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**Stereochemistry of Microbial Hydrogenation of (–)- α -Santonin
to (+)-1,2-Dihydro- α -santonin by *Streptomyces
cinereocrocatu*s NRRL 3443***

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We reported the microbial transformation of (–)- and (+)-dehydrogriseofulvin and their analogs by *Streptomyces cinereocrocatu*s NRRL 3443 and it was demonstrated that hydrogenations of the dienones proceed in *trans*-diaxial manner to give the corresponding dihydro derivatives. In order to elucidate the microbial transformation activity of *S. cinereocrocatu*s, (–)- α -santonin (1) was selected as a cross-conjugated dienone compound. The microbial transformation of (–)- α -santonin (1) by *S. cinereocrocatu*s was performed under the same conditions as described in the previous paper. The mass spectrum (MS) and $^1\text{H-NMR}$ spectrum data indicated that the microbial transformation product might be the 1,2-dihydro derivative (2) of (–)- α -santonin (Chart 1). Therefore, (–)- α -santonin was partially hydrogenated over 5% palladium-charcoal catalyst in ethyl acetate to give (+)-1,2-dihydro- α -santonin (2). The $^1\text{H-NMR}$, MS and circular dichroism (CD) data of the microbial transformation product were identical with those of 2, demonstrating that the microbial hydrogenation of 1 by *S. cinereocrocatu*s occurs at the 1 and 2 positions. Since Inayama *et al.* have shown that 2 is in a half-chair conformation with respect to the cyclohexenone ring on the basis of the CD spectrum, which exhibited a negative CD Cotton effect, 400 MHz $^1\text{H-NMR}$ spectroscopy with selective proton decoupling established the assignments of all of the proton chemical shifts of (+)-1,2-dihydro- α -santonin (2).

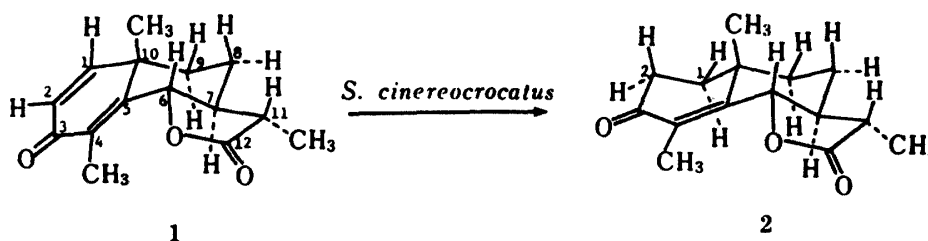


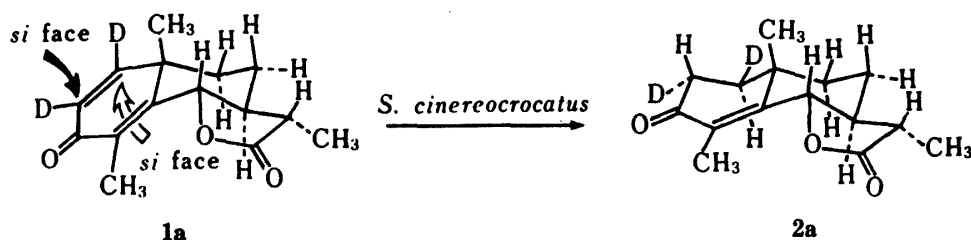
Chart 1

Consequently, to elucidate the stereochemistry of microbial hydrogenation of (–)- α -

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santonin (**1**) by *S. cinereocrocatu*s, the deuterated substrate, (-)-[1,2-²H]- α -santonin (**1a**), was synthesized. Thus, the microbial transformation of (-)-[1,2-²H]- α -santonin (**1a**) by *S. cinereocrocatu*s was performed under the same conditions as described above. The transformation product (**2a**) was proved to be deuterated (+)-1,2-dihydro- α -santonin by MS and gas liquid chromatography comparisons with the standard compound (**2**). The 400 MHz ¹H-NMR spectrum of **2a** was almost identical with that of **2** except that decreases of the signal intensities at the 2 α - and 1 β -H regions and some differences in the 1 α -, 1 β -, 2 α -, and 2 β -H regions. Further, a coupling pattern was clearly observed at the 2 β -H region, demonstrating the configurations of the deuterons of the microbial transformation product (**2a**) as 1 β and 2 α , respectively (Chart 2). Thus, the structure of **2a** was concluded to be (+)-[1 β ,2 α -²H]-1,2-dihydro- α -santonin.



Comparison of the above results with those for griseofulvin derivatives indicates that the microbial hydrogenations of dienone compounds by *S. cinereocrocatu*s proceed with the same stereochemistry, *i. e.*, in a *trans* diaxial manner.