

THE TOTAL SYNTHESIS OF RACEMIC

DAVANONE

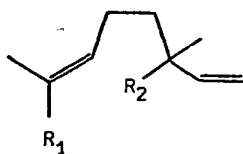
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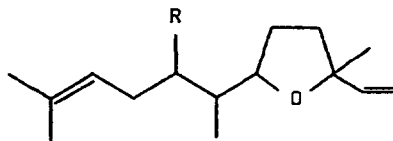
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Davanone, a dextrorotatory sesquiterpene ketone from the essential oil of *Artemisia pallens*, Wall., has recently been assigned structure I with no stereochemical specifications (1).

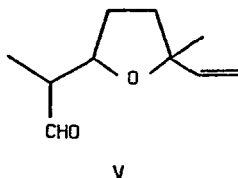
We wish to report a total synthesis of rac. davanone, starting from rac. linalyl acetate (II).



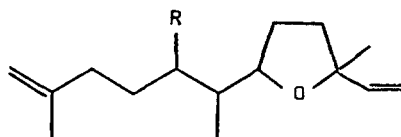
II : R<sub>1</sub> = CH<sub>3</sub>; R<sub>2</sub> = OAc  
III : R<sub>1</sub> = CHO; R<sub>2</sub> = OAc  
IV : R<sub>1</sub> = CHO; R<sub>2</sub> = OH



Ia-Id : R = O  
VIII : R = OAc  
IXa-IXd : R = OH



V



VI : R = OH  
VII : R = OAc

Treatment of the latter with an equimolar amount of SeO<sub>2</sub> in 95% dioxane at 70°C gave, after chromatographic and distillative purification, the acetoxy-aldehyde III (35% yield), most probably as the trans form (2).

$\lambda_{\max}$ : 224 nm,  $\epsilon = 18700$  (3).

$\nu_{\max}$ : 2720, 1735, 1685, 1640, 1365, 1250, 1170, 1105, 1020, 940, 930  $\text{cm}^{-1}$  (4).

NMR ( $\text{CDCl}_3 + \text{TMS}$ ):  $\delta = 9.37$  (1H, s); 6.52 (1H, m); 6.03 (1H, dd,  $J_1 = 18\text{cps}$ ,  $J_2 = 10\text{cps}$ ); 5.30 and 5.06 (2H, 2m); 2.03 (3H, s); 1.76 (3H, broad s); 1.61 ppm (3H, s).

NMR ( $\text{C}_6\text{D}_6 + \text{TMS}$ ):  $\delta = 9.27$  (1H, s); 5.91 (1H, dd); 1.76 (3H, s); 1.67 (3H, broad s); 1.47 ppm (3H, s) (5).

This was reacted with a 5% sodium carbonate solution in 75% MeOH at 50°C, yielding after chromatography on silica a 60% yield of compounds IV and V (in a ratio of about 1:1).

Cyclic aldehyde V proved to be a mixture of four diastereoisomers (ratio 24:30:19:27) on a polar glasscapillary VPC-column.

$\nu_{\max}$ : 2720, 1727, 1644, 1455, 1370, 1126, 1100, 1040, 994, 920  $\text{cm}^{-1}$ .

NMR ( $\text{CDCl}_3 + \text{TMS}$ ):  $\delta = 9.83$  (1H, m); 5.94 and 5.88 (1H, 2dd,  $J_1 = 18\text{cps}$ ,  $J_2 = 10\text{cps}$ ); 4.18 (1H, m); 1.28 (3H, s); 1.14/1.11/1.06/1.03 ppm (3H, 4d,  $J = 7\text{cps}$ ).

NMR ( $\text{C}_6\text{D}_6 + \text{TMS}$ ):  $\delta = 9.66$  and 9.50 (1H, 2m); 5.87 and 5.80 (1H, 2dd,  $J_1 = 18\text{cps}$ ,  $J_2 = 10\text{cps}$ ); 5.31/5.02/4.86 (2H, 3m); 3.93 (1H, m); 2.25 (1H, m); 1.20 (3H, s); 1.04/0.99/0.87/0.82 ppm (3H, 4d,  $J = 7\text{cps}$ ).

Subsequent reaction with the Grignard reagent of 3-methyl-but-3-en-1-yl bromide [synthesized from the corresponding alcohol (6) via the tosylate and treatment with lithium bromide] in THF furnished a mixture of diastereomeric alcohols VI.

$\nu_{\max}$ : 3450, 1650, 1450, 1372, 1100, 1040, 1030, 995, 925, 890  $\text{cm}^{-1}$ .

NMR ( $\text{CDCl}_3 + \text{TMS}$ ):  $\delta = 5.96$  and 5.90 (1H, 2dd,  $J_1 = 18\text{cps}$ ,  $J_2 = 10.5\text{cps}$ ); 5.31/5.05/4.90 (2H, 3m); 4.72 (2H, dd); 1.75 (3H, broad s); 1.30 and 1.28 (3H, 2s); centre 0.90 ppm (3H, 4d,  $J = 7\text{cps}$ ).

Acetylation with pyridine-acetic anhydride led to the corresponding acetates VII.

$\nu_{\max}$ : 1742, 1655, 1453, 1375, 1245, 1196, 1050, 1025, 1000, 927, 895  $\text{cm}^{-1}$ .

NMR ( $\text{CDCl}_3 + \text{TMS}$ ):  $\delta = 5.92$  and 5.86 (1H, 2dd,  $J_1 = 18\text{cps}$ ,  $J_2 = 10\text{cps}$ ); 4.70 (2H, broad s); 3.82 (1H, m); 2.03 (3H, s); 1.73 (3H, m); 1.28 (3H, s); centre 0.96 ppm (3H, 4d,  $J = 7\text{cps}$ ).

Transformation of these into the diastereomeric acetates VIII was effected by 5% p-toluene sulfonic acid in refluxing benzene.

$\nu_{\max}$ : 1742, 1645, 1453, 1375, 1245, 1050, 1025, 1000, 927, 858  $\text{cm}^{-1}$ .

NMR ( $\text{CDCl}_3 + \text{TMS}$ ):  $\delta = 5.94$  and 5.86 (1H, 2dd,  $J_1 = 17\text{cps}$ ,  $J_2 = 10\text{cps}$ ); 3.84 (1H, m); 2.28 (2H, broad t); 2.01 (3H, s); 1.28 (3H, s); 1.06/0.98/0.90/0.88 ppm (3H, 4d,  $J = 7\text{cps}$ ).

Careful chromatography on silica allowed the separation into four components, which were hydrolyzed individually by 5% methanolic KOH giving four davanol fractions (IXa-IXd in order of elution from silica). Each of them showed only one peak on a glasscapillary VPC-column.

$\nu_{\max}$ : 3470, 1645, 1450, 1375, 1305, 1245, 1180, 1100, 1045, 995, 922, 862  $\text{cm}^{-1}$  (7).

NMR of IXa ( $\text{C}_6\text{D}_6 + \text{TMS}$ ):  $\delta = 5.78$  (1H, dd,  $J_1 = 17.5\text{cps}$ ,  $J_2 = 10\text{cps}$ ); 2.30 (3H, m); 1.18 (3H, s); 1.02 ppm (3H, d,  $J = 7\text{cps}$ ).

NMR of IXb ( $C_6D_6$ +TMS):  $\delta$  = 5,80 (1H,dd,  $J_1=17,5$  cps,  $J_2=10$ cps); 2,30 (2H,m); 1,20 (3H,s);  
0,90 ppm (3H,d,  $J=7$ cps).

NMR of IXc ( $C_6D_6$ +TMS):  $\delta$  = 5,88 (1H,dd,  $J_1=17$ cps,  $J_2=10$ cps); 2,30 (2H,m); 1,19 (3H,s);  
1,05 ppm (3H,d,  $J=6,5$ cps).

NMR of IXd ( $C_6D_6$ +TMS):  $\delta$  = 5,86 (1H,dd,  $J_1=17$ cps,  $J_2=10$ cps); 2,25 (2H,broad t); 1,22 (3H,s);  
0,86 ppm (3H,d,  $J=7$ cps).

IXd, the fraction eluted last from the silica column, shows identical IR, MS and NMR spectra as well as VPC-retention time as the minor epimer of davanol, obtained by reducing natural davanone with  $LiAlH_4$  in ether.

Finally all of the four davanol fractions (IXa - IXd) were converted to the four racemic davanones Ia - Id by rapid oxydation with Jones reagent in acetone solution at  $-5^\circ C$ .

$\lambda_{max}$ : 207 nm,  $\epsilon$  = 4000.

$\nu_{max}$ : 1713,1645,1452,1372,1185,1125,1110,1100,(1045),1030,995,920  $cm^{-1}$  (7).

NMR of Ia ( $C_6D_6$ +TMS):  $\delta$  = 5,78 (1H,dd,  $J_1=17$ cps,  $J_2=10$ cps); 4,06 (1H,m); 3,12 (2H,broad d);  
1,20 (3H,s); 1,08 ppm (3H,d,  $J=7$ cps).

NMR of Ib ( $C_6D_6$ +TMS):  $\delta$  = 5,76 (1H,dd,  $J_1=17$ cps,  $J_2=10$ cps); 4,01 (1H,m); 3,18 (2H,broad d);  
1,21 (3H,s); 0,88 ppm (3H,d,  $J=7$ cps).

NMR of Ic ( $C_6D_6$ +TMS):  $\delta$  = 5,89 (1H,dd,  $J_1=17$ cps,  $J_2=10$ cps); 4,10 (1H,m); 3,07 (2H,broad d);  
1,20 (3H,s); 1,14 ppm (3H,d,  $J=7$ cps).

NMR of Id ( $C_6D_6$ +TMS):  $\delta$  = 5,88 (1H,dd,  $J_1=17$ cps,  $J_2=10$ cps); 4,01 (1H,m); 3,24 (2H, broad d);  
1,18 (3H,s); 0,88 (3H,d,  $J=7$ cps).

The isomer Id (obtained from IXd) shows identical UV, IR, MS and NMR spectra as well as identical retention time on a glasscapillary VPC-column as natural davanone (8).

If one compares the downfield shift of the centre of the lowfield vinylic hydrogen NMR resonances going from trans-linalool oxyde to cis-linalool oxyde [ $\Delta\delta = 0,08$  ppm (9)] with the one observed going from IXb to IXc or IXa to IXd and bearing in mind that the vinyl groups in the linalool oxydes and the davanols are in a similar molecular environment, one is tempted to assign a cis relationship to the vinyl and the ketonic side chain groupings at the tetrahydrofuran moiety of natural davanone.

Further work in this direction is continued and will be reported later.

We are much obliged to Dres. P. Schudel and M. Pesaro for helpful discussion.

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- (3) UV spectra are given for cyclohexane solutions.
- (4) IR spectra were measured for liquids on PE 157 and 257 spectrometers.
- (5) NMR spectra were measured on a Varian A 60 A instrument.
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- (7) IR spectra of isomers show slight but distinct differences.
- (8) We thank Dr. Klimeš of our laboratory for providing us with natural davanone.
- (9) D. Felix et al., Helv. Chim. Acta 46, 1513 (1963).