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

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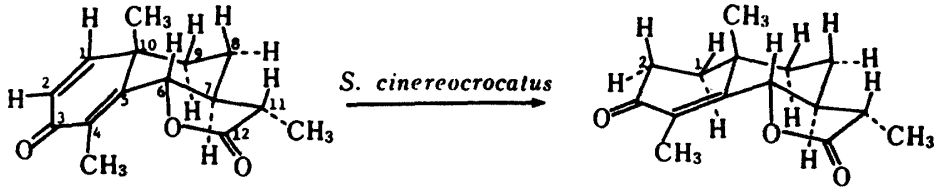
We reported the microbial transformation of (−)- and (+)-dehydrogriseofulvin and their analogs by *Streptomyces cinereocrocatus* NRRL 3443 and it was demonstrated that hydrogenations of the dienones proceed in *trans*-diaxial manner to give the corresponding dihydro derivatives. In order to elucidate the microbial transformation activity of *S. cinereocrocatus*, (−)-α-santonin (**1**) was selected as a cross-conjugated dienone compound. The microbial transformation of (−)-α-santonin (**1**) by *S. cinereocrocatus* was performed under the same conditions as described in the previous paper. The mass spectrum (MS) and ^{1}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}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. cinereocrocatus* 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}H-NMR spectroscopy with selective proton decoupling established the assignments of all of the proton chemical shifts of (+)-1,2-dihydro-α-santonin (**2**).



1 2

Chart 1

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

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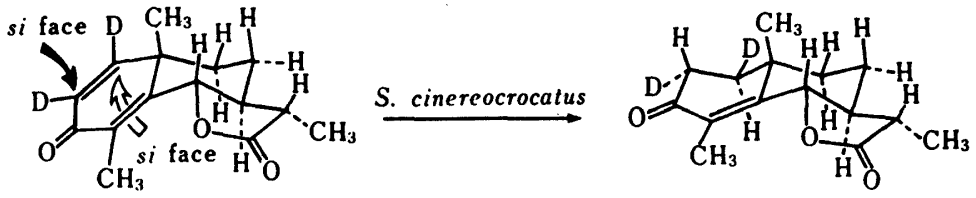
santonin (**1**) by *S. cinereocrocatus*, the deuterated substrate, (−)-[1,2-^{2}H]-α-santonin (**1a**), was synthesized. Thus, the microbial transformation of (−)-[1,2-^{2}H]-α-santonin (**1a**) by *S. cinereocrocatus* was performed under the same conditions as described above. The transformation product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



1a **2a**

Chart 2

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