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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 from **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 ($^1\text{H-NMR}$), 41.41 MHz $^2\text{H-NMR}$ and circular dichroism (CD) spectral data.

The microbial transformations of (-)-[2'- ^2H]- and [3'- ^2H]-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'-

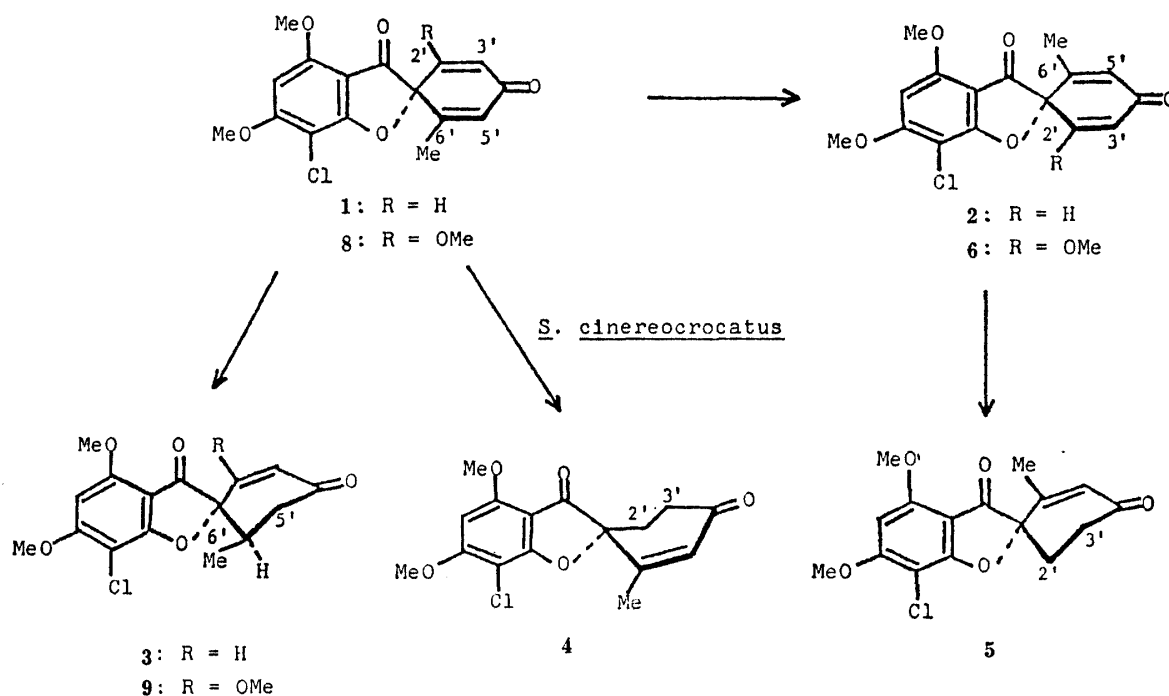


Chart 1.

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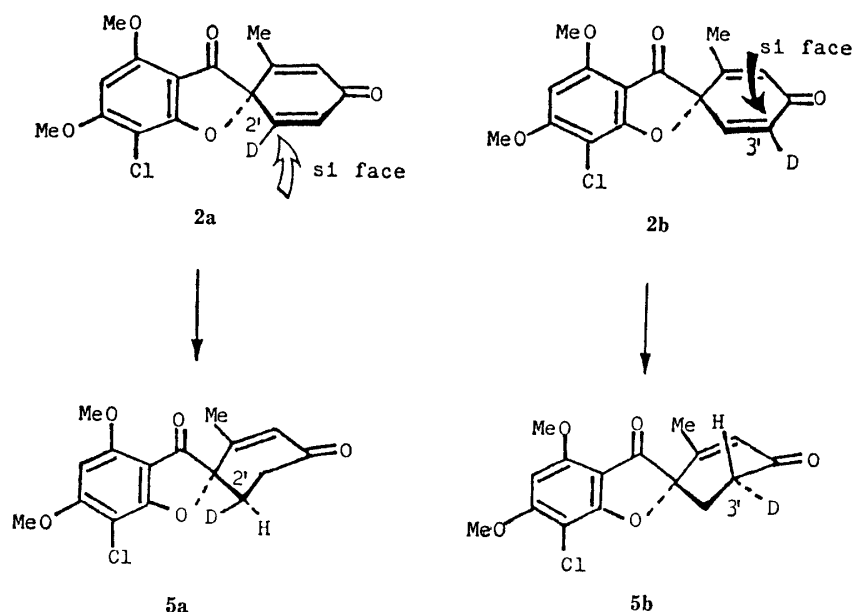


Chart 2.

demethoxy-2',3'-dihydrodehydrogriseofulvin (5a) was isolated as the transformation product from the broth. The configuration of the deuterium of 5a was unequivocally assignable as $2'\beta$ (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 deuterium of 5b was also unequivocally assignable as $3'\alpha$. 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. cinereocrocutus* 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 and 4). The configuration of the deuterium of the microbial transformation products (5c 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 deuterium 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 1a and 1b to 4e and 4f proceed with *anti*-addition of hydrogens *via re* attacks at the 2' and 3' positions. That is, in the microbial

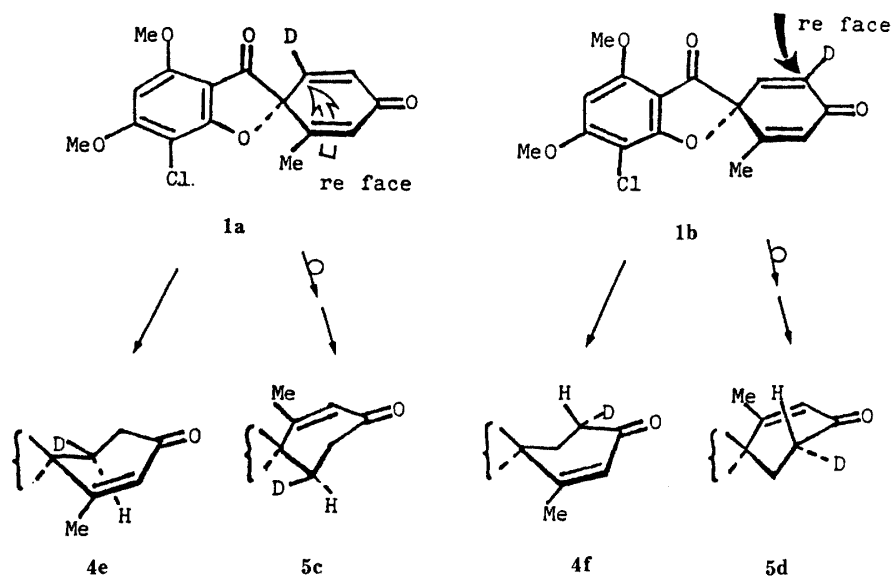


Chart 3.

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.