Hydrogen Rearrangements in the Biosynthesis of the Sesquiterpenoid, Alliacolide

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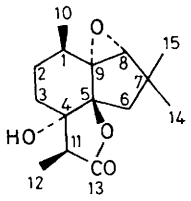
The occurrence of hydrogen rearrangements to C-1 and from C-5 to C-6 during the biosynthesis of alliacolide has been demonstrated by ^2H n.m.r. experiments.

Alliacolide (**1**) is one of a group of biologically active metabolites of the Basidiomycete, *Marasmius alliaceus*.[1–3] Recently we have shown[4] that the labelling pattern from [1-^{13}C]- and [1,2-^{13}C]-acetate is consistent with the formation of the sesquiterpenoid carbon skeleton from the three isoprene units as shown in (**2**). Examination of the mevalonoid hydrogen labelling pattern now reveals that a number of rearrangements are involved in this biosynthesis.

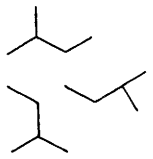
[4(*R*)-4-^{3}H,2-^{14}C]- and [5-$^3H_2$,2-^{14}C]-mevalonic acids (MVA's) were fed to *Marasmius alliaceus* after 14 days growth. The alliacolide (**1**) was isolated after a further 21 days and converted into dehydroalliacolide (**3**). The ^3H:^{14}C results are given in Table 1. Two of the three centres (C-4 and C-9) which would be expected to be labelled by [4(*R*)-4-^{3}H]MVA are fully substituted and hence, in order to account for the incorporation of two labels, one *pro*-4(*R*)-mevalonoid hydrogen atom must be involved in a rearrangement. The site of the 4-mevalonoid labels was determined using [4-$^2H_2$]mevalonate.

Careful proton spin decoupling studies at 360 MHz enabled the proton resonances of dehydroalliacolide to be assigned [see (**3**)]. Signals in the ^2H n.m.r. spectrum at δ 1.83 and 1.03, corresponding to 1-H and 6-H respectively, were found to be enriched in samples prepared biosynthetically from [4-$^2H_2$]mevalonate. C-1 was thus the terminus of a hydrogen rearrangement involving a *pro*-4(*R*)-mevalonoid hydrogen atom.

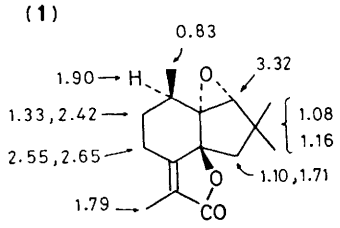
One of the centres (C-5) which would be expected to be labelled by a [5-^{3}H]mevalonate is fully substituted and another (C-8) bears only one hydrogen atom. Therefore in order to account for the incorporation of the fourth [5-^{3}H]-mevalonoid label, it must also be involved in a rearrange-



(1)



(2)



(3)

^{1}H N.m.r. signals (from Me_4Si) of dehydroalliacolide were determined in $CDCl_3$ at 360 MHz.

Table 1. Incorporation of mevalonates into alliacolide (**1**) and dehydroalliacolide (**3**).

	[4(*R*)-4-^{3}H,2-^{14}C]MVA	[5-$^3H_2$,2-^{14}C]MVA
^{3}H:^{14}C ratio in MVA	12.98:1	22.6:1
Atom ratio	3:3	6:3
Quantity fed (μCi ^{14}C)	11.8	13.15
^{3}H:^{14}C ratio in (**1**)	8.22:1	14.93:1
Atom ratio	1.90:3	3.96:3
% Incorporation (^{14}C)	0.99	1.59
^{3}H:^{14}C ratio in (**3**)	8.14:1	15.09:1
Atom ratio	1.9:3	4:3

ment. Since there was no change in the ^{3}H:^{14}C atom ratio in the formation of dehydroalliacolide (**3**), the extra label is not at C-11 (*cf.* avocettin biosynthesis).[5] The sites of labelling were located by feeding [5-$^2H_2$]mevalonate to *Marasmius alliaceus*. Signals assigned to 3-H (α and β) (δ 2.62), 6-H (δ 1.71), and 8-H (δ 3.34) in the ^{2}H n.m.r. spectrum of the resultant dehydroalliacolide were enriched. Hence the rearrangement has led to a label at C-6. This rearrangement may involve a 1,2-shift (C-5 → C-6) or a 1,3-shift (C-8 → C-6). The former occurs within an isoprene unit and may therefore be distinguished from the latter by the use of [5-$^2H_2$,4-^{13}C]-mevalonate. In the case of a 1,2-shift, a ^{2}H:^{13}C coupling will be generated whilst, provided there is a sufficient dilution with unlabelled material, a 1,3-shift will occur between labelled and unlabelled isoprene units and no such coupling will result. Since deuterium has a spin of 1 and carbon-13 a spin of $\frac{1}{2}$, these couplings are more easily observed in the deuterium spectrum. The dehydroalliacolide (**3**) derived from [5-$^2H_2$,4-^{13}C]mevalonate, showed a doublet, J 21 Hz, in place of a singlet at δ 1.71 in accordance with a 1,2-shift.

Alliacolide joins the increasing number of terpenoid substances in which a secondary methyl group has been shown to be generated by a hydrogen rearrangement.[6] Furthermore many sesquiterpenoids derived from the Basidiomycetes contain a cyclopentane ring bearing a methylene group which is probably labelled by C-4 of mevalonate. The present results suggest these methylenes might also be generated by a hydrogen shift.

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