Incorporation of [2-$^3H_2$]- and [4(*R*)-4-^{3}H]-Mevalonoid Hydrogen Atoms into the Sesquiterpenoid Illudin M

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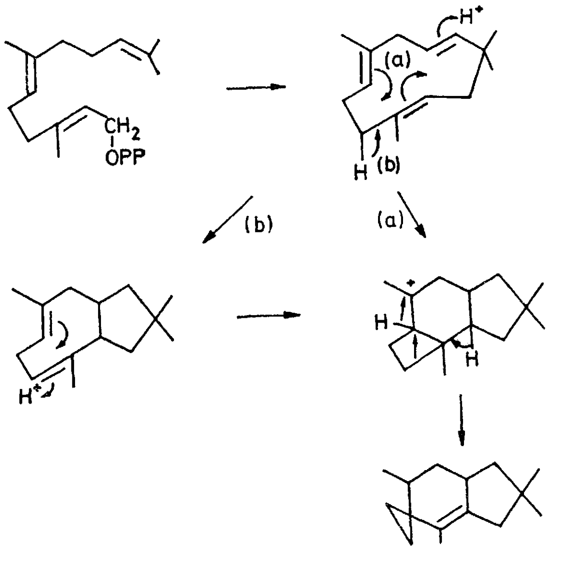
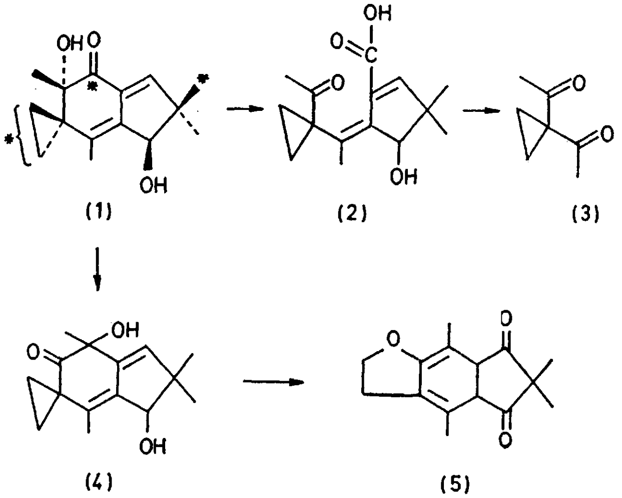
Summary Three [2-$^3H_2$]- and one [4(*R*)-4-^{3}H]-mevalonoid hydrogen atoms are incorporated into the sesquiterpenoid, illudin M in *Clitocybe illudens*.

Information on stages in sesquiterpenoid biosynthesis may be obtained from the established chirality of mevalonoid hydrogen atoms in *trans,trans*-farnesyl pyrophosphate[1] and their subsequent location in the sesquiterpenoid natural product. In the trichothecane series the cyclization of the farnesyl pyrophosphate has been shown[2—5] to take place with the involvement of the central and distal double bonds. In the illudin series, it has been suggested[6] that a humulene type of precursor forms the first cyclic intermediate. The formation of this requires cyclization only at the distal double bond (see Scheme). The [2-^{14}C]mevalonate labelling pattern, illustrated in (**1**), is in accord with this suggestion.[7] In the light of our work in the trichothecane series,[2] we have examined the biosynthesis of illudin M (**1**) using doubly-labelled mevalonates.



Scheme



Clitocybe illudens was grown on surface culture for 8—10 weeks and then fed with [^{3}H,^{14}C]mevalonic acid. The illudin M was isolated after a further 10—21 days. The ^{3}H : ^{14}C ratios are tabulated.

Degradation of the labelled metabolites was undertaken in the following way. The illudin M (^{3}H : ^{14}C, 5·95 : 1) from the [2-$^3H_2$,2-^{14}C]mevalonate experiment, was oxidized with sodium metaperiodate to the acid (**2**) which was then ozonized to give diacetylcyclopropane (**3**), (^{3}H : ^{14}C, 6·1 : 1). This ratio corresponds to the presence of only one tritium label in this part of the molecule. The illudin M from the [4(*R*)-4-^{3}H]mevalonate experiment was converted into isoilludin M (**4**)[7] (^{3}H : ^{14}C, 3·0 : 1) with alumina. Oxidation of the isoilludin M with the chromium trioxide–pyridine complex in pyridine afforded the dihydrobenzofuran (**5**) with the complete loss of the tritium label.

TABLE

Incorporation of mevalonoid hydrogen atoms into illudin M

Mevalonate	Initial ratio $^3H:^{14}C$	Ratio in illudin M	Number of ^3H labels	% Incorporation of ^{14}C(0·1mCi fed)
$2\text{-}^3H_2,2\text{-}^{14}C$	9·6 : 1	4·7 : 1	3·1	0·06
$2\text{-}^3H_2,2\text{-}^{14}C$	11·1 : 1	5·9 : 1	3·2	0·03
$4(R)\text{-}4\text{-}^3H,2\text{-}^{14}C$	9·8 : 1	3·1 : 1	0·9	0·1

The retention of one of the [4(*R*)-4-^{3}H]mevalonoid hydrogen atoms is in accord with the suggested mode of cyclization of farnesyl pyrophosphate. However, the loss of a [2-$^3H_2$]mevalonoid label in the cyclopropane ring requires a modification of the present theory, possibly in terms of a non-concerted cyclization of humulene to form the illudene skeleton (pathway b).

(*Received*, 10*th January* 1973; *Com.* 034.)

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