Tobacco Chemistry. 59. * Six New Cembratrienetriols from Tobacco

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Six new cembratrienetriols have been isolated from Greek tobacco. They have been identified as the (1S,2E,4R,6R,7E,11S)- and (1S,2E,4S,6R,7E,11R)-2,7,12(20)-cembratriene-4,6,11-triols (I,2), the (1S,2E,4R,6R,7E,10E,12S)-, (1S,2E,4R,6R,7E,10E,12R)- and (1S,2E,4S,6R,7E,-10E,12R)-2,7,10-cembratriene-4,6,12-triols (3-5) and (1S,2E,4R,6E,8S,11S)-2,6,12(20)-cembratriene-4,8,11-triol (6) by spectral and chemical methods. The biogeneses of these compounds are discussed in the light of results obtained from biomimetic reactions involving sensitized photo-oxygenation of the (1S,2E,4R,6R,7E,11E)- and (1S,2E,4S,6R,7E,11E)-2,7,11-cembratriene-4,6-diols (7, 8) and of (1S,2E,4R,6E,8S,11E)-cembratriene-4,8-diol (9). A discussion on the conformation about the 5,6-bond in various cembrane alcohols and acetates is also presented.

RESULTS

**Structure determination of triols 1–5.** Triols 1 and 2, C_{20}H_{34}O_{3}, gave rise to ^1H and ^13C NMR spectra reminiscent of those of (1S,2E,4S,6R,7E,11S)-2,7,12(20)-cembratriene-4,6,11-triol (10) and indicative of the presence of an iso-propyl group, a methyl group attached to a carbon atom carrying a tertiary hydroxyl group, a vinylc methyl group and two secondary hydroxyl groups. Of the three double bonds, one extends to an exocyclic methylene group, one is E-disubstituted and one is trisubstituted. Triols 1 and 2 were hence tentatively identified as 2E,7,12(20)-cembratriene-4,6,11-triols.

In contrast to triols 1 and 2, triols 3–5 (C_{20}H_{34}O_{3}) contain one secondary and two tertiary hydroxyl groups, two E-disubstituted and one trisubstituted double bond. These results and a spectral comparison with (1S,2E,4S,6R,7E,-10E,12S)-2,7,10-cembratriene-4,6,12-triol (II) led to a provisional formulation of triols 3–5 as stereoisomers of 2E,7,10E-cembratriene-4,6,12-triol.

The tentative structural assignments of triols 1, 3 and 5 were verified and their stereochemistries determined by simple chemical correlations. Thus, rearrangement of (1S,2E,4R,6R,7E,11S)-12S)-11,12-epoxy-2,7-cembradiene-4,6-diol (I2) using Sharpless’ method afforded (1S,2E,4R,6R,7E,10E,12S)-2,7,10-cembratriene-4,6,12-triol as the major and (1S,2E,4R,6R,7E,11S)-2,7,12(20)-cembratriene-4,6,11-triol as the minor product. These proved to be identical to triols 3 and 1, respectively. Structural evidence for triol I was also provided by its cyclization to (1S,-

* For part 58 see Ref. 1.
Table 1. $^{13}$C NMR chemical shifts and assignments for compounds 1–8, 10, 11, 15, 16, 18–23.$^a$

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$^a$ δ-values in CDCl₃ relative to TMS. $^b,c$ Assignment may be reversed. $^d$ OCOCH₃ 170.8; OCOCH₃ 21.5. $^e$ OCOCH₃ 170.6; OCOCH₃ 21.4. $^f$ OCOCH₃ 170.7; OCOCH₃ 21.4. $^g$ OCOCH₃ 170.4 and 169.8; OCOCH₃ 21.4 and 21.3. $^h$ OCOCH₃ 170.0; OCOCH₃ 21.4. $^i$ OCOCH₃ 169.9; OCOCH₃ 21.4. $^j$ OCOCH₃ 170.2; OCOCH₃ 21.4.
By analogy, the 4S,6R-diol (8) gave rise to (1S,2E,4S,6R,7E,11S)-2,7,12(20)-cembretriene-4,6,11-triol (10), the (1S,2E,4S,6R,7E,10E,12S)- and (1S,2E,4S,6R,7E,10E,12R)-2,7,10-cembretriene-4,6,12-triols (11,5) as well as (1S,2E,4S,6R,7E,11R)-2,7,12(20)-cembretriene-4,6,11-triol, which was identical in all respects to triol 2.

It follows from the results summarized in Table 2 that in the reactions of the 4R,6R- and 4S,6R-diols (7,8) with singlet oxygen the hydroperoxides corresponding to the 11S- and 12S-triols are formed in preference to their 11R- and 12R-counterparts. This stereoselectivity may be accounted for by conformational arguments similar to those presented previously for acetate 15.

It is also evident that the generation of all four products from each 4,6-diol (7,8) occurs with hydrogen abstraction from the 1,2-disubstituted side of the trisubstituted 11,12 double bond. This result is consistent with the recent finding that syn ene additions are favoured in acyclic and most cyclic systems.

Structure determination of triol 6. The spectral data demonstrated that compound 6, C_{20}H_{34}O_{3}, contains an isopropyl group (two methyl doublets at δ 0.85 and 0.88; IR bands at 1385 and 1375 cm\(^{-1}\)), two methyl groups attached to the same carbon atoms as the two tertiary hydroxyl groups (\(^1\)H NMR singlets at δ 1.27 and 1.39; \(^13\)C NMR signals at δ 73.0 (s) and 73.3 (s); OH-absorption in the IR spectrum of the monoacetate 17) and one secondary hydroxyl group (one-proton multiplet at δ 4.24 shifted to δ 5.38 in the \(^1\)H NMR spectrum of 17). Of the three double bonds, one extends to an exocyclic methylene group and two are E-disubstituted. These results demonstrate that triol 6 is monocyclic and incorporates a fourteen-membered ring. A 2,6,12(20)-cembre-
triene-4,8,11-triol structure seemed most likely from a biogenetic point of view.

This assignment was readily verified, since triol 6 proved to be identical to the 4,8,11-triol obtained as the minor product on treatment of the 4R,6R,11S-triol I with weak acid (vidi supra). This conversion also determines that triol 6 has a 1S,2E,6E,11S-stereochemistry but does not allow an unambiguous assignment of the chiralities of C-4 and C-8. The reason for this is that in the analogous acid-induced conversion of 4,6-diols (7,8) to 4,8-diols epimerization does occur at C-4, and in addition to the major 4R,8S- and 4S,8S-diols, a 4S,8R-diol is formed.9

In order to resolve these stereochemical uncertainties the 4R,8S-diol 9 was reacted with singlet oxygen. Following reduction of the reaction mixture with triethyl phosphate and separation by HPLC the major product was isolated. This compound was indistinguishable from triol 6 and was hence formulated as (1S,2E,4R,6E,8S,11S)-2,6,12(20)-cembretriene-4,8,11-triol.

Biogenesis. The results obtained by the biomimetic reactions described above support the view that the 4,6,11- and 4,6,12-triols (7-5, 10, 11), which are present in the cuticular wax of the leaf and flower, are formed in tobacco via sensitized photo-oxygenation or enzyme-assisted oxidation of the 11,12 double bond in the 4,6-diols (7, 8; cf. Scheme 1).3 The biogenesis of the 4R,8S,11S-triol 6 may take place by an initial conversion of the 4R,6R-diol (7) to the 4R,8S-diol (9) with subsequent oxidation or by an acid-induced rearrangement of a preformed 4R,6R,11S-triol (1).

Comments upon the conformation about the 5,6 bond in various cembrene alcohols and acetates. A comparison of the 1H and 13C NMR data as well as results from X-ray diffraction determinations have led us to focus our attention on the conformation about the 5,6 bond in various cembrene alcohols and acetates. Thus, (1S,2E,4R,6R,7E,11S,12S)-11,12-epoxy-6-acetoxy-2,7-cembradien-4-ol (18) exists in the crystalline state as conformer A, in which the dihedral angle involving the pro-R hydrogen at C-5 and H-6 is 94° and that involving the pro-S hydrogen and H-6 is 147° (Scheme 2).4 The 4S,6R,11S-triol 10, on the other hand, has conformation B and the corresponding angles are 54 and 64°.2

An analysis of the 1H NMR spectra suggests that these conformations are retained in solution.

The two hydrogens at C-5, which resonate at δ 1.90 and 2.03 in epoxide 18 and at δ 1.80 and 2.22 in triol 10, have vicinal couplings (J) to H-6 of 8.7 and 1.6 Hz (18) and 2.7 and 5.5 Hz (10), respectively (cf. Table 3). These couplings are in conformity with the dihedral angles in conformers A and B, respectively. As a result, the downfield H-5 signal in the spectra of both compounds can be ascribed to the pro-R hydrogen and the upfield signal to the pro-S hydrogen.

The assignments made for epoxide 18 were reinforced by lanthanide induced shift (LIS) measurements using Eu(dpm)3. The hydroxyl group at C-4 proved to be the preferential complexing site. H-6 (100)* and the pro-R hydrogen at C-5 (74) suffered the largest induced shifts, whereas a considerably smaller effect (39) was observed on the pro-S hydrogen. This result is in accordance with the conclusion that the pro-R hydrogen is exo to the carbocyclic ring and more favourably oriented spatially for interaction with the shift reagent than the pro-S hydrogen.

In order to avoid competing complex formation with all three hydroxyl groups, LIS experiments were not performed on triol 10 itself but on the diacetylated derivative 19.2 The latter compound was judged from relevant chemical shift values and coupling constants to have a similar orientation around the 5,6 bond as triol 10. As expected preferential LIS interaction was observed at the hydroxyl group at C-4. However, the two hydrogens at C-5 were found to undergo induced shifts (100, 99) of equal magnitudes, a result which is best accommodated by a conformer of type B.

With these results at hand, the 1H NMR data compiled in Table 3 indicate that triols 1, 16, 3 and 4 as well as acetate 20, all of which have 4R-configurations, are conformationally reminiscent of epoxide 18 (conformer A), whereas the triols and acetates of the 4S-series (10, 2, 11, 5, 19, 21, 22) are likely to exist in a conformation of type B. It is particularly noteworthy that the 1H NMR results for both the 4R,6R- and 4S,6R-diols (7, 8) and their corresponding monoacetates (23, 15) are consistent with a conformer such as B.


* The measurements were made with the linear LIS range (shift reagent/substrate ca. 0-0.5) and were normalized by assigning the value 100 to the proton signal exhibiting the largest shift.
Scheme 1. Probable biogenesis of triols 1–6, 10 and 11.

These conformational differences are also reflected, in a diagnostic manner, in the $^{13}$C NMR spectra (Table 1). Thus, the C-4, C-5 and C-6 signals are present at virtually invariant positions in the spectra of the 4R,6R-diol (7) and the triols of the 4R-series (1, 16, 3, 4). In the 4S-series, however, the diol (8) proved to differ significantly from the triols (10, 2, 11, 5) with respect to the shieldings of these carbon atoms, i.e. C-4: δ 72.5 (dil 8) as against δ 74.0–74.4 (triols), C-5: δ 52.5 as against δ 46.5–47.2 and C-6: δ 66.2 as against δ 68.5–69.4. An analogous situation is encountered for C-5 in the spectra of acetates 15, 18–23.

Scheme 2. Conformation about the 5,6 bond in compound 18 (A) and in compound 10 (B).
Table 3. Chemical shift values (δ) and coupling constants (J in Hz) for the H-5α, H-5β, H-6 and H-7 signals in the 1H NMR spectra of compounds 1–5, 7, 8, 10, 11, 15, 16 and 18–23.

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**EXPERIMENTAL**

With the exception of accurate mass measurements, which were carried out on a Kratos MS50 Stereo DS55 SM/DS 55S mass spectrometer-computer system and the NMR spectra, which were recorded on a Varian XL-200 spectrometer, the instruments specified in Ref. 10 were used.

*Isolation.* An extract (83 g) obtained by immersing flowers of Greek *Nicotiana tabacum* (Basma Drama) in chloroform was initially separated into five fractions, A (12.7 g), B (4.7 g), C (8.0 g), D (30 g) and E (3.6 g) by flash chromatography using a column packed with silica gel and gradients of hexane—ethyl acetate—methanol as eluent. Part of fraction C (6.2 g) was separated further into eight fractions, Cl–C8, using a PrepPak 500/C18 cartridge and methanol—water (65:35) as an eluent. Repeated HPLC of fraction C3 (272 mg) using columns packed with Spherisorb 5 and Spherisorb/5 CN led to the isolation of 7.5 mg of (1S,2E,4R,6R,7E,11S)-2,7,12(20)-cembratriene-4,6,11-triol (1) and 17 mg of (1S,2E,4S,6R,7E,10E,12R)-2,7,10-cembratriene-4,6,12-triol (2).

Flash chromatography (silica gel; hexane—ethyl acetate 30:70) was used to separate fraction D into six fractions, D1–D6. Fraction D5 (5.7 g) was subjected to repeated HPLC using columns packed with PrepPak 500/C18, Spherisorb 5, Spherisorb/5 CN and Spherisorb 5 ODS, which gave 30 mg of (1S,2E,4R,6R,7E,11S)-2,7,12(20)-cembratriene-4,6,11-triol (1), 18 mg of (1S,2E,4R,6R,7E,10E,12S)-2,7,10-cembratriene-4,6,12-triol (4) and 12 mg of (1S,2E,4R,6E,8S,11S)-2,6,12(20)-cembratriene-4,8,11-triol (6).

(1S,2E,4R,6R,7E,11S)-2,7,12(20)-Cembratriene-4,6,11-triol (1) had m.p. 146–147 °C; [α]D +37° (c 0.69, EtOH); (Found: [M−18] + 304.2391). Calc. for C_{30}H_{48}O_{2}: 304.2402; IR (KBr) bands at 3300, 3080, 1665, 1645, 1385 and 1365 cm⁻¹; 1H NMR (CDCl₃): δ 0.82 (d, J = 6.7 Hz) / 0.85 (d, J = 6.7 Hz) (H-16/H-17), 1.36 (s, H-18), 1.74 (d, J = 1.2 Hz, H-19), 1.93 (dd, J = 8.6 and −14.0 Hz, H-5a), 2.04 (dd, J = 3.0 and −14.0 Hz, H-5b), 4.03 (dd, J = 0.8 and 6.5 Hz, H-11), 4.70 (dd, J = 3.0, 8.6 and 8.9 Hz, H-6), 4.90 (q, J = 1.4 Hz, H-20a), 5.06 (dd, J = 0.8 and 1.4 Hz, H-20b), 5.24 (dd, J = 1.2 and 8.9 Hz, H-7), 5.38 (dd, J = 8.0 and 16.0 Hz, H-2) and 5.44 (d, J = 16.0 Hz, H-3); MS [m/z (% composition)]: 304 (2), 286 (21, C_{29}H_{48}O), 268 (4), 253 (3, C_{29}H_{48}S), 243 (15), 225 (10, C_{28}H_{42}), 215 (7), 203 (8, C_{11}H_{25}O), 159 (19, C_{23}H_{31}), 147 (24, C_{15}H_{15}), 133 (28, C_{10}H_{11}), 121 (36, C_{9}H_{13}), 105 (38, C_{8}H_{9}), 93 (44, C_{7}H_{9}), 81 (56), 69 (39), 55 (47).
and 43 (100).

\((1S,2E,4S,6R,7E,11R)-2,7,12(20)-\text{Cembratriene-4,6,11-triol} (2)\) was an oil and had [\(\alpha\)]\(_D^{21\circ}\) +44° (c 0.61, CHCl\(_3\)) ; (Found: [M−18]+ 304.2404. Calc. for C\(_{29}H\(_{32}O\(_5\)) : 304.2402); IR (CHCl\(_3\)) bands at 3600, 3450, 3080, 1665, 1645, 1385 and 1370 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)) : \(\delta\) 0.82 (d, \(J=6.8\) Hz)/0.84 (d, \(J=6.7\) Hz) (H-16/H-17), 1.26 (s, H-18), 1.67 (d, \(J=1.3\) Hz, H-19), 1.68 (dd, \(J=2.6\) and \(-14.2\) Hz, H-5a), 2.24 (dd, \(J=6.0\) and \(-14.2\) Hz, H-5b), 4.09 (m, H-11), 4.78 (dd, \(J=2.6, 6.0\) and 8.7 Hz, H-6), 4.92 (broad s, H-20a), 5.16 (broad s, H-20b), 5.4–5.6 (overlapping signals, H-2 and H-3) and 5.55 (dd, \(J=1.3\) and 8.7 Hz, H-7); \(^1\)H NMR (CD\(_3\)OD) : \(\delta\) 3.54 (d, \(J=15.4\) Hz, H-3) and 5.66 (dd, \(J=9.8\) and 15.4 Hz, H-2); MS \([m/z\) (\%, composition)]: 304 (0.2), 286 (1, C\(_{19}H\(_{20}O\(_2\))\), 271 (1), 261 (1), 243 (2), 225 (1), C\(_{17}H\(_{18}\))\), 215 (1), 203 (2), 136 (15, C\(_{15}H\(_{16}\) and C\(_{16}H\(_{16}\))\), 121 (12, CH\(_3\)C\(_{10}H\(_{22}\))\), 109 (18, CH\(_3\)C\(_{10}H\(_{20}\)) and C\(_{16}H\(_{16}\)\), 93 (21, CH\(_{2}H\(_{16}\)\), 81 (23, CH\(_{2}H\(_{16}\) and C\(_{15}H\(_{18}\))\), 69 (20, CH\(_{3}H\(_{18}\) and C\(_{16}H\(_{20}\))\), 55 (22, CH\(_{2}H\(_{18}\) and C\(_{16}H\(_{20}\))\) and 43 (100, C\(_{12}H\(_{18}\) and C\(_{13}H\(_{18}\))\).}

\((1S,2E,4R,6R,7E,10E,12R)-2,7,10-Cembratriene-4,6,12-triol (3)\) was an oil and had [\(\alpha\)]\(_D^{21\circ}\) +86° (c 0.51, EtOH); (Found: [M−18]+ 304.2442. Calc. for C\(_{29}H\(_{32}O\(_5\)) : 304.2402); IR (CHCl\(_3\)) bands at 3610, 3430, 1670, 1390 and 1375 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)) : \(\delta\) 0.77 (d, \(J=6.7\) Hz)/0.84 (d, \(J=6.7\) Hz) (H-16/H-17), 1.29 (s, H-20), 2.36 (s, H-18), 1.80 (d, \(J=1.2\) Hz, H-19), 1.80 (dd, \(J=10.4\) and \(-13.4\) Hz, H-5a), 2.07 (dd, \(J=3.0\) and \(-13.4\) Hz, H-5b), 2.62 (dd, \(J=8.8\) and \(-16.2\) Hz, H-9a), 2.82 (dd, \(J=5.3\) and \(-16.2\) Hz, H-9b), 4.72 (dd, \(J=3.0, 8.9\) and 10.4 Hz, H-6), 5.27 (d, \(J=8.9\) Hz, H-7), 5.30 (dd, \(J=7.5\) and 16.1 Hz, H-2), 5.45 (d, \(J=16.1\) Hz, H-3), 5.45 (d, \(J=15.4\) Hz, H-11) and 5.73 (dd, \(J=5.3, 8.7\) and 15.4 Hz, H-10); MS \([m/z\) (\%, composition)]: 304 (1), 289 (1, C\(_{19}H\(_{20}O\(_2\))\), 286 (2, C\(_{19}H\(_{20}O\(_2\))\), 271 (1, C\(_{19}H\(_{20}O\(_2\))\), 261 (2), 243 (5), 215 (2), 203 (4, C\(_{14}H\(_{16}\) and C\(_{14}H\(_{16}\))\), 136 (25, C\(_{14}H\(_{16}\)), 121 (22, CH\(_{3}C\(_{10}H\(_{22}\))\), 109 (34, CH\(_{3}H\(_{18}\) and C\(_{13}H\(_{18}\))\), 95 (32), 81 (33), 69 (33), 55 (30) and 43 (100).}

\((1S,2E,4R,6R,7E,10E,12R)-2,7,10-Cembratriene-4,6,12-triol (4)\) had m.p. 164–165°C; [\(\alpha\)]\(_D^{21\circ}\) +42° (c 0.41, EtOH); (Found: [M−18]+ 304.2419. Calc. for C\(_{29}H\(_{32}O\(_5\)) : 304.2402); IR (CHCl\(_3\)) bands at 3500, 3400, 3080, 1645, 1385 and 1375 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)) : \(\delta\) 0.85 (d, \(J=6.6\) Hz)/0.88 (d, \(J=6.4\) Hz) (H-16/H-17), 1.27 (s, H-18), 4.13 (s, H-19), 4.98 (broad s, H-20b), 5.25 (dd, \(J=8.3\) and 15.8 Hz, H-2), 5.39 (dd, \(J=15.8\) Hz, H-3) and 5.5–5.6 (overlapping signals, H-6 and H-7); \(^1\)H NMR (CD\(_3\)OD) : \(\delta\) 3.24 (dd, \(J=0.6, 9.0\) and \(-13.6\) Hz, H-5a), 2.32 (dd, \(J=1.2\) and 5.7, \(-13.6\) Hz, H-5b), 5.25 (dd, \(J=0.6, 1.2\) and 15.4 Hz, H-7) and 5.50 (dd, \(J=5.7, 9.0\) and 15.4 Hz, H-6); MS \([m/z\) (\%, composition)]: 304 (0.5), 286 (2, C\(_{19}H\(_{20}O\(_2\))\), 271 (1, C\(_{19}H\(_{20}O\(_2\))\), 261 (2), 243 (4), 233 (2, C\(_{14}H\(_{16}O\(_2\))\), 203 (5, C\(_{14}H\(_{16}O\(_2\))\), 195 (8, C\(_{12}H\(_{15}\))\), 147 (10), 133 (13, C\(_{13}H\(_{13}\))\), 123 (16, C\(_{12}H\(_{15}\))\), 109 (18, C\(_{13}H\(_{15}\) and C\(_{13}H\(_{15}\))\), 95 (22, 81
Conversion of (1S,2E,4R,6R,7E,11S,12S)-11,12-epoxy-2,7-cembratriene-4,6-diol (12) to (1S,-
2E,4R,6R,7E,10E,12S)-2,7,10-cembratriene-4,6,-
12-triol (3) and (1S,2E,4R,6R,7E,11S)-2,7,12
(20)-cembratriene-4,6,11-triol (1). A stirred suspension of 21 mg of diphenyl diselenide in 5
ml of isopropanol was added, under nitrogen, 5.5
mg of NaBH₄. After addition of 35 mg of 12 the
reaction mixture was refluxed for 30 h. The
reaction mixture was cooled (0 °C) and 2.5 ml of
tetrahydrofuran was added, followed by drop-
wise addition of 0.3 ml of hydrogen peroxide
(30 %). After 4 h the resulting slurry was diluted
with water and extracted with ether. The organic
phase was washed with aqueous sodium carbonate
(10 %) and water, dried and concentrated.
The residue was separated by flash chromatog-
raphy over silica gel and HPLC (Spherisorb 5
hexane—ethyl acetate 20:80) to give 9.4 mg of
starting material (12), 4.0 mg of (1S,-
2E,4R,6R,7E,10E,12S)-2,7,10-cembratriene-4,
6,12-triol, whose ¹H NMR and mass spectra
agreed with those of triol 3, and 0.8 mg of
(1S,2E,4R,6R,7E,11S)-2,6,12(20)-cembratriene-
4,6,11-triol, whose ¹H NMR and mass spectra
were identical with those of triol 1.

Treatment of (1S,2E,4R,6R,7E,11S)-2,7,-
12(20)-cembratriene-4,6,11-triol (1) with acid.
To a solution of 44 mg of 1 in 5 ml of chloroform was
added 0.3 ml of aqueous HCl (10 %). The
reaction mixture was kept at room temperature for
24 h, washed with water and aqueous sodium carbonate,
dried and evaporated. The residue was separated
by HPLC using a column packed with Spherisorb 5 ODS
and methanol—water (80:20) to give 7.0 mg of (1S,2E,4R,6E,8R,11S)-
8,11-epoxy-2,6,12(20)-cembratrien-4-ol (13),
whose m.p., optical rotation, IR, ¹H NMR and
MS data agreed with those of an authentic sample, and
7.8 mg of (1S,2E,4R,6E,8S,-
11S)-2,6,12(20)-cembratriene-4,8,11-triol, which
was identical to the naturally occurring triol 6.

Acetylation of (1S,2E,4S,6R,7E,10E,12R)-
2,7,10-cembratriene-4,6,12-triol (9). Treatment
of 8 mg of triol 5 with acetic anhydride in pyridine
for 3.5 h at room temperature followed by
work-up and purification by HPLC using a column packed with Spherisorb 5 ODS gave 2.4
mg of (1S,2E,4S,6R,7E,10E,12R)-6-acetoxy-
2,7,10-cembratriene-4,12-diol (14), whose optical
rotation, IR, ¹H NMR and mass spectra were
identical with those of an authentic sample.²

Photo-oxygenation of the (1S,2E,4R,6R,7E,-
11E)- and (1S,2E,4S,6R,7E,11E)-2,7,11-
cembratriene-4,6-diols (7, 8). A solution of 400 mg of
7 and 30 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 1 h when TLC
showed that all starting material had been
consumed, 1 ml of triethyl phosphite was added,
and the reaction mixture was kept at room
temperature for 4 h. The solvent was removed
under reduced pressure, and the residue was
recrystallized from ethyl acetate to give 83 mg of
(1S,2E,4R,6R,7E,11S)-2,7,12(20)-cembratriene-
4,6,11-triol (1). Part of the mother liquor was
separated by HPLC using columns packed with
Spherisorb 5 Nitrile and Spherisorb to afford
29 mg of I, 3.5 mg of (1S,2E,4R,6R,7E,11R)-2,7,12
(20)-cembratriene-4,6,11-triol (16), 22 mg
of (1S,2E,4R,6R,7E,10E,12S)-2,7,10-cembratri-
ene-4,6,12-triol (3) and 5.2 mg of (1S,2E,-
4R,6R,7E,10E,12R)-2,7,10-cembratriene-4,6,12-
trio (4).

A solution of 1.6 g of (1S,2E,4S,6R,7E,11E)-
2,7,11-cembratriene-4,6-diol (8) and 50 mg of
Rose Bengal in 25 ml of methanol was reacted with
singlet oxygen for 50 min using the apparatus
described above. After addition of 1.9 ml of
trichlorophosphate the reaction mixture was kept
at room temperature for 3 h. Removal of the solvent and separation of the residue by flash chromatography over silica gel and HPLC using columns packed with PrePak-500/C₁₈,
Spherisorb and Spherisorb 5 Nitrile yielded 113 mg of
starting material (8), 247 mg of (1S,2E,4S,6R,-
7E,11S)-2,7,12(20)-cembratriene-4,6,11-triol
(10), m.p. 112 °C, [α]D+54° (c 0.17, EtOH), 1.2
mg of (1S,2E,4S,6R,7E,11R)-2,7,12(20)-
cembratriene-4,6,11-triol (2), 125 mg of (1S,2E,4S,-
6R,7E,10E,12S)-2,7,10-cembratriene-4,6,12-triol
(11), m.p. 143—144 °C, [α]D+167° (c 0.90
EtOH)² and 27.6 mg of (1S,2E,4S,6R,7E,10E,-
12R)-2,7,10-cembratriene-4,6,12-triol (5).

Of these, the (1S,2E,4R,6R,7E,11S)- and
(1S,2E,4S,6R,7E,11R)-2,7,12(20)-cembratriene-
4,6,11-triols were identical (optical rotation, IR,
¹H NMR and MS) to triols 1 and 2 and the (1S,-
2E,4R,6R,7E,10E,12S)-, (1S,2E,4R,6R,7E,-
10E,12R)- and (1S,2E,4S,6R,7E,10E,12R)-
2,7,10-cembratriene-4,6,12-triols to 3, 4 and 5,
respectively.

(1S,2E,4R,6R,7E,11R)-2,7,12(20)-Cembratrie-
ne-4,6,11-triol (16) had m.p. 82—84 °C; [α]D+63° (c 0.57, EtOH); IR (CHCl₃): 3600,
3410, 3080, 1660, 1645, 1385 and 1375 cm⁻¹. ¹H
NMR (CDCl₃): δ 0.80 (d, J = 6.7 Hz)(0.84 (d,
J = 6.2 Hz) (H-16/H-17), 1.40 (s, H-18), 1.83 (d,
J = 1.2 Hz, H-19), 1.90 (dd, J = 10.1 and —13.6 Hz,
H-5a), 2.11 (dd, J = 2.8 and —13.6 Hz, H-5b),
4.04 (t, J = 6.0 Hz, H-11), 4.82 (dd, J = 2.8, 8.6
and 10.1 Hz, H-6), 4.93 (broad s, H-20a), 5.18

Acetylation of (1S,2E,4R,6E,8S,11S)-2,6,12-(20)-cembretriene-4,8,11-triol (6). Treatment of 6 mg of triol 6 with acetic anhydride in pyridine for 3 h at room temperature followed by work-up and chromatography over silica gel gave 1.6 mg of (1S,2E,4R,6E,8S,11S)-11-acetoxy-2,6,12-(20)-cembretriene-4,8-diol (I7), which was an oil and had IR (CHCl₃) bands at 3600, 3420, 3090, 1730, 1650 and 1245 cm⁻¹; ¹H NMR (CDCl₃): δ 0.85 (d, J=6.5 Hz)/0.88 (d, J=6.5 Hz) (H-16/H-17), 1.27 (s)/1.39 (s) (H-18/H-19), 2.07 (s, OCOC₂H₅), 2.29 (dd, J=8.0 and –13.9 Hz, H-5a), 2.41 (dd, J=5.0 and –13.9 Hz, H-5b), 4.90 (broad s, H-20a), 4.93 (broad s, H-20b), 5.25 (dd, J=8.4 and 15.9 Hz, H-2), 5.38 (m, H-11), 5.40 (d, J=15.9 Hz, H-3), 5.48 (d, J=15.4 Hz, H-7) and 5.56 (dd, J=5.0, 8.0 and 15.4 Hz, H-6); MS m/z (%): 346 (M-, 18), 304 (0.1), 286 (1), 243 (3), 228 (2), 203 (2), 185 (8), 173 (3), 159 (10), 133 (23), 119 (11), 107 (18), 93 (24), 81 (25), 71 (32), 55 (24) and 43 (100).

Photo-oxygenation of (1S,2E,4R,6E,8S,11E)-2,6,11-cembretriene-4,8-diol (9). A solution of 37 mg of 9 and 10 mg of Rose Bengal in 25 ml of methanol was reacted with singlet oxygen for 1 h using the apparatus described above. After addition of 100 μl of triethyl phosphate the reaction mixture was kept at room temperature for 30 min. Concentration in vacuo and separation by HPLC using a column packed with Spherisorb 5 afforded 12 mg of (1S,2E,4R,6E,8S,11S)-2,6,12-(20)-cembretriene-4,8,11-triol, which was identical to tobacco triol 6.

LIS measurements. The relative induced shifts were for 18: H-6 (100), H-5b (74), H-5a (39), H-3 (36), H-7 (26), H-11 (24), H-18 (19), H-2 (17), H-19 (12), OCOC₂H₅ (10), H-20 (8) and H-16/H-17 (4) and for 19: H-5b (100), H-5a (99), H-18 (84), H-6 (76), H-2 (74), H-3 (67), H-7 (46), H-11 (46), H-19 (27), OCOC₂H₅ (23), H-20a (16), H-20a (12), OCOC₂H₅ (10), H-16/H-17 (8/6).

Acetylation of (1S,2E,4R,6R,7E,10E,12S)-2,7,10-cembretriene-4,6,12-triol (3). A solution of 35 mg of 3 in 0.5 ml of acetic anhydride and 1 ml of pyridine was left at 4°C overnight. Work-up and separation by HPLC (Spherisorb 5 ODS, methanol-water 80:20) gave 11 mg of (1S,2E,-4R,6R,7E,10E,12S)-6-acetoxy-2,7,10-cembretriene-4,12-diol (20), which had m.p. 115-116°C; [α]D+28 (c 0.35, EtOH), IR (CHCl₃) bands at 3680, 3430, 1725, 1625 and 1247 cm⁻¹; ¹H NMR (CDCl₃): δ 0.77 (d, J=6.7 Hz)/0.86 (d, J=6.7 Hz) (H-16/H-17), 1.30 (s)/1.34 (s) (H-18/H-20), 1.76 (d, J=1.2 Hz, H-19), 1.91 (dd, J=8.7 and –13.6 Hz, H-5a), 2.00 (dd, J=3.3 and –13.6 Hz, H-5b), 2.02 (s, OCOC₂H₅), 2.61 (dd, J=8.5 and –15.7 Hz, H-9a), 2.81 (dd, J=5.6 and –15.7 Hz, H-9b), 5.20 (broad d, J=9.1 Hz, H-7), 5.4-5.6 (overlapping signals, H-2, H-3), 5.44 (d, J=15.3 Hz, H-11), 5.70 (dd, J=5.6, 8.5 and 15.3 Hz, H-10) and 5.74 (dd, J=3.3, 8.7 and 9.1 Hz, H-6); MS m/z (%): 304 (M–60, 1), 286 (1), 271 (0.2), 243 (2), 225 (0.5), 215 (1), 203 (1), 163 (4), 151 (3), 137 (5), 123 (21), 109 (20), 95 (33), 81 (42), 71 (25), 55 (24) and 43 (100).

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REFERENCES


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