Biosynthesis of Illudin Sesquiterpenoids from [1,2-$^{13}C_2$]Acetate

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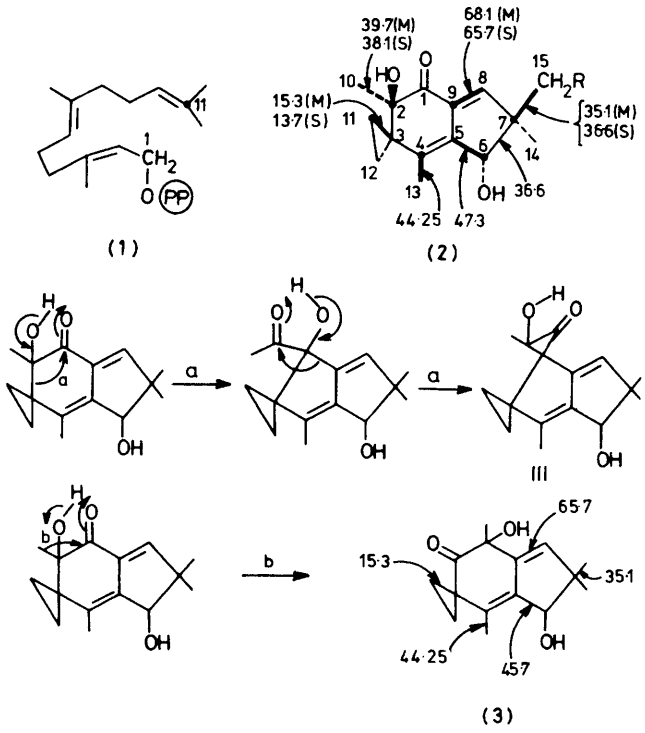
Summary The coupling pattern of illudin M and S, derived from [1,2-$^{13}C_2$]acetate, and the induced coupling from [1-^{13}C]acetate, support their biosynthesis from farnesyl pyrophosphate; the illudin M–isoilludin M rearrangement has been shown to be a 1:2 methyl shift rather than a pinacolic rearrangement.

SESQUITERPENOIDS of the illudin skeleton [*e.g.* illudin M (**2**, R = H) and illudin S (**2**, R = OH)] may be formed by a primary cyclization of farnesyl pyrophosphate (**1**) between C-1 and the distal C-10–C-11 double bond.[1,2] Labelling studies involving the partial degradation of material biosynthesized from ^{14}C-acetate and variously labelled mevalonates are compatible with this but without fully defining it.[3,4] In this communication we present results based on carbon-13 experiments which extend these studies.

The ^{13}C n.m.r. resonances of illudins M and S were assigned utilizing the single-frequency off-resonance decoupled spectra and by a study of variation of the chemical shift in a number of derivatives. Sodium [1,2-$^{13}C_2$]acetate, diluted with unlabelled acetate, was fed to the fungus *Clitocybe illudens* after 4 weeks growth. The illudins M and S were isolated after a further 3 weeks growth. The coupling patterns are shown in the Scheme. The cyclopropane methylene carbons, C-11 and C-12, were distinguished by the use of the shift reagent Pr(fod-d_9)$_3$[5] with illudin M acetate. The signal which showed the greater upfield shift was assigned to C-11 which lies on the same face of the molecule as the C-2 hydroxy-group. This signal, which is the higher field of the two cyclopropane methylene resonances, is also experiencing the greater γ-shielding from the adjacent hydroxy-group.[6] In the material biosynthesized from [1,2-$^{13}C_2$]acetate, it was this signal which was coupled to C-3 thus defining the stereochemistry of the folding of farnesyl pyrophosphate in this portion of the molecule. The distinction between these two cyclopropane methylene carbons has not been achieved by chemical means.

Sodium [1-^{13}C]-acetate was fed in one batch to *Clitocybe illudens* at the time of metabolite production. Apart from the anticipated enrichments shown in the Scheme, there was an induced coupling[7] between C-6 and C-7 (J 36·6 Hz) arising from farnesyl pyrophosphate precursor molecules which were formed from more than one labelled acetate unit. This induced coupling is compatible with C-6 originating from C-1 and C-7 from C-11 of farnesyl pyrophosphate. Both C-1 and C-11 would be labelled by C-1 of acetate.

Illudin M undergoes a rearrangement on alumina to form isoilludin M (**3**).[1] This may either take the form of a double pinacolic shift (pathway a) or a 1,2-methyl group migration (pathway b). The former would retain the coupling between the ring A methyl (C-10) and the tertiary carbinol (C-2) present in the [1,2-$^{13}C_2$]acetate labelled material, whilst in the latter this coupling would be lost. When the reaction was carried out, the isoilludin M (**3**) had lost this coupling whilst the other couplings in the molecule remained intact. Hence despite the reaction conditions, this rearrangement is a simple 1,2-shift.



SCHEME. Coupling constants in Hz; — denotes pairs of coupled atoms in the $^{13}C_2$-acetate experiment; ● denotes enriched atoms in the 1-^{13}C-acetate experiment. PP = pyrophosphate.

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