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Tobacco Chemistry. 43. Sensitized Photo-oxygenation of (12*Z*)-Abienol. Biomimetic Synthesis of Tobacco Labdanoids

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The reaction of (12*Z*)-abienol (*1*) with singlet oxygen was found to occur with competition between four processes. The predominant route (68 %) is an ene-process involving attack at C-13 and yielding, after reduction, the (11*E*,13*S*)- and (11*E*,13*R*)-11,14-labdadiene-8,13-diols (*2*, *3*). Less favoured are an ene-process (3 %) involving attack at C-12 and leading to the formation of the (12*S*)- and (12*R*)-13(16),14-labdadiene-8,12-diols (*4*, *5*) and a Diels-Alder process (5 %) furnishing, *i.a.* (12*R*)-12,15-epidioxy-13-labden-8-ol (*10*). The remaining process, accounting for some 12 % of the overall yield, is proposed to involve an attack on the 12,13 double bond and to proceed through intermediate peroxiranes to give the (12*R*,13*R*)- and (12*S*,13*S*)-8,12-epoxy-14-labden-13-ols (*6*, *7*) as well as the (12*S*,13*S*)- and (12*R*,13*R*)-8,13-epoxy-14-labden-12-ols (*8*, *9*). Exhaustive photo-oxygenation affected the concentrations of all these compounds and resulted in the generation of some additional products, *i.e.* 15,16-epoxy-8-hydroxy-13(16),14-labdadien-12-one (*14*), the (12*S*)- and (12*R*)-15,16-epoxy-13(16),14-labdadiene-8,12-diols (*15*, *16*) and norambreinolide (*17*).

Since several of the photo-oxygenation products obtained have previously been identified as tobacco constituents, the present results provide experimental support for the view that (12*Z*)-abienol (*1*) may be a precursor of the labdanic compounds found in processed tobacco.

Recent studies have disclosed that tobacco cultivars often produce diterpenoids of either the labdane or thunbergane types.[1,2] These diterpenoids, which are present in the cuticular wax of the tobacco leaf, are highly susceptible to light and oxidation and their concentrations are markedly reduced during the aerobic post-harvest treatment of the tobacco.[2,3] These findings are of particular interest from a flavour point of view, since it seems likely that the products of the catabolism of these diterpenoids are low-molecular weight odoriferous compounds.

It has been suggested that (12*Z*)-abienol (*1*) is an appropriate precursor of the labdanic compounds found in processed tobacco and a hypothetical route accounting for the conversion of *1* to some of these compounds has been formulated.[4] However, since no experimental evidence was available, we found it desirable to undertake a biomimetic study of the reactions of (12*Z*)-abienol (*1*) with singlet oxygen. The present paper gives an account of the products thus obtained.

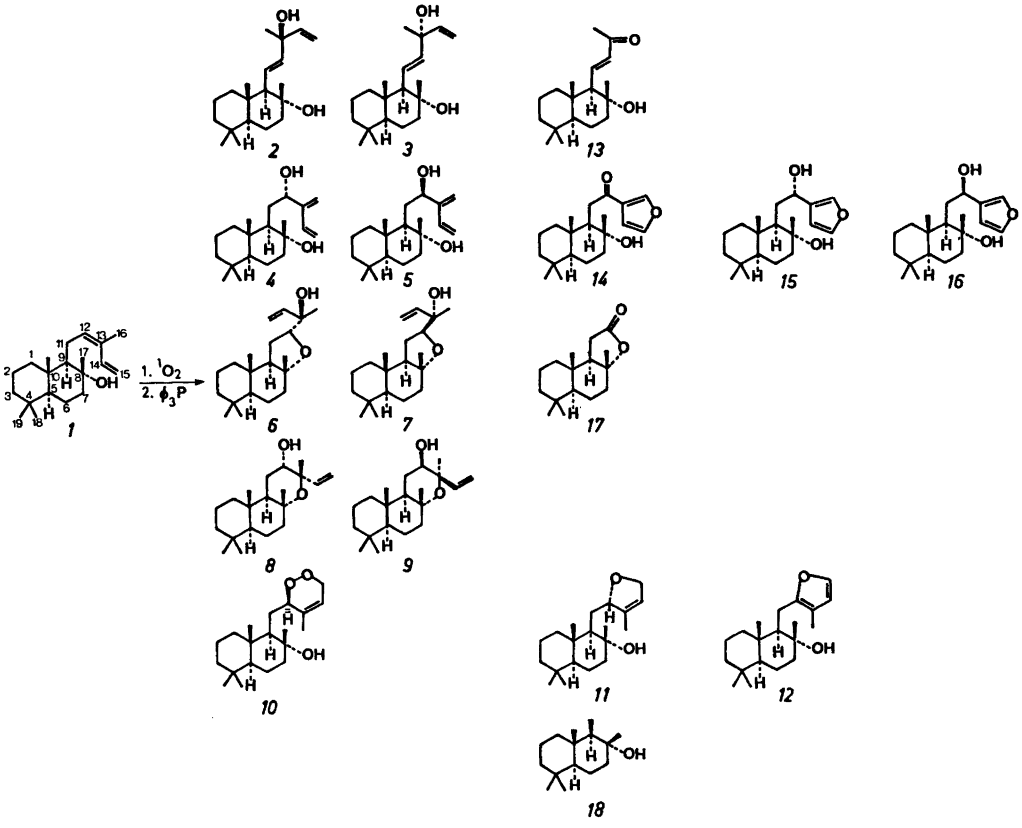
RESULTS

(12*Z*)-Abienol (*1*) is a 1,3-diene incorporating one trisubstituted and one monosubstituted double bond. Since the reactivity of acyclic olefins toward singlet oxygen is known to be in the order: tetrasubstituted mono-olefin > trisubstituted mono-olefin > 1,3-diene ≫ di- and monosubstituted mono-olefin,[5,6] an ene reaction involving the trisubstituted double bond is expected to be somewhat favoured over a 1,4-addition of oxygen across the conjugated double bond system. An ene reaction involving the monosubstituted 14,15 double bond of (12*Z*)-abienol (*1*), may, however, be excluded.

In agreement with this, (12*Z*)-abienol (*1*) proved to react smoothly with singlet oxygen and the reaction was complete after 6.5 h.

Reduction of the reaction mixture with triphenylphosphine and subsequent separation by liquid chromatography afforded a series of products, *2*–*13* and *18* (Scheme 1). Of these, the diols *2*–*5* represent the products of the ene reactions involving the 12,13 double bond, whereas the 12,15 oxygen-bridged compounds *10*–*12* are likely to arise *via* the 1,4 addition process. The reaction leading to the generation of the tetrahydrofurans and tetrahydropyrans *6*–*9* is evidently more complex. Since the formation of the two nor-labdanoids *13* and *18*, seemed to involve subsequent chemical alterations of the initially generated products, it was also of interest to study the products obtained on exhaustive (75 h) photo-oxygenation. As shown in Table 1 prolonged exposure of (12*Z*)-abienol (*1*) to singlet oxygen not only affected the relative proportions of the products presented above but also resulted in the appearance of the furano labdanoids *14*–*16* and norambreinolide (*17*).

Products of ene reactions. The major products obtained on photo-oxygenation of (12*Z*)-abienol (*1*) were identified as the (11*E*,13*S*)- and (11*E*,13*R*)-11,14-labdadiene-8,13-diols (*2*, *3*) on the basis of the following evidence. Both compounds had the composition $C_{20}H_{34}O_2$ (MS) and exhibited spectral properties indicating that they were isomers. The ^{13}C and ^1H NMR spectra demonstrated that diols *2* and *3* incorporate one monosubstituted and one disubstituted double bond. Three of the signals due to the vinylic hydrogens were doublets of doublets showing the splitting pattern typical of a vinyl group attached to a fully substituted carbon atom, *i.e.* $J_{AB}=1.5$, $J_{AX}=10.5$ and $J_{BX}=17.5$ Hz. Hence, they were identified as the resonances due to H-14, H-15a and H-15b. The protons of the disubstituted double bond



Scheme 1. Compounds formed by sensitized photo-oxygenation of (12*Z*)-abienol (*1*).

Table 1. Relative proportions (%), as determined by GC integration, of the various products obtained on normal and exhaustive photo-oxygenation of (12*Z*)-abienol (*1*).

Photo-oxygenation	Compound No. 2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Normal (6.5 h) [a]	46	22	2	1	5	1	0.5	6	[b]	1	[b]	0.2	—	—	—	—	[d]
Exhaustive (75 h)	7	3	—	—	4	3	1	8	[c]	5	[c]	5	1	5	2	5	—

[a] The reaction was stopped when all starting material had been consumed. [b] *10* plus *12* integrate for 4 %. [c] *10* plus *12* integrate for 13 %. [d] *18* integrates for 10 % on analysis of the Na_2SO_3-treated reaction mixture and for 0.5 % on analysis of the triphenylphosphine-treated reaction mixture.

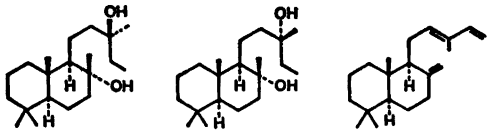
Table 2. Carbon-13 chemical shifts and assignments for compounds *2*—*5*, *10*—*16*, *19*, *20*, *22*, *23* and *30*.[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15	C-16	C-17	C-18	C-19	C-20
2	40.7	18.5	42.0	33.3	55.8	20.2	42.7	73.0 [b]	65.8	37.5	124.2	141.2	72.4 [b]	144.8	111.9	27.2	24.7	33.4	21.6	15.9
3	40.8	18.5	42.0	33.4	55.9	20.2	42.7	73.1 [b]	65.9	37.5	125.0	141.8	72.3 [b]	144.0	112.4	28.5	24.8	33.4	21.6	16.0
4	39.5	18.4	41.9	33.3	56.0	20.5	44.1	73.2	59.0	39.3	33.6	72.9	150.3	136.6	113.9	113.5	25.0	33.4	21.4	15.4
5	39.5	18.5	41 9	33.5	56.0	20.5	45.0	73.9	54.4	38.5	31.2	69.8	149.5	137.1	113.7	114.8	24.6	33.5	21.6	15.7
10	39.3	18.6	42.0	33.5	56.1	20.6	45.7	74.9	56.7	38.7	27.1	83.6	135.7	117.6	69.8	19.1	23.8	33.5	21.6	15.8
30	39.9	18.5	41.9	33.2	56.0	20.5	43.8	72.7	58.3	39.6	26.4	84.1	134.4	118.3	70.0	19.1	24.1	33.5	21.5	15.3
11	39.4	18.4	42.0	33.3	56.1	20.5	44.0	71.9	58.6	39.3	29.9	89.8	138.2	120.0	73.6	12.5	24.5	33.4	21.5	15.3
12	39.4	18.6	41.8	33.3	56.0	20.4	44.1	73.4	59.9	38.8	21.2	151.9	113.0	113.0	139.5	10.1	23.9	33.5	21.6	15.2
13	41.0	18.4	41.8	33.4	55.6	20.2	43.1	72.4	65.9	37.9	144.8	135.5	197.7			27.6	24.9	33.4	21.6	16.0
14	39.5	18.4	41.7	33.3	55.9	20.6	44.7	73.1	55.9	38.7	36.4	196.3	128.3	108.9	144.1	147.0	23.4	33.3	21.4	15.7
15	39.3	18.4	41.9	33.3	56.0	20.5	44.1	73.2	58.8	39.2	34.8	68.7	130.2	108.6	143.0	138.6	24.9	33.4	21.5	15.3
16	39.7	18.5	41.7	33.4	55.9	20.4	44.9	73.8	54.6	38.6	33.0	66.4	129.5	109.1	142.9	139.2	24.3	33.4	21.6	15.5
19	39.7	18.5	42.1	33.2	56.1	20.5	44.1	74.7	62.1	39.2	18.8	44.0	73.4	36.1	8.3	25.1	24.2	33.4	21.5	15.5
20	39.8	18.5	42.1	33.3	56.2	20.6	44.2	74.8	62.2	39.3	18.9	44.3	73.7	33.3	8.6	27.2	24.3	33.4	21.5	15.5
22	39.9	18.4	42.5	33.1	57.2	20.6	39.9	81.0	58.2	36.1	29.9	73.9	148.3	137.2	113.8	113.1	21.7	33.6	21.1	15.2
23	40.6	18.4	42.5	33.1	57.2	21.0	40.1	80.7	61.1	36.3	30.3	77.1	148.9	137.1	113.5	112.9	24.6	33.5	21.0	15.7

[a] δ-Values relative to TMS. [b] Assignment may be reversed.

gave rise to overlapping signals at δ 5.7, which on addition of Eu(dpm)$_3$ were resolved into the AB part of an ABX system with $J_{AB} = 15.5$, $J_{AX} = 10.0$ and $J_{BX} < 0.3$ Hz. This is compatible with the presence of the 11,12 double bond of *E*-configuration adjacent to the non-protonated C-13 in diols *2* and *3*. The two oxygen atoms were accommodated by hydroxyl substituents attached to C-8 and C-13, a conclusion supported by the fact that the ^{13}C NMR spectra included signals due to two oxygen-carrying, fully substituted sp^3 carbons and the ^{1}H NMR spectra showed methyl singlets at δ 1.21 and 1.41 (*2*) and at δ 1.18 and 1.39 (*3*).

Catalytic hydrogenation of diol *2* gave a low yield of a tetrahydro derivative, which proved to be identical to dihydrosclareol, (13*S*)-8,13-labdanediol (*19*). This established the structure of diol *2* as (11*E*,13*S*)-11,14-labdadiene-8,13-diol. Hydrogenation of diol *3* afforded a tetrahydro derivative (*20*), whose ^{13}C NMR spectrum differed from that of (13*S*)-8,13-labdanediol (*19*) with respect to the chemical shift values of the C-14 and C-16 signals: 33.3 and 27.2 ppm for *20* as against 36.1 and 25.1 ppm for *19* (Table 2). In view of this and since other spectral data were markedly similar, it was concluded that the two tetrahydro derivatives *19* and *20*, and hence diols *2* and *3*, were epimeric at C-13, *i.e.* diol *3* could be assigned the structure (11*E*,13*R*)-11,14-labdadiene-8,13-diol.



19 *20* *21*

These two diols (*2*, *3*) are evidently formed by ene processes involving attack of singlet oxygen at C-13 and migration of a hydrogen from C-11. Since the *cis*-cyclic mechanism of the ene process would require that the plane of the 12,13 double bond is roughly perpendicular to the C-H(11) bond,[7] it is necessary to include a brief discussion on the conformers around the 11,12 bond of (12*Z*)-abienol. In principle, the butene substituent at C-12 can occupy a position in any of the three sectors **a**, **b** and **c**, defined by the bonds between C-11 and the 11β-hydrogen, C-11 and the 11α-hydrogen, and C-11 and C-9; the corresponding conformers are designated by A, B and C respectively (Fig. 1). However, due to the *anti*-arrangement of the two large groups, conformers of type A may be more populated than those of type B, which have a *gauche* arrangement and those of type C, which have a severe interaction between the vinyl group and the methyl group at C-8.

Four conformers, A_1, A_2, B_2 and C_2 fulfil the steric requirements of the ene process, but conformers B_2 and C_2, which are sterically crowded, can be ruled out, since they would furnish 11*Z*-derivatives. In conformer A_1 one side of the double bond is shielded by the hydroxyl and methyl substituents at C-8, which strongly favours attack of oxygen from the side indicated (Fig. 1). Abstraction of the 11α-hydrogen would produce the (13*S*)-hydroperoxide of (11*E*)-11,14-labdadien-8-ol (*2a*). Conformer A_2 allows attack of oxygen from both faces, but only attack at the top face and migration of the 11β-hydrogen would afford the 13*R*-hydroperoxide (*3a*). The corresponding diols (*2*, *3*) are obtained in the ratio 2:1, which

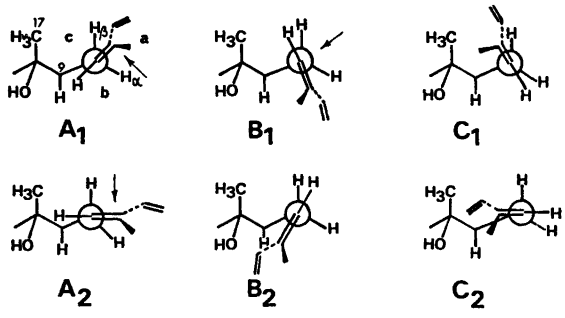


Fig. 1. Conformers about the 11,12 bond in (12*Z*)-abienol (*1*).

demonstrates that the process involving conformer A_1 is favoured over that involving conformer A_2.

Attack of oxygen at C-12 in a conformer such as A_1, and abstraction of an allylic hydrogen from C-16 yield the (12*R*)-hydroperoxide of 13(16),14-labdadien-8-ol (*5a*), whereas conformers such as A_2 and B_1 may be the precursors of the 12*S*-derivative (*4a*) (Fig. 1). However, since the corresponding alcohols are obtained in low yields (*cf.* Table 1) it can be concluded that this process is considerably less favoured than the ene reaction involving attack at C-13 and migration of a hydrogen from C-11. This finding contrasts with the situation for *trans*-biformene (*21*), which has recently been shown to undergo a preferential ene reaction with participation of a hydrogen from C-16.[6]

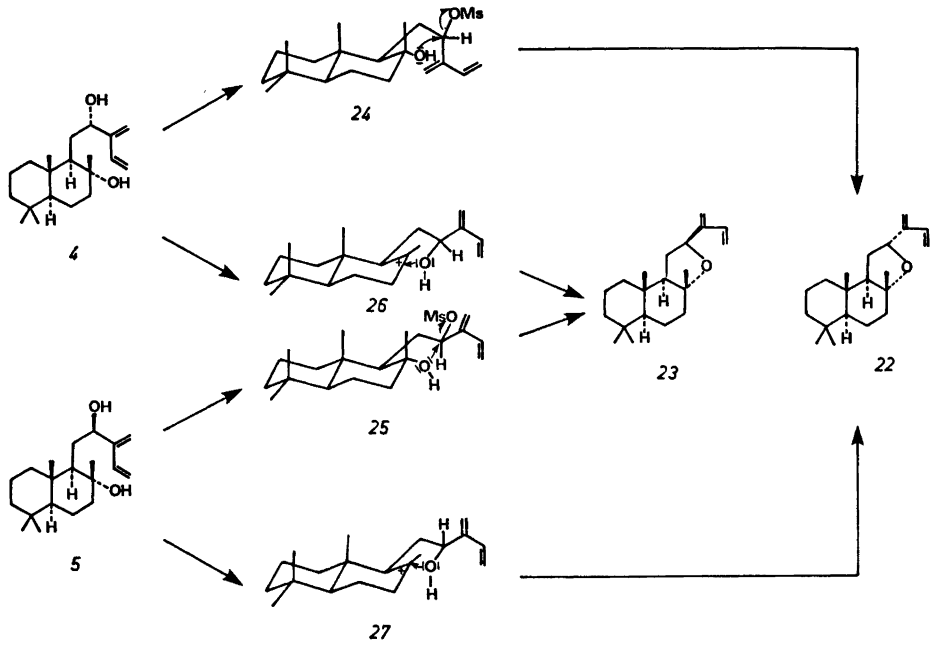
The (12*S*)- and (12*R*)-13(16),14-labdadiene-8,12-diols (*4*, *5*) had the composition $C_{20}H_{34}O_2$ (MS) and gave ^{1}H NMR spectra containing four methyl singlets and signals due to five hydrogens in the olefinic regions. Thus two broadened singlets, present at δ 5.14 and 5.32 for *4* and at δ 5.20 and 5.30 for *5*, were assigned to H-16a and H-16b, whereas two broadened doublets at δ 5.10 and 5.37 for *4* and at δ 5.09 and 5.36 for *5*, were identified as the H-15a and H-15b resonances. A doublet of doublets ($J = 11$ and 18 Hz) at δ 6.37 for *4* and at δ 6.36 for *5* was ascribed to H-14. The ^{13}C NMR spectra containing signals due to two sp^2 methylene, one sp^2 methine and one fully substituted sp^2 carbon atom, and the UV spectra having maxima at 225 nm were also in accordance with the presence of the 13(16),14(15) diene system in *4* and *5*.

The IR spectra, which exhibited absorption at 3300 cm^{-1} and were devoid of carbonyl bands, showed that the two oxygen atoms were present as hydroxyl substituents. The allocation of these to C-8 and C-12 followed from the NMR data. Thus, the H-12 signal appeared as a doublet of doublets at δ 4.27 ($J = 3$ and 9 Hz) in the ^{1}H NMR spectrum of diol *4* and as a triplet at δ 4.74 ($J = 5$ Hz) for diol *5*, whereas C-8 and C-12 resonated at δ 73.2 (s) and 72.9 (d) in the ^{13}C NMR spectrum of diol *4* and at δ 73.9 (s) and 69.8 (d) for diol *5*.

The configuration at C-12 in the two diols (*4*, *5*) was elucidated by chemical means (Scheme 2). Treatment of diol *4* with mesyl chloride in pyridine proceeded smoothly with direct cyclisation to (12*R*)-13(16),14-labdadien-8,12-epoxide (*22*), while under the same conditions the epimeric diol *5* afforded the corresponding (12*S*)-derivative (*23*) in almost quantitative yield. Since, conversely, the reaction of diols *4* and *5* with stannic chloride in chloroform yielded the (12*S*)- and (12*R*)-derivatives (*23*, *22*), respectively, these results may be rationalised as depicted in Scheme 2. The mesylates expected to be formed initially (*24*, *25*) undergo an S_N2-type of cyclisation by attack of the 8α-hydroxyl group with formation of (12*R*)- and (12*S*)-13(16),14-labdadien-8,12-epoxide (*22*, *23*), respectively. This requires that diol *4* has the (12*S*)- and diol *5* the (12*R*)-configuration. The reaction of diols *4* and *5* with stannic chloride, on the other hand, proceeds *via* the tertiary carbonium ions (*26*, *27*), which are attacked by the hydroxyl substituent at C-12. The products thus obtained, the (12*S*)- and (12*R*)-13(16),14-labdadien-8,12-epoxides (*23*, *22*) should then derive from the 12*S*- and 12*R*-diols (*4*, *5*) respectively.

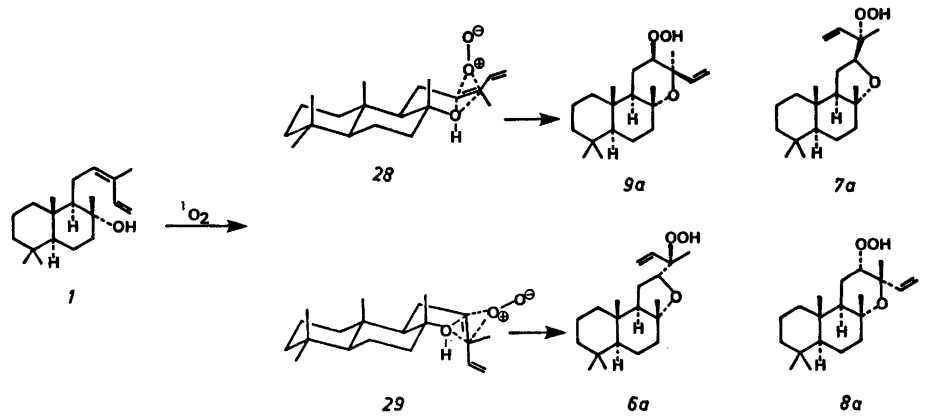
The (12*R*)- and (12*S*)-13(16),14-labdadien-8,12-epoxides (*22*, *23*), M^+ 288, gave IR spectra devoid of hydroxyl and carbonyl absorptions. Their ^{1}H NMR spectra displayed five signals in the olefinic region which, due to the typical splitting patterns, were assigned to the protons of the 13(16),14(15)-diene systems. A multiplet, present at δ 4.79 for *22* and at δ 4.67 for *23*, was identified as the H-12 signal. The ^{13}C NMR spectra, which contained signals due to two oxygen-carrying carbons, one methine and one fully substituted carbon, confirmed the presence of the 8,12-epoxide group. Moreover, the chemical shift values of the C-12 and C-17 signals, 73.9 and 21.7 ppm for *22* and 77.1 and 24.6 ppm for *23*, respectively, provided the basis for the assignment of the 12*R*-configuration to *22* and the 12*S*-configuration to *23*.[8]

The (12*R*,13*R*)- and (12*S*,13*S*)-8,12-epoxy-14-labden-13-ols (*6*, *7*) as well as the (12*S*,13*S*)- and (12*R*,13*R*)-8,13-epoxy-14-labden-12-ols (*8*, *9*), identified by spectral comparison with corresponding authentic samples,[8] were obtained after reduction, as products of the sensitized photo-oxygenation of (12*Z*)-abienol (*1*). The reaction leading to the formation of these compounds is evidently more complex than



Scheme 2. Cyclisation of the (12*S*)- and (12*R*)-13(16),14-labdadiene-8,12-diols (*4*, *5*).

the normal ene reaction. However, since compounds *6* – *9* are also obtained on peracid oxidation of (12*Z*)-abienol (*1*),[8] it seems likely that the reaction involves attack of singlet oxygen at the 12,13 double bond of conformers B_3 and C_1 (Fig. 1) and proceeds with anchimeric assistance of the 8α-hydroxyl group through the peroxirane type of intermediates shown in Scheme 3. Although nearly equal amounts of products are generated *via* the two intermediates (*28*, *29*), it is evident that intermediate *28* affords the tetrahydropyran *9a* in preference to the tetrahydrofuran *7a*, while the diastereomeric intermediate *29* gives the tetrahydrofuran *6a* in preference to the tetrahydropyran *8a*. This may partly be ascribed to

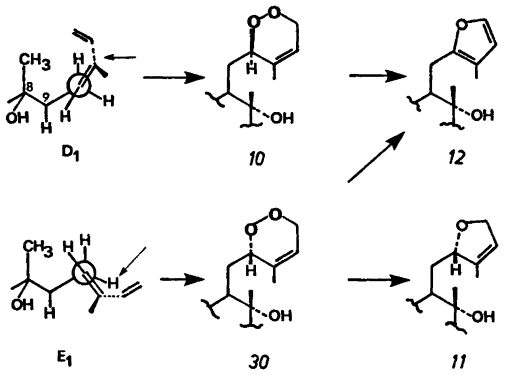


Scheme 3. Mechanism for the formation of the (12*R*,13*R*)- and (12*S*,13*S*)-8,12-epoxy-14-labden-13-hydroperoxides (*6a*, *7a*) and the (12*S*,13*S*)- and (12*R*,13*R*)-8,13-epoxy-14-labden-12-hydroperoxides (*8a*, *9a*) from (12*Z*)-abienol (*1*).

the fact that in the conversion of intermediate *28* to *9a* the tetrahydropyran ring will be generated in the chair form having the hydroperoxide group equatorially oriented and the vinyl group in an axial position. The conversion of intermediate *29* to *8a*, on the other hand, will involve a boat conformation of the tetrahydropyran ring, which on reversion to the chair form will have the hydroperoxide and C-13 methyl groups axially oriented. Moreover, the steric congestion is smaller in the tetrahydrofuran *6a* than in the diastereomer *7a*, where the C-12 substituent is quasiaxial and interacts with the axial methyl group at C-8.[8]

Products of 1,4-addition reactions. Although ene reactions are the major routes for photooxygenation of (12*Z*)-abienol (*1*), the isolation of (12*R*)-12,15-epidioxy-13-labden-8-ol (*10*), (12*S*)-12,15-epoxy-13-labden-8-ol (*11*) and 12,15-epoxy-12,14-labdadien-8-ol (*12*) indicates that the 1,4 addition reaction, which requires an energetically unfavoured *s-cis* configuration of the 1,3-diene system, makes a small contribution to the overall yield (*cf.* Table 1). This result thus represents an addition to the relatively few reports of the formation of unsaturated cyclic peroxides from acyclic 1,3-dienes.[6,9–11]

Since a 1:1 mixture of the two C-12 epimers of 12,15-epidioxy-13-labden-8-ol (*10*, *30*) was obtained in an experiment where aqueous Na_2SO_3 replaced triphenylphosphine in the work-up procedure, it seems likely that the

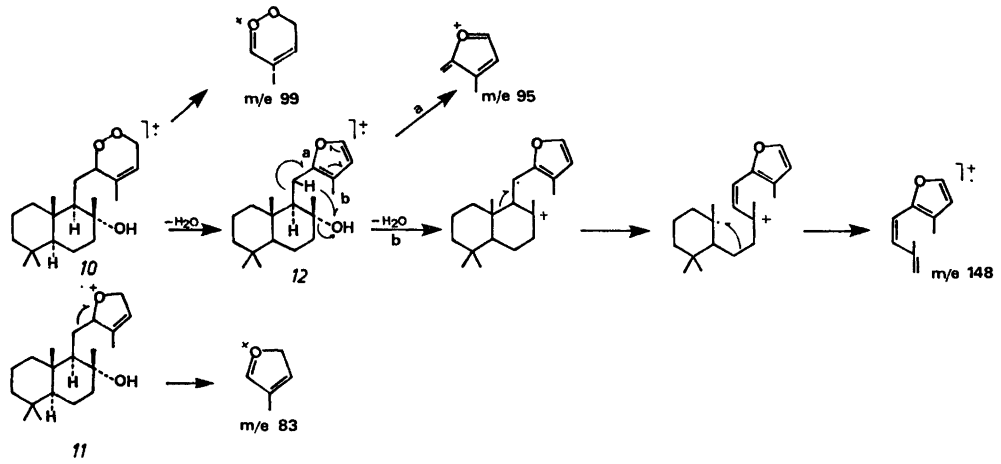


Scheme 4. Mechanism for the formation of the (12*R*)- and (12*S*)-12,15-epidioxy-13-labden-8-ols (*10*, *30*), (12*S*)-12,15-epoxy-13-labden-8-ol (*11*) and 12,15-epoxy-12,14-labdadien-8-ol (*12*) from (12*Z*)-abienol (*1*).

formation of compounds *10* – *12* proceeds as shown in Scheme 4. Attack of singlet oxygen at the unhindered side of a conformer such as D_1 yields the 12*R*-epidioxide *10*, while attack at the unhindered side of a conformer such as E_1 furnishes the 12*S*-epidioxide *30*. The latter is the obvious precursor of (12*S*)-12,15-epoxy-13-labden-8-ol (*11*), whereas 12,15-epoxy-12,14-labdadien-8-ol (*12*) may be formed from either epidioxide.

(12*R*)-12,15-Epidioxy-13-labden-8-ol (*10*) had the composition $C_{20}H_{34}O_3$ (MS) and showed hydroxyl absorption at 3600 and 3490 cm^{-1} in the IR spectrum. The ^{13}C NMR spectrum with signals δ 69.8 (t), 74.9 (s) and 83.6 (d) due to three oxygen-carrying carbon atoms and at δ 117.6 (d) and 135.7 (s) due to two sp^2 carbon atoms was consistent with the presence of one hydroxyl substituent, one epidioxy group and one trisubstituted double bond. A three-proton multiplet at δ 1.78 in the ^1H NMR spectrum, sharpened on irradiation at the frequency of a multiplet at δ 5.55, was assigned to H-16. Conversely, irradiation at the frequency of the methyl multiplet sharpened the multiplet at δ 5.55, which was hence identified as the H-14 signal, as well as the AB part of an ABX system centered at δ 4.5, which was ascribed to H-15a and H-15b. An obscured signal at δ 4.6 was assigned to H-12. The mass spectrum, which in addition to prominent peaks at *m/e* 95 and 148 (*vide infra*) exhibited a peak at *m/e* 99 due to a $C_5H_7O_2$ species formed by rupture of the 11,12-bond, supported the formulation of the epidioxide (*10*) (Scheme 5).

The tentative assignment of the 12*R*- and 12*S*-configuration to the epidioxides *10* and *30*, respectively, rested on a comparison of the ^{13}C NMR data of these compounds with those of the 12*S*- and 12*R*-diols *4* and *5* and requires comment. As shown in Table 2, the C-7 and C-8 signals for the 12*S*-diol (*4*) are upfield of those for the 12*R*-diol (*5*), while the reverse is true for the C-9 to C-12 and C-17 signals. The shift difference is particularly marked for the C-9 signals, δ 59.0 for diol *4* and δ 54.4 for diol *5*, a result which may be accounted for by an inspection of the conformers about the 11,12-bond. Of the conformers likely to be of importance,[6,12] *i.e.* the 12*S*-conformers F and G and the 12*R*-conformers H and I (Fig. 2), only H has an interaction between the hydroxyl



Scheme 5. Mass spectral fragmentation reactions characteristic of compounds *10* – *12*.

group at C-12 and the C-H(9) bond (*syn*-arrangement) which is expected to cause an appreciable shielding of C-9.[13] Since the ^{13}C NMR spectra of the two epimeric epidioxides (*10*, *30*) showed shift differences for the C-7 to C-12 and C-17 signals similar to those observed for the corresponding signals for the 12*S*- and 12*R*-diols (*4*, *5*) and since a *syn*-arrangement of one of the oxygens of the epidioxide group and the C-H(9) bond is only of importance for the 12*R*-epidioxide (*30*), the ^{13}C NMR results were used for the configurational assignment.

The presence of the dihydrofuran ring system in (12*S*)-12,15-epoxy-13-labden-8-ol (*11*), $C_{20}H_{34}O_2$ (MS), followed from the ^1H NMR spectrum, which displayed the methyl multiplet due to H-16 at δ 1.74 and the H-14 multiplet at δ 5.45, whereas the signals due to H-12, H-15a and H-15b overlapped at δ 4.4 – 4.7. Evidence was also obtained from the mass spectrum, whose base peak at *m/e* 83 was due to a C_5H_7O species comprising the dihydrofuran moiety (Scheme 5). The assignment of the *S*-configuration to C-12 followed from a comparison of the ^{13}C NMR data with those of the 12*R*- and 12*S*-epidioxides (*10*, *30*).

12,15-Epoxy-12,14-labdadien-8-ol (*12*) had the composition $C_{20}H_{32}O_2$ (MS) and showed absorption due to hydroxyl (3590 and 3430 cm^{-1}) and furan (1512 cm^{-1}) groups in the IR spectrum. The ^1H NMR spectrum exhibited the three-proton signal due to H-16 at δ 1.98, whereas one-proton doublets ($J = 2$ H) at δ 6.13 and 7.22 were assigned to H-14 and H-15 respectively, which agrees with previously published values.[14] Structural information was also provided by the mass spectrum, which contained prominent peaks at *m/e* 95 (C_6H_7O) and 148 ($C_{10}H_{12}O$) corresponding to ions formed by the reactions outlined in Scheme 5.

Secondary products. (11*E*)-14,15-Bisnor-8-hydroxy-11-labden-13-one (*13*), identified by direct comparison with an authentic sample,[15] is probably generated by degradation of the 13-hydroperoxides of (11*E*)-11,14-labdadien-8-ol (*2a*, *3a*). This view was supported by the fact that the relative proportion of the nor-ketone *13* increases and those of the presumed pre-

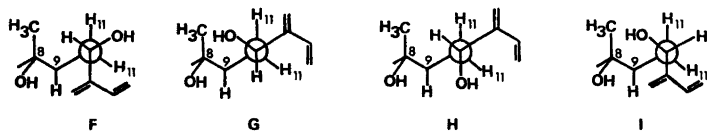


Fig. 2. Conformers about the (11,12) bond in the (12*S*-) and (12*R*)-13(16),14-labdadiene-8,12-diols (*4*, *5*).

cursors (*2a*, *3a*) decrease on exhaustive photo-oxygenation of (12*Z*)-abienol (*1*) (*cf.* Table 1).

By analogy with the formation of (12*R*)-12-hydroxy-8(17),13-labdadien-15,16-epidioxide by exposure of (12*R*)-8(17),13(16),14-labdatrien-12-ol to singlet oxygen,[6] the 15,16-epoxy-13(16),14-labdadien-8-ol derivatives *14*–*16*, obtained only on exhaustive photo-oxygenation, are presumably derived from the hydroperoxides of 13(16),14-labdadien-8-ol (*4a*, *5a*) *via* the corresponding 15,16-epidioxides.

15,16-Epoxy-8-hydroxy-13(16),14-labdadien-12-one (*14*), $C_{20}H_{30}O_3$ (MS), gave rise to IR bands at 3450, 1675, 1512 and 880 cm^{-1}, which is consistent with the presence of the hydroxyl, α,β-unsaturated carbonyl and furan groups. The protons of the latter group, H-14, H-15 and H-16, resonated as typical doublets of doublets at δ 6.78 ($J = 0.8$ and 1.9 Hz), 7.44 ($J = 1.4$ and 1.9 Hz) and 8.11 ($J = 0.8$ and 1.4 Hz). Moreover, the chemical shift values of the H-14 and H-16 signals were indicative of the presence of the carbonyl group at C-12. Support for the structure of the ketofuran *14* was also provided by the mass spectrum. Thus, the base peak at *m/e* 95 was mainly due to a $C_5H_3O_2$ ion, which is likely to arise by a favoured cleavage of the 11,12 bond with charge retention on the smaller fragment.

The ^1H NMR spectra of the corresponding alcohols, the (12*S*)- and (12*R*)-15,16-epoxy-13(16),14-labdadiene-8,12-diols (*15*, *16*), displayed the signals due to the protons of the furan group at δ 6.40 (H-14) and 7.38 (H-15 and H-16) and at δ 6.36 (H-14) and 7.38 (H-15 and H-16), respectively, while the H-12 triplet was present at δ 4.50 ($J = 6.5$ Hz) and at δ 4.98 ($J = 6$ Hz). The C-9 signal appeared at δ 58.8 and at δ 54.6 in the ^{13}C NMR spectra of the hydroxyfurans *15* and *16*, respectively. This shift difference, and also those observed for the C-7, C-8, C-10 to C-12 and C-17 signals, provided the basis for the assignment of the 12*S*- and 12*R*-configuration to *15* and *16*, respectively (*vide supra*).

Norambreinolide (*17*), identified by comparison with an authentic sample,[16] was a product of the exhaustive photo-oxygenation. It may be derived from the 13-hydroperoxides of 14-labden-8,12-epoxide (*6a*, *7a*).

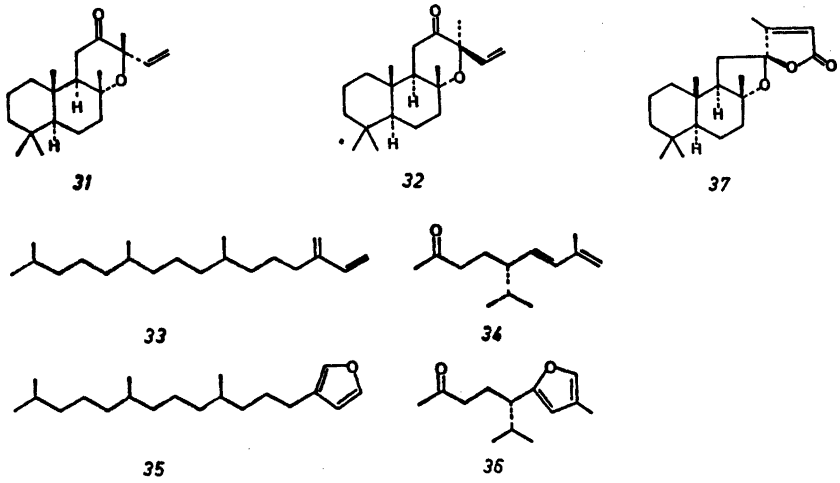
8-Drimanol (*18*), identified by comparison of the mass spectrum and GC-retention time on a capillary column with those of an authentic sample,[17] was detected as a minor component on GC analysis of the triphenyl phosphine-treated reaction mixture and as a fairly abundant component on analysis of the Na_2SO_3-reduced reaction mixture (Table 1). In view of this and since various attempts to isolate this sesquiterpenoid (*18*) were unsuccessful, it seems likely that it may be generated in the injector of the gas chromatograph by thermal degradation of an unreduced hydroperoxide or epidioxide precursor.

DISCUSSION

Our examination demonstrates that the reaction between singlet oxygen and (12*Z*)-abienol (*1*) occurs with competition between an ene-process involving attack at C-13, which is the main pathway, an ene-process involving attack at C-12 and a Diels-Alder addition process and results in the generation of a number of products. Several of these were identified as previously known tobacco constituents, or were closely related to such constituents, thus supporting the view that (12*Z*)-abienol (*1*) may be a precursor of some of the labdane, nor-labdane, drimane and nor-drimane constituents of tobacco.[4]

Thus, the 8,12-epoxy alcohols *6* and *7*,[18] as well as the (13*S*)- and (13*R*)-8,13-epoxy-14-labden-12-ones (*31*, *32*),[19] readily obtained from the 8,13-epoxy alcohols *8* and *9* respectively,[8] have previously been detected in Greek tobacco. Similarly, the nor-labdanoids identified, (11*E*)-14,15-bisnor-8-hydroxy-11-labden-13-one (*13*),[15] norambreinolide (*17*)[20] and 8-drimanol (*18*),[17] are all constituents of various tobaccos.

None of the remaining products have so far been found in tobacco, but it may well be that a thorough examination of the diterpene fraction of an appropriate tobacco will reveal the presence of some of them. This is particularly true of the furans, since furano diterpenoids are of common occurrence in nature and since the furans obtained by photo-oxygenation of neophytadiene (*33*) and solanone (*34*), phytofuran (*35*) and solanofuran (*36*), have recently been found in tobacco.[11,21] Another possibility is that the primary photo-oxygenation products are rapidly degraded further. This view is



corroborated by the observation that the relative yields of the (11*E*,13*S*)- and (11*E*,13*R*)-11,14-labdadiene-8,13-diols (*2*, *3*) are drastically reduced on exhaustive photo-oxygenation, while that of the nor-ketone (*13*), their presumed degradation product, is increased (*cf.* Table 1). Moreover, one of the furan products, 12,15-epoxy-12,14-labdadien-8-ol (*12*) has recently been shown to give α-levantenolide (*37*), a constituent of Turkish tobacco,[22] on treatment with *m*-chloroperbenzoic acid.[14]

EXPERIMENTAL

For instrumental details: see Ref. 8.

Photo-oxygenation A. A solution of 1.1 g of (12*Z*)-abienol (*1*) [23] and 100 mg of Rose Bengal in 25 ml of methanol in a tube cooled by a water jacket was irradiated with a 400 W sodium high pressure lamp placed outside the tube, while oxygen was bubbled through the reaction mixture. After 6.5 h, when TLC showed that all (12*Z*)-abienol (*1*) had been consumed, the solvent was removed at reduced pressure and the residue was dissolved in 30 ml of toluene and stirred with 1.2 g of triphenylphosphine at 40° for 20 h. The reaction mixture was diluted with water and extracted with ether. The washed and dried ether extract was evaporated and separated into ten fractions by chromatography over silica gel using a light petroleum/acetone gradient. Each fraction was separated further by high performance liquid chromatography to give compounds *2*–*13*.

B. A solution of 1.55 g of (12*Z*)-abienol (*1*) and 150 mg of Rose Bengal in 30 ml of methanol was subjected to prolonged photo-oxygenation, 75 h, using the apparatus and conditions described above. After removal of the solvent, the residue was dissolved in 50 ml of toluene and stirred with 1.8 g of triphenylphosphine at room temperature for 60 h. Work-up, chromatography over silica gel and further purification by high performance liquid chromatography resulted in the isolation of compounds *14*–*16*.

(11E,13S)-11,14-Labdadiene-8,13-diol (2) had m.p. 108–112 °C (Found: $[M-18]^+$ 288.2439; Calc. for $C_{20}H_{32}O$: 288.2453); $[\alpha]_D$ −9.4° (*c* 1.9); IR ($CHCl_3$) bands at 3580 and 3390 cm^{-1}; ^1H NMR peaks at δ 0.82 (3 H, s), 0.88 (3 H, s), 0.91 (3 H, s), 1.21 (3 H, s), 1.41 (3 H, s), 5.04 (1 H, dd, J = 1.5 and 10.5 Hz), 5.22 (1 H, dd, J = 1.5 and 17.5 Hz), 5.7 (2 H, overlapping signals) and 5.98 (1 H, dd, J = 10.5 and 17.5 Hz); MS peaks at *m/e* (%, composition): 288 (M−18, 66), 273 (21), 270 (12) 255 (10, $C_{19}H_{27}$) 245 (13, $C_{17}H_{25}O$ and $C_{18}H_{29}$), 230 (17, $C_{17}H_{26}$) 207 (25, $C_{14}H_{23}O$), 195 (22, $C_{13}H_{23}O$), 189 (38), 177 (60), 161 (57, $C_{12}H_{17}$), 147 (56, $C_{11}H_{15}$), 133 (68, $C_{10}H_{13}$), 119 (66, C_9H_{11}), 108 (73, C_8H_{12}), 93 (63), 81 (60), 69 (66), 55 (65) and 43 (100).

(11E,13R)-11,14-Labdadiene-8,13-diol (3) had m.p. 115–117 °C (Found: $[M-18]^+$ 288.2456. Calc. for $C_{20}H_{32}O$: 288.2453); $[\alpha]_D$ +10.2° (*c* 1.6); IR ($CHCl_3$) bands at 3590 and 3390 cm^{-1}; ^1H NMR peaks at δ 0.81 (3 H, s), 0.87 (3 H, s), 0.89 (3 H, s), 1.18 (3 H, s), 1.39 (3 H, s), 5.10 (1 H, dd, J = 1.5 and 10.5 Hz), 5.28 (1 H, dd, J = 1.5 and 17.5 Hz), 5.7 (2 H, overlapping signals) and 6.01 (1 H, dd, J = 10.5 and 17.5 Hz); MS peaks at *m/e* (%, composition): 288 (M−18, 65), 273 (20), 270 (12), 255 (14), 245 (16, $C_{17}H_{25}O$ and $C_{18}H_{29}$), 230 (20, $C_{17}H_{26}$), 207 (24, $C_{14}H_{23}O$), 195 (19, $C_{13}H_{23}O$), 189 (35), 177 (46), 161 (57, $C_{12}H_{17}$), 147 (63, $C_{11}H_{15}$), 133 (82, $C_{10}H_{13}$), 119 (72, C_9H_{11}), 108 (95, C_8H_{12}), 93 (69), 81 (57), 69 (68), 55 (64) and 43 (100).

(12S)-13(16),14-Labdadiene-8,12-diol (4) had m.p. 147–149 °C (Found: M^+ 306.2546. Calc. for $C_{20}H_{34}O_2$: mol. wt. 306.2558); UV (EtOH) maximum at 225 nm, $\varepsilon = 15\,800$; IR (CCl_4) bands at 3300 and 1595 cm^{-1}; ^1H NMR peaks at δ 0.78 (3 H, s) 0.80 (3 H, s), 0.89 (3 H, s), 1.19 (3 H, s), 4.27 (1 H, dd, $J = 3$ and 9 Hz), 5.10 (1 H, d, $J = 11$ Hz), 5.14 (1 H, broad s), 5.32 (1 H, broad s), 5.37 (1 H, d, $J =$ 18 Hz) and 6.37 (1 H, dd, $J = 11$ and 18 Hz); MS peaks at *m/e* (%, composition): 306 (M, 15), 288 (20, $C_{20}H_{32}O$), 273 (18), 255 (9), 245 (11), 206 (25, $C_{15}H_{26}$), 191 (65), 177 (73), 161 (15), 150 (36, $C_{10}H_{14}O$ and $C_{11}H_{18}$), 137 (56), 123 (62), 109 (65), 95 (54), 82 (58), 81 (70), 69 (98), 55 (82) and 43 (100).

(12R)-13(16),14-Labdadiene-8,12-diol (5) had m.p. 114–115 °C (Found: M^+ 306.2557. Calc. for $C_{20}H_{34}O_2$: mol wt. 306. 2558); UV (EtOH) maximum at 225 nm, $\varepsilon = 13\,900$; IR (CCl_4) bands at 3320 and 1595 cm^{-1}; ^1H NMR peaks at δ 0.76 (3 H, s), 0.78 (3 H, s), 0.87 (3 H, s), 1.24 (3 H, s), 4.74 (1 H, t, $J = 5$ Hz), 5.09 (1 H, broad d, $J = 11$ Hz), 5.20 (1 H, broad s), 5.30 (1 H, broad s), 5.36 (1 H, broad d, $J = 18$ Hz) and 6.36 (1 H, dd, $J = 11$ and 18 Hz); MS peaks at *m/e* (%, composition): 306 (M, 2), 288 (20, $C_{20}H_{32}O$), 273 (15), 255 (8), 245 (5), 206 (21, $C_{15}H_{26}$), 191 (70), 177 (64), 163 (15), 150 (27, $C_{10}H_{14}O$ and $C_{11}H_{18}$), 137 (50), 123 (58), 109 (55), 95 (61), 82 (48), 81 (63), 69 (78), 55 (65) and 43 (100).

The (12R,13R)- and (12S,13S)-8,12-epoxy-14-labden-13-ols (6 and 7) as well as the (12S,13S)- and (12R,13R)-8,13-epoxy-14-labden-12-ols (8 and 9) gave IR, mass, ^1H and ^{13}C NMR spectra identical to those of the corresponding authentic samples.[8]

(12R)-12,15-Epidioxy-13-labden-8-ol (10) had m.p. 75–78 °C (Found: M^+ 322.2463. Calc. for $C_{20}H_{34}O_3$: mol. wt. 322.2507); IR (CCl_4) bands at 3600 and 3490 cm^{-1}; ^1H NMR peaks at δ 0.78 (3 H, s), 0.79 (3 H, s), 0.88 (3 H, s), 1.23 (3 H, s), 1.78 (3 H, m), 4.28 (1 H, m), 4.5–4.8 (2 H, overlapping signals) and 5.55 (1 H, m, $W_{1/2} = 8$ Hz); MS peaks at *m/e* (%, composition): 322 (M, 2), 304 (7, $C_{20}H_{32}O_2$), 286 (12, $C_{20}H_{30}O$), 250 (3, $C_{16}H_{26}O_2$), 221 (2), 191 (18, $C_{14}H_{23}$), 177 (17, $C_{13}H_{21}$), 161 (10), 148 (100, $C_{10}H_{12}O$), 137 (13), 123 (14), 109 (25, C_8H_{13}), 99 (9, $C_5H_7O_2$), 95 (65, C_6H_7O and C_7H_{11}), 82 (25, C_5H_6O and C_6H_{10}), 69 (28) and 55 (20).

(12S)-12,15-Epidioxy-13-labden-8-ol (30) was obtained as a 1:1 mixture with *10* from a photooxygenation experiment, in which the reaction mixture was reduced by stirring overnight with aqueous Na_2SO_3. Subtraction of the signals due to *10* from the ^{13}C NMR spectrum of the mixture left the signals listed in Table 1 for *30*.

(12S)-12,15-Epoxy-13-labden-8-ol (11) had m.p. 108–110 °C (Found: M^+ 306.2539. Calc. for $C_{20}H_{34}O_2$: mol. wt. 306.2558); IR (CCl_4) bands at 3460 and 1670 cm^{-1}; ^1H NMR peaks at δ 0.81 (6 H, s), 0.88 (3 H, s), 1.12 (3 H, s), 1.74 (3 H, m), 4.4–4.7 (3 H, overlapping signals) and 5.45 (1 H, m, $W_{1/2} = 4$ Hz); MS peaks at *m/e* (%, composition): 306 (M, 10), 288 (7, $C_{20}H_{32}O$), 273 (3, $C_{19}H_{29}O$), 235 (6, $C_{16}H_{27}O$), 206 (5, $C_{15}H_{26}$), 192 (18, $C_{14}H_{24}$), 191 (18, $C_{14}H_{23}$), 177 (23, $C_{13}H_{21}$), 137 (19, $C_{10}H_{17}$), 123 (20, C_9H_{15}), 111 (25, $C_7H_{11}O$), 109 (26, C_7H_9O and C_8H_{13}), 96 (45, C_6H_8O), 83 (100, C_5H_7O), 69 (30) and 55 (30).

12,15-Epoxy-12,14-labdadien-8-ol (12) was a gum (Found: M^+ 304.2388. Calc. for $C_{20}H_{32}O_2$: mol. wt. 304.2402); IR (CCl_4) bands at 3590, 3430 and 1512 cm^{-1}; MS peaks at *m/e* (%, composition): 304 (M, 3), 286 (10), 271 (1), 191 (6), 178 (6), 161 (9), 148 (100, $C_{10}H_{12}O$), 133 (15), 121 (5), 109 (11), 95 (55, C_6H_7O and C_7H_{11}), 81 (11), 69 (16), 55 (13) and 43 (39). *12* had ^1H NMR peaks at δ 0.81 (3 H, s), 0.87 (3 H, s), 0.89 (3 H, s), 1.24 (3 H, s), 1.98 (3 H, broad s), 2.67 (2 H, m, $W_{1/2} = 10$ Hz), 6.13 (1 H, d, $J =$ 2 Hz) and 7.22 (1 H, d, $J = 2$ Hz).

(11E)-14,15-Bisnor-8-hydroxy-11-labden-13-one (13) had m.p. 125–127 °C, which was not depressed on admixture with an authentic sample. The IR, ^1H NMR and mass spectra were identical to those of the authentic sample.[15]

15,16-Epoxy-8-hydroxy-13(16),14-labdadien-12-one (14) had m.p. 148–151 °C (Found: M^+ 318.2208. Calc. for $C_{20}H_{30}O_3$: mol. wt. 318.2195); IR (CCl_4) bands at 3450, 1675, 1512 and 880 cm^{-1}; ^1H NMR peaks at δ 0.81 (3 H, s), 0.87 (3 H, s), 0.89 (3 H, s), 1.17 (3 H, s), 2.83 (2 H, d, $J = 5$ Hz), 6.78 (1 H, dd, $J = 0.8$ and 1.9 Hz), 7.44 (1 H, dd, $J = 1.4$ and 1.9 Hz) and 8.11 (1 H, dd, $J = 0.8$ and 1.4 Hz); MS peaks at *m/e* (%, composition): 318 (M, 40), 300 (31, $C_{20}H_{28}O_2$), 285 (8, $C_{19}H_{25}O_2$), 267 (2, $C_{19}H_{23}O$) 215 (4, $C_{14}H_{15}O_2$), 203 (3, $C_{15}H_{23}$), 190 (27, $C_{14}H_{22}$), 177 (38), 175 (21, $C_{13}H_{19}$), 163 (18, $C_{10}H_{11}O_2$), 137 (20, $C_{10}H_{17}$), 124 (27), 123 (27), 109 (19), 95 (100, $C_5H_3O_2$ and C_7H_{11}), 81 (25), 69 (42), 55 (25) and 41 (36).

(12S)-15,16-Epoxy-13(16),14-labdadiene-8,12-diol (15) had m.p. 155–158 °C (dec.) (Found M^+ 320.2321. Calc. for $C_{20}H_{32}O_3$: mol. wt. 320.2351); IR (CCl_4) bands at 3300, 1500 and 875 cm^{-1}; ^1H NMR peaks at δ 0.78 (3 H, s), 0.79 (3 H, s), 0.89 (3 H, s), 1.19 (3 H, s), 4.50 (1 H, t, $J = 6.5$ Hz), 6.40 (1 H, broad s) and 7.38 (2 H, overlapping signals); MS peaks at *m/e* (%, composition): 320 (M, 3), 302 (31, $C_{20}H_{30}O_2$), 287 (34, $C_{19}H_{27}O_2$), 269 (12, $C_{19}H_{25}O$), 206 (42, $C_{15}H_{26}$), 192 (41), 191 (35, $C_{14}H_{23}$), 177 (94, $C_{13}H_{21}$), 163 (15, $C_{12}H_{19}$ and $C_{10}H_{11}O_2$), 150 (27, $C_{11}H_{18}$), 137 (43, $C_{10}H_{17}$), 123 (65, C_9H_{15}), 109 (50, C_8H_{13}), 97 (38, $C_5H_5O_2$), 95 (84, C_7H_{11} and $C_5H_3O_2$), 81 (63, C_6H_9 and C_5H_5O), 69 (100), 55 (46), and 43 (97).

(12R)-15,16-Epoxy-13(16),14-labdadiene-8,12-diol (16) had m.p. 122–124 °C (Found: M^+ 320.2354. Calc. for $C_{20}H_{32}O_3$: mol. wt. 320.2351); IR (CCl_4) bands at 3320, 1505 and 880 cm^{-1}; ^1H NMR peaks at δ 0.79 (6 H, s), 0.86 (3 H, s), 1.24 (3 H, s), 4.98 (1 H, t, $J =$ 6 Hz), 6.36 (1 H, t, $J = 1$ Hz) and 7.38 (2 H,

d, $J = 1.5$ Hz); MS peaks at *m/e* (%, composition): 320 (M, 1), 302 (38, $C_{20}H_{30}O_2$), 287 (70, $C_{19}H_{27}O_2$), 269 (10, $C_{19}H_{25}O$), 206 (44, $C_{15}H_{26}$), 192 (57), 191 (38, $C_{14}H_{23}$), 177 (100, $C_{13}H_{21}$), 163 (10, $C_{12}H_{19}$), 150 (24, $C_{11}H_{18}$), 137 (44, $C_{10}H_{17}$), 136 (27, $C_{10}H_{16}$), 123 (63, C_9H_{15}), 110 (63), 95 (56, C_7H_{11}), 81 (57), 69 (73), 55 (40) and 43 (61).

Norambreinolide (17) and 8-drimanol (18) had GC retention time and mass spectra identical to those of the corresponding authentic samples.[16,17]

Hydrogenation of sclareol. A solution of 100 mg of sclareol [24] in 20 ml of ethanol was stirred with 10 mg of 10 % Pd/C in a hydrogen atmosphere for 2 h. The reaction mixture was filtered, evaporated and chromatographed over silica gel to afford 62 mg of (13*S*)-8,13-labdanediol (*19*), which had m.p. 112 – 114 °C (reported m.p. 114 – 115 °C);[25] IR (CCl_4) bands at 3610 and 3480 cm^{-1}; ^1H NMR peaks at δ 0.80 (6 H, s), 0.87 (3 H, s), 0.90 (3 H, t, J = 7 Hz), 1.16 (3 H, s) and 1.18 (3 H, s); MS peaks at *m/e* (%): 292 (M – 18, 42), 277 (8), 274 (5), 259 (25), 245 (35), 204 (28), 195 (62), 177 (70), 164 (30), 149 (33), 137 (53), 123 (58), 109 (69), 95 (79), 82 (63), 69 (85), 55 (62) and 43 (100).

Hydrogenation of the (11E,13S)- and (11E,13R)-11,14-labdadiene-8,13-diols (2, 3). A solution of 45 mg of (11*E*,13*S*)-11,14-labdadiene-8,13-diol (*2*) in 10 ml of ethanol was stirred with 10 mg of 5 % Pd/C in a hydrogen atmosphere for 72 h. Work-up and chromatography over silica gel gave 8 mg of a product, m.p. 113 – 114 °C, which was identical in all respects (m.p., IR, ^1H and ^{13}C NMR, MS) to (13*S*)-8,13-labdanediol (*19*). Hydrogenation under the same conditions converted (11*E*,13*R*)-11,14-labdadiene-8,13-diol (*3*) to (13*R*)-8,13-labdanediol (*20*), m.p. 137 – 139 °C; IR (CCl_4) bands at 3610 and 3360 cm^{-1}; ^1H NMR peaks at δ 0.80 (6 H, s), 0.87 (3 H, s), 0.87 (3 H, t, J = 7 Hz), 1.15 (3 H, s), 1.17 (3 H, s); MS peaks at *m/e* (%): 292 (M – 18, 36), 277 (4), 274 (9), 259 (17), 245 (36), 204 (21), 195 (50), 177 (59), 164 (19), 149 (25), 137 (61), 123 (56), 109 (71), 95 (78), 81 (61), 69 (81), 55 (66) and 43 (100).

Cyclisation of (12S)-13(16),14-labdadiene-8,12-diol (4). A solution of 65 mg of (12*S*)-13(16),14-labdadiene-8,12-diol (*4*) in 5 ml of pyridine was left with 50 µl of methanesulfonyl chloride at room temperature for 1 h. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed with aqueous H_2SO_4 (10 %), $NaHCO_3$ and water. Evaporation afforded 52 mg of (12*R*)-13(16),14-labdadien-8,12-epoxide (*22*), which had m.p. 65 – 67 °C; IR (CCl_4) bands at 3080 and 1585 cm^{-1}; ^1H NMR peaks at δ 0.83 (3 H, s), 0.85 (3 H, s), 0.88 (3 H, s), 1.20 (3 H, s), 4.79 (1 H, m), 5.06 (1 H, broad s), 5.08 (1 H, broad d, J = 11 Hz), 5.16 (1 H, broad d, J = 17 Hz), 5.34 (1 H, broad s) and 6.39 (1 H, dd, J = 11 and 17 Hz); MS peaks at *m/e* (%), 288 (M, 17), 273 (62), 255 (10), 245 (3), 217 (7), 206 (31), 191 (100), 177 (20), 163 (17), 149 (23), 137 (72), 123 (72), 109 (61), 95 (68), 82 (77), 69 (66), 55 (58) and 43 (65).

A solution of 35 mg of (12*S*)-13(16),14-labdadiene-8,12-diol (*4*) in 4 ml of chloroform was treated with 40 µl of stannic chloride [26] at 0 °C for 30 min. Work-up gave 23 mg of (12*S*)-13(16),14-labdadien-8,12-epoxide (*23*), which had m.p. 68.5 – 70 °C; IR (CCl_4) bands at 3090 and 1595 cm^{-1}; ^1H NMR peaks at δ 0.83 (6 H, s), 0.88 (3 H, s) 1.14 (3 H, s), 4.67 (1 H, m), 5.05 (1 H, broad s), 5.06 (1 H, broad d, J = 11 Hz), 5.21 (1 H, broad d, J = 18 Hz), 5.39 (1 H, broad s), and 6.38 (1 H, dd, J = 11 and 18 Hz); MS peaks at *m/e* (%): 288 (M, 12), 273 (57), 255 (5), 245 (2), 217 (3), 191 (100), 177 (12), 163 (7), 149 (15), 137 (49), 123 (29), 109 (31), 95 (37), 82 (50), 69 (47), 55 (37) and 43 (44).

Cyclisation of (12R)-13(16),14-labdadiene-8,12-diol (5). Treatment of 100 mg of (12*R*)-13(16),14-labdadiene-8,12-diol (*5*) with 70 µl of methanesulfonyl chloride in 5 ml of pyridine at room temperature for 3 h yielded, after work-up, 92 mg of (12*S*)-13(16),14-labdadien-8,12-epoxide (*23*).

Treatment of 30 mg of (12*R*)-13(16),14-labdadiene-8,12-diol (*5*) with 40 µl of stannic chloride in 4 ml of chloroform at 0 °C for 1 h afforded 25 mg of (12*R*)-13(16),14-labdadien-8,12-epoxide (*22*).

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