

The Preparation and Microbiological Hydroxylation of the Sesquiterpenoid Nootkatone

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The sesquiterpenoid nootkatone has been prepared from valencene by copper(I) iodide catalysed oxidation with *tert*-butyl hydroperoxide and hydroxylated at C-9 by *Mucor plumbeus* and *Cephalosporium aphidicola*.

The sesquiterpenoid nootkatone **3** is a major contributor to the aroma of grapefruit and it is present in commercial flavourings.^{1,2} Consequently its synthesis has attracted considerable interest.^{3,4} Recently it has been reported⁵ to show inhibitory activity against a range of cytochrome P₄₅₀ enzymes responsible for drug inactivation. However, little is known of the metabolism of nootkatone. Consequently it was of interest to see if nootkatone was hydroxylated by microbial systems.

Although nootkatone **3** is available commercially, it has been prepared by oxidation of the more readily available valencene **1** with *tert*-butyl chromate.^{6,7} An alternative cleaner oxidation of valencene **1** was based on the copper(I) iodide catalysed reaction with *tert*-butyl hydroperoxide.⁸ The major product (49%) was nootkatone **3** which was identified by its ¹H and ¹³C NMR spectra. Two minor products were the *tert*-butylperoxy ethers **2** and **4**. Application of the same reaction to valerianol **8** gave the unsaturated ketone **9**.^{9,10} Reduction of nootkatone **3** with sodium borohydride in methanol gave 2 α -hydroxy-4 α ,5 α -eremophil-1(10),11-diene **10**.

Incubation of nootkatone **3** with *Mucor plumbeus* gave the 9 α - and 9 β -hydroxy-2-oxo-4 α ,5 α -eremophila-1(10),11-dienes **5** and **6**, respectively whilst incubation of 2 α -hydroxy-4 α ,5 α -eremophila-1(10),11-diene **10** with *M. plumbeus* gave the nootkatone **3** and the epimeric C-9 alcohols **5** and **6**. However incubation of 11-hydroxy-2-oxo-4 α ,5 α -eremophila-1(10)-ene **9** with *M. plumbeus* gave no transformation products and the starting material was recovered. Incubation of nootkatone with *Cephalosporium aphidicola* gave 9 α -hydroxynootkatone **5**, and 11,12-dihydroxynootkatone **11**.

The microbiological hydroxylation of $\alpha\beta$ -unsaturated ketones typically affords the axial allylic alcohol.¹¹ The formation of both epimers in the case of the hydroxylation of nootkatone may be the result of a facile epimerization. It is interesting to note that although nootkatone underwent microbiological hydroxylation, 2-oxovalerianol **9** was resistant to attack by *M. plumbeus*.

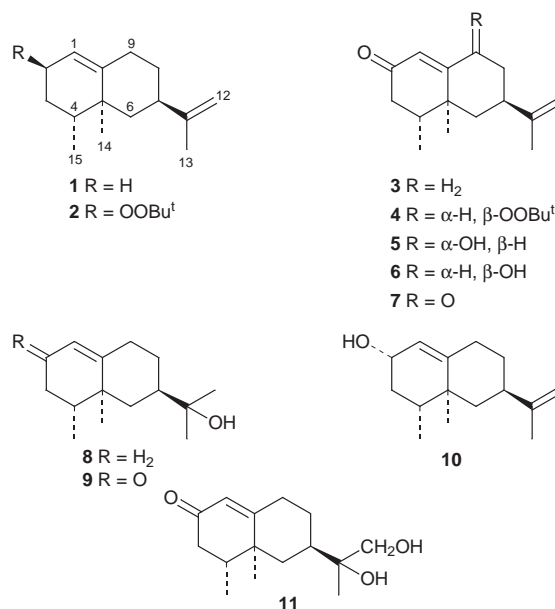
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Techniques used: ¹H and ¹³C NMR, MS, chromatography, microbiological transformation

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Table 1: ¹³C NMR data for the reaction products of valencene

Table 2: ¹³C NMR data for nootkatone and its metabolites



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