The Biosynthesis of the Sesquiterpenoid Tricothecane Antibiotics

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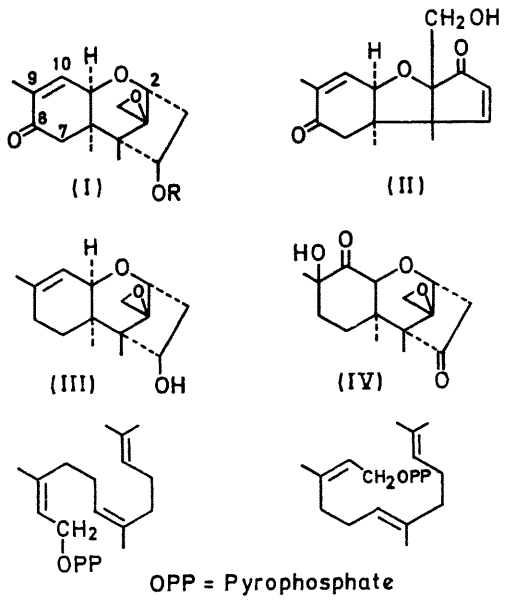
Summary The location of the 4(*R*)-[4-^{3}H]mevalonoid hydrogen atoms at C-2 and C-10, and the incorporation of tritium from 1- and 2-^{3}H-farnesol pyrosphosphate, suggest that a 6,7-*trans*-farnesol pyrophosphate acts as a precursor of the Tricothecane antibiotics.

THE antibiotic tricothecin (I; R = CO·CH=CHMe), which is produced by *Tricothecium roseum*, has been shown[1] to incorporate three molecules of 2-^{14}C-mevalonic acid and its sesquiterpenoid nature was confirmed[2] by the incorporation of farnesol pyrophosphate. The earlier work[1] suggested that a 6,7-*cis*-isomer of farnesol was involved in the biosynthesis. The experiments reported in this communication were initially directed at establishing the fate of the hydrogen atoms on the double bond during this biosynthesis.

4(*R*)-[4-^{3}H,2-^{14}C]Mevalonic acid (^{3}H : ^{14}C, 13·4 : 1) was fed to *Tricothecium roseum*. Tricothecin showed (^{3}H : ^{14}C, 9·05 : 1) and tricothecolone (I; R = H) (^{3}H : ^{14}C, 8·7 : 1) having incorporated two of the three possible labels. Degradation through tricothecolone glycol to the ketone (II)[3] (^{3}H : ^{14}C, 4·7 : 1) established the presence of one label at C-2. 4(*R*)-[4-^{3}H,2-^{14}C]Mevalonic acid (^{3}H : ^{14}C, 8·68 : 1) was fed to a *Trichoderma sp.* to afford trichodermol[4] (roridin C[5]) (III) (^{3}H : ^{14}C, 5·83 : 1). Again two out of the three possible labels were incorporated. Oxidation afforded trichodermone (^{3}H : ^{14}C, 5·83 : 1) which was converted with osmium tetroxide into its 9,10-glycol (^{3}H : ^{14}C, 6·03 : 1). Oxidation of this with chromium trioxide afforded a low yield of the ketol (IV) (^{3}H : ^{14}C, 2·87 : 1) thus locating one tritium atom at C-10. This result is in apparent conflict with the earlier work.[1]

The two ways of folding farnesol pyrophosphate may be distinguished by the number of 1-^{3}H and 2-^{3}H farnesol atoms that are retained in the final product. The first folding involving a *cis*-configuration about the central double bond, would place 1-^{3}H and 2-^{3}H farnesol labels at C-7 and C-8 respectively, whilst the *trans*-configuration would place these labels at C-10 and C-11 respectively. [1-$^3H_2$,2-^{14}C]Farnesol pyrophosphate (^{3}H : ^{14}C, 37·7 : 1) was fed to *Tricothecium roseum*. Tricothecolone showed (^{3}H : ^{14}C, 20·8 : 1); *i.e.* one label was lost. [2-^{3}H,2-^{14}C]Farnesol pyrophosphate (^{3}H : ^{14}C, 7·4 : 1) was also fed to *Tricothecium roseum*. Tricothecolone showed (^{3}H : ^{14}C, 7·0 : 1), and thus no label was lost. Unless there are complex hydrogen migrations during the late stages of the biosynthesis, this supports the *trans*-folding of the pyrophosphate.



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