

SYNTHESIS OF SESQUITERPENOIDS RELATED TO NOOTKATONE--STRUCTURE DETERMINATION
BY NMR USING TRIS(DIPIVALOMETHANATO)EUROPIUM

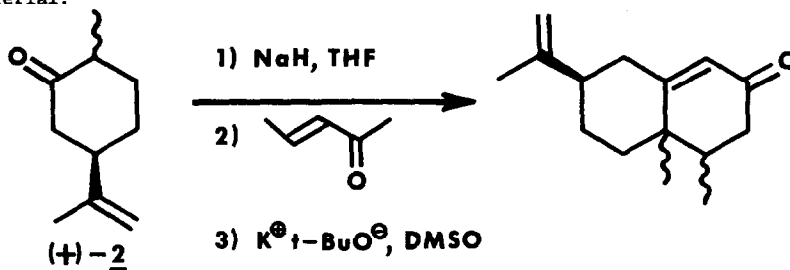
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The total synthesis of racemic nootkatone (1), a sesquiterpenoid whose (+)-antipode is found in grapefruit¹, has been reported independently by Schudel² and Marshall³. The following describes a synthesis leading to a series of compounds related to 1.

(+)-Dihydrocarvone⁴ (2) was prepared from (-)-carvone by reduction⁵ or from (+)-limonene by oxidation⁶. The anion of (+)-2 (method of McQuillin⁷) was condensed with trans-3-penten-2-one. Dehydration with potassium tert-butoxide in DMSO afforded a mixture of enones and starting material.



Unchanged (+)-2 (47% by weight) was removed by distillation and a mixture of products was obtained, bp 85-115° (3μHg); spectral data indicated that these products were isomers having the general structure drawn above.

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The major component (61% by glc) was separated by preparative glc, and structure 3 was assigned from spectroscopic properties. The IR spectrum of 3 exhibits bands at 1670 cm^{-1} (shoulder at 1680 cm^{-1} , $>\text{C}=\text{O}$) and 895 cm^{-1} ($>\text{C}=\text{CH}_2$); the molecular weight is 218 (obtained from mass spectrometry). The nmr spectrum (100 MHz) in CCl_4 of 3 shows a doublet at 0.96-0.89 ppm (3H), a singlet at 1.09 (3H), a singlet (slightly split) at 1.69 (3H), a doublet at 4.83-4.75 (2H), and a singlet (slightly split) at 5.68 (1H).

Figure 1 illustrates the nmr spectrum of 1, whose absolute configuration is known^{1,8}, in CCl_4 with tris(dipivalomethanato)europium⁹ [$\text{Eu}(\text{DPM})_3$] present as a shift reagent. The nmr spectrum of 3 under the same conditions is shown in Figure 2. The splitting pattern for H_1 , H_2 , and H_3 in both are superimposable; the gem $J_{1,2} = 17$ cps, the transdiaxial $J_{2,3} = 14$, and the equatorial-axial $J_{1,3} = 5$. Therefore, the vicinal methyls in 3 must be cis as in 1. In addition, H_7 must be equatorial since the twelve line pattern for H_5 and H_6 (assigned on the basis of decoupling experiments) does not show any transdiaxial coupling between H_6 and H_7 ($J_{5,6} = 14$; $J_{5,7} = 2$; $J_{6,7} = 2$; and $J_{4,5} = 6$). Thus, the isopropenyl group is axial. The use of $\text{Eu}(\text{DPM})_3$ as a shift reagent provides a simple, convenient, and rapid method of determining the structure of a complex molecule.

Hydrogenation of 3 in acetic acid with Pd-C (conditions which are known to isomerize axial isopropenyl substituents to the equatorial position¹⁰) gave a different product than the hydrogenation of 3 in ethanol with Pt-C (conditions which do not bring about isomerization). This chemical evidence supports the conclusion that the isopropenyl group is indeed axial.

A further investigation of this reaction and the structures of the other isomeric products is underway.

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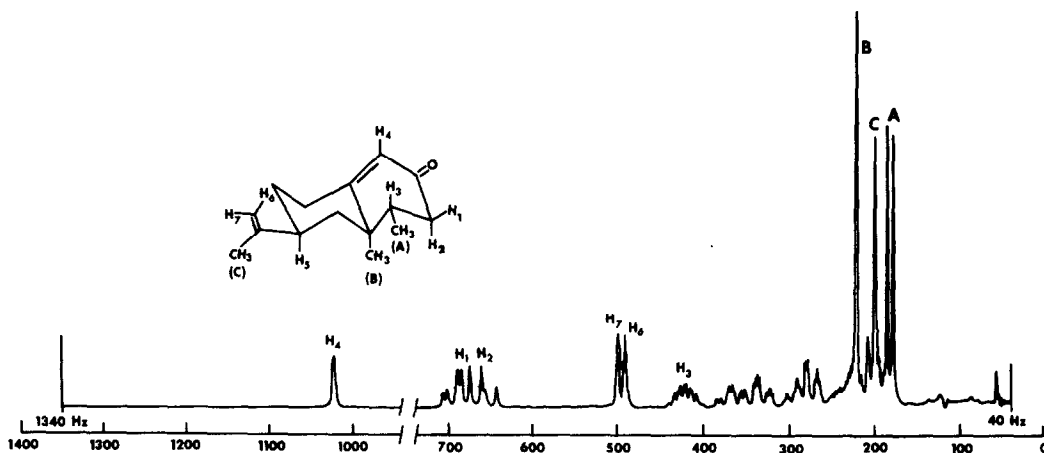


Figure 1. NMR spectrum (100 MHz) of nootkatone (1) in CCl_4 with TMS and $\text{Eu}(\text{DPM})_3$ present. The ratio of moles of substrate to moles of $\text{Eu}(\text{DPM})_3$ was 3 to 1.

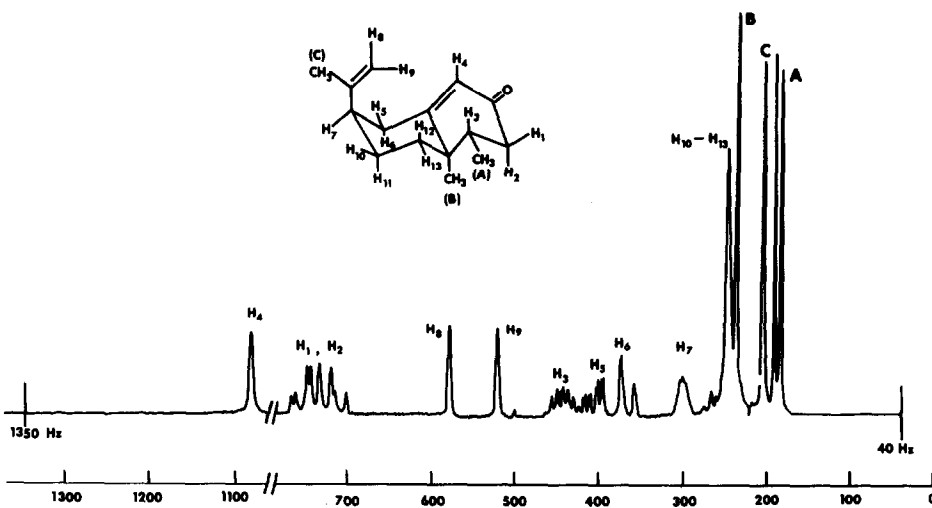


Figure 2. NMR spectrum (100 MHz) of 3 in CCl_4 with TMS and $\text{Eu}(\text{DPM})_3$ present. The ratio of moles of 3 to moles of $\text{Eu}(\text{DPM})_3$ was 3 to 1.