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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 cinereocrocatius* 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. cinereocrocatius* 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, $[\alpha]_D^{25} +336.9^\circ$, which was inferred from ^1H NMR and mass spectral data together with gas liquid chromatography (GLC) and thin-layer 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'- ^2H]DGF (**4c**) which was obtained by dehydrogenation of (+)-[5' α ,5' β - ^2H]epigriseofulvin, was subjected to microbial transformation by *S. cinereocrocatius* 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 ($^2\text{H}_0$ 57.4, $^2\text{H}_1$ 42.6%) (**2e**). The ^2H NMR spectrum of **2e** was compared with that of (+)-[5' α ,5' β - ^2H]GF (**2f**) as described previously, and the configuration of the deuterium was unequivocally ascribed as 5' α , establishing the structure of **2e** as (+)-[5' α - ^2H]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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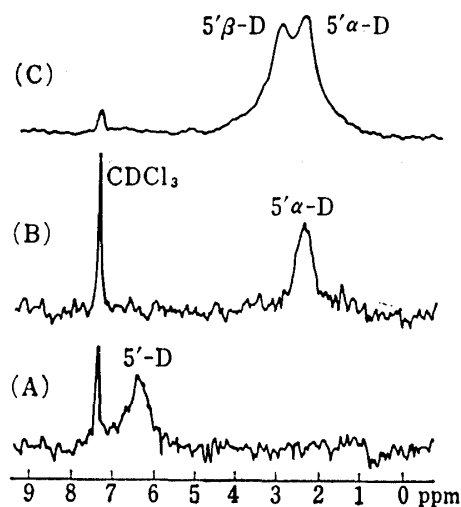


Fig. 1. ^2H NMR Spectra of Deuterated Griseofulvin Derivatives
 (A): 4c, 10 mg, 2200 transients.
 (B): 2c, 8 mg, 6400 transients.
 (C): 2f, 22 mg, 706 transients.

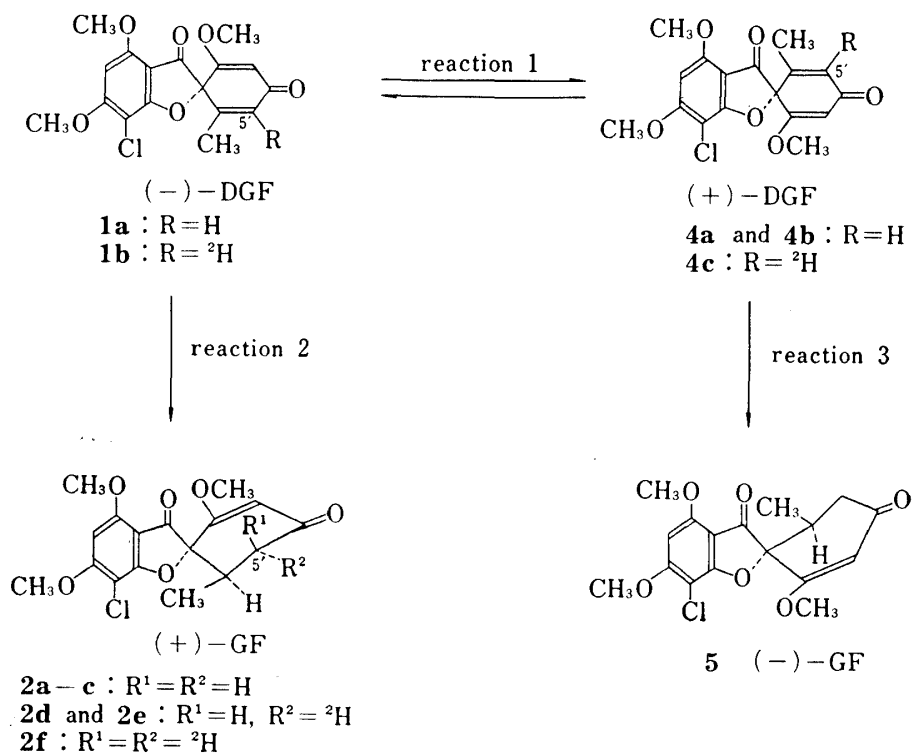


Chart 1

by other *Streptomyces* species. When (-)-DGF and (+)-DGF were incubated with *Streptomyces* species (*S. cinereocrocutus*, *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→2 (reaction 2) and 4→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 cinereoruber* Corbaz et al. (IFO 12756) was found to be very different from the *Streptomyces* species described above. When (–)-DGF was incubated with *S. cinereoruber*, GF ($[\alpha]_D^{25} +254.5^\circ$) 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 (±)-DGF, which is an important intermediate in the total synthesis of (±)-GF.