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TETRAHYDROFURAN-TYPE TERPENOIDS FROM *TANACETUM VULGARE*

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Key Word Index—*Tanacetum vulgare*, Compositae, sesquiterpenes, davanone, hydroperoxides, peroxyhemiketals, chemotaxonomy

Abstract—Investigation of a rare genotype of *Tanacetum vulgare* afforded a series of tetrahydrofuran-type terpenoids, whose pattern was different in flowers and leaves The major constituent of the flowers was the *trans* $\Delta^{3,4}$-hydroperoxide of davanone, whereas the leaves gave mostly a peroxyhemiketalic compound resulting from the intramolecular cyclization of the *cis* $\Delta^{3,4}$-hydroperoxide of davanone Structures were elucidated by spectral data and chemical reactions, including correlation with natural (+)-davanone The peroxyhemiketalic compound upon acylation of its hydroxyl group gave an instantaneous complex reaction, resulting in the formation of a β-acyloxyenone and loss of one molecule of acetone Among the minor constituents of the leaves, a C-10 carboxylic acid biogenetically related with davanone was isolated

INTRODUCTION

Many studies have shown that *Tanacetum vulgare* L displays a noteworthy infraspecific variation in the terpene constituents of its essential oil [1, 2] Furthermore, a wide range of non-volatile sesquiterpenes have been isolated from different collections of this plant [3–10], showing that the species is characterized by an abnormally high infraspecific variability of its whole terpenoid pattern As a part of a joint chemosystematic study on *T vulgare*, we have now investigated the extractive constituents of a rare genotype, whose flowerheads have been reported to afford an essential oil made up almost exclusively (95%) [1] by the sesquiterpene ketone davanone (**1**) [11] Preliminary analysis of different parts of the plant revealed that only the flowers contained davanone, whereas the leaves gave a complex mixture of oxygenated terpenoids, some of which were also present in flowers, five sesquiterpenes and one terpene carboxylic acid biogenetically related with davanone were isolated We present here the structural elucidation and chemical properties of these compounds

RESULTS AND DISCUSSION

The flowers and the leaves were extracted separately, and the extracts were chromatographed on a silica gel column, the compounds isolated and the respective yields are listed in Table 1

Compound **2**, the major constituent of the leaves, gave positive reactions for the presence of a peroxide bond (liberation of iodine from alcoholic potassium iodide, blood-red colour with ferrous thiocyanate) This bond was part of a peroxide bridge, as shown by the failure of the reduction with triphenyl phosphine, which ruled out the presence of a hydroperoxyl group The electron-impact mass spectrum (EIMS) showed a prominent peak (57%) at *m/z* 236, resulting from the loss of one molecule of oxygen from a low-intensity (1%) ion at *m/z* 268, the latter was the molecular ion, as shown by the chemical ionization mass spectrum (CIMS) using ammonia as a reaction gas (peak at *m/z* 286 $[M + NH_4]^+$) The molecular formula $C_{15}H_{24}O_4$ was deduced from exact mass measurements on the peak at *m/z* 268 in the EIMS Overall, the EIMS of **2** was very similar to that of davanone (**1**), the major difference being, besides the presence of the peak at *m/z* 268, the greater intensity of the peaks at *m/z* 236 and 125

Table 1 Terpenoid compositions of leaves and flowers of *Tanacetum vulgare**

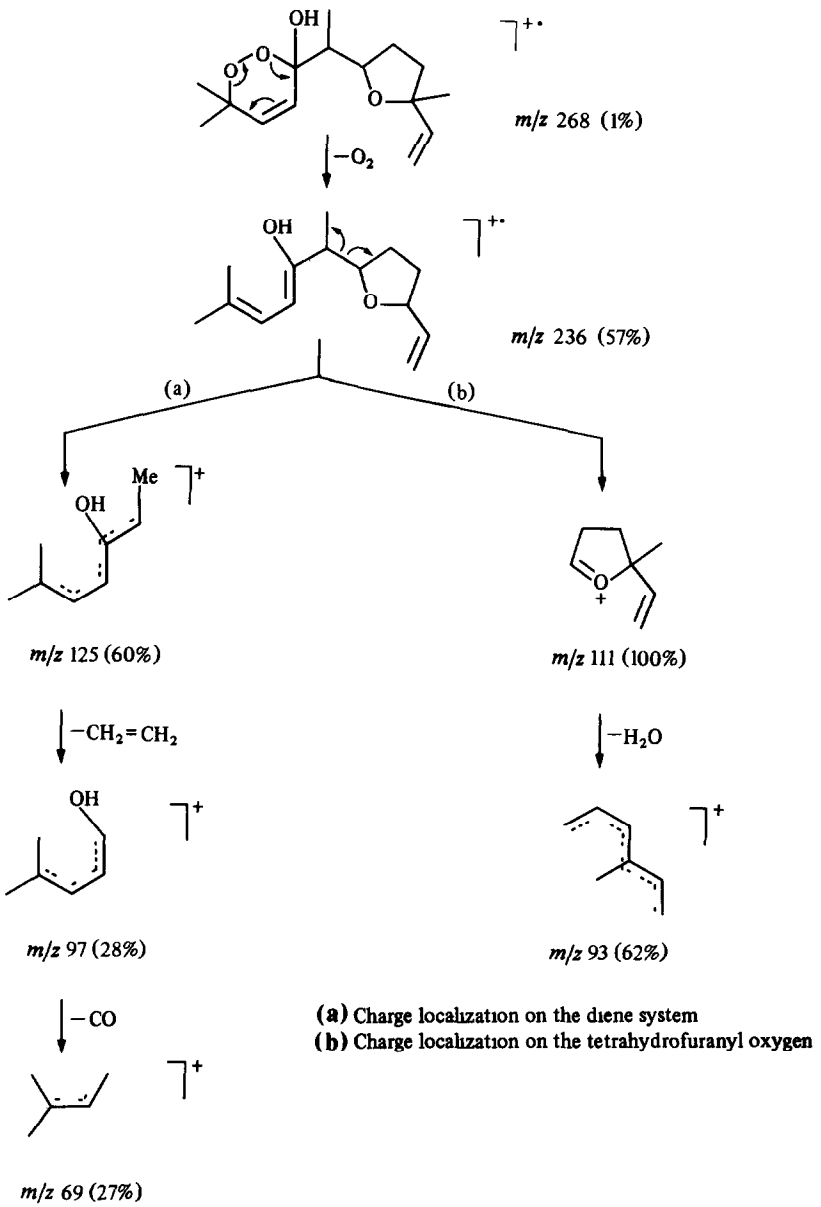
Compound	Leaves	Flowers
1	—	0 28%
2	0 75%	0 20%
9	0 06%	0 31%
10 + **11**	0 04%	—
12	0 10%	0 12%
13	0 17%	—

*Yields are referred to dried plant material

The IR spectrum of **2** showed the presence of one tertiary hydroxyl (sharp band at 3400 cm^{-1}) and the absence of carbonyl groups The ^{13}C NMR spectrum displayed signals characteristic of the 1-(5-methyl-5-vinyltetrahydrofuran-2-yl)ethyl moiety (**A**) of davanones and their derivatives [12] (Table 3) Multiplicity and chemical shift considerations as well as the molecular formula required the remaining six carbons to be accommodated in a 6,6-dimethyl-3-hydroxy-$\Delta^{4,5}$-1,2-dioxan-3-yl structure (**B**) Formula **2** (exclusive of stereochemistry) was thus assigned to the major constituent of the leaves This formula was in accordance with the close similarity between the EIMS of **1** and **2** Loss of one molecule of oxygen from **2** gives in fact the enol form of davanone

(Scheme 1) Structure **2** was further confirmed by treatment of **2** with an excess of lithium aluminium hydride in THF, which afforded the epimeric diols **3** and **4** These compounds were separated by preparative TLC The ^{1}H NMR and ^{13}C NMR spectra of **3** and **4** showed that one of the two newly-formed hydroxyls was tertiary, trichloroacetyl isocyanate (TAI) induced shifts [13] in the ^{1}H NMR spectra of **3** and **4** further verified that the geminal methyl groups were adjacent to the tertiary hydroxyl [13]

The peroxyhemiketalic hydroxyl group of **2** was not silylated upon treatment with trimethylchlorosilane (TMCS) or *N,O*-bis(trimethylsilylacetamide) (BSA) in standard conditions [14] Acetylation with acetic anhydride–pyridine or acetic anhydride–dimethylaminopyridine furnished no product that could be isolated When **2** was treated with the powerful acylating agent TAI [13] directly in the NMR sample tube, a complex reaction took place, resulting in the loss of acetone and the formation of the enol ester **5** (Scheme 2) The β-acyloxyenone structure of the latter was evident from the characteristic chemical shift of the enone olefinic carbons and protons (Tables 2 and 3) The formation of **5** from **2** can be rationalized in terms of acylation of the hydroxyl group of **2**, followed by a pericyclic (3,3)-sigmatropic shift of the 'ethereal' ester bond, and cycloelimination of the resulting $\Delta^{3,4}$-1,2-dioxane derivative to the enolester **5** and one molecule of acetone (Scheme 2) Compound **5** could not be isolated from the reaction mixture, the attempted work-up (pouring into a cold 5% sodium bicarbonate solution or a phosphate buffer, pH 7, and extraction with pentane) resulted in the hydrolysis of the ester moiety, with formation of the β-ketoaldehyde **6** The latter was a very unstable product, existing in solution at



(a) Charge localization on the diene system
(b) Charge localization on the tetrahydrofuranyl oxygen

Scheme 1 Mass spectral fragmentation pattern of compound **2**

Table 2 ^{1}H NMR data for compounds 2–7 and 9–13*

Protons†	2	2 (C_6D_6)	3, 4	Δ TAI		Δ TAI	5	7	9	10, 11	12	Δ TAI	13
H-1	1 28 *s*‡	1 05 *s*‡	1 33 *s*‡	+0 44§	1 29 *s*‡	+0 45§	—	—	1 38 *s*‡	5 04, 4 84 *br s*	1 36 *s*‡	+0 28§	—
H-3	5 96 *d*	4 63 *d*	5 61 *dd*	+0 04	5 65 *dd*	0	8 17 *d*	7 90 *d*	6 86 *d*	4 54, 4 50 *br t*	6 88 *d*	+0 01	—
	(10 5)	(10 0)	(13 0)		(13 0)		(12 4)	(4 2)	(16 0)	(8 8)	(16 0)		
			(1 0)		(2 0)					(8 8)			
H-4	5 62 *d*	4 59 *d*	5 31 *dd*	+0 11	5 37 *dd*	+0 16	5 21 *d*	5 60 *d*	6 39 *d*	*ca* 2 75 *dq*	6 39 *d*	0	—
	(10 5)	(10 0)	(13 0)		(13 0)		(12 4)	(4 2)	(16 0)	(16 0)	(16 0)		
			(7 5)		(5 5)					(8 8)			
H-5	—		4 90 *td*	+1 60	4 78 *td*	+1 71	—	—	—	—	—		—
			(7 5)		(7 5)								
			(7 5)		(5 5)								
			(1 0)		(2 0)								
H-6	1 97 *m*	1 82 *m*	1 95 *m*	||	1 99 *m*	||	2 70 *m*	2 50 *m*	2 95 *m*	2 65 *m*	2 90 *m*	0	2 65 *m*
H-7	4 19 *dt*	4 22 *dt*	3 88 *dt*	−0 20	4 02 *dt*	−0 18	4 05 *dt*	4 11 *dt*	4 15 *dt*	4 10, 4 07 *dt*	4 21 *dt*	−0 04	4 15 *td*
	(10 0)	(10 0)	(9 5)		(9 5)		(9 5)	(10)	(8 0)	(9 5)	(8 0)		(8 4)
	(10 0)	(10 0)	(9 5)		(9 5)		(9 5)	(10)	(8 0)	(7 5)	(8 0)		(8 4)
	(5 0)	(7 0)	(5 5)		(5 5)		(5 5)	(5 5)	(6 0)		(6 0)		(6 0)
H-11	5 93 *q*	5 64 *q*	5 83 *q*	−0 01	5 88 *dd*	−0 03	5 78 *q*	5 88 *q*	5 88 *q*	5 89, 5 86 *q*	5 88 *q*	+0 01	5 87 *q*
	(17 5)	(17 0)	(17 0)		(17 0)		(17 0)	(17 0)	(17 0)	(17 0)	(17 0)		(17 0)
	(11 0)	(11 0)	(11 0)		(11 0)		(11 0)	1 5)	(11 0)	(11 0)	(11 0)		(11 0)
H-12a	5 17 *dd*	5 23 *dd*	5 21 *dd*	−0 03	5 21 *dd*	−0 09	5 06 *dd*	5 10 *dd*	5 16 *dd*	5 16, 5 13 *dd*	5 15 *dd*	−0 04	5 21 *dd*
	(17 5)	(17 0)	(17 0)		(17 0)		(17 0)	(17 0)	(17 0)	(17 0)	(17 0)		(17 0)
	(1 5)	(2 0)	(1 5)		(1 5)		(1 5)	(1 5)	(1 5)	(1 5)	(1 5)		(1 5)
H-12b	4 95 *dd*	4 86 *dd*	4 98 *dd*	−0 05	4 98 *dd*	−0 05	4 85 *dd*	4 92 *dd*	4 97 *dd*	4 98, 4 96 *dd*	4 94 *dd*	−0 04	4 97 *dd*
	(11 0)	(11 0)	(11 0)		(11 0)		(11 0)	(11 0)	(11 0)	(11 0)	(11 0)		(11 0)
	(1 5)	(2 0)	(1 5)		(1 5)		(1 5)	(1 5)	(1 5)	(1 5)	(1 5)		(1 5)
H-13	1 34 *s*‡	1 07 *s*‡	1 32 *s*‡	+0 45§	1 36 *s*‡	+0 38§	—	—	1 38 *s*‡	1 25 *s*	1 36 *s*‡	+0 28§	—
H-14	0 83 *d*	0 77 *d*	0 80 *d*	+0 11	0 88 *d*	+0 12	0 92 *d*	1 03 *d*	1 03 *d*	1 01 *d*	1 03 *d*	+0 01	1 15 *d*
	(7 5)	(7 0)	(7 4)		(7 0)		(7 0)	(7 0)	(7 3)	(7 0)	(7 3)		(7 3)
H-15	1 40 *s*‡	1 32 *s*‡	1 33 *s*‡	−0 11§	1 33 *s*‡	−0 13§	1 10 *s*	1 12 *s*	1 24 *s*‡	1 75 *br s*	1 24 *s*‡	+0 02	1 31 *s*
OH	6 63 *s*	6 40 *s*	4 65 *br s*		4 80 *br s*								
OOH									8 40 *br s*				
NH							9 15 *br s*						

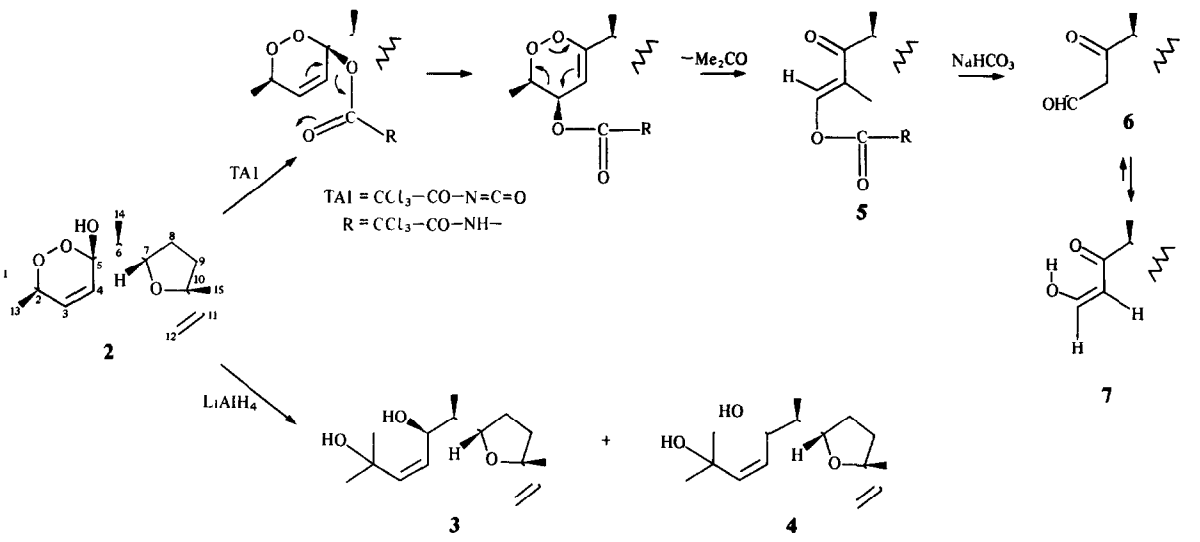
*Run at 200 MHz in $CDCl_3$, shifts are in δ-values (ppm) downfield from TMS

†The protons at C-8 and C-9 gave a complex system, not analysable by first-order rules

‡Assignments in the same column are interchangeable

§As the chemical shift values of the corresponding protons in the parent compound are interchangeable, these values are only approximate The two positive shifts in each spectrum have been assigned to the two geminal methyl groups, and the negative shift to H-15

||The signal could not be observed owing to overlapping



Scheme 2 Reactions of compound **2**

room temperature mostly as its hydrogen-bonded β-hydroxyenone form (**7**) The hydrogen bonding stabilizing **7** over **6** requires a *cis*-relationship between the enone olefinic protons, this is in accordance with the dramatic decrease of their vicinal coupling observed when going from **5** to **7** (ΔJ = 8 2 Hz)

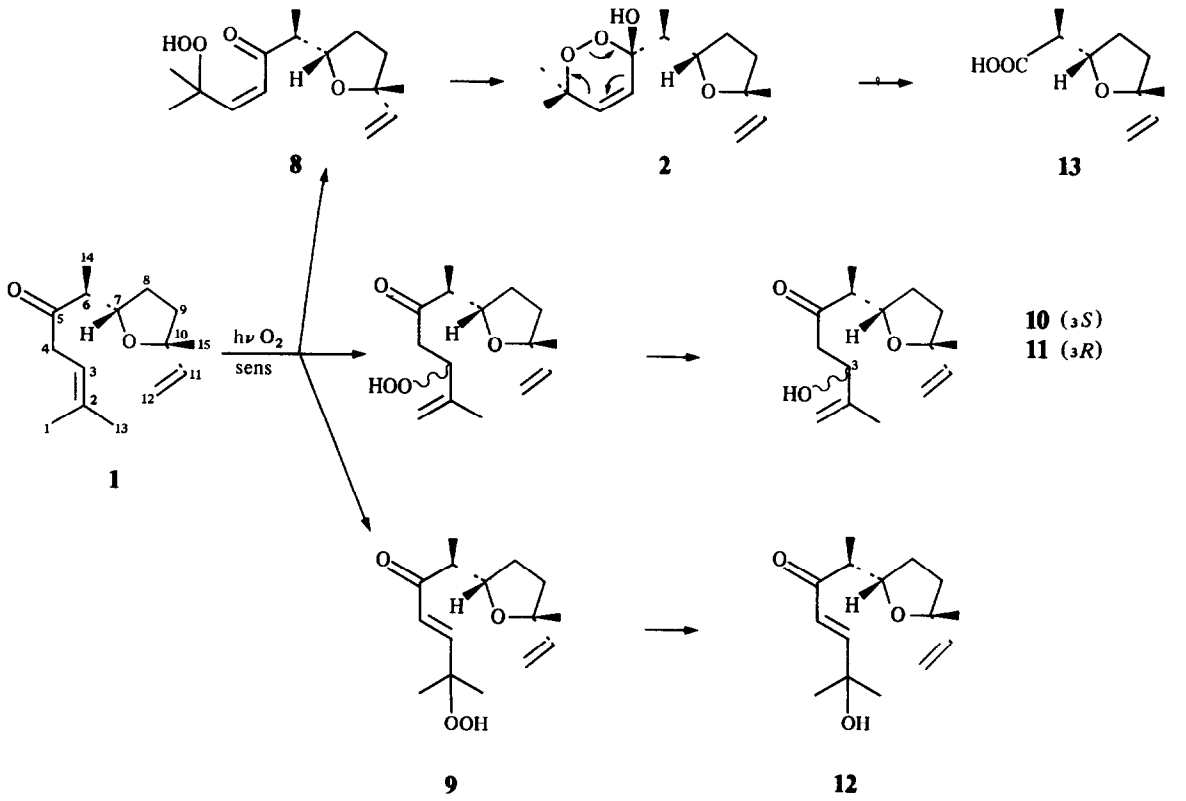
The stereochemistry of **2** was deduced as follows the value of $J_{6,7}$ (9 5 Hz) showed that **2** belonged to the *l* (6*S**, 7*S**) series of davanone derivatives [12] (this series has been referred to in the literature as '*threo*' [12] or '*anti*' [15] The descriptor *threo* is evidently to be intended according to the 'aldol notation' [16], as application of the definition found in the textbooks on stereochemistry [17] would lead to an *erythro* descriptor for the (6*S**, 7*S**) series The recently introduced *l/u* configurational notation [18] allows unambiguous specification of this series, and has therefore been adopted) The high-field position of H-6 (δ1 97) in the ^{1}H NMR spectrum of **2** suggested a β-orientation (assuming the same absolute configuration as davanone at C-6) for the hydroxyl group a strong intramolecular hydrogen bonding was in fact present between this hydroxyl and the tetrahydrofuranyl oxygen (It is well known that hemiacetal hydroxyls form strong hydrogen bondings [19], the –OH stretching pattern in the IR spectrum and both position and shape of the sharp signal of the hydroxylic proton in the ^{1}H NMR spectrum of **2** were practically unaffected by dilution) This bonding requires locking of the molecule in a 'spirane-like' conformation, with the two hetero-rings lying on approximately perpendicular planes The intramolecular hydrogen-bonded conformation expected for the 5β-hydroxy derivative (**C**) has H-6 *gauche* to one oxygen, whereas the corresponding one for its C-5 epimer (**D**), has H-6 *gauche* to two oxygen atoms, and so subjected to more considerable deshielding As the chemical shift of H-6 was virtually the same in **2** and the diols **3**

Table 3 ^{13}C NMR spectral data for compounds **2–7** and **9–13***

Carbon	2	3, 4		5	7	9	10, 11	12	13
C-1	24 24 *q*†	31 27 *q*	30 68 *q*†	—	—	29 62 *q*†	110 66 *t*	29 28 *q*	—
C-2	76 47 *s*	71 29 *s*	70 79 *s*	—	—	80 71 *s*	145 86 *s*	70 80 *s*	—
C-3	134 45 *d*‡	140 49 *d*†	140 60 *d*‡	148 10 *d*	175 50 *d*	148 51 *d*	71 43, 70 89 *d*	152 50 *d*	—
C-4	125 48 *d*‡	127 03 *d*†	127 20 *d*‡	114 76 *d*	101 70 *d*	128 31 *d*	48 12, 47 76 *t*	125 14 *d*	—
C-5	98 64 *s*	71 42 *d*	70 99 *d*	201 57 *s*	201 53 *s*	202 62 *s*	214 04, 214 00 *s*	202 74 *s*	179 02 *s*
C-6	45 96 *d*	44 93 *d*	43 53 *d*	50 46 *d*	49 26 *d*	49 60 *d*	52 83, 52 60 *d*	49 70 *d*	45 33 *d*
C-7	80 69 *d*	84 38 *d*	81 86 *d*	80 65 *d*	80 38 *s*	80 39 *d*	81 16, 80 96 *d*	80 33 *d*	80 21 *d*
C-8	32 10 *t*	31 01 *t*	32 03 *d*	37 36 *t*	37 55 *t*	29 62 *t*	30 13 *t*	29 61 *t*	37 62 *t*
C-9	36 93 *t*	37 33 *t*	37 43 *t*	29 80 *t*	29 56 *t*	37 50 *t*	37 33 *t*	37 54 *t*	29 31 *t*
C-10	84 56 *s*	84 38 *s*	83 65 *s*	83 07 *s*	83 00 *s*	83 08 *s*	83 35 *s*	82 83 *s*	83 67 *s*
C-11	143 80 *d*	143 67 *d*	144 00 *d*	144 38 *d*	144 34 *d*	144 28 *d*	144 01 *d*	144 42 *d*	143 86 *d*
C-12	111 74 *t*	112 14 *t*	111 92 *t*	111 38 *t*	111 60 *t*	111 32 *t*	111 54 *t*	111 32 *t*	111 92 *t*
C-13	24 69 *q*†	31 27 *q*	30 93 *q*†	—	—	24 09 *q*†	18 40 *q*	29 28 *q*	—
C-14	13 03 *q*	12 30 *q*	12 96 *q*	13 16 *q*	13 76 *q*	12 95 *q*	12 92 *q*	12 99 *q*	13 19 *q*
C-15	27 00 *q*	26 91 *q*	26 47 *q*	26 46 *q*	26 51 *q*	26 46 *q*	26 51 *q*	26 46 *q*	26 52 *q*

*Run at 25 18 MHz in $CDCl_3$, shifts are in parts per million downfield from TMS

†,‡Assignments in the same column are interchangeable

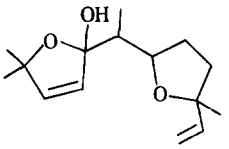


Scheme 3 Possible biogenetic relationships among the tetrahydrofuran-type terpenoid isolated from *T vulgare*

and **4**, in which H-6 can be *gauche* only to one oxygen atom, the β-orientation for the hydroxyl group seems likely

The stereochemistry at C-10 could not be established on the basis of spectral data alone, as in compounds of the linalyl oxide-type there is a surprising similarity of ^{13}C NMR chemical shift values between compounds belonging to the *cis* and *trans* series [12] The stereochemistry at this centre as well as the absolute configuration, were assessed by correlation of **2** with natural (+)-davanone (**1**) A plausible biogenetic route to **2** would involve photo-oxygenation of davanone (**1**) to afford the *cis*-$\Delta^{3,4}$-hydroperoxide **8**, and then direct [1, 2] attack of the highly nucleophilic hydroperoxyl group on the enone group (Scheme 3) Photo-oxygenation of (+)-davanone and chromatography of the reaction mixture gave mostly the *trans*-$\Delta^{3\ 4}$-hydroperoxide (**9**) However, small amounts of **2** were directly obtained from less polar fractions Therefore these results allowed us to assign a (5*S*,6*S*,7*S*,10*R*)-2,6,10-trimethyl-2,5-epidioxy-7,10-epoxydodeca-3,11-dien-5-ol structure to compound **2** Previous studies on the photo-oxygenation of davanone had shown that different compounds could be obtained according to the way in which the reaction mixture was reduced [20] When the latter was directly chromatographed on a silica gel column, it yielded small amounts of a compound believed to be the hemiketal **14** and 10% of a compound to which the structure of hydroxydavanone (**12**) was assigned [20] The coupling constant between H-3 and H-4 (J = 10 5 Hz, the same value as in **2**) in the published spectrum of **14** is scarcely consistent with the structure assigned [21] No samples of the compounds obtained in these studies were available for direct comparison with **2** and **9**, and we were unable to obtain compounds corresponding to **14** and **12** from the direct photo-oxygenation of **1**

Further elution during the column chromatography of the extract from the leaves gave the epimeric alcohols **10** and **11**, the hydroperoxide **9**, its corresponding alcohol **12** and the carboxylic acid **13** Compounds **10** and **11** could not be separated The assigned structures followed from ^{1}H NMR and ^{13}C NMR analysis of their mixture (Tables 2 and 3) These alcohols are known compounds [20], but to our knowledge have not been isolated previously from natural sources Only minute amounts of the hydroperoxide **9** were present in the leaves, but this compound was the major constituent of the flowers (Table 1) Reduction of **9** gave the known alcohol **12** (hydroxydavanone) [22] Compounds **9** and **12** were identical to the main product which we obtained during the photo-oxygenation of (+)-davanone and its reduction product, respectively A compound having the same constitution as **9** has recently been isolated from *Artemisia inculta* [23] The published spectral and physical data for this compound, whose stereochemistry was not established, are in good accordance with those of **9**, and it is therefore likely that these compounds are the same Comparison of the ^{13}C NMR spectra of **9** and **12** revealed the characteristic β-upfield and γ-downfield shifts typical of the allyl hydroperoxides relative to their corresponding alcohols [24] The ^{13}C NMR spectrum of **13** displayed only ten signals Besides the ones corresponding to the moiety **A**, a



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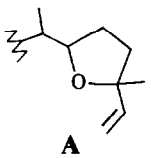

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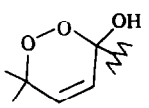

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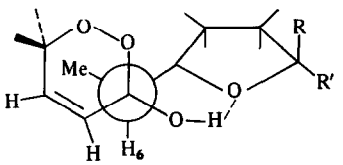

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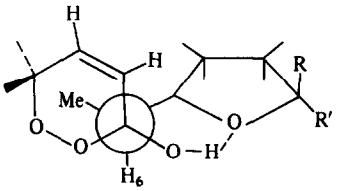

D

singlet at 179 02 ppm was present The latter was assigned to a carboxylic group owing to the presence of diagnostic bands at 3300–2700 and 1710 cm^{-1} in its IR spectrum Compound **13** has previously been obtained from the oxidation of davanone [11], and it has recently been synthesized stereospecifically [15] However, as far as we know, it has not been reported as a natural product Compound **13** might be formed from **2** through a cycloelimination reaction (Scheme 3) Compounds **10**, **11** and **13** are synthetically related to davanone [11, 20] However, the $[\alpha]_D$ values for these compounds have not been reported The absolute configuration of natural **10**, **11** and **13** is thus not known The fact that compounds **10**, **11** and **13** co-occur in *T vulgare* with compounds **1**, **2**, **9** and **12**, all having the absolute configuration 6*S*, 7*S* and 10*R*, might suggest that the absolute configuration at these centres is the same also for natural **10**, **11** and **13**

A possible biogenetic relationship among the compounds isolated from this genotype of *T vulgare* is depicted in Scheme 3 It is worth noting that the stereoselectivity of the first step (photo-oxygenation of davanone) is different in flowers and leaves In the flowers mostly the *trans*-$\Delta^{3,4}$-hydroperoxide (**9**) is formed (Table 1), while in the leaves formation of the *cis*-$\Delta^{3,4}$-hydroperoxide (**8**) prevails, and only small amounts of compounds derived from the *cis*-$\Delta^{3,4}$-hydroperoxide **9** are present

The genotype of *T vulgare* described here is most unusual in several aspects The mevalonate pathway is shifted towards the formation of sesquiterpenes, and consequently monoterpenes, which are the characteristic constituents of the oils from *T vulgare* [1, 2], are present only in small amounts Furthermore the sesquiterpenes produced are atypical for this species, as the other genotypes so far investigated gave mostly sesquiterpene lactones [3–9] or unlactonized analogues of them [10]

EXPERIMENTAL

High- and low-resolution mass spectra were determined on a Cratos MS80 and Varian MAT CH7 apparatus, respectively ^1H NMR and ^{13}C NMR spectra were obtained on a Varian XL 200 and Varian XL 100 spectrometer, respectively Kieselgel 60 (70–230 mesh, Merck) was employed for column chromatography, and pre-coated Kieselgel 60 F_{254} plates (Merck) were used for TLC and preparative TLC (thickness 2 mm) Spots were revealed by spraying with H_2SO_4–EtOH (1 1) and heating.

Plant material T vulgare came from experimental cultivations at the Research Institute for Medicinal Plants of Budakalász (Hungary), and was collected during the years 1982–1983 The flowers were collected in August, and the leaves in September Samples of leaves collected monthly from May to September during the year 1983 showed the same terpenoid pattern

Isolation of constituents Dried, powdered leaves (315 g) and flowers (50 g) were extracted separately with $CHCl_3$ at room temp The extracts so obtained were worked up by standard procedures [25] to give 6 2 g and 0 98 g of purified extracts, respectively, that were separated by CC on silica gel Compounds were eluted in the following order **1**, **2** [petrol (bp 50–70°)–$CHCl_3$, 3 1], **10**, **11** (petrol–$CHCl_3$, 1 1), **9**, **12**, **13** ($CHCl_3$) The yields are listed in Table 1

(5*S*,6*S*, 7*S*,10*R*)-2, 6, 10-*Trimethyl*-2,5-*epidioxy*-7,10-*epoxydodeca*-3,11-*dien*-5-*ol* (**2**) Colorless oil, $[\alpha]_D^{25}$ +0 45° ($CHCl_3$, *c* 2 16), $[\alpha]_{578}^{25}$ −2 02° ($CHCl_3$, *c* 2 16), IR $\nu_{max}^{liquid\ film}$ cm^{-1} 3400, 3080, no band in the carbonyl region, 1140, EIMS see Scheme 1, CIMS (NH_3) *m/z* (rel int) 286 $[M+NH_4]^+$ (10), 268 $[M]^+$ (18), 111 (100) Anal calc for $C_{15}H_{24}O_4$ mol wt 268 1674, found mol wt (mass spectrometry) 268 1679

Reduction of **2** *with* $LiAlH_4$ To a stirred suspension of $LiAlH_4$ (250 mg) in dry THF (2 ml), was added 185 mg of **2** dissolved in 3 ml of dry THF The mixture was stirred at room temp for 45 min, and then the excess of reagent was destroyed by addition of a few drops of EtOAc, followed by 10 ml of a cold satd $MgSO_4$ soln The mixture was extracted with $CHCl_3$ (4 × 10 ml), affording 161 mg of a mixture of compounds **3** and **4** This mixture (80 mg) was separated by prep TLC ($CHCl_3$–Me_2CO, 6 1) to yield 46 4 mg and 17 3 mg of pure diols as colorless oils The major diol had $[\alpha]_D^{25}$ +49 9° ($CHCl_3$, *c* 0 80), IR $\nu_{max}^{liquid\ film}$ cm^{-1} 3600, 3100, 1180 EIMS 70 eV, *m/z* (rel int) 239 $[M-15]^+$ (1), 221 $[M-15-18]^+$ (3), 203 $[M-15-18-18]^+$ (2), 125 (40), 111 (90), 97 (100), 93 (80), 69 (40), 55 (50) The spectral data for this compound are presented in Tables 2 and 3 before the ones of the minor diol The minor diol had $[\alpha]_D^{25}$ −27 5° ($CHCl_3$, *c* 0 41), IR $\nu_{max}^{liquid\ film}$ cm^{-1} 3600, 3100, 1160 EIMS 70 eV, *m/z* (rel int) 239 (0 5), 221 (3), 203 (6), 125 (40), 111 (97), 97 (100), 69 (50), 55 (46) The spectral data of this compound are presented in Tables 2 and 3 after the ones of the major diol

Fragmentation reaction of **2** To a soln of **2** (108 mg, 0 4 mM) in 0 5 ml $CDCl_3$ in a NMR sample tube, five drops of TAI were added This resulted in an exothermic reaction, and the soln became yellowish The ^1H NMR spectrum revealed the quantitative disappearance of compound **2**, and the formation of compound **5** After the registration of the spectrum, the contents of the NMR sample tube were poured into a cold 5% $NaHCO_3$ soln (or phosphate buffer, pH 7), which was extracted with

pentane (3 × 10 ml) The organic phase was dried ($MgSO_4$) and evaporated at 0° to yield 70 mg of **7** as a yellowish oil This compound was very unstable, and decomposed at room temp in $CDCl_3$ soln in 2 days

Photo-oxygenation of (+)-*davanone* Natural (+)-davanone (**1**) (820 mg), 96% purity by GLC, $[\alpha]_D^{25}$ +71° ($CHCl_3$, *c* 0 80) (lit values from +69° [26] to +77 7° [11]) was dissolved in MeOH (20 ml) containing 10 mg of methylene blue The mixture was irradiated with a 700 W halogen lamp with introduction of oxygen and cooling After 2 hr all of compound **1** had reacted, and the reaction mixture was worked-up by evaporating the solvent The residue was then dissolved in CH_2Cl_2 (25 ml) and passed through a short column of silica gel to remove the dye A yellowish oil (760 mg) was obtained The latter, when analysed by ^1H NMR spectroscopy, was found to be almost exclusively the hydroperoxide **9** The reaction mixture was then separated by CC on silica gel (45 g), 50 ml eluates were collected, and fractions were eluted in the following order petrol (bp 50–70°)–$CHCl_3$, 3 1 (fr 1–5), $CHCl_3$ (fr 6–16) and $CHCl_3$–Me_2CO, 9 1 (fr 17–22) Fractions 9–12 gave 28 mg of **2**, $[\alpha]_D^{25}$ +0 80°, $[\alpha]_{578}^{25}$ −1 60° ($CHCl_3$, *c* 0 70), fractions 17–20 gave 360 mg of **9** (yield 44%) $[\alpha]_D^{25}$ +48° ($CHCl_3$, *c* 1 2) The IR and ^1H NMR spectra of synthetic **2** and **9** were identical with those of the natural compounds Addition of TAI to synthetic **2** gave the enol ester **5**

(6S*,7S*, 10R*)-3-*Hydroxy*-2,6,10-*trimethyl*-7,10-*epoxydeca*-1,11-*dien*-5-*one* (ca 3 2 *mixture of* C-3 *epimers*) **10** + **11** Yellowish oil, $[\alpha]_D^{25}$ +10° ($CHCl_3$, *c* 0 60), IR $\nu_{max}^{liquid\ film}$ cm^{-1} 3500, 1705, 1360, EIMS 70 eV, *m/z* (rel int) 234 $[M-18]^+$ (1), 219 $[M-18-15]^+$ (2), 167 (5), 111 (50), 93 (40), 71 (38), 43 (100)

(6S,7S,10R)-2-*Hydroperoxy*-2,6,10-*trimethyl*-7,10-*epoxydeca*-3,11-*dien*-5-*one* (**9**) Colourless oil, $[\alpha]_D^{25}$ +48° ($CHCl_3$, *c* 0 83), IR $\nu_{max}^{liquid\ film}$ cm^{-1} 3300, 3090, 1690, 1660, 1640, UV λ_{max}^{EtOH} nm (log ε) 232 (3 2), EIMS 70 eV, *m/z* (rel int) 236 $[M-O_2]^+$ (2), 234 $[M-H_2O_2]^+$ (4), 129 (20), 111 (100), 93 (80), 71 (36)

Reduction of compound **9** A 20 mg sample of **9** (0 075 mM) was dissolved in 2 ml MeOH and the soln was treated with 22 mg (0 080 mM) of Ph_3P for 5 min at room temp The soln was evaporated to dryness, and the residue was purified by prep TLC ($CHCl_3$–Me_2CO, 6 1), affording 12 mg of compound **12**, $[\alpha]_D^{25}$ +38° ($CHCl_3$, *c* 0 5), IR, mass and ^1H NMR spectra superimposable with those of natural (+)-hydroxydavanone obtained from the extract of *T vulgare*

(6S,7S,10R)-2-*Hydroxy*-2,6,10-*trimethyl*-7,10-*epoxydodeca*-3,11-*dien*-5-*one* (*hydroxydavanone*) Colourless oil, $[\alpha]_D^{25}$ +44° ($CHCl_3$, *c* 0 35), IR $\nu_{max}^{liquid\ film}$ cm^{-1} 3300, 3090, 1690, 1660, 1640, UV λ_{max}^{EtOH} nm (log ε) 230 (3 0), EIMS 70 eV, *m/z* (rel int) 252 $[M]^+$ (1), 237 $[M-15]^+$ (11), 234 $[M-H_2O]^+$ (8), 193 (8), 166 (15), 142 (16), 138 (22), 111 (100), 93 (83)

(2S*,3S*,6R*)-2,6-*Dimethyl*-3,6-*epoxyocta*-7-*enoic acid* (**13**) Yellow gum, $[\alpha]_D^{25}$ +27° ($CHCl_3$, *c* 0 10), IR $\nu_{max}^{CHCl_3}$ cm^{-1} broad band between 3300 and 2700, 1710, 910, EIMS 70 eV, *m/z* (rel int) 184 $[M]^+$ (6), 169 $[M-15]^+$ (80), 111 (100), 93 (70), 81 (60), 55 (80)

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