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

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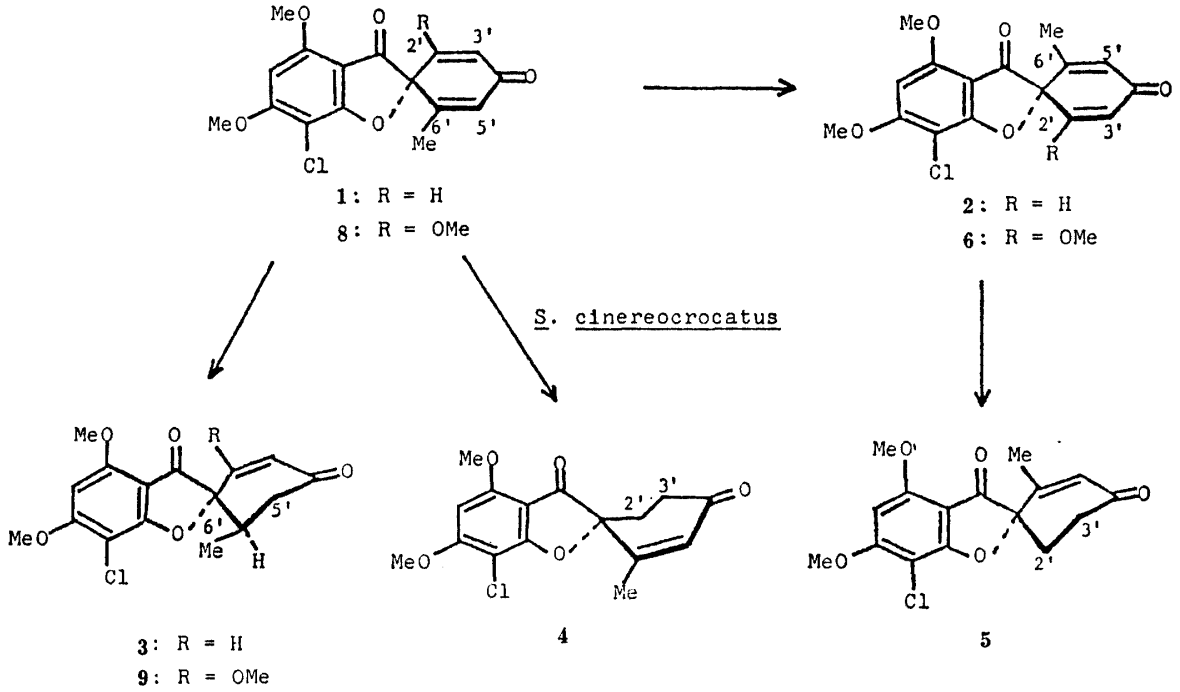
In a preceding paper, we reported studies on the microbial transformation of (+)- and (−)-2′-demethoxydehydrogriseofulvin (**1** and **2**) by *Streptomyces cinereocrocatus*, which demonstrated that the products formed from **1** were (+)-2′-demethoxygriseofulvin (**3**) and (−)- and (+)-2′-demethoxy-2′,3′-dihydrodehydrogriseofulvin (**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 (^{1}H-NMR), 41.41 MHz ^{2}H-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′-



1: R = H
8: R = OMe

2: R = H
6: R = OMe

3: R = H
9: R = OMe

4

5

Chart 1.

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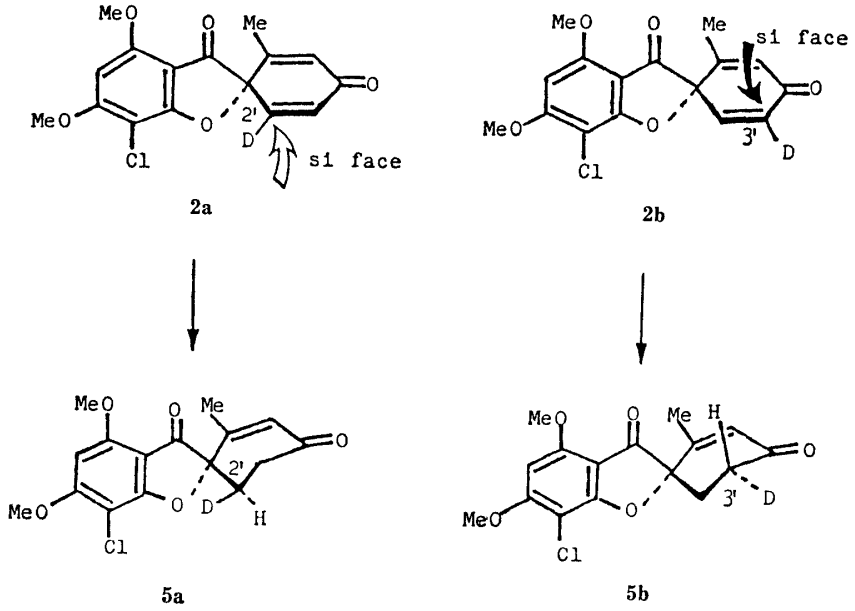

Chart 2.

demethoxy-2′,3′-dihydrodehydrogriseofulvin (**5a**) was isolated as the transformation product from the broth. The configuration of the 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′-^{2}H]- and [3′-^{2}H]-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** and **4**). The configuration of the deuteron of the microbial transformation products (**5c** and **4e**) was unequivocally assignable as 2′β (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′α (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

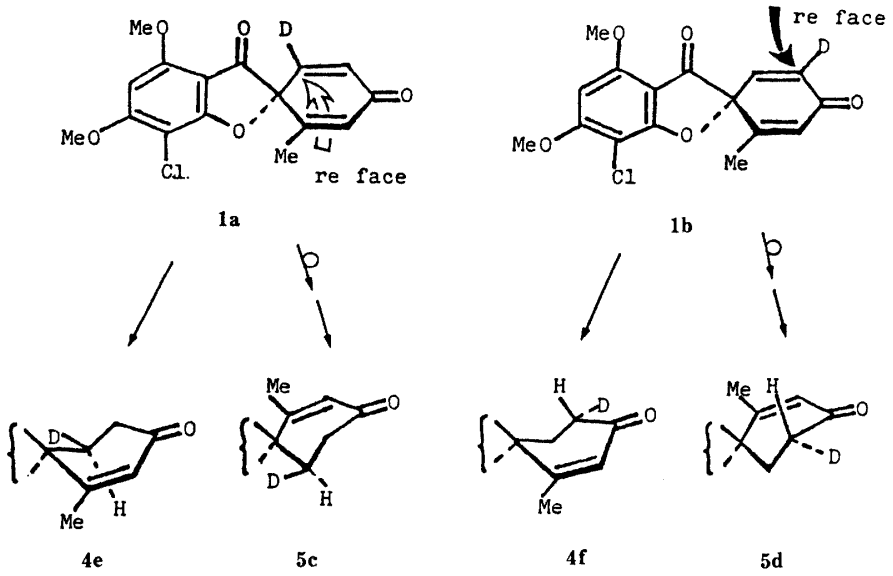

Chart 3.

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 ^{2}H-NMR and 400 MHz ^{1}H-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.