# Biosynthesis of the Terpenoid Dendrobine. Early Stages of the Pathway

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*Summary* 2-*trans*,6-*trans*-farnesol is shown to be a precursor in the biosynthesis of dendrobine rather than the 2-*cis*, 6-*trans*-isomer; the 1-*pro-R* hydrogen of farnesol is involved in a 1,3-shift in the early stages of the pathway.

A COMMENT[1] on our work on the biosynthesis of dendrobine[2] prompts us to present further results.†

[1-$^3H_2$]-2-*trans*,6-*trans*-farnesol (10 mCi) was fed to living plants of *Dendrobium nobile* as a water suspension with Tween 80 as emulsifier. After 15 days the plants were extracted as usual and the resulting dendrobine (**1**) showed an incorporation of tritium of 0·01% (12·8 × $10^5$ d.p.m. $mmol^{-1}$). Chemical degradation to the already described[2] diphenylolefin (**2**) (6·14 × $10^5$ d.p.m. $mmol^{-1}$) and

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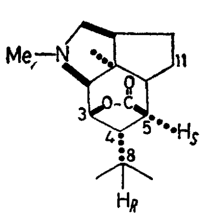
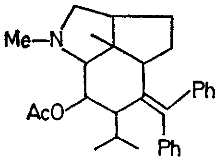
† Some of these results were discussed at the EUCHEM Conference on the Chemistry and Biosynthesis of Steroids and Terpenoids, La Laguna, Canary Isles, Spain, September 1974.

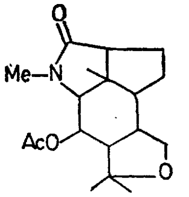
the tetrahydrofuran derivative (**3**) ($6{\cdot}8 \times 10^6$ d.p.m. $\text{mmol}^{-1}$) localized 52% of the label at C(5) and 47% at C(8). Feeding of [1-$^3H_2$]-2-*cis*,6-*trans*-farnesol resulted in a negligible incorporation of radioactivity into dendrobine.



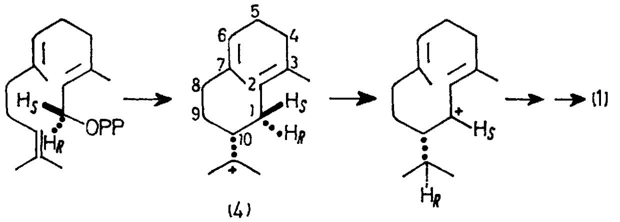
(1)



(2)



(3)



(4)

(1*S*)-[1-$^3$H]-2-*trans*,6-*trans*-farnesol (5 mCi) was also given to *D. nobile* and the extracted dendrobine showed an incorporation of tritium of the same magnitude as the racemic precursor (0·015% and 0·020% in two parallel experiments). The transformation of (**1**) into (**2**) resulted in the loss of more than 88% of tritium from C(5). Again, feeding (1*S*)-[1-$^3$H]-2-*cis*,6-*trans*-farnesol resulted in no appreciable labelling of dendrobine.

The experiment with [1-$^3H_2$]2-*trans*,6-*trans*-farnesol unambiguously establishes that the hydrogen atom at C(8) of dendrobine originates from C(1) of farnesol; the existence of many muurolanes and cardinanes with both hydrogens at C(9)‡ and the need for a reactive centre at C(1) of the germacrene intermediate (**4**) to accomplish the second cyclization was largely in favour of this proposal[2,3] which has now been confirmed. The incorporation of (1*S*)-[1-$^3$H]-2-*trans*,6-*trans*-farnesol reveals that this hydride shift has a high degree of stereospecificity, the 1-*pro-R* hydrogen being transferred.§

These results confirm that in our system farnesal is not mediating *trans-cis* isomerization of farnesol,[4] and also substantiate the hypothesis previously presented[2] about the configuration of double bonds in dendrobine precursors. The lack of incorporation of 2-*cis*,6-*trans*-farnesol into dendrobine suggests that the germacradiene (**4**) is formed in a *trans*,*trans*-configuration and only in the following steps is the configuration or the position of the 2,3-double bond modified to fulfil the geometrical requirements for the ring closure of the muurolane intermediate.[5]

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‡ Numbering in germacranes and muurolanes refers to the corresponding carbon atoms in farnesol, according to the proposed scheme of cyclization.

§ At the 9th IUPAC Symposium on the Chemistry of Natural Products (Ottawa, June 1974), D. Arigoni described feeding experiments in *D. nobile* with (5*R*)- and (5*S*)-[5-$^3$H]mevalonic acid; from these precursors, the 1,3-hydride shift also involves transfer of the 1-*pro-R* hydrogen.

[1] E. McDonald, *Ann. Reports* (*B*), 1973, **70**, 600.
[2] A. Corbella, P. Gariboldi, and G. Jommi, *J.C.S. Chem. Comm.*, 1973, 729.
[3] A. Corbella, P. Gariboldi, and G. Jommi, *J.C.S. Chem. Comm.*, 1972, 600.
[4] K. H. Overton and F. M. Roberts, *Phytochemistry*, 1974, **13**, 2741; R. Evans, A. M. Holton, and J. R. Hanson, *J.C.S. Chem. Comm.*, 1973, 465; L. Chayet, R. Pont-Lezica, C. George-Nascimento, and O. Cori, *Phytochemistry*, 1973, **12**, 95.
[5] K. Yoshihara, Y. Ohta, T. Sakui, and Y. Hirose, *Tetrahedron Letters*, 1969, 2263.