# Biosynthesis of Sclerin, a Metabolite of *Sclerotinia sclerotiorum*: Incorporation of [1-$^{13}$C]- and [1,2-$^{13}C_2$]-Acetates

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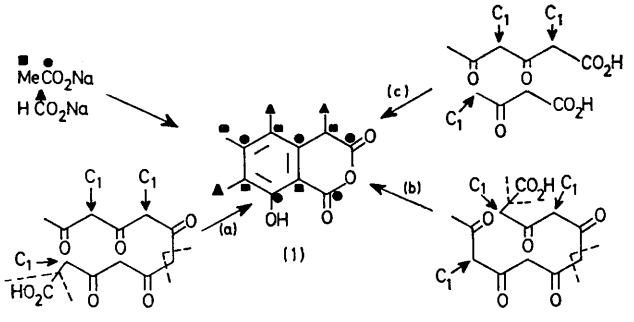
*Summary* Sclerin, a metabolite of *Sclerotinia sclerotiorum*, incorporates five intact acetate units; the results are in accord with a biosynthesis from two separately formed polyketide chains but an alternative pathway involving a single polyketide chain is proposed.

ON the basis of an earlier biosynthetic study it has been proposed that sclerin (**1**), a metabolite of the fungus *S. sclerotiorum*, incorporates activity from isotopically labelled carbon in acetate and formate as shown in Scheme 1.[1] Three biosynthetic routes have been proposed to account for this intriguing labelling pattern:[1,2] pathways (a) and (b) show alternative ways in which the sclerin nucleus might be formed by cyclisation of a single polyketide chain containing six acetate units, followed by the loss of two carbons; according to pathway (c) the nucleus would be generated by a remarkable condensation between two separately formed polyketide residues.




SCHEME 1

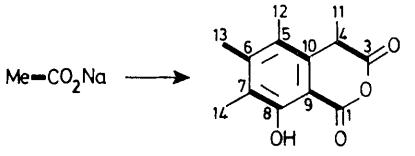
TABLE. $^{13}$C n.m.r. data for sclerin[a]

| Carbon | Carbon chemical shifts/p.p.m. (rel to $Me_4Si$) | $^{13}C$–$^{13}C$ coupling in sclerin labelled with [1,2-$^{13}C_2$]acetate/Hz. |
|---|---|---|
| 1 | 165·2[b] | 71·0 |
| 3 | 167·5[b] | 53·9 |
| 4 | 37·8 | 54·0 |
| 5 | 122·9 | 63·7 |
| 6 | 146·6[b] | 43·9 |
| 7 | 123·7 | 67·4 |
| 8 | 157·8[b] | 67·5 |
| 9 | 100·5 | 70·9 |
| 10 | 133·6[b] | 63·5 |
| 13 | 16·6 | 43·4 |
| 11,12,14 | 11·0, 13·6, 21·4 | — |

[a] In $CDCl_3$ containing 0·1M-Cr(acac)$_3$ [b] Enhanced in intensity after incorporated of [1-$^{13}$C]acetate.

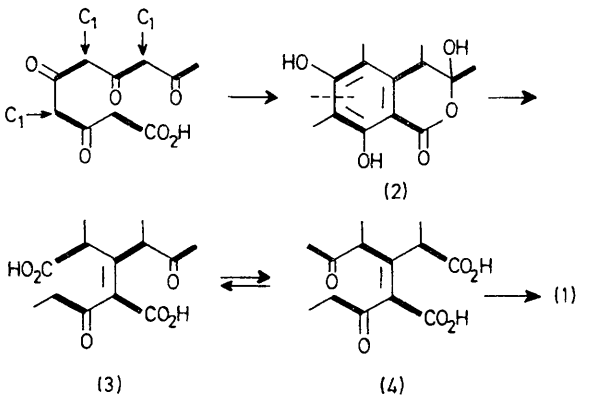
We have now determined the orientation of the acetate units by carrying out incorporation experiments with [1-$^{13}$C]- and [1,2-$^{13}C_2$]-acetates. The results are shown in the Table where the signals in the $^{13}$C n.m.r. spectra

are assigned from calculated values of chemical shifts, off-resonance decoupling experiments, and the $^{13}C$–$^{13}C$ couplings in the spectrum of sclerin derived from [1,2-$^{13}C_2$]-acetate. They confirm the pattern of incorporation shown in Scheme 1 and show further that the nucleus incorporates five intact $C_2$ units whose orientation is shown in Scheme 2.



SCHEME 2

Of the three pathways shown in Scheme 1 only (c) is consistent with this labelling pattern.† However, as has been pointed out,[1,2a] this biosynthetic scheme seems doubtful because it involves an aldol condensation and a methylation at the methyl group of one of the polyketide chains: though these are standard reactions of polyketide chains at the chain building units there is almost no precedent for their occurrence at a chain starter unit. We therefore propose in Scheme 3 an alternative pathway in which sclerotinin A (**2**) serves as an intermediate in sclerin biosynthesis: cleavage of the benzenoid ring of (**2**) would produce an open-chain intermediate such as (**3**); isomerisation of (**3**) to (**4**) followed by recyclisation would then give sclerin. Though it is unprecedented, the proposed transformation of (**2**) to (**1**) is mechanistically plausible, and, as indicated it would satisfactorily account for all the incorporation data obtained so far. Moreover, sclerotinin A has been isolated along with sclerin from cultures of *S. sclerotiorum*.[3]



SCHEME 3

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† In ref. 2(b) there is a report that evidence in support of pathway (a) has been obtained in a $^{13}C$ n.m.r. experiment. Unfortunately no details are given. Our own work excludes this pattern of chain folding.

[1] T. Kubota, T. Tokoroyama, S. Oi, and Y. Satomura, *Tetrahedron Letters*, 1969, 631; T. Tokoroyama and T. Kubota, *J. Chem. Soc.* (*C*), 1971, 2703.

[2] (a) W. B. Turner, 'Fungal Metabolites', Academic Press, London and New York, 1972, p. 194; (b) K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, 'Natural Products Chemistry', Vol. 2, Academic Press, London and New York, 1975, p. 201.

[3] T. Sassa, H. Aoki, M. Namiki, and K. Munakata, *Agric. and Biol. Chem.* (*Japan*), 1968, **32**, 1432.