220. Terpenoids Derived from Linalyl Oxide. Part 1. The Stereochemistry of the Davanones

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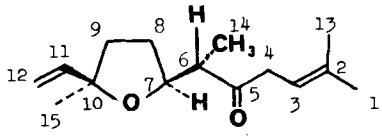
Summary. Natural (+)-davanone is 6*S*,7*S*,10*R*-2,6,10-trimethyl-7,10-oxidododeca-2,11-dien-5-one (**1**). Equilibration of davanone with base leads to the four possible isomers, but only a single deuterium atom is exchanged when deuterium oxide is the solvent.

Davanone (**1**) is the main component of the essential oil of *Artemisia pallens*, [1] and its synthesis has been accomplished [2]. The stereochemistry about the tetrahydrofuran ring is suggested to be *cis*, [2a, 2b] but rigorous proof is lacking, and there is no report of the stereochemistry about the other asymmetric center. In this communication, we show that the stereochemistry about the ring is definitely *cis*, and suggest that the most likely stereochemistry about the other center is *S*, thus making (+)-davanone 6*S*,7*S*,10*R*-2,6,10-trimethyl-7,10-oxidododeca-2,11-dien-5-one (**1**), the *cis,threo* isomer.



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The evidence for this assignment is based on the behavior of davanone on base-catalyzed equilibration, and on the NMR. spectra of the isomers of davanone.

Base-catalyzed equilibration of natural (+)-davanone in *t*-butyl alcohol leads within 30 minutes to a mixture of the four possible davanones in the proportions of about 12:7:30:50 (listed in order of elution on a column of Carbowax), natural davanone corresponding to the major isomer[2]). Use of methanol-d gives davanones containing only a single deuterium atom, presumably on the ring side of the carbonyl group, but not on the ring itself (although this position was epimerized) since the main fragment of the mass spectrum of deuterated davanone remains at *m/e* 111. If the exchange reaction is 'forced', by heating or by increasing the time of contact with base, the four isomers of the lower homolog of davanone, 3,7-dimethyl-4,7-

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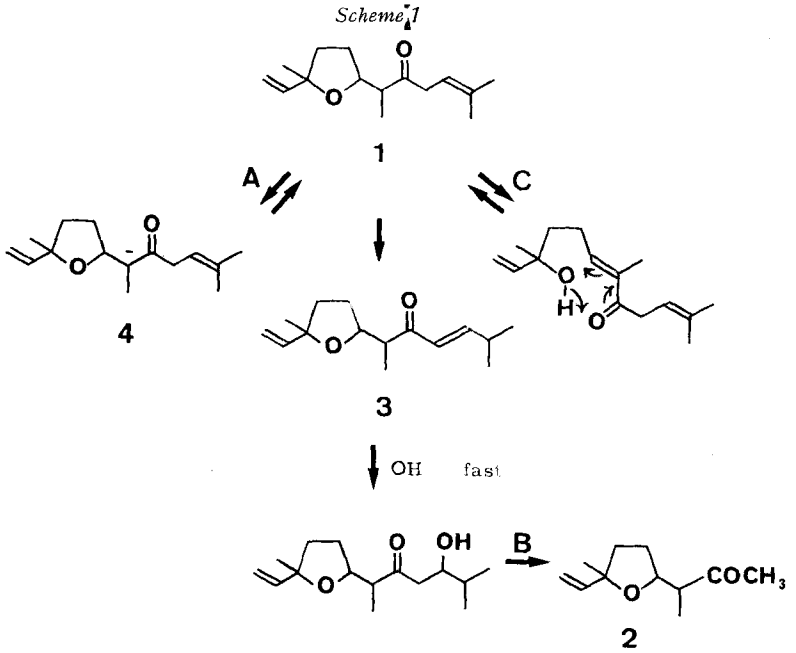
[2]) The order of retention times of the four davanone isomers on our polar packed Carbowax columns is not the same as that of *Naegeli & Weber* [2b] on their capillary columns, but natural davanone has the longest time in both cases.

oxido-oct-7-en-2-one (**2**), were isolated; these contained four deuterium atoms per molecule when deuterium oxide was used. One of these methyl ketones (the most polar on a Carbowax column) was identical with a substance isolated from the natural Davana oil [3].

Scheme 1



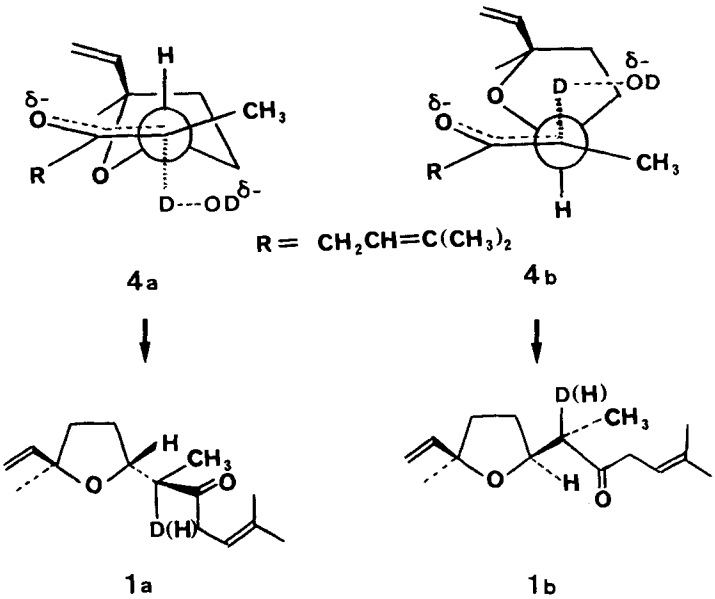
These facts can be explained following *Scheme 1*. Enolization of davanone apparently occurs preferentially on the side of the carbonyl group away from the double bond (reaction A), enolization on the double bond side of the carbonyl leading to the known [2a] isomer (**3**) which can undergo a rapid retro-aldol reaction (reaction B). Epimerization at the point of attachement to the tetrahydrofuran ring must occur through ring-opening (reaction C).

Considering the stereochemistry of the protonation of the enolates (**4**) formed by reaction A (*Scheme 2*), we can project the enolates from *trans*- or *cis*-davanones as **4a** and **4b** respectively, with the bulkier side chain lying towards the ring oxygen, this position possibly being also favored by hydrogen bonding with solvent. Torsional considerations [4] make it appear likely that the incoming proton will be placed in such a way that torsional interactions are at a minimum, *i.e.* as shown in *Scheme 2*[3]). In the case of both *trans*- and *cis*-enolates, this reasoning leads to the conclusion that the *threo* isomers (**1a**) and (**1b**) will be the major products.

The positioning of the carbonyl group towards the side of the molecule carrying the oxygen atom of the tetrahydrofuran ring is supported by the difference of chemical shift of representative protons between the value measured in deuteriochloroform

[3]) Several examples of the use of this idea to predict the stereochemistry of protonation of enolates have been quoted [5]; the stereoselective monodeuteration of (7α*H*)-longifolan-3-one [6] can also be explained in this way.

Scheme 2



(δ_{CDCl_3}) and benzene [2b] ($\delta_{C_6H_6}$). Fig. 1 illustrates values of $\Delta = \delta_{CDCl_3} - \delta_{C_6H_6}$ observed, and these show that the whole of the molecule lies behind the plane at right angles to the carbonyl group [7]. A corrolary of these measurements is that the major isomer, both of the *cis* and *trans* series has a Δ-value much greater than the minor

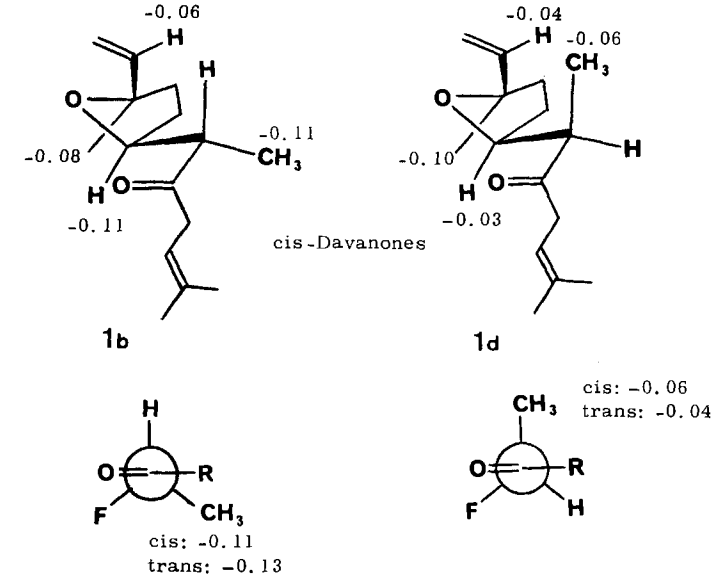


Fig. 1. *Values of Δ observed for davanones. Only the cis isomers are shown complete. The projections are drawn about the 5,6 bond.* F = tetrahydrofuran ring

isomer, *i.e.* the adjacent methyl group is further from the plane bisecting the carbonyl bond in the major isomer, which must therefore be *threo* (**1a**, **1b**) in both cases.

cis-Linalyl oxide (**5a**) has the double doublet for which the vinyl hydrogen is responsible at lower field than *trans*-linalyl oxide (**5b**) [8], and this has been quoted as evidence that natural davanone, having this double doublet at lower field than the other major isomer after equilibration, is *cis* and the other isomer *trans* [2a, 2b]. We have carried out measurements in the presence of the shift agent, $Eu(fod)_3$ [9], and find that the protons that are most displaced are those in the neighborhood of the carbonyl group, but the greatest proportional difference in shift between the two isomers is exhibited by the protons of the vinyl group, all being more affected in the davanone case than that of the isomer, confirming the fact that natural davanone is the *cis*-isomer (see Fig. 2). Double irradiation enabled the coupling constant be-

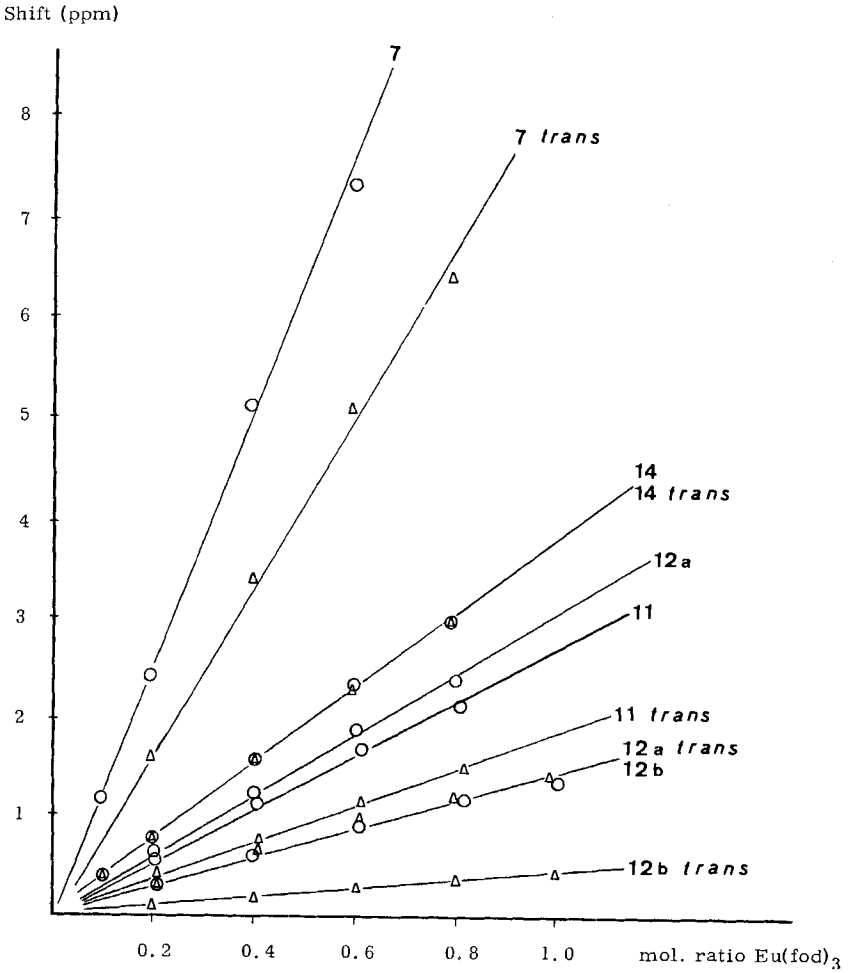
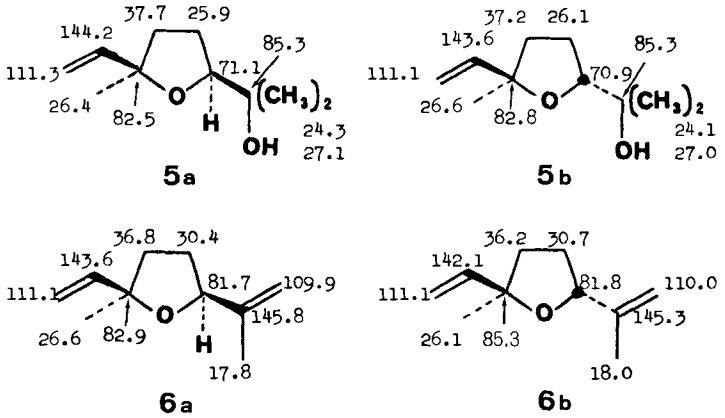


Fig. 2. *NMR.-values for certain protons in the presence of a shift agent.* ○ = davanone (**1b**), △ = *trans* davanone (**1a**). Numbers refer to the carbon atom to which the proton is attached

tween the protons at C(6) and C(7) to be measured, and this turned out to be distinctly higher (9 Hz) in the case of the major (*threo*) isomers (**1a**, **1b**) (6.5 Hz). Furthermore, the secondary methyl group on C(6) is more shielded in the case of the *erythro* isomers (**1c**, *trans* at 1.14, **1d**, *cis* at 1.20) than in that of the *threo* isomers (**1a**, *trans* at 1.01, **1b**, *cis* at 0.99), the two *cis* isomers showing the greater difference on account of the greater effect of the vinyl group.

For further confirmation of the stereochemistry of the davanones, natural abundance ^{13}C-NMR.-spectra of the natural products and structural models were inspected and chemical shift assignments performed[4]).

The proton-decoupled spectra and the single-frequency, off-resonance decoupled spectra revealed all carbon signals of chloroform solutions of *cis*-linalyl oxide (**5a**) and its dehydration product (**6a**) [8] and differentiated their various carbon atom types. The non-protonated carbon atoms in **6a** are unique permitting their shift assignment as well as that of the related centers in **5a**. The environment of the vinyl group being the same in both substances allows the determination of its shifts and the δ-value of the remaining olefinic methylene group in **6a**. The environmental dissimilarity of the methyl groups in **6a** distinguishes their shifts and, as a consequence, the methyl shifts of **5a**. The oxymethine is unique in both substances and the methylene group nearest the fully substituted ring carbon least perturbed by the side chain alterations in the two compounds. The larger number of β-effects and smaller number of γ-effects exerted on this methylene group by the substituents of its neighboring ring carbon deshield it with respect to the remaining ring methylene group. The latter is more shielded in **5a** than in **6a** in view of an additional γ-effect from the neighboring side chain.

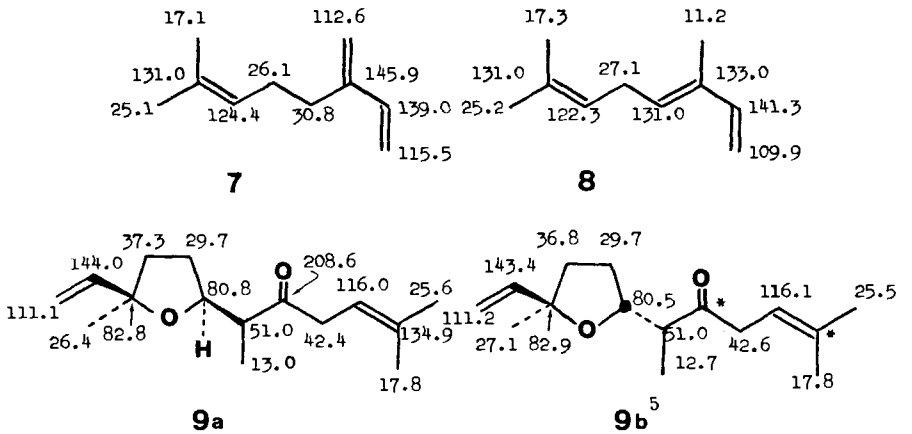


Chemical shift analysis of *trans*-linalyl oxide (**5b**) and its dehydration product (**6b**) followed the arguments advanced for the analysis of their *cis* isomers. The carbon shifts for all four substances are denoted on their formulas. Comparison of the shift data of the stereoisomer pairs indicates that three carbon atoms respond to

[4]) Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XXVII. For the preceding paper, see [11].

stereochemical changes, albeit only minimally. The olefinic methine and its nearest ring methylene group in the *cis* series are deshielded relative to these centers in the *trans*-series, while the non-protonated oxycarbon atom is shielded in the *cis*-series. The limited shift changes with stereochemistry in compounds **5** and **6** are in contrast with the striking shift differences encountered in more heavily substituted tetrahydrofurans, *e.g.* the furanoses [12].

The chemical shift analysis of the davanones is facilitated by compounds **6** and acyclic monoterpenes [11], *e.g.* myrcene (**7**) and *trans*-ocimene (**8**), acting as models for the methylvinyltetrahydrofuran unit and part of the side chain, respectively. Thus, the shifts of the non-protonated oxycarbonatom and its attached methyl, vinyl and methylene groups of *cis*-davanone (**9a**) and *trans*-davanone (**9b**) are nearly identical to the shifts of like centers in **6a** and **6b**, respectively. The methyl groups of the isopropylidene moiety have δ-values like those of related sites in **7** and **8**. The remaining ring methylene group can be differentiated from the methylene unit in the side chain by the latter being deshielded by the adjacent carbonyl group and by the similarity of the shifts of the former with those in models **6**. All other carbon atoms are distinguished by field position and/or multiplicity. As in the case of the substances **5** and **6**, the difference of the stereochemistry of the davanones is reflected in the shifts of the non-protonated oxycarbon and its adjacent methylene and olefinic methine groups.



Experimental Part

^{1}H-NMR.-spectra were recorded with a *Bruker* HX-90 spectrometer in $CDCl_3$, and chemical shifts are given in ppm with tetramethylsilane as 0.00 ppm. IR.-spectra were measured with a *Perkin-Elmer* type 125 spectrophotometer. Mass-spectra (MS.) were measured on an *Atlas* CH 4 mass spectrometer; using an inlet temperature of about 150° and electrons of 70 eV; alternatively, measurement was made by injection onto a capillary gas chromatography column coupled with the mass spectrometer. MS. are given as *m/e* (% most important fragment), and, generally, the ten most important fragments are listed. Gas chromatography (GLPC) was carried out on a *Carlo Erba* type GT instrument, using Carbowax 20M, 15% on Chromosorb W 60–80 mesh, acid washed, packed either in 3 m × 8 mm, or 5 m × 4 mm columns.

[5] The signals of the starred carbons were not observed because of the long relaxation times of the carbons and the low concentration of the ketone.

The ^{13}C-NMR.-spectra were recorded on a *Fourier* transform spectrometer operating at 15.08 MHz with a *Varian* Associates DP-60 magnet. The samples were spun in 13 mm o.d. tubes and the solvent signal used as internal standard. Chloroform was used as solvent and the δ-values denoted on the formulas are in ppm downfield from TMS; $\delta^{TMS} = \delta^{CHCl_3} + 77.2$ ppm.

Equilibration of (+)-*davanone.* To a solution of 0.4 g of potassium in 20 ml of dry *t*-butyl alcohol was added 1 g of (+)-davanone. The mixture was stirred for 26 h, then pentane and water were added, and the organic layer was washed to neutrality, dried, and concentrated. The residue was distilled, b.p. 82°/0.01 Torr, and purified by GLPC. The proportions of the isomers (see theoretical part) were essentially the same when 1 g of davanone was warmed for 30 min to 60° with a solution of 0.1 g of sodium in 5 ml of dioxan and 5 ml of water. After purification, the recovered davanone had $[\alpha]_D^{20} = +81° \pm 3°$ (7.4% in $CHCl_3$), and the *trans,threo* isomer, with a slightly shorter retention time on Carbowax, had $[\alpha]_D^{20} = -66° \pm 3°$ (7.6% in $CHCl_3$).

The reaction was carried out in the presence of deuterium by allowing 0.5 g of (+)-davanone to react for 2 h at room temperature with about 0.1 g of sodium dissolved in 10 ml of methanol-O-d. The MS. of the recovered davanone had the molecular ion (M^+) at *m/e* 237, representing over 90% d_1, and the most important fragment at *m/e* 111 [1]. A similar result was obtained when the equilibration in aqueous dioxan described above was carried out using deuterium oxide in place of water.

In all these reactions, traces of substances with much shorter retention times were observed; these corresponded to the retention times of the nordavanones [3]; the following is more convenient to have larger amounts.

A mixture of 2 g of (+)-davanone was heated at reflux with 250 ml of ethanol and 250 ml of 10% aqueous sodium hydroxide for 5 h. The products were isolated in pentane and distilled. There was obtained a fraction (0.7 g) with b.p. 36°/0.02 Torr, that corresponded in retention times and spectrally with the equilibrium mixture of the four nordavanones [3].

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