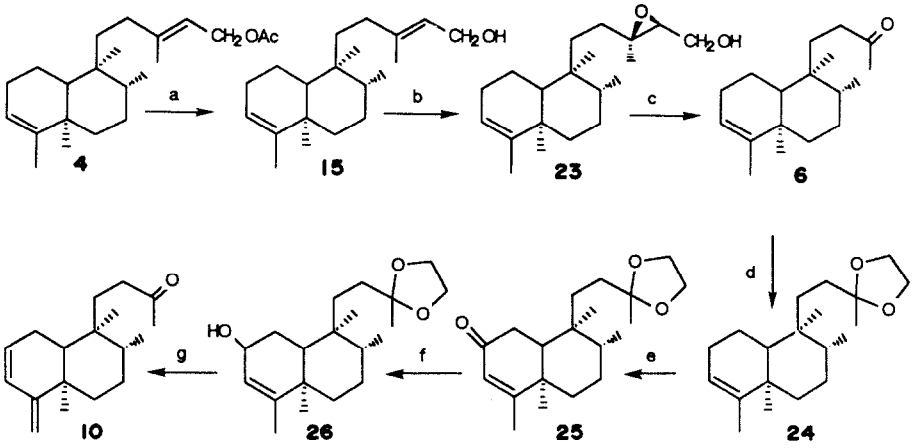
3 RCH_2OAc
4 $R'CH_2OAc$
7 $RCH_2OCO\text{-}CH_2\text{-}COOCH_2R$
8 $RCH_2OCO\text{-}CH_2COOCH_2R'$
9 $R'CH_2OCO\text{-}CH_2\text{-}COOCH_2R'$
12 $RCH_2OCO\text{-}CH_2\text{-}COOMe$
13 $R'CH_2OCO\text{-}CH_2\text{-}COOMe$
14 RCH_2OH
15 $R'CH_2OH$



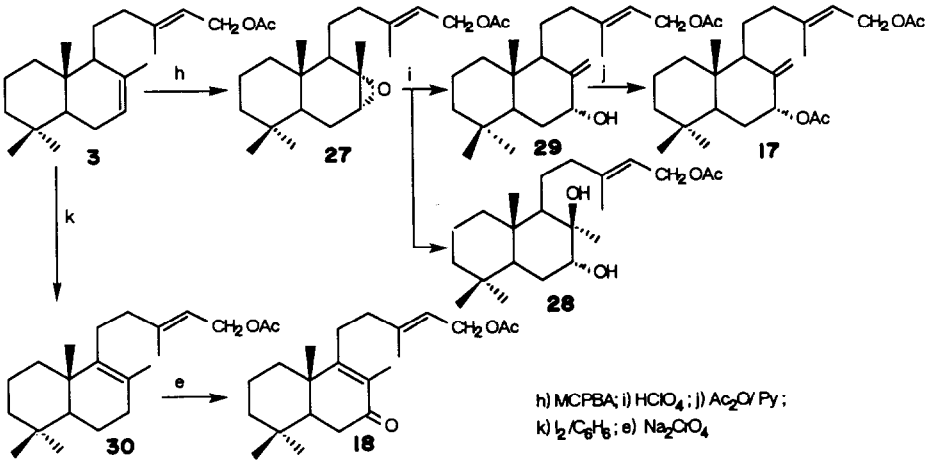


a) KOH/MeOH (10 %); b)$Ti(iPrO)_4$, L(+)DET, tBuOOH, CH_2Cl_2; c) H_5IO_6

Scheme 1.



a) KOH/MeOH (10 %); b)$Ti(iPrO)_4$, L(+)DET, tBuOOH, CH_2Cl_2; c) H_5IO_6;
d) $HO\text{-}CH_2\text{-}CH_2OH$/ p-TsOH; e) Na_2CrO_4; f) LAH; g) HCl



Scheme 3.

4.68, 4.68, 2H, *d*, $J=6.8$ Hz; 1.72, 3H, *s*), three methyl singlets on an sp^3 carbon atom and a singlet (2H) at $\delta 3.38$ characteristic of a malonate moiety [ROCO–CH_2–COOR]. The ^{13}C NMR spectrum showed 22 signals, five methyls, eight methylenes, four methines (two of them olefinic) and four tetrasubstituted carbon atoms (three of them sp^2, two of them olefinic and one carbonyl). The structure of **7** as di-(7,13*E*-labdadien-15-yl) malonate was confirmed by its hydrolysis to give **14**.

Compounds **8** and **9** also showed a 2H singlet at $\delta 3.38$ characteristic of the malonate moiety in the ^1H NMR spectrum. Alkaline hydrolysis of **8** afforded **14** and **15** and that of **9** afforded **15**, such that **8** can be identified as 7,13*E*-labdadien-15-yl and *ent*-3,13*E*-clerodadien-15-yl malonic acid diester and **9** as the malonate of di-(*ent*-3,13*E*-clerodadien-15-yl).

Compound **10** is a ketone with two conjugated double bonds (IR: 3100, 1720, 1640, 1600, 890, 790 cm^{-1}) (UV 231 nm). Its ^1H NMR spectrum showed signals of the groupings: $CH_2=C-CH=CH-$ ($\delta 6.03$, 1H, *d*, $J=9.3$ Hz; 5.76, 1H, *m*; 4.80, 1H, *s*; 4.66, 1H, *s*); Ac–($\delta 2.13$, 3H, *s*) and of three methyls ($\delta 0.97$, 3H, *s*; 0.83, 3H, *s*; 0.81, 3H, *d*, $J=6.3$ Hz).
atoms, four methyls, six methylenes (one of them sp^2), four methines (two of them sp^2) and four tetrasubstituted carbon atoms (two sp^2, one olefinic and another carbonyl). The presence of three methyls, two singlets and one doublet, suggests that **10** is a compound similar to **6** with the two double bonds on the A ring. The structure of 14,15-dinor-*ent*-2,4(18)-clerodadien-13-one is proposed for **10**; this was confirmed by hemisynthesis (Scheme 2).

Treatment of **6** with ethyleneglycol in the presence of *p*-TsOH afforded the ethylenedioxyderivative **24**, whose oxidation with Na_2CrO_4 afforded **25**. Reduction of **25** with $LiAlH_4$ gave **26**, which following treatment with HCl yielded **10** [14,15-dinor-*ent*-2,4(18)-clerodadien-13-one].

Compound **17** was an acetyl derivative (IR: 3100, 1750, 1665, 1245, 890, 845 cm^{-1}) whose ^1H NMR spectrum showed signals of three methyls and of two allylic acetoxyl groups situated in the following groupings: Me–C=CH–CH_2OAc ($\delta 5.37$, 1H, *t*, $J=6.8$ Hz; 4.58, 2H, *d*, $J=6.8$ Hz; 1.68, 3H, *s*) and $CH_2=C$–CHOAc (5.54, 1H, *br s*; 5.20, 1H, *s*; 4.78, 1H, *s*). The ^{13}C NMR spectrum showed signals of 24 carbon atoms, six methyls, eight methylenes (one of them sp^2), four methines (one of them sp^2) and six completely substituted carbon atoms (two of them carbonyl and two olefinic).

Treatment of **3** (Scheme 3) with MCPBA afforded the epoxide **27**, whose cleavage with perchloric acid [7] gave the diol **28** and its elimination product **29**. Acetylation of **29** afforded **17**, the diacetate of 8(17),13*E*-labdadien-7α,15-diol.

The IR spectrum of **18** corresponded to an unsaturated α-β ketone (IR: 1680, 1670, 840 cm^{-1}). The ^1H NMR spectrum showed signals of a Me–C=CH–CH_2–OAc grouping ($\delta 5.39$, 1H, *t*, $J=6.8$ Hz; 4.60, 2H, *d*, $J=6.8$ Hz; 1.76, 3H, *s*) similar to **3**, and of four singlet methyls, one of them on an sp^2 carbon atom ($\delta 1.76$, 3H, *s*) α to a carbonyl group (C=CMe–CO). The ^{13}C NMR spectrum showed signals of 22 carbon atoms, six methyls, seven methylenes, two methines (one of them olefinic) and seven tetrasubstituted carbon atoms (5 of them sp^2, 3 olefinic and 2 carbonyl). Treatment of **3** with I_2 [8] afforded **30** (Scheme 3), whose oxidation with sodium chromate [9] led to **18** (15, acetoxy-8,13*E*-labdadien-7-one).

Compound **19** was an unsaturated hydroxyacetate (IR: 3340, 1740, 1640, 1240, 1150, 880, 845 cm^{-1}) whose ^1H NMR spectrum showed signals identical to those of the side chain of **3** and **18** (Table 1). On the two-ring system there must be four singlet methyls, one of them geminal to a hydroxyl group. **19** has the structure of 15 acetoxy-13*E*-labden-8-β-ol according to the deshielding of Me-17 ($\delta 1.14$) in the ^1H NMR spectrum, and its displacement to $\delta 23.9$ in the ^{13}C NMR [10] and the deshielding of the Me-20 ($\delta 0.95$) [11].

EXPERIMENTAL

Mps: uncorr. ^1H NMR: 200 MHz, $CDCl_3$, TMS as int. standard; ^{13}C NMR: 50.3 MHz.

Extraction and isolation. The neutral fraction (15 g) of the hexane extract of *Parentucellia latifolia*, as described in ref. [1], was fractionated on CC yielding three fractions: I (4.5 g, *n*-hexane–EtOAc, 9:1), II (6.2 g, *n*-hexane–EtOAc, 4:1), III (4.3 g, *n*-hexane–EtOAc, 1:1). Fraction I was rechromatographed, giving four fractions: I_1 (0.50 g, *n*-hexane), I_2 (2.55 g, *n*-hexane–Et_2O, 19:1), I_3 (0.98 g, *n*-hexane–Et_2O, 9:1), I_4 (0.47 g, *n*-hexane–Et_2O, 17:3). Fraction I_1 (0.5 g) was hydrolysed with 5 ml KOH in MeOH (10%) giving phytol (**1**) (51 mg).

Table 1. ^{13}C NMR data of compounds **5–10**, **17–19**, **22–25** and **27–30** (50.3 MHz, $CDCl_3$, TMS as int. standard)

C	**5**	**22**	**6**	**23**	**7**	**8**		**9**	**10**	**24**	**25**	**17**	**27**	**29**	**28**	**18**	**30**	**19**
1	39.5	39.4	18.3	18.4	39.3	39.3	18.4	18.4	35.9	18.3	35.0	39.1	38.9	38.9	39.1	36.4	40.2	39.3
2	18.9	18.9	26.9	26.9	18.9	18.9	26.9	26.9	128.3	26.9	200.0	19.4	18.7	18.7	18.2	18.7	19.1	18.4
3	42.4	42.4	120.5	120.4	42.4	42.4	120.5	120.5	128.9	120.5	125.6	42.1	42.2	42.2	42.1	41.4	41.8	42.2
4	33.0	33.0	144.5	144.5	33.0	33.0	144.5	144.5	157.1	144.5	172.0	33.0	32.9	33.2	32.8	33.0	33.3	33.5
5	50.3	50.3	38.3	38.2	50.3	50.3	38.3	38.3	37.0	38.3	40.0	49.5	46.1	47.9	47.0	50.4	51.9	56.1
6	23.9	23.9	36.9	36.9	23.9	23.9	36.9	36.9	37.5	37.0	37.2	29.8	23.0	31.1	26.1	38.3	26.8	18.3
7	123.1	122.6	27.6	27.5	122.5	122.5	27.6	27.6	27.3	27.6	27.0	74.1	60.8	74.2	75.8	200.0	33.6	43.3
8	134.5	134.5	36.6	36.5	135.2	135.2	36.4	36.4	37.2	36.5	36.2	147.4	58.3	149.8	75.4	130.3	125.8	73.2
9	54.5	55.1	38.4	38.4	54.6	54.6	38.7	38.7	38.6	38.4	38.3	51.2	55.1	50.1	53.4	167.2	140.2	59.0
10	37.0	37.0	46.8	46.5	36.9	36.9	46.6	46.6	44.0	44.6	45.9	39.4	36.0	39.9	39.1	41.0	39.0	39.1
11	21.0	22.3	37.7	33.2	25.5	25.5	36.7	36.7	37.8	32.1	32.5	21.2	24.2	21.0	23.5	28.2	19.1	23.8
12	45.9	41.1	31.8	32.1	42.1	42.1	32.9	32.9	31.3	32.1	31.9	37.8	41.5	37.9	43.0	35.3	37.0	42.4
13	208.6	61.5	209.2	61.6	143.5	143.5	143.4	143.4	209.0	110.6	110.2	143.7	142.6	142.6	142.8	141.4	141.5	142.8
14		63.1		63.1	117.4	117.4	118.0	118.0				118.0	118.8	118.5	118.3	119.0	118.9	118.3
15		61.4		61.4	62.4	62.4	62.5	62.5				61.2	61.3	61.4	61.4	61.2	61.3	61.4
16	29.9	16.9	29.9	16.6	16.6	16.6	16.8	16.8	30.0	23.7	23.7	16.3	16.6	16.4	16.6	16.5	16.6	16.6
17	22.2	22.0	16.0	15.9	22.2	22.2	16.0	16.0	15.8	15.9	15.7	110.5	18.7	109.6	27.0	18.3	20.1	30.7
18	33.2	33.1	17.9	17.9	33.2	33.2	17.9	17.9	107.1	17.9	18.0	33.6	33.1	33.3	33.3	32.6	32.5	33.4
19	21.8	21.9	20.0	20.0	21.8	21.8	20.0	20.0	21.9	20.0	18.9	21.7	21.9	21.6	21.7	21.4	21.7	21.6
20	13.7	13.8	18.2	18.4	13.6	13.6	18.4	18.4	18.0	18.4	18.4	14.7	14.3	13.5	15.0	11.4	11.5	15.2
$COCH_2CO$					41.3	41.3		41.3										
$COCH_2CO$					166.6	166.6		166.6										
OCH_2CH_2O										64.6	64.6							
Me CO												20.7	21.0	21.0	21.0	21.0	20.9	21.0
Me CO												21.0						
MeCO												170.9	170.9	170.9	170.9	170.9	171.0	170.9

Assignments based on DEPT experiments and, particularly in the case of **3** and **4**[1], on C/H (HCCORR) normal and long range two dimensional correlations.

Fraction I_2 (2.55 g) was chromatographed over silica gel impregnated with 10% $AgNO_3$, yielding: sitosterol acetate (**2**) (407 mg, *n*-hexane–Et_2O, 19:1), **3** (1171 mg, *n*-hexane–Et_2O, 19:1) and **4** (970 mg, *n*-hexane–Et_2O, 19:1). Upon subjecting I_3 to the above procedure, **5** (151 mg, *n*-hexane–Et_2O, 19:1), **7** (87 mg, *n*-hexane–Et_2O, 9:1), **8** (120 mg, *n*-hexane–Et_2O, 9:1), **9** (111 mg, *n*-hexane–Et_2O, 9:1), **10** (112 mg, *n*-hexane–Et_2O, 17:3) and α-tocopherylquinone (**11**) (219 mg) were obtained. Fraction I_4 was also treated as above. Elution with *n*-hexane–Et_2O (9:1) gave compounds **12** (241 mg) and **13** (219 mg). Fraction II (1.7 g) was chromatographed over silica gel impregnated with 10% $AgNO_3$. Elution with *n*-hexane–EtOAc (4:1) gave compounds **14** (509 mg), **15** (637 mg) and **16** (549 mg). Fraction III (3.1 g) was treated with 20 ml KOH in MeOH (10%) for 24 hr at room temp. Usual work-up afforded 1.8 g of neutral fraction, which was treated with pyridine (3 ml) Ac_2O (2 ml) and the mixture kept at room temp. overnight. Usual work-up yielded 1.8 g of acetyl derivatives, which were chromatographed on silica gel yielding **17** (190 mg, *n*-hexane–EtOAc, 9:1), **18** (163 mg, *n*-hexane–EtOAc, 17:3), **19** (212 mg, *n*-hexane–EtOAc, 4:1), **20** (212 mg, *n*-hexane–EtOAc, 4:1) and **21** (370 mg, *n*-hexane–EtOAc, 7:3).

14,15-*Dinor*-ent-3-*cleroden*-13-*one* (**6**). Oil. $[\alpha]_D^{22}+16°$ ($CHCl_3$; *c* 1.0); IR ν_{max}^{film} cm^{-1}: 1710, 1660 and 850. ^1H NMR: δ5.35 (1H, *br s*, H-7), 2.12 (3H, *s*, Ac), 1.65 (3H, *s*, Me-17), 0,87 (3H, *s* Me-19), 0.84 (3H, *s*, Me-18), 0.77 (3H, *s*, Me-20); ^{13}C NMR: see Table 1.

14,15-*Dinor-ent-cleroden*-13-*one* (**6**). Oil. $[\alpha]_D^{22}+16°$ ($CHCl_3$; *c* 1.0); IR ν_{max}^{film} cm^{-1}: 1710, 1670 and 850. ^1H NMR: δ5.18 (1H, *br s*, H-3), 2.15 (3H, *s*, Ac), 1.70 (3H, *s*, Me-18), 1.00 (3H, *s*, Me-19), 0.80 (3H, *d*, *J* = 5.9 Hz, Me-17), 0.70 (3H, *s*, Me-20); ^{13}C NMR: see Table 1.

Di (-7,13E-*labdadien*-15-*yl*) *malonate* (**7**). Oil. IR ν_{max}^{film} cm^{-1}: 1750, 1660 and 845. ^1H NMR, δ5.39 (2H, *br s*, H-7, H′-7), 5.35 (2H, *t*, *J* = 6.8 Hz, H-14, H′-14), 4.68 (4H, *d*, *J* = 6.8 Hz, H-15, H′-15), 3.38 (2H, *s*, –CO–CH_2–CO–), 1.72 (6H, *s*, Me-16, Me′-16), 1.69 (6H, *s*, Me-17, Me′-17), 0.88 (6H, *s*, Me-19, Me′-19), 0.86 (6H, *s*, Me-18, Me′-18) and 0.76 (6H, *s*, Me-20, Me′-20); ^{13}C NMR: see Table 1.

7,13E-*Labdadien*-15-*yl and* ent-3,13E-*clerodadien*-15-*yl-malonic acid diester* (**8**). Oil. IR ν_{max}^{film} cm^{-1}: 1750, 1600 and 845. ^1H NMR: δ5.39 (1H, *br s*, H-7), 5.35 (1H, *t*, *J* = 6.8 Hz, H-14), 5.33 (1H, *t*, *J* = 7.3 Hz, H′-14), 5.19 (1H, *br s*, H′-3), 4.67 (2H, *d*, *J* = 6.8 Hz, H-15), 4.65 (2H, *d*, *J* = 7.3 Hz, H′-15), 3.38 (2H, *s*, –CO–CH_2–CO–), 1.72 (3H, *s*, Me-16), 1.71 (3H, *s*, Me′-16), 1.69 (3H, *s*, Me-17), 1.59 (3H, *s*, Me′-18), 1.00 (3H, *s*, Me′-19), 0.88 (3H, *s*, Me-19), 0.86 (3H, *s*, Me-18), 0.81 (3H, *d*, *J* = 6.3 Hz, Me′-17), 0.76 (3H, *s*, Me-20), 0.73 (3H, *s*, Me′-20); ^{13}C NMR: see Table 1.

Di-[ent-3,13E-*clerodadien*-15-*yl*]-*malonate* (**9**). IR ν_{max}^{film} cm^{-1}: 1750, 1660 and 850. ^1H NMR: δ5.33 (2H, *t*, *J* = 7.3 Hz, H-14), 5.19 (2H, *br s*, H-3), 4.65 (4H, *d*, *J* = 7.3 Hz, H-15), 3.38 (2H, *s*, –CO–CH_2–CO), 1.71 (6H, *s*, Me-16), 1.59 (6H, *s*, Me-18), 1.00 (6H, *s*, Me-19), 0.81 (6H, *d*, *J* = 6.3 Hz, Me-17), 0.73 (6H, *s*, Me-20); ^{13}C NMR: see Table 1.

14,15-*Dinor*-ent-2,4(18)-*clerodadien*-13-*one* (**10**). Oil; UV λ_{max}^{EtOH} nm (log ε): 231 (4.15). IR ν_{max}^{film} cm^{-1}: 3100, 1720, 1640, 1600, 890 and 790. ^1H NMR: δ 6.03 (1H, *d*, *J* = 9.3 Hz, H-3), 5.76 (1H, *m*, H-2), 4.80 (1H, *s*, H_A-18), 4.66 (1H, *s*, H_B-18), 2.13 (3H, *s*, Me-16), 0.97 (3H, *s*, Me-19), 0.83 (3H, *s*, Me-20), 0.81 (3H, *d*, *J* = 6.3 Hz, Me-17); ^{13}C NMR: see Table 1.

α-*Tocopherylquinone* (**11**). Yellow oil. $[\alpha]_D^{22}+3°$ ($CHCl_3$; *c* 1.4); UV λ_{max}^{EtOH} nm (log ε): 263. (4.21); IR ν_{max}^{film} cm^{-1}: 3550, 1660, 1480, 1320 and 730. ^1H NMR: δ 2.55 (2H, *m*, H′-1), 2.03 (3H, *s*, Me-5), 1.99 (6H, *s*, Me-2, Me-3), 1.23 (3H, *s*, Me-1′), 0.86 (9H, *d*, *J* = 6.3 Hz, Me-7′, Me-11′, Me-15′), 0.84 (3H, *d*, *J* = 6.3 Hz, Me-15′); ^{13}C NMR: δ187.7 (C-1), 140.5 (C-2), 140.3 (C-3), 187.2 (C-4), 144.6 (C-5), 140.6 (C-6), 21.5 (C′-1), 40.4 (C′-2), 72.7 (C′-3), 42.4 (C′-4), 21.4 (C′-5), 37.7 (C′-6), 32.8 (C′-7), 37.5 (C′-8), 24.5 (C′-9), 37.5 (C′-10), 32.8 (C′-11), 37.4 (C′-12), 24.8 (C′-13), 39.4 (C′-14), 28.0 (C′-15), 12.3 (Me-C2), 12.3 (Me-C3), 12.0 (Me-C5), 26.7 (Me-C3′), 19.7 (Me-C7′), 19.8 (Me-C11′), 22.6 (Me-C15′), 22.7 (Me-C15′).

Diacetate of 8 (17),13E-*labdadien*-7α,15-*diol* (**17**). Oil. $[\alpha]_D^{22}-31°$ ($CHCl_3$; *c* 1.1); IR ν_{max}^{film} cm^{-1}: 3100, 1750, 1665, 1245, 890 and 845. ^1H NMR: δ 5.54 (1H, *br s*, H-7), 5.37 (1H, *t*, *J* = 6.8 Hz, H-14), 5.20 (1H, *s*, H_B-17), 4.78 (1H, *s*, H_A-17), 4.58 (2H, *d*, *J* = 6.8 Hz, H-15), 2.06 (3H, *s*, O–Ac), 2.03 (3H, *s*, O–Ac), 1.68 (3H, *s*, Me-16), 0.87 (3H, *s*, Me-19), 0.84 (3H, *s*, Me-18), 0.75 (3H, *s*, Me-20); ^{13}C NMR: see Table 1.

15-*Acetoxy*-8,13E-*labdadien*-7-*one* (**18**). Oil. $[\alpha]_D^{22}-45°$ ($CHCl_3$; *c* 1.0); IR ν_{max}^{film} cm^{-1}: 1745, 1680, 1670, 1245 and 840. ^1H NMR: δ 5.39 (1H, *t*, *J* = 6.8 Hz, H-14), 4.60 (2H, *d*, *J* = 6.8 Hz, H-15), 2.05 (3H, *s*, O–Ac), 1.76 (6H, *s*, Me-16, Me-17), 1.07 (3H, *s*, Me-20), 0.88 (3H, *s*, Me-19), 0.83 (3H, *s*, Me-18); ^{13}C NMR: see Table 1.

15-*Acetoxy*-13E-*labden*-8β-*ol* (**19**). Oil. $[\alpha]_D^{22}+42°$ ($CHCl_3$; *c* 1.1); IR ν_{max}^{film} cm^{-1}: 3340, 1740, 1640, 1240, 1150, 880 and 850. ^1H NMR: δ 5.35 (1H, *t*, *J* = 6.8 Hz, H-14), 4.58 (2H, *d*, *J* = 6.8 Hz, H-15), 2.05 (3H, *s*, O–Ac), 1.72 (3H, *s*, Me-16), 1.14 (3H, *s*, Me-17), 0.95 (3H, *s*, Me-20), 0.87 (3H, *s*, Me-19), 0.82 (3H, *s*, Me-18); ^{13}C NMR: see Table 1.

15-*Acetoxy*-13E-*labden*-8-*ol* (**20**). Oil. $[\alpha]_D^{22}-22°$ ($CHCl_3$; *c* 1.1); IR ν_{max}^{film} cm^{-1}: 3450, 1750, 1670, 1250, 880 and 840. ^1H NMR: δ 5.34 (1H, *t*, *J* = 6.8 Hz, H-14), 4.58 (1H, *d*, *J* = 6.8 Hz, H-15), 2.05 (3H, *s*, O–Ac), 1.71 (3H, *s*, Me-16), 1.13 (3H, *s*, Me-17), 0.86 (3H, *s*, Me-19), 0.79 (3H, *s*, Me-18), 0.78 (3H, *s*, Me-20); ^{13}C NMR: see Table 1.

15-*Acetoxy*-ent-3,13E-*clerodadien*-2-*one* (**21**). Oil. $[\alpha]_D^{22}-11°$ ($CHCl_3$; *c* 1.0); IR ν_{max}^{film} cm^{-1}: 1745, 1680, 1660, 1620, 1254 and 850. ^1H NMR: δ 5.71 (1H, *d*, *J* = 1.0 Hz, H-3), 5.30 (1H, *t*, *J* = 6.8 Hz, H-14), 4.54 (2H, *d*, *J* = 6.8 Hz, H-15); 2.34 (2H, *m*, H-1), 2.05 (3H, *s*, O–Ac), 1.87 (3H, *d*, *J* = 1.0 Hz, Me-18), 1.67 (3H, *s*, Me-16), 1.10 (3H, *s*, Me-19), 0.82 (3H, *d*, *J* = 6.3 Hz, Me-17), 0.80 (3H, *s*, Me-20); ^{13}C NMR: see Table 1.

Alkaline hydrolysis of **3**. Compound **3** (450 mg) was treated with 5 ml KOH in MeOH (10%) for 24 hr at room temp. Usual work-up gave **14** (375 mg).

Sharpless reaction of **14**. A 100 ml flask equipped with a Teflon-coated magnetic stirring bar was oven-dried, then flushed with N_2. The flask was charged with dry CH_2Cl_2 (15 ml) and cooled by stirring in a −23° bath. The following liquids were then added sequentially via syringe while stirring in the cooling bath: Ti(*i*PrO)$_4$ (0.45 ml, 1.5 mmol), L-(+)-diethyl tartrate [L-(+)-DET, 0.24 ml, 1.5 mmol]; the mixture was stirred 45 min before the next addition of **14** (375 mg) in dry CH_2Cl_2 (2 ml). The mixture was stirred for 25 min and then *t*BuOOH (0.30 ml) was added. The resulting homogeneous soln was kept (4 hr) in the freezer at −20° in the sealed reaction vessel. The flask was then placed in a −23° bath and 10% aq. tartaric acid soln (10 ml) was added with stirring; the aq. layer solidified. After 30 min, the cooling bath was removed and stirring continued at room temp. until the aq. layer became clear. After separation of the aq. layer, the organic layer was washed once with water, dried (Na_2SO_4) and concd to give a yellow oil (350 mg); this was chromatographed on silica gel eluting with *n*-hexane–EtOAc (7:3) to afford **22** (280 mg). Oil. IR ν_{max}^{film} cm^{-1}: 3450, 1360, 1310, 1050, 1010 and 840. ^1H NMR: δ 5.35 (1H, *br s*, H-7), 3.80 (1H, *dd*, J_1 = 12.1 Hz, J_2 = 3.6 Hz, H_A-15), 3.65 (1H, *dd*, J_1 = 12.1 Hz and J_2 = 4.3 Hz H_B-15), 2.91 (1H, *dd*, J_1 = 4.3 Hz and J_2 = 3.6 Hz, H_X-14), 1.61 (3H, *s*, Me-17), 1.23 (3H, *s*, Me-16), 0.87 (3H, *s*, Me-19), 0.84 (3H, *s*, Me-18), 0.72 (3H, *s*, Me-20); ^{13}C NMR: see Table 1.

Oxidation of **22** *with periodic acid*. A soln of 240 mg periodic acid ($HIO_4 \cdot 2H_2O$) in 9 ml aq. (60%) tetrahydrofuran was

stirred while 280 mg **22** in 5 ml tetrahydrofuran were added dropwise. After 2 hr, the mixture was extracted into Et_2O, washed ($Na_2S_2O_3$ and H_2O) and dried (Na_2SO_4). The Product obtained, by evapn of the solvent, was **5** (192 mg).

Alkaline hydrolysis of **4**. Compound **4** (215 mg) was treated with 3 ml KOH in MeOH (10%) for 24 hr at room temp. Usual work-up gave **15** (199 mg).

Sharpless reaction of **15**. Upon subjecting 199 mg **15** to Sharpless treatment (see above with Ti(*i*PrO)$_4$ (0.3 ml), L(+)-DET (0.2 ml) and *t*BuOOH (0.2 ml) 150 mg **23** were obtained. Oil; IR ν_{max}^{film} cm^{-1}: 3450, 1360; 1310, 1050, 1010 and 840. ^{1}H NMR: δ 5.18 (1H, *br s*, H-3), 3.81 (1H, *dd*, $J_1 = 12.1$ Hz and $J_2 = 3{,}6$ Hz, H_A-15), 3.68 (1H, *dd*, $J_1 = 12.1$ Hz and $J_2 = 4.2$ Hz, H_B-15), 2.95 (1H, *dd*, $J_1 = 4.2$ Hz and $J_2 = 3.6$ Hz, H_X-14), 1.48 (3H, *s*, Me-18), 1.24 (3H, *s*, Me-16), 0.96 (3H, *s*, Me-19), 0.78 (2H, *d*, $J = 6.4$ Hz, Me-17), 0.71 (3H, *s*, Me-20); ^{13}C NMR: see Table 1.

Oxidation of **23** *with periodic acid*. Upon subjecting **23** (150 mg) to oxidation with periodic acid, 110 mg **6** were obtained.

Alkaline hydrolysis of **7**. Compound **7** (70 mg) was treated with 2 ml KOH in MeOH (10%) for 24 hr at room temp. Usual work-up gave **14** (61 mg).

Alkaline hydrolysis of **8**. Compound **8** (80 mg) was treated with 1 ml KOH in MeOH (10%) for 24 hr at room temp. Usual work-up gave 79 mg reaction product which on CC over silica gel impregnated with $AgNO_3$ (10%), yielded **14** (34 mg, *n*-hexane–EtOAc, 4:1) and **15** (36 mg, *n*-hexane–EtOAc, 4:1).

Alkaline hydrolysis of **9**. Compound **9** (87 mg) was treated with 1 ml KOH in MeOH (10%) for 24 hr at room temp. Usual work-up gave **15** (73 mg).

Reaction of **6** *with ethylene glycol*. *p*-Toluenesulphonic acid (10 mg) and ethylene glycol (15 ml) were added to a soln of **6** (110 mg) in C_6H_6 (15 ml). The mixture was refluxed (with a continuous water removal adapter) for 4 hr. The C_6H_6 was then evapd off, H_2O added and the product extracted with Et_2O. The organic layer was washed with $NaHCO_3$ (10%) and H_2O and dried over Na_2SO_4. The solvent was removed to give **24** (70 mg). Oil; ^{1}H NMR: δ 5.18 (1H, *br s*, H-3), 3.86 (4H, *m*, $(OCH_2)_2$), 1.50 (3H, *s*, Me-18), 1.30 (3H, *s*, Me-16), 0.91 (3H, *s*, Me-19), 0.69 (3H, *d*, $J = 6.3$ Hz, Me-17), 0.66 (3H, *s*, Me-20); ^{13}C NMR: see Table 1.

Oxidation of **24** *with* Na_2CrO_4. Dry Na_2CrO_4 (66 mg), 0.25 ml Ac_2O, 0.25 ml glacial HOAc and 66 mg dry NaOAc were added to 70 mg **24** dissolved in 5 ml of C_6H_6. The mixture was kept at 60° for 2 hr. Then, H_2O was added and after 1 hr the mixture was extracted with Et_2O. The ethereal extract was washed with $NaHCO_3$ and H_2O. CC on silica gel of the reaction product yielded 55 mg **25**. Oil; ^{1}H NMR: δ 5.70 (1H, *d*, $J = 0.9$ Hz, H-3), 3.86 (4H, *m*, O–CH_2–CH_2–O), 2.33 (2H, *m*, H-1), 1.68 (3H, *d*, $J = 0.9$ Hz, Me-18), 1.30 (3H, *s*, Me-16), 1.09 (3H, *s*, Me-19), 0.82 (3H, *d*, $J = 6.3$ Hz, Me-17), 0.79 (3H, *s*, Me-20); ^{13}C NMR: see Table 1.

Reduction of **25** *with* $LiAlH_4$. $LiAlH_4$ (10 mg) was added to a stirred, ice-cooled soln of **25** (55 mg) in dry Et_2O (3 ml) and the mixture was stirred for 1 hr under N_2. Then Et_2O (30 ml) and Na_2SO_4 (200 mg) were added, the mixture was kept for 15 min. Following this, it was filtered and the solvent evapd off to give **26** (40 mg).

Reaction of **26** *with* HCl (1 M). Three ml of 2 M HCl was added to **14** (40 mg), the mixture was stirred for 24 hr at room temp. After this the reaction product was extracted with Et_2O. The organic layer was washed with H_2O and dried over Na_2SO_4. Then the solvent was evapd off to give the reaction product (35 mg) which on prep. TLC gave **10** (20 mg).

Treatment of **3** *with m-chloroperbenzoic acid*. *m*-Chloroperbenzoic acid (60 mg) dissolved in 1 ml CH_2Cl_2 was added slowly to a soln of 100 mg **3** in 5 ml of CH_2Cl_2. The mixture was then shaken at room temp. for 5 hr, after which work-up in the usual fashion yielded **27** (93 mg). Oil; ^{1}H NMR: δ 5.35 (1H, *t*, $J = 6.8$ Hz, H-14), 4.58 (2H, *d*, $J = 6.8$ Hz, H-15), 2.93 (1H, *br s*, H-7), 2.03 (3H, *s*, OAc), 1.70 (3H, *s*, Me-16), 1.31 (3H, *s*, Me-17), 0.84 (3H, *s*, Me-19), 0.82 (3H, *s*, Me-18), 0.72 (3H, *s*, Me-20); ^{13}C NMR: see Table 1.

Treatment of **27** *with* $HClO_4$. Compound **27** (93 mg) was dissolved in 1,2-dimethoxyethane (5 ml) and 0.2 ml of $HClO_4$ (5%) were added and the mixture was kept at room temp. for 26 hr. The reaction mixture was extracted with Et_2O and the Et_2O washed with 10% Na_2CO_3, H_2O, dried and evapd to give a mixture which on silica gel CC yielded the following compounds **28** (34 mg) and **29** (37 mg) (*n*-hexane–EtOAc).

Compound **28**. Oil; ^{1}H NMR: δ 5.35 (1H, *t*, $J = 6.8$ Hz, H-14), 4.58 (2H, *d*, $J = 6.8$ Hz, H-15), 3.61 (1H, *br s*, H-7), 2.05 (3H, *s*, OAc), 1.70 (3H, *s*, Me-16), 1.23 (3H, *s*, Me-17), 0.94 (3H, *s*, Me-20), 0.87 (3H, *s*, Me-19), 0.82 (3H, *s*, Me-18); ^{13}C NMR: see Table 1.

Compound **29**. Oil; ^{1}H NMR: δ 5.31 (1H, *t*, $J = 6.8$ Hz, H-14), 5.06 (1H, *s*, H_A-17), 4.65 (1H, *s*, H_B-17), 4.59 (2H, *d*, $J = 6.8$ Hz, H-15), 4.37 (1H, *br s*, H-7), 2.03 (3H, *s*, OAc), 1.70 (3H, *s*, Me-16), 0.88 (3H, *s*, Me-19), 0.81 (3H, *s*, Me-18), 0.67 (3H, *s*, Me-20); ^{13}C NMR: see Table 1.

Acetylation of **29**. Compound **29** (37 mg) was treated with pyridine (2 ml) and Ac_2O (2 ml) for 5.5 hr at room temp. Usual work-up gave **17** (30 mg).

Isomerization of **3** *with* I_2. Compound **3** (100 mg) in dry C_6H_6 (10 ml) and I_2 (10 mg) was refluxed for 4 hr, ^{1}H NMR of the reaction mixture showed that compound **3** was completely transformed. The reaction mixture was purified on silica gel CC, yielding **30** (82 mg). Oil; ^{1}H NMR: δ 5.31 (1H, *t*, $J = 6.8$ Hz, H-14), 4.59 (2H, *d*, $J = 6.8$ Hz, H-15), 2.03 (3H, *s*, OAc), 1.71 (3H, *s*, Me-16), 1.69 (3H, *s*, Me-17), 0.93 (3H, *s*, Me-20), 0.88 (3H, *s*, Me-19), 0.82 (3H, *s*, Me-18); ^{13}C NMR: see Table 1.

Oxidation of **30** *with* Na_2CrO_4. Dry Na_2CrO_4 (64 mg), 0.25 ml Ac_2O, 0.25 ml glacial HOAc and 35 mg dry NaOAc were added to 82 mg **27** dissolved in 5 ml C_6H_6. The mixture was kept at 60° for 5 hr, H_2O was added and after 1 hr the mixture was extracted with Et_2O. The ethereal extract was washed with $NaHCO_3$ and H_2O. CC on silica gel of the reaction product yielded 84 mg **18**.

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