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Stereochemistry of Microbial Transformation of (+)- and (-)-2'-Demethoxydehydrogriseofulvin by Streptomyces cinereocrocatus*

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In a preceding paper, we reported studies on the microbial transformation of (+)and (-)-2'-demethoxydehydrogriseofulvin (1 and 2) by *Streptomyces cinereocrocatus*, which demonstrated that the products formed from 1 were (+)-2'-demethoxygriseofulvin (3) and (-)- and (+)-2'-demethoxy-2',3'-dihydrodehydrogriseofulvin (4 and 5), whereas only 5 was obtained fom 2.

In this paper, therefore, the microbial transformations of the deuterated substrates (1a, 1b, 2a, and 2b) were performed using *Streptomyces cinereocrocatus*, and the stereochemistry of the transformation products was elucidated from 400 MHz proton nuclear magnetic resonance (¹H-NMR), 41. 41 MHz ²H-NMR and circular dichroism (CD) spectral data.

The microbial transformations of $(-)-[2'-{}^{2}H]$ - and $[3'-{}^{2}H]-2'$ -demethoxydehydrogriseofulvins (2a and 2b) by S. cinereocrocatus were performed under the same conditions as described in the previous paper. After a 12 h fermentation of 2a, deuterated (+)-2'-



Chart 1.

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demethoxy-2',3'-dihydrodehydrogriseofulvin (5a) was isolated as the transformation product from the broth. The configuration of the deuteron of 5a was unequivocally assignable as 2' β (Chart 2). On the other hand, after the 12 h fermentation of 2b, deuterated (+)-2'demethoxy-2',3'-dihydrodehydrogriseofulvin (5b) was isolated from the broth. The configuration of the deuteron of 5b was also unequivocally assignable as 3' α . The results clearly demonstrated that the microbial hydrogenation of (-)-2'-demethoxydehydrogriseofulvin (2) proceeds with *anti*-addition of hydrogens *via si* attacks at the 2' and 3' position (Chart 2).

On the other hand, the microbial transformations of (+)-[2'-2H]- and [3'-2H]-2'demethoxydehydrogriseofulvins (1a and 1b) by S. cinereocrocatus were performed under the same conditions as described above for the (-)-isomers. After 12 h, the transformation product from 1a was isolated from the broth, and shown to be composed of (+)- and (-)-2'-demethoxy-2',3'-dihydrodehydrogriseofulvin (5c and 4e) in a relative ratio of 8 : 11 by comparisons of its CD spectrum with those of standard (+)- and (-)-compounds (5) The configuration of the deuteron of the microbial transformation products (5cand 4). and 4e) was unequivocally assignable as $2'\beta$ (Chart 3). Next, in the microbial transformation of 1b, the products consisted of (+)- and (-)-2'-demethoxy-2',3'-dihydrodehydrogriseofulvin (5b and 4f) in a relative ratio of 91:9, based on comparisons of its CD spectrum with those of standard (+)- and (-)-compounds, after 12 h incubation. The configuration of the deuteron of the microbial transformation products (5b and 4f)was unequivocally assignable as $3'\alpha$ (Chart 3). The results mentioned above clearly indicate that the microbial hydrogenations of la and lb to 4e and 4f proceed with antiaddition of hydrogens via re attacks at the 2' and 3' positions. That is, in the microbial

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hydrogenations of 1a and 1b, the compounds were first converted to their corresponding enantiomers (2a and 2b), followed by *anti*-addition of hydrogens *via si* attacks at the 2' and 3' positions to give 5c and 5d.

In conclusion, the 41.41 MHz ²H-NMR and 400 MHz ¹H-NMR studies clearly showed that the microbial hydrogenations of (+)- and (-)-2'-demethoxydehydrogriseofulvin (1 and 2) proceed stereospecifically with *anti*-addition of hydrogens at the 2', 3' positions. Comparison of the above results with those for (-)- and (+)-dehydrogriseofulvin (8 and 6) indicates that the microbial hydrogenation of dehydrogriseofulvin analogs by S. *cinereocrocatus* proceeds with the same stereochemistry in a *trans* diaxial manner regardless of the 2'-substituent.