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Microbial Transformation of (+)- and (-)-Dehydrogriseofulvin by Streptomyces Species Analyzed by ²H Nuclear Magnetic Resonance Spectroscopy*

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The microbial transformation of (-)-dehydrogriseofulvin (DGF) (1a) to (+)-griseofulvin (GF) (2a) was initially investigated by Andres and his co-workers using *Streptomyces cinereocrocatus* NRRL 3443. Previously, we deduced by means of ²H NMR spectroscopy the stereochemical course of the microbial hydrogenation of natural (-)-[5'-²H]DGF (1b) into natural (+)-[5' α -2H]GF (2d) by the same microorganism. This paper describes the results of incubations of (-)- and (+)-DGF with eight *streptomyces* species.

Firstly, (+)-DGF (4a) was administered to a shaken culture of S. cinereocrocatus on the 4th day of the fermentation as described previously. After 3 days, GF (2b) was obtained in 35-45% yields from the broth, and DGF (4b) was recovered in 10-15%yields. The structure of 2b, mp 228–229°C, $[\alpha]_{\rm p}^{21}$ +336.9°, which was inferred from ¹H NMR and mass spectral data together with gas liquid chromatography (GLC) and thinlayer chromatography (TLC) data, was confirmed to be (+)-GF by comparison of its CD spectrum with those of natural (+)-GF and (-)-GF (5). The recovered 4b, on the other hand, was pure (+)-DGF without any contamination by (-)-DGF in spite of the fermentation conditions under which (+)-GF was formed. When the incubation period was shortened by one day, on the other hand, GF (2b) and DGF (4b) were obtained in 12 and 40% yields, respectively. To elucidate the stereochemical course of the microbial transformation of (+)-DGF by Streptomyces species, (+)- $[5'-^{2}H]$ DGF (4c) which was obtained by dehydrogenation of (+)- $[5'\alpha, 5'\beta^{-2}H]$ epigriseofulvin, was subjected to microbial transformation by S. cinereocrocatus under the same conditions as described above for the undeuterated substrate (4a). After an additional 3 days, the cultures were harvested and deuterium-labeled GF was extracted, followed by column chromatographic separation to give 14 mg of deuterated GF, mp 229-230°C (²H₀ 57.4, ²H₁ 42.6%) (2e). The ²H NMR spectrum of 2e was compared with that of (+)- $[5'\alpha, 5'\beta^{-2}H]GF$ (2f) as described previously, and the configuration of the deuterium was unequivocally ascribed as $5'\alpha$, establishing the structure of **2e** as (+)- $[5'\alpha^{-2}H]$ GF (Fig. 1). The results suggest that during the microbial transformation, (+)-DGF (4a) is converted first to its enantiomer, natural (-)-DGF (1a), followed by hydrogenation of the 5'-6' double bond to yield natural (+)-GF (2b).

The above results prompted us to investigate the microbial transformation of DGF's

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by other Streptomyces species. When (-)-DGF and (+)-DGF were incubated with Streptomyces species (S. cinereocrocatus, S. roseochromogenus, S. bikiniensis, S. griseinus, S. durhamensis, S. californicus. S. fimbriatus, and S. cinereoruber), mutual interconversion (reaction 1 in Chart 1) occurred, although in the fermentation of (+)-DGF with S. cinereocro-

catus and S. roseochromogenus (+)-DGF was recovered without any contamination by (-)-DGF. The results presented here led us to propose a scheme for the transformation of (-)- and (+)-DGF by Streptomyces species (Chart 1). The processes comprise isomerization between (-)- and (+)-DGF and hydrogenation to the corresponding (+)- and (-)-GF, respectively. Except for S. cinereoruber which shows almost the same hydrogenation activities in both $1\rightarrow 2$ (reaction 2) and $4\rightarrow 5$ (reaction 3) processes, other Streptomyces species showed very much higher activities in reaction 2 than in reaction 3. During the course of the screening test, Streptomyces species described above. When (-)-DGF was incubated with S. cinereoruber, GF ($[\alpha]_{p}^{10}$ +254.5°) was obtained, corresponding to a mixture consisting of 88% (+)-GF and 12% (-)-GF (5) on the basis of optical activities. When (+)-DGF was incubated under the same conditions, an enantiomer mixture of GF consisting of 87% (-)-enantiomer and 13% (+)-enantiomer was produced.

Chemical isomerization of DGF has been reported by MacMillan. The results indicate that the microbial transformation of (-)- and (+)-DGF by *Streptomyces* species is a new type of isomerization to afford the corresponding enantiomer. Using some microbial systems it is possible to obtain natural (+)-GF both directly and stereospecifically from (\pm) -DGF, which is an important intermediate in the total synthesis of (\pm) -GF.