Alternariol is not Biosynthesised *via* Norlichexanthone

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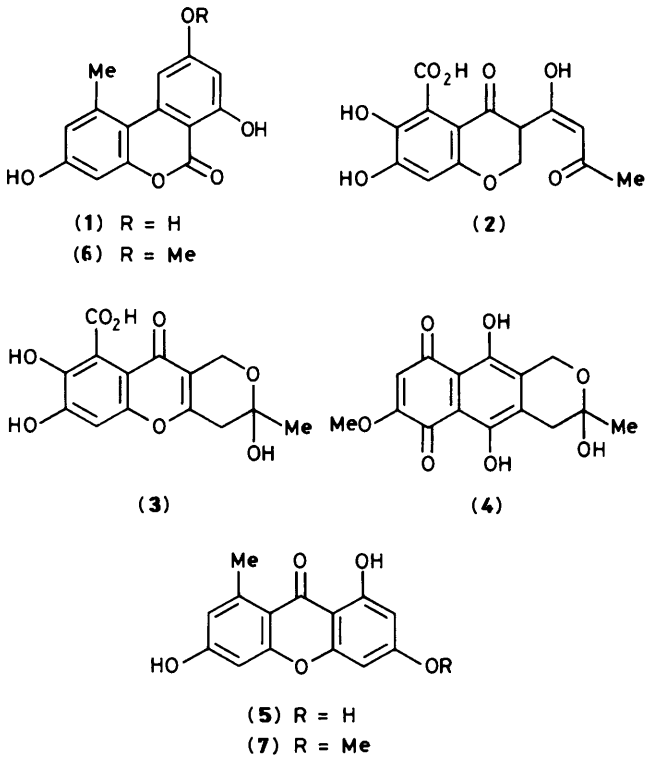
Incorporation of [1-^{13}C,$^{18}O_2$]acetate into alternariol in *Alternaria tenuis* establishes that all the oxygen atoms are acetate-derived and so disproves proposals for the biosynthesis of alternariol *via* ring cleavage of norlichexanthone or related pathways.

Alternariol (**1**) has long been regarded as an archetypal example of an aromatic metabolite biosynthesised by cyclisation and aromatisation of a simple polyketide precursor[1] as shown in Scheme 1, and this pathway has provided the basis for successful biomimetic syntheses of alternariol.[2,3] However, longstanding biogenetic speculations[4,5] exist concerning the derivation of structurally diverse fungal metabolites, including alternariol, by modification of a common heptaketide-derived precursor, and evidence has been obtained for the biosynthesis of polivione (**2**)[6] and fulvic acid (**3**)[7] from a precursor related to fusarubin (**4**). It was recently proposed[8,9] that alternariol could be biosynthesised *via* norlichexanthone (**5**), as shown in Scheme 2, where the necessary ring fragmenation would occur either (a) by oxidative scission or (b) by a retro-aldol process. Indirect evidence for this proposal is the co-occurrence of alternariol

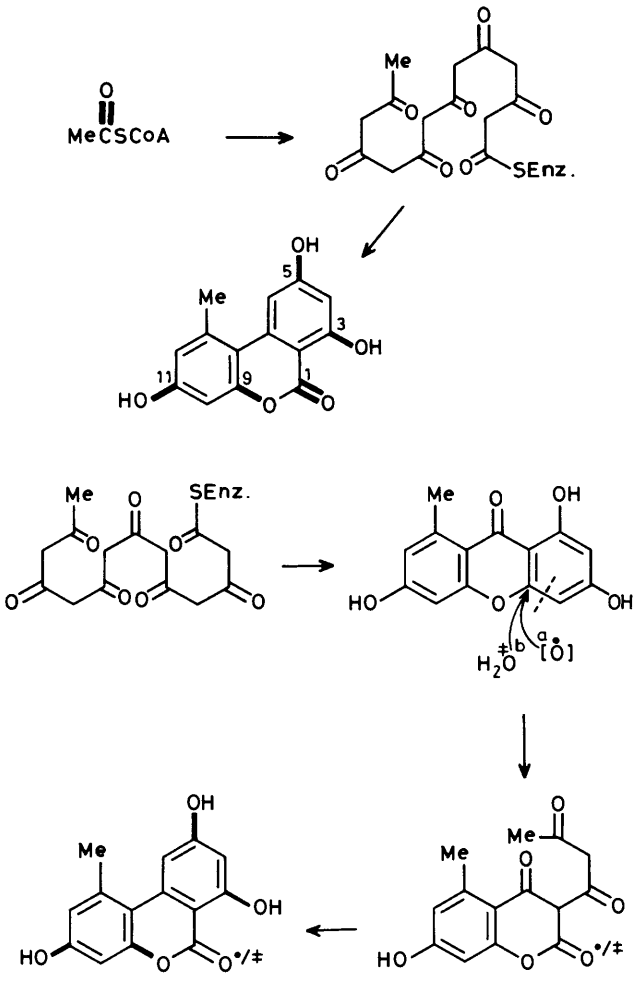


Scheme 1

Table 1. ^{18}O Isotopically shifted resonances in the 90.6 MHz ^{13}C n.m.r. spectrum of [1-^{13}C, $^{18}O_2$]acetate-enriched alternariol (**1**).

Carbon	δ/p.p.m.[a]	Δδ[b]	^{16}O : ^{18}O
1	164.5	3.0	59 : 41
3	164.0	1.0	56 : 44
5	165.1	1.1	55 : 45
9	152.5	2.3	57 : 43
11	158.1	1.0	59 : 41

[a] In $(CD_3)_2SO$. [b] p.p.m. × 100.



Scheme 2

methyl ether (**6**) and lichexanthone (**7**) in *Penicillium diversum*,[10] and direct evidence was provided by the incorporation (3.8%) of ^{14}C-labelled norlichexanthone into alternariol by cultures of *Alternaria tenuis*.[9] If correct these proposals would render untenable several presently held assumptions on the cyclisation modes leading to many polyketide-derived metabolites. We therefore sought to obtain more evidence for the biosynthesis of alternariol.

The pathways shown in Schemes 1 and 2 can be distinguished by determining the biosynthetic origins of the oxygen atoms, in particular the carbonyl oxygen of the benzopyrone ring which would be derived from acetate according to Scheme 1 or from the atmosphere (path a) or the medium (path b) according to Scheme 2. Sodium [1-^{13}C,$^{18}O_2$]acetate was fed to a high alternariol producing strain of *A. tenuis* and the proton noise decoupled ^{13}C n.m.r. spectrum of the enriched alternariol was determined. This showed high incorporation of acetate-derived oxygen into all the oxygen bearing carbons (see Table 1). The incorporation of ^{18}O-labels into the benzopyrone carbonyl group is not significantly different from that into the other positions and clearly precludes either of the ring cleavage pathways shown in Scheme 2. Therefore, norlichexanthone or other metabolites necessitating ring cleavage cannot be implicated in the biosynthesis of alternariol. The observed[9] incorporation of ^{14}C-labelled norlichexanthone presumably occurs *via* prior degradation to ^{14}C labelled acetyl CoA.

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References

1 R. Thomas, *Biochem. J.*, 1981, **78**, 748.
2 C. Abell, B. D. Bush, and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 1986, 15.
3 T. M. Harris and C. M. Harris, *Pure Appl. Chem.*, 1986, **58**, 283.
4 W. B. Turner, 'Fungal Metabolites,' Academic Press, London, 1971, p. 154.
5 F. M. Dean, R. A. Eade, R. A. Moubasher, and A. Robertson, *Nature*, 1957, **179**, 366.
6 A. K. Demetriadou, E. D. Laue, and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 1985, 764.
7 I. Kurobane, C. R. Hutchinson, and L. C. Vining, *Tetrahedron Lett.*, 1981, **22**, 493.
8 E. E. Stinson, W. B. Wise, and P. E. Pfeffer, 'Alternariol: Biosynthesis from norlichexanthone investigated by 2D ^{13}C NMR,' in Abstracts of the Phytochemical Society of North America Meeting, 12—16 June 1985, Pacific Grove, Georgia, U.S.A.
9 E. E. Stinson, W. B. Wise, R. A. Moreau, A. J. Jurewicz, and P. E. Pfeffer, *Can. J. Chem.*, 1986, **64**, 1590.
10 J. S. E. Holker, E. O'Brien, and T. J. Simpson, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1365.