Tetrahedron Letters No.47, pp. 4657-4659, 1967. Pergamon Press Ltd. Printed in Great Britain.

THE STEREOCHEMICAL COURSE OF THE 1,5-SHIFT OF HYDROGEN IN THE BIOSYNTHESIS OF OPHIOBOLINS

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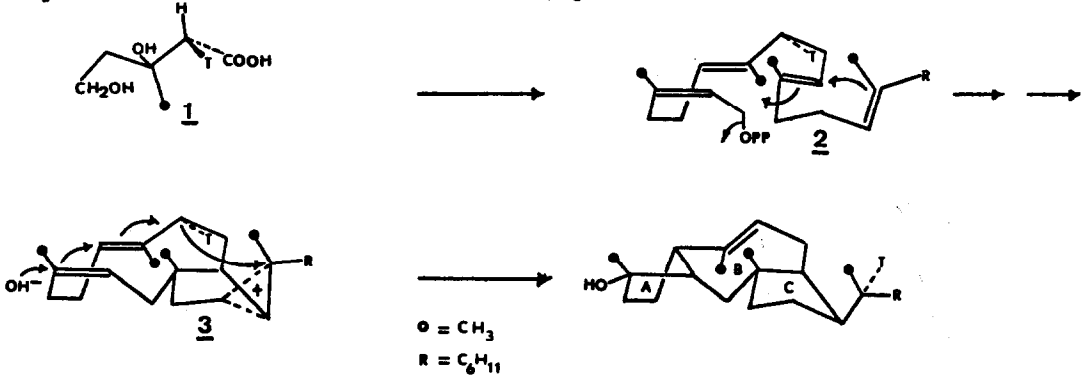
(Received in UK 27 July 1967)

As we have previously proved (1) the cyclization of geranylfarnesylpyrophosphate or its biological equivalent 2 to ophiobolins occurs with the unespected 1,5 shift of one hydrogen atom from 8-C to 15-C.

This fact allowed us to hypothize that the ionic intermediate 3 is saturated by a hydride ion arising from 8-α-C.

To prove this hypothesis we biosynthetized ophiobolins culturing Cochliobolus miyabeanus in presence of DL [2-R-2^{3}H$_1$] mevalonic acid lactone 1 and DL [2--S-2^{3}H$_1$] mevalonic acid lactone. The precursor 3 will contain five tritium atoms linked to 4-C, 8-C, 12-C, 16-C and 24-C (1); besides tritium will be linked to 8-α position in the former case and to 8-β position in the latter one.

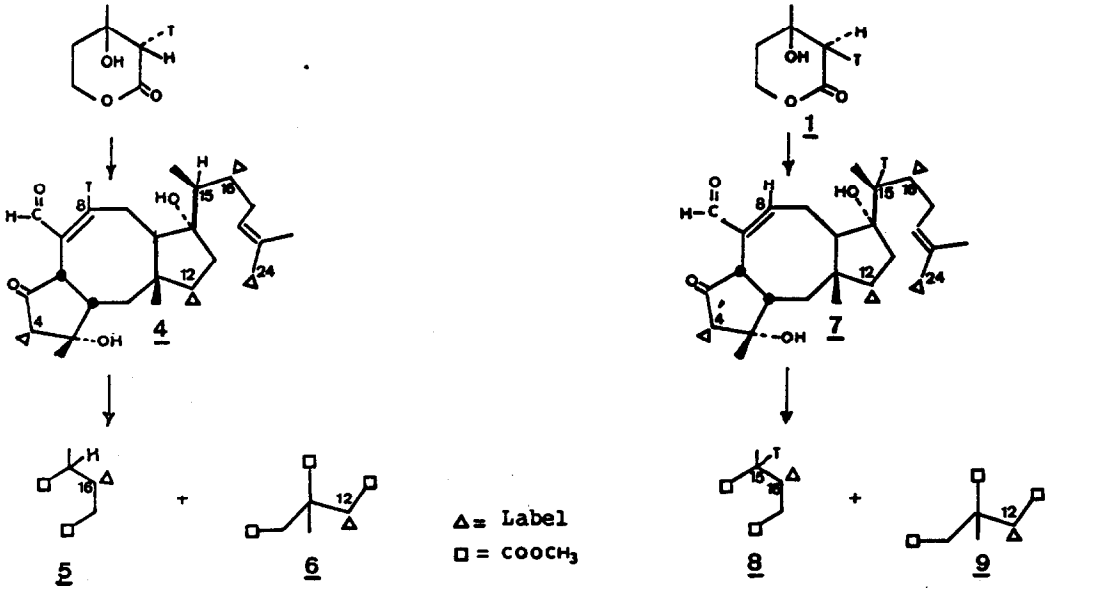


Cochliobolus miyabeanus was cultured as previously described (1), DL [2-S--2^{3}H$_1$] mevalonic acid lactone (0.1 mC) being added. Ophiobolin A (98 mg, 2.91 μC/mmole, incorporation 1.4%) and ophiobolin B 4 (375 mg, 3.33 μC/mmole, incorporation 6.2%) were obtained.

After dilution with inactive material ophiobolin B 4 was oxidized with nitric acid, yielding a mixture of polycarboxylic acids, whose methyl esters were

isolated by preparative gas-chromatography (2). In this way we obtained dimethyl S(+)-2-methylglutarate 5 and trimethyl 2-methyl-1,2,3-propanetricarboxylate 6. Their molar radioactivities are almost identical (respectively 21.5% and 23.5% of molar radioactivity of 4), showing that in 5 only one tritium atom is present. The radioactivity must be localized on 16-C of 4 as previously demonstrated (1,3).

These results prove that no shift of tritium occurs, therefore the 8-β-hydrogen of 3 does not migrate



Cochliobolus miyabeanus was cultured as previously described (1), DL [2-R--2^3H_1] mevalonic acid lactone (0.1 mC) 1 being added. Ophiobolin A (135 mg, 3.35 μC/mmole, incorporation 2.26%) and ophiobolin B 7 (303 mg, 3.28 μC/mmole, incorporation 4.94%) were obtained.

After dilution with inactive material ophiobolin B 7 was degraded as described above. In this case the molar radioactivity of dimethyl S(+)-2-methylglutarate 8 (42.4% of molar radioactivity of 7) was almost the double of that we found for trimethyl 2-methyl-1,2,3-propanetricarboxylate 9 (23.0% of molar radioactivity of 7), showing that in 8 two tritium atoms are present. The radioactivity must be localized on hydrogens linked to 15-C and 16-C of 7 as previously demonstrated (1,3).

Our present results undoubtly prove that the shift of tritium occurs only when tritium is on 8-α position of 3.

Acknowledgements.- Grateful acknowledgements are made to prof. E. Grossi Paoletti, University of Milan, for measurements with liquid scintillation spectrometer.

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