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Tobacco Chemistry. 56.* The Stereochemistries of the Tobacco Diterpenoids: The (1*S*,2*E*,4*S*,6*E*,8*S*,11*E*)- and (1*S*,2*E*,4*R*,6*E*,8*S*,11*E*)-2,6,11-Cembratriene-4,8-diols. Acid-induced Transformations of Cembratrienediols

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The stereochemistries of the (1*S*,2*E*,4*S*,6*E*,8*S*,11*E*)- and (1*S*,2*E*,4*R*,6*E*,8*S*,11*E*)-2,6,11-cembratriene-4,8-diols (*1*,*2*) have been determined by X-ray analyses.

Acid-induced transformations of the 4,8-diols (*1*, *2*) and the (1*S*,2*E*,4*S*,6*R*,7*E*,11*E*)- and (1*S*,2*E*,4*R*,-6*R*,7*E*,11*E*)-2,7,11-cembratriene-4,6-diols (*3*,*4*) have been studied. The results show that the 4*S*,6*R*- and 4*R*,6*R*-diols (*3*, *4*) are interconvertible with the 4*S*,8*S*- and 4*S*,8*R*-diols (*1*, *7*) and with the 4*R*,8*S*-diol (*2*), respectively. The 4,6-diols (*3*,*4*) also undergo epimerization reactions and a fragmentation reaction yielding a *seco*-aldehyde (*6*).

The pioneer studies on the tobacco cembranoids carried out in the 1960:s led to the isolation of the two major components,[2] which were later fully identified as the (1*S*,2*E*,4*S*,6*R*,7*E*,11*E*)- and (1*S*,2*E*,-4*R*,6*R*,7*E*,11*E*)-2,7,11-cembratriene-4,6-diols (*3*, *4*).[1,3,4] A series of minor components, which included *inter alia* two diastereoisomers of 2,6,11-cembratriene-4,8-diol (*1*, *2*), was also found to be present.[5] Although results obtained later have shown that the two 4,8-diols (*1*, *2*) have (1*S*,2*E*,4*S*,11*E*)- and (1*S*,2*E*,-4*R*,11*E*)-configurations, respectively,[4] the geometries of their 6,7 double bonds and their chiralities at C-8 have remained unknown.

Our recent isolation of these two 4,8-diols (*1*, *2*) from a wax extract of green leaves of Greek tobacco has encouraged studies on their stereostructures and their generation *via* acid-induced rearrangements of the 4,6-diols *3* and *4*.

RESULTS

Stereochemistry. A detailed analysis of the ^{1}H NMR spectra using spin decoupling and spin simulation techniques revealed that the 6,7 as well as the 2,3 double bonds in the two 4,8-diols (*1*, *2*) have *E*-geometries ($J_{6,7}=16.1$ Hz, $J_{2,3}=16.0$ Hz for *1* and $J_{6,7}=16.4$ Hz, $J_{2,3}=15.7$ Hz for *2*). However, since conclusive evidence for the C-8 configurations was not obtainable from the ^{1}H and ^{13}C NMR spectra, X-ray analyses were carried out on the 4*S*,8-diol (*1*) and the epoxide (*5*) derived from the 4*R*,8-diol (*2*).

Diol *1* forms orthorhombic crystals of the monoclinic space group $P2_1$. The crystal data, obtained on a Philips PW 1100 diffractometer, were: $a=9.492$, $b=11.305$ and $c=10.577$ Å, $\beta=119.18°$, $Z=2$. The present *R*-value including thermal parameters for all non-hydrogen atoms is 0.183; location of the hydrogen atoms and further refinement being under way.[6] A stereoscopic view, which summarizes the *X*-ray results and demonstrates that diol *1* is (1*S*,2*E*,4*S*,6*E*,8*S*,11*E*)-2,6,11-cembratriene-4,8-diol, is shown in Fig. 1.

Epoxide *5* crystallizes in the orthorhombic space group $P2_1$ with $a=12.479$, $b=8.483$, $c=9.580$ Å, $\beta=110.92°$, $Z=2$. The structure, shown in Fig. 2,

*For part 55 see Ref. 1.

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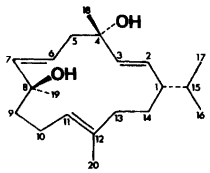

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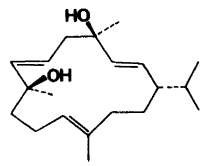

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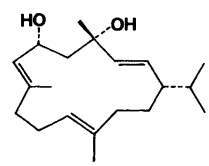

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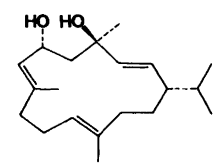

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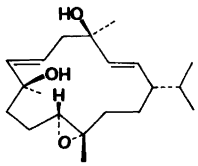

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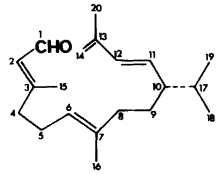

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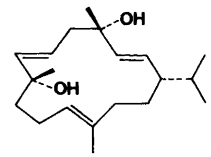

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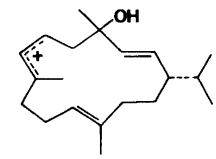


8a 4*R*
8b 4*S*

has so far been refined to an *R*-value of 0.093 with anisotropic thermal parameters assigned for all non-hydrogen atoms.[6] The analysis shows that epoxide *5* is (1*S*,2*E*,4*R*,6*E*,8*S*,11*S*,12*S*)-11,12-epoxy-2,6-cembradiene-4,8-diol and hence that diol *2* has an *S*-configuration at C-8.

Acid-induced transformations. A plausible biogenetic route to the 4*S*,8*S*- and 4*R*,8*S*-diols (*1*, *2*) would involve allylic rearrangements of the 4*S*,6*R*- and 4*R*,6*R*-diols (*3*, *4*), respectively. Roberts and

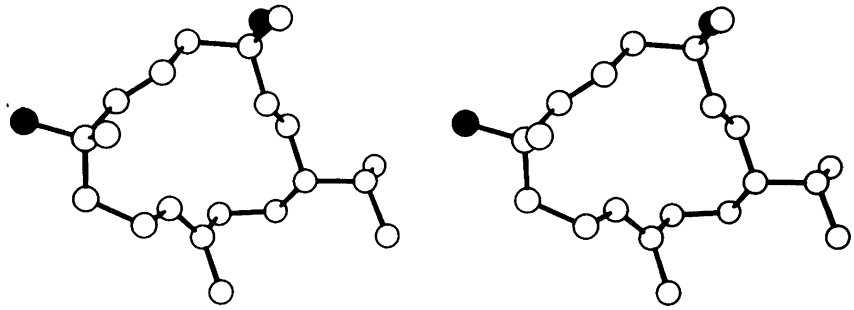


Fig. 1. Stereoscopic view of (1*S*,2*E*,4*S*,6*E*,8*S*,11*E*)-2,6,11-cembratriene-4,8-diol (*1*).

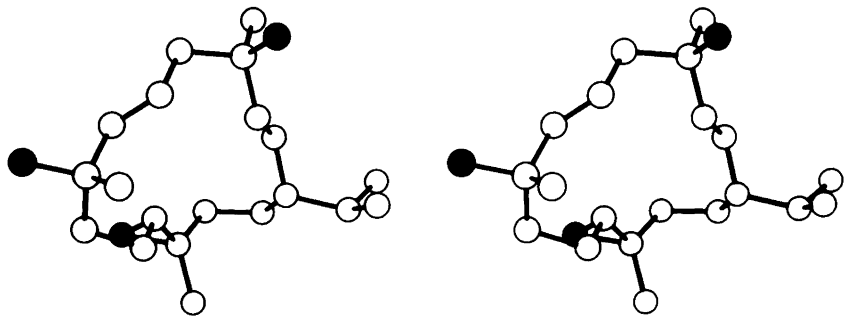


Fig. 2. Stereoscopic view of (1*S*,2*E*,4*R*,6*E*,8*S*,11*S*,12*S*)-11,12-epoxy-2,6-cembradiene-4,8-diol (*5*).

Table 1. Carbon-13 chemical shifts and assignments for compounds *1*, *2*, *6* and *7*.[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
1	47.4	128.2	138.4	73.1[c]	47.5	123.2	140.4	73.4[c]	42.3	22.8	126.5	132.6	37.5	27.9	33.1	20.6	19.6	29.8	28.2	14.6
2	47.2	130.0	137.4	72.7[c]	47.1	123.6	140.3	73.3[c]	42.9	22.7	126.9	132.2	37.2	27.4	32.8	20.3	19.7	27.3[d]	27.4[d]	14.4
6	193.4	128.4	166.8	41.6	26.7	124.0	137.6	38.7	31.8	50.3	135.5	133.7	143.3	114.8	17.7	16.2	33.3	21.2	19.6	19.0
7	47.3[b]	127.2	138.8	73.4[c]	48.0[b]	121.7	140.8	73.3[c]	42.1	22.2	126.9	132.0	37.3	27.7	32.9	20.7	19.6	30.0[d]	29.3[d]	14.3

[a] δ-Values in $CDCl_3$ (*1*, *2* and *7*) or CD_3OD (*6*) relative to TMS. [b,c,d] Assignments may be reversed.

Rowland carried out these conversions synthetically simply by subjecting each of the 4,6-diols (*3*,*4*) to slow chromatography over acidic alumina and obtained a 20 % yield of the corresponding 4,8-diol (*1* and *2*, respectively).[5]

In our hands, treatment of the 4*S*,6*R*-diol (*3*) with dilute sulfuric acid in dioxane – water for 6 h afforded, in addition to starting material (*3*, 24 % isolated yield), five major products, which were isolated. Four of these were identified as the 4*S*,8*S*- and 4*R*,8*S*-diols (*1*, *2*; 15 % and 10 %), the 4*R*, 6*R*-diol (*4*; 12 %) and 10-isopropyl-3,7,13-trimethyl-2,6,11,13-tetradecatetraen-1-al (*6*; 5 %).[7] The fifth product was assigned the structure (1*S*,2*E*,4*S*,6*E*,-8*R*,11*E*)-2,6,11-cembratriene-4,8-diol (*7*; 3 %) on the basis of the following evidence.

The ^{1}H NMR spectrum displayed signals due to two methyl groups on fully substituted, oxygen-carrying carbon atoms and one vinylic methyl group, which were ascribed to H-18, H-19 and H-20, respectively. An analysis of the olefinic region by spin decoupling and spin simulation methods established the presence of the disubstituted 2,3 and 6,7 double bonds and revealed that these have *E*-geometries, $J_{2,3}=15.4$ Hz and $J_{6,7}=14.0$ Hz.

The assignment of an *E*-stereochemistry to the trisubstituted 11,12 double bond rests on a comparison, which showed that the C-9 to C-14 and C-20 signals were present at virtually invariant positions in the ^{13}C NMR spectra of diols *1*, *2* and *7* (*cf.* Table 1). ^{13}C NMR results were also used to determine the stereochemistry at C-4 and C-8. Thus, the chemical shift values of the C-2 and C-18 signals, δ 127.2 and 30.0, were consistent with a 4*S*-configuration, whereas the shieldings of C-6 and C-19, δ 121.7 and 29.3 for diol 7 as against 123.2 – 123.6 and 28.0 – 27.4 for diols *1* and *2*, indicated that the configuration at C-8 in diol 7 is *R*.

Treatment of the 4*R*,6*R*-diol (*4*) with sulfuric acid in dioxane – water for 6 h, yielded in addition to starting material (*4*, 10 %) again five major products: *1*, *2*, *3*, *6* and *7*; 11, 26, 14, 6 and 2 %, respectively.

It is evident, therefore, that treatment of a 4,6-diol (*3*, *4*) with weak acid occurs with participation of several competing reactions. In order to gain some insight into these, each of the 4,6-diols (*3*, *4*) was again treated with sulfuric acid in dioxane – water. Aliquots were taken after various reaction times and analyzed by HPLC. The results obtained are summarized in Table 2.

It follows that in the interconversions of the 4,6-

Table 2. Relative yields, as determined by integration of HPLC traces, of the products obtained by treatment of *1*–*4* with dilute acid for different reaction times.

Reaction	Product (%)					
	1	*2*	*3*	*4*	*6*	*7*
4*S*,6*R*-Diol (*3*); H_2SO_4–dioxane–H_2O; 20 °C						
15 min	4.6	1.0	87	7.6	–	–
30 min	6.2	1.9	83	8.7	–	–
1 h	8.4	2.8	72	14	1.7	1.7
2 h	13	5.8	58	17	3.9	2.6
4 h	21	12	38	15	8.2	4.9
6 h	22	14	31	15	11	6.5
24 h	29	25	5.6	3.7	23	13
48 h	30	17	2.5	1.7	32	17
4*R*,6*R*-Diol (*4*); H_2SO_4–dioxane–H_2O; 20 °C						
15 min	–	6.5	3.9	86	3.6	–
30 min	1.6	10	6.1	77	5.4	–
1 h	2.0	16	12	62	7.7	–
2 h	3.6	24	16	43	14	–
4 h	6.5	31	19	22	21	1.2
6 h	9.2	34	16	13	25	1.9
24 h	26	31	4.6	3.2	29	6.3
48 h	26	20	3.0	1.7	39	11
4*S*,8*S*-Diol (*1*); H_2SO_4–dioxane–H_2O; 20 °C						
6 h	72	12	3.9	2.5	–	10
48 h	39	16	2.5	2.8	12	27
96 h	32	12	6.6	4.1	24	22
4*R*,8*S*-Diol (*2*); H_2SO_4–dioxane–H_2O; 20 °C						
6 h	14	78	3.9	3.2	–	–
48 h	30	29	2.3	2.7	20	15
96 h	21	21	4.5	3.7	35	15

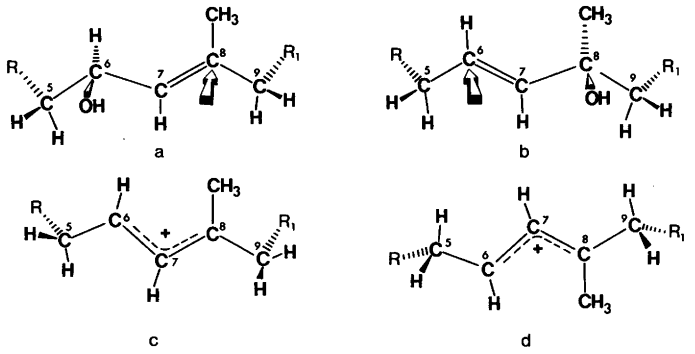
and the 4,8-diols (*e.g.* *3*⇄*1* and *4*⇄*2*) the equilibrium positions favour the formation of the latter. This conclusion is substantiated by the observation that the 4,8-diols *1* and *2* when treated with weak acid give rise to minute quantities of 4,6-diols (*3*, *4*) only (*cf.* Table 2).

Inspection of Dreiding models revealed that an allylic rearrangement of S_N2' type taking place with the well-documented *cis*-stereochemistry[8] in conformer *a* of the 4,6-diols *3* and *4* would explain the formation of the 4*S*,8*S*- and 4*R*,8*S*-diols *1* and *2*, respectively (*cf.* Scheme 1). Conversely, conformer *b* of the 4*S*,8*S*- and 4*R*,8*S*-diols (*1*, *2*), whose existence is corroborated by the results from the X-ray analyses, would be amenable to an S_N2' reaction yielding the 4*S*,6R- and 4*R*,6*R* diols *3* and *4*.

In cannot be excluded, however, that the interconversions of the 4,6- and 4,8-diols (*1*–*4*) may take place by S_N1 types of reactions. Thus, attack of hydroxyl ions on C-8 of carbonium ions *8a* and *8b*, when these exist in conformation *c*, would afforld the 4*S*,8*S*- and 4*R*,8*S*-diols (*1*, *2*), respectively, whereas the 4*S*,6*R*- and 4*R*,6*R*-diols (*3*, *4*) would arise by attachment of hydroxyl ions to C-6.

The generation of the 4*S*,8*R*-diol *7*, which is not consistent with the S_N2' mechanism, may also be rationalized by an S_N1 reaction occurring in conformer *d* of carbonium ion *8a*. For reasons not readily understood, the corresponding reaction is not favoured in the 4*R*-series.

The *seco*-aldehyde (*6*) was first reported as a constituent of tobacco flowers and has been pre-



Scheme 1.

pared from the 4*R*,6*R*-diol (*4*) by the use of *p*-toluenesulphonic acid.[7] It is formed, in our case, by a competing fragmentation reaction, which although occurring in both the 4*S*,6*R*- and 4*R*,6*R*-diols (*3*, *4*) is more effective in the latter (*cf.* Table 2). Attempted acid-induced cyclization of *6* showed that this fragmentation reaction is irreversible, a result which concurs with the observed accumulation of *6* on exposure of the 4,6-diols (*3*, *4*) and also of the 4,8-diols (*1*, *2*; *i.e.* $1 \rightleftarrows 3 \rightarrow 6$) to acid for prolonged reaction times.

Use of BF_3-etherate in toluene as the acidic agent was found to promote the fragmentation reaction and not to involve competing formation of 4,8-diols. Thus, a 10% yield of *6* was obtained from the 4*S*,6*R*-diol (*3*) under these conditions.

It follows from Table 2 that in addition to the allylic rearrangement and fragmentation reactions the 4*S*,6*R*- and 4*R*,6*R*-diols (*3*, *4*) are prone to undergo epimerization of the allylic hydroxyl group at *C*-4 on treatment with weak acid. This process is evidently also part of the reaction sequence, in which the 4*S*,8*S*- and 4*R*,8*S*-diols (*1*, *2*) are interconverted, *i.e.* $1 \rightleftarrows 3 \rightleftarrows 4 \rightleftarrows 2$. Whether a direct epimerization at C-4 occurs in the 4,8-diols *1* and *2* is unclear.

Although oxidative processes are predominant,[9] it seems likely that acid-induced reactions of the types described above, which can be carried out under mild conditions, are involved in the biotransformations of the 4,6-diols *3* and *4*. This view is supported by the fact that the 4,8-diols *1* and *2*,[5] a metabolite derived from *1* [10] and the *seco*-aldehyde *6* [7] are tobacco constituents.

EXPERIMENTAL

With the exception of accurate mass measurements, which were carried out on a Kratos MS50 Stereo DS55SM/DS55S mass spectrometer-computer system and some of the NMR spectra, which were recorded on a Varian XL-200 spectrometer, the instruments specified in Ref. 11 were used.

Isolation. An extract (24 g) obtained by immersing green leaves of Greek *Nicotiana tabacum* (Basma Drama) in chloroform was distributed between hexane and methanol–water (80:20). The polar material obtained (16 g) was chromatographed over silica gel using a gradient of hexane–ethyl acetate as eluent to give fractions 1 (1 g), 2 (8 g) and 3 (6 g). Fraction 1 was a complex mixture, which was separated further by chromatography over silica gel and HPLC using columns packed with μ-Porasil and μ-Bondapak/CN to give 12.6 mg of (1*S*,2*E*,4*S*,6*E*,8*S*,11*E*)-2,6,11-cembratriene-4,8-diol (*1*) and 6.6 mg of (1*S*,2*E*,4*R*,6*E*,8*S*,11*E*)-2,6,11-cembratriene-4,8-diol (*2*).

(1*S*,2*E*,4*S*,6*E*,8*S*,11*E*)-2,6,11-Cembratriene-4,8-diol (*1*) had m.p. 116–119 °C and $[\alpha]_D$ +72° (*c* 0.57, $CHCl_3$) (reported m.p. 118–120 °C; $[\alpha]_D$ +100°);[5] IR ($CHCl_3$) bands at 3600, 3450 and 985 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.80 (d, J = 6.8 Hz)/0.84 (d, J = 6.7 Hz) (H-16/H-17), 1.33 (s, H-18 + H-19), 1.50 (broad s, H-20), 2.29 (dd, J = 8.0 and −13.6 Hz, H-5_A), 2.43 (ddd, J = 1.0, 5.2 and −13.6 Hz, H-5_B), 5.31 (broad t, J = 6 Hz, H-11), 5.32 (dd, J = 6.0 and 16.0 Hz, H-2), 5.39 (d, J = 16.0 Hz, H-3), 5.52 (ddd, J = 5.2, 8.0 and 16.1 Hz, H-6) and 5.69 (dd, J = 1.0 and 16.1 Hz, H-7); MS[*m*/*z*(%)]: 288 (M−18, 3), 270 (9), 255 (5), 245 (6), 227 (13), 187 (6), 159 (12), 135 (19), 121 (17), 107 (41), 93 (28), 81 (56), 71 (36), 55 (30) and 43 (100).

(1*S*,2*E*,4*R*,6*E*,8*S*,11*E*)-2,6,11-Cembratriene-4,8-diol (*2*) had m.p. 146–148 °C and $[\alpha]_D$ +38° (c 0.37, $CHCl_3$) (reported m.p. 150–152 °C and $[\alpha]_D$ +40°);[5]

IR ($CHCl_3$) bands at 3600, 3440 and 985 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.81 (d, J = 6.5 Hz)/0.84 (d, J = 6.2 Hz) (H-16/H-17), 1.37 (s)/1.40 (s) (H-18/H-19), 1.49 (broad s, H-20), 2.20 (dd, J = 7.1 and −13.7 Hz, H-5_A), 2.49 (dd, J = 3.8 and −13.7 Hz, H-5_B), 5.26 (dd, J = 8.6 and 15.7 Hz, H-2), 5.31 (broad t, J = 5 Hz, H-11), 5.47 (d, J = 15.7 Hz, H-3), 5.66 (d, J = 16.4 Hz, H-7) and 5.71 (ddd, J = 3.8, 7.1 and 16.4 Hz, H-6); MS [*m/z* (%)]: 288 (M − 18, 3), 270 (13), 255 (9), 245 (8), 227 (19), 187 (9), 159 (16), 133 (24), 119 (21), 107 (48), 93 (38), 81 (74), 71 (35), 55 (32) and 43 (100).

Preparation of (1S,2E,4R,6E,8S,11S,12S)-11,12-epoxy-2,6-cembradiene-4,8-diol (5). To a cooled (0 °C) solution of 12.0 mg of (1*S*,2*E*,4*R*,6*E*,8*S*,11*E*)-2,6,11-cembratriene-4,8-diol (*2*) and 19.5 mg of sodium acetate in 4 ml of chloroform was added 7.6 mg of *m*-chloroperbenzoic acid. The reaction mixture was kept at 0 °C for 45 min. Work-up and separation by HPLC using a column packed with Spherisorb/CN gave 8.2 mg of (1*S*,2*E*,4*R*,6*E*,8*S*,11*S*,12*S*)-11,12-epoxy-2,6-cembradiene-4,8-diol (*5*), which had m.p. 128 − 130 °C; $[\alpha]_D$ −12° (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) bands at 3600 and 3450 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.83 (d, J = 7.0 Hz)/0.87 (d, J = 6.9 Hz) (H-16/H-17), 1.19 (s, H-20), 1.36 (s)/1.43 (s) (H-18/H-19), 2.30 (dd, J = 6.3 and −13.0 Hz, H-5_A), 2.47 (dd, J = 6.1 and −13.0 Hz, H-5_B), 2.98 (dd, J = 2.5 and 10.7 Hz, H-11), 5.32 (dd, J = 8.6 and 15.9 Hz, H-2), 5.53 (d, J = 15.9 Hz, H-3), 5.63 (d, J = 15.6 Hz, H-7) and 5.77 (ddd, J = 6.1, 6.3 and 15.6 Hz, H-6); MS [*m/z* (%)]: 304 (M − 18, 2), 286 (13), 268 (11), 243 (11), 225 (12), 215 (5), 201 (5), 185 (7), 173 (12), 159 (15), 145 (25), 133 (23), 119 (28), 105 (32), 95 (35), 81 (43), 69 (26), 55 (32) and 43 (100).

Treatment of (1S,2E,4S,6R,7E,11E)-2,7,11-cembratriene-4,6-diol (3) with acid. I. A solution of 194 mg of *3* in 12 ml of dioxane − water (3:1) and 0.4 ml of dilute H_2SO_4 (5 %) was kept under nitrogen and at room temperature (20 °C) for 5.5 h. The reaction mixture was diluted with water and extracted with diethyl ether. The ether phase was washed with aqueous $NaHCO_3$ and water, dried and concentrated. The residue was separated by HPLC using a column packed with Spherisorb/CN and hexane − ethyl acetate (60:40) as an eluent to give 9.3 mg of 10-isopropyl-3,7,13-trimethyl-2,6,11,13-tetradecatetraen-1-al (*6*),[7] 6.0 mg of (1*S*,2*E*,4*S*,6*E*,8*R*,11*E*)-2,6,11-cembratriene-4,8-diol (*7*), 28.8 mg of (1*S*,2*E*,4*S*,6*E*,8*S*,11*E*)-2,6,11-cembratriene-4,8-diol (*1*), 18.9 mg of (1*S*,2*E*,4*R*,6*E*,8*S*,11*E*)-2,6,11-cembratriene-4,8-diol (*2*), 46.6 mg of starting material (*3*) and 24.1 mg of (1*S*,2*E*,4*R*,6*R*,7*E*,11*E*)-2,7,11-cembratriene-4,6-diol (*4*).

(1*S*,2*E*,4*S*,6*E*,8*R*,11*E*)-2,6,11-Cembratriene-4,8-diol (*7*) was an oil and had $[\alpha]_D$ +54° (*c* 0.33, $CHCl_3$); IR ($CHCl_3$) bands at 3600, 3540 and 985 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.80 (d, J = 6.8 Hz)/0.83 (d, J = 6.8 Hz) (H-16/H-17), 1.29 (s)/1.35 (s) (H-18/H-19), 1.49 (broad s, H-20), 2.27 (dd, J = 7.0 and −13.1 Hz, H-5_A), 2.49 (dd, J = 2.5 and −13.1 Hz, H-5_B), 5.27 (dd, J = 9.0 and 15.4 Hz, H-2), 5.32 (broad t, J = 6 Hz, H-11), 5.44 (d, J = 15.4 Hz, H-3), 5.57 (ddd, J = 2.5, 7.0 and 14.0 Hz, H-6) and 5.64 (d, J = 14.0 Hz, H-7); MS [*m/z* (%)]: 288 (M − 18, 3), 270 (4), 255 (2), 245 (3), 227 (5), 187 (4), 163 (8), 147 (12), 135 (18), 121 (19), 107 (38), 93 (31), 81 (50), 71 (33), 55 (26) and 43 (100).

II. A solution of 200 mg of *3* in 12 ml of dioxane − water (3:1) and 0.4 ml of dilute H_2SO_4 (5 %) was kept under nitrogen and at room temperature. Aliquots containing 1 ml of the reaction mixture were taken after various reaction times, worked up and examined by HPLC using the conditions described above. The results obtained are summarized in Table 2.

Treatment of (1S,2E,4R,6R,7E,11E)-2,7,11-cembratriene-4,6-diol (4) with acid. I. A solution of 109 mg of *4* in 6 ml of dioxane − water (3:1) and 0.2 ml of dilute H_2SO_4 (5 %) was kept under nitrogen and at room temperature for 5.5 h. Work-up and separation by HPLC using a column packed with Spherisorb/CN and hexane − ethyl acetate (60:40) as an eluent afforded 6.9 mg of *6*, 2.0 mg of *7*, 11.7 mg of *1*, 28.5 mg of *2*, 15.2 mg of *3* and 11.2 mg of *4*.

II. A solution of 185 mg of *4* in 12 ml of dioxane − water (3:1) and 0.4 ml of dilute H_2SO_4 (5 %) was kept under nitrogen and at room temperature. Aliquots containing 1 ml of the reaction mixture were taken after the reaction times indicated in Table 2, worked up and examined by HPLC using the conditions described above (*cf.* Table 2).

Treatment of the (1S,2E,4S,6E,8S,11E)- and (1S,-2E,4R,6E,8S,11E)-2,6,11-cembratriene-4,8-diols (1, 2) with acid. A solution of 8.8 mg of *1* in 4 ml of dioxane − water (3:1) and 0.2 ml of aqueous H_2SO_4 (5 %) was kept under nitrogen and at room temperature. Aliquots containing 1 ml of the reaction mixture were taken after 6, 48 and 96 h. They were worked up and analyzed by HPLC using a column packed with Spherisorb/CN and hexane − ethyl acetate (60:40) as an eluent. The results are summarized in Table 2.

A solution of 6.3 mg of *2* in 4 ml of dioxane − water (3:1) and 0.2 ml of aqueous H_2SO_4 (5 %) was kept under nitrogen and at room temperature. Aliquots were taken and analyzed in the same manner as described above (*cf.* Table 2).

Treatment of 10-isopropyl-3,7,13-trimethyl-2,6,11,13-tetradecatetraen-1-al (6) with acid. A solution of 14.2 mg of *6* in 5 ml of dioxane − water (3:1) and 0.2 ml of aqueous H_2SO_4 (5 %) was kept under nitrogen and at room temperature for 5 h. Work-up and examination by TLC and ^1H NMR showed that *6* was recovered unchanged.

Preparation of 10-isopropyl-3,7,13-trimethyl-2,6,11,13-tetradecatetraen-1-al (6). To a solution of 102 mg of *3* in 9 ml of toluene, which was kept at

−45 °C, was added a solution of 0.1 ml of BF_3-etherate in 6 ml of toluene. The reaction mixture was kept at −45 °C for 30 min, then diluted with ice-water and extracted with ether. The organic phase was washed with aqueous $NaHCO_3$ and water and dried. The residue was chromatographed over silica gel using a gradient of hexane – ethyl acetate as an eluent to give 12.3 mg of starting material (*3*) and 12.9 mg of *6*, whose IR, MS and ^1H NMR spectra agreed with published spectral data.[7]

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