

UTILIZATION OF ^{13}C - ^{13}C COUPLING IN STRUCTURAL AND BIOSYNTHETIC STUDIES. VIII.¹⁾

THE CYCLIZATION PATTERN OF A FUNGAL METABOLITE, SCYTALONE.

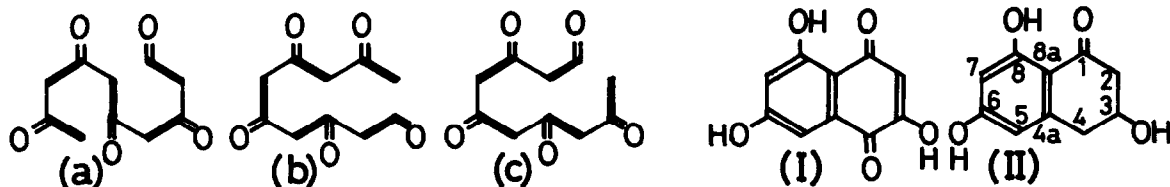
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Naphthoquinones lacking any C-alkyl substituents such as flaviolin (I) are biosynthetically very unique among polyketide metabolites in that they do not possess the clear starter unit of a polyketide chain. This structural feature has allowed the proposal of several cyclization patterns for pentaketides as shown below.²⁾

Fig.1



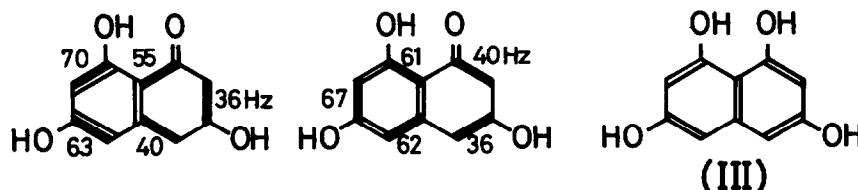
In order to investigate the cyclization pattern in question of these metabolites by the double labeling method³⁾, we chose a fungal metabolite, scytalone (II) as a model compound, since the polyketide origin of which has been proved by making use of $\text{CH}_3^{13}\text{CO}_2\text{Na}$ and ^{13}C -nmr spectroscopy.⁴⁾ The metabolite was isolated for the first time from *Scytalidium* sp.⁵⁾ however, *Phialophora lagerbergii*, more recently reported to be a producing organism of scytalone⁴⁾, was used for our experiment because of higher production yield.

The scytalone labeled with $^{13}\text{CH}_3^{13}\text{CO}_2\text{Na}$ was obtained as reported by Turner et al.⁴⁾ and the ^{13}C - ^{13}C coupling constants observed in the ^{13}C -nmr spectrum are summarized in Table together with the chemical shifts of carbon signals which were, within experimental error, in agreement with the reported values⁴⁾ with one exception (observed 165.4 ppm, reported 160.9 ppm). Although the assignment of the ^{13}C -nmr spectrum of scytalone has been previously made, two pairs of signals, i.e. C-2 and C-4, and C-6 and C-8, remained to be differentiated. The comparison of the magnitude of ^{13}C - ^{13}C coupling constants facilitated the unambiguous assignment to be made (*vide infra*) as shown in Table.

Table⁸⁾

carbon	δ_C	J_{C-C} (Hz)	signals but one at 66.4 ppm showed two kinds of ^{13}C - ^{13}C coupling of equal signal intensities. For example, C-1 ($\delta_C=202.1$ ppm) is coupled to C-8a ($\delta_C=111.5$ ppm, $J_{C-C}=55$ Hz) as well as to a signal at $\delta_C=47.1$ ppm ($J_{C-C}=40$ Hz) which, therefore, must be assigned to C-2. ⁶⁾ By elimination, the remaining signal at 38.9 ppm is ascribed to C-4. Likewise, C-8 was differentiated from C-6 based on the coupling between C-8a.
4	38.9	37, 40	
2	47.1	36, 40	
3	66.4	36	
7	101.3	67, 70	
5	108.9	62, 63	
8a	111.5	56*, 61*	This splitting pattern can be explained by assuming that C-1 was coupled only to either of C-2 and C-8a and not both of them in a given molecule, otherwise the splitting pattern of C-1 would be a doublet of doublets instead of two independent doublets as really observed. Thus, the labeled scytalone is a mixture of two differently labeled molecules
4a	145.8	41, 62	
6	165.4	64, 67	
8	166.0	61, 70	
1	202.1	40, 55	

*Due to the overlapping of the C-5 signal, these values were obtained by taking a noise off-resonance spectrum.



This phenomenon implies the involvement of a symmetric intermediate such as 1,3,6,8-tetrahydroxynaphthalene (III) in the biosynthesis of scytalone and excludes the folding pattern (a) in Fig. 1. Although flaviolin (I) has been believed to be formed from scytalone via (III)⁷⁾, our experiment demonstrates that (III) is most likely a common intermediate for both scytalone and flaviolin.

References and Footnotes

- 1) For part VII, see, H. Seto, T. Satō, S. Urano, J. Uzawa and H. Yonehara, *Tetrahedron Lett.* **1976**, 4367.
- 2) W. B. Turner, "Fungal Metabolites" p.130. Academic Press. London. 1971.
- 3) H. Seto, T. Satō and H. Yonehara, *J. Amer. Chem. Soc.* **95**, 8461 (1973).
- 4) D. C. Aldridge, A. B. Davies, M. R. Jackson and W. B. Turner, *J.C.S. Perkin I.* **1974**, 1540.
- 5) J. A. Findley and D. Kwan, *Can. J. Chem.* **51**, 1617 (1973).
- 6) This assignment was corroborated by observing characteristic 1,3-coupling ($^2J_{C-C}=9$ Hz) between C-2 and C-8a which are connected by a carbonyl carbon. This long range coupling is caused by the simultaneous incorporation of two $^{13}CH_3$, $^{13}CO_2H$ molecules into the adjacent positions (C-2 and C-3, and C-1 and C-8a) of a polyketide chain.
- 7) A. A. Bell, R. D. Stipnovic and J. E. Puhall, *Tetrahedron*, **32**, 1353 (1976).
- 8) Determined on a JEOL FX-100 nmr spectrometer operating at 25.05 MHz, in d_6 -acetone, relative to internal TMS. Data points 16K, pulse width $\pi/4$, spectral width; for measurement of ^{13}C - ^{13}C coupling constants, 3KHz; for a whole spectrum, 6KHz.