TERPENE AND STEROID BIOTRANSFORMATIONS

BY

WHETZELINIA, PHANEROCHAETE

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ABSTRACT

The research described herein is divided into five chapters. In chapter 1 the phenomenon of biotransformation, specifically its functions, causative agents, mechanisms and exploitation by mankind was investigated. In Chapters 2, 3 and 4 the focus was on the bioconversion of bioactive sesquiterpenes, diterpenes, tetraterpenes and steroids by *Whetzelinia sclerotiorum* ATCC 18687, *Phanerochaete chrysosporium* ATCC 24725, and *Cunninghamella echinulata* var. *elegans* ATCC 8688a respectively. In Chapter 5 the phytochemical investigation of the plant *Capparis ferruginea* is reported.

The evergreen shrub *Stemodia maritima* was collected and extracted to yield three biologically significant diterpenes (stemodin, stemodinone and stemarin). The

diterpenes, the anthelmintic sesquiterpene santonin, and eight bioactive steroids were used as substrates in these investigations.

The pathogenic fungus *Whetzelinia sclerotiorum* ATCC 18687, for which there were no previous reports of bioconversion, was explored for its potential in this area. The production of seven stemodane and twelve steroid metabolites by the growing fungus was observed. The previously unreported compounds were 2α,11β,13-trihydroxystemodane, 7β,13-dihydroxystemodan-2-one, 13,19-dihydroxystemaran-2-one, 13,15-dihydroxystemaran-19-oic acid and 7β,13,19-trihydroxystemarane. Incubation of eight steroids gave twelve metabolites of which five were novel. These new compounds were 3β,16β-dihydroxypregn-5-ene-7,20-dione (from pregnenolone), 2β,16β,17β-trihydroxyandrost-4-en-3-one (from testosterone), 2β,17α,21-trihydroxypregn-4-ene-3,11,20-trione (from cortisone), 2β-hydroxypregn-4-ene-3,15,20-trione and 2β,15β-dihydroxypregn-4-ene-3,20-dione (both from progesterone). This represents the first such biotransformations with this fungus.

Phanerochaete chrysosporium ATCC 24725, though utilized in only a very limited number of medicinal biotransformations in the past, was also examined. Although this microorganism produced five eudesmane and four stemodane analogues, the low yields hindered further study. The fermentation of nine steroids, however, gave nine metabolites of which 15α,17β-dihydroxyandrosta-

1,4-dien-3-one (from 17β-hydroxyandrosta-1,4-dien-3-one) was hitherto unreported.

Bioconversion of santonin with *Cunninghamella echinulata* var. *elegans* yielded only one metabolite. Incubation of stemodin gave three metabolites, whereas stemodinone gave four products of which two were new. These were 13,14-dihydroxystemodan-2-one and 7β,13-dihydroxystemodan-2-one. Incubation of 2α-(*N*,*N*-dimethylcarbamoxy)-13-hydroxystemodane gave two novel products: 2α-(*N*,*N*-dimethylcarbamoxy)-6α,13-dihydroxystemodane and 2α-(*N*,*N*-dimethylcarbamoxy)-7α,13-dihydroxystemodane. Fermentation of stemarin gave the new compound 6α-hydroxystemaran-19-oic acid, while feeding 19-(*N*,*N*-dimethylcarbamoxy)-13-hydroxystemarane yielded two novel compounds, namely 19-(*N*,*N*-dimethylcarbamoxy)-2β,13-dihydroxystemarane and 19-(*N*,*N*-dimethylcarbamoxy)-2β,8β,13-trihydroxystemarane.