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BIOCONVERSION OF SESQUITERPENES

VÉRONIQUE LAMARE and ROLAND FURSTOSS*
Laboratoire de Chimie Organique et Bioorganique, Faculté des Sciences de Luminy-70, route Léon Lachamp, case 901, 13288 Marseille Cedex 9, France

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1. INTRODUCTION

Sesquiterpenes are very widespread constituents of essential oils. Some of them are of considerable industrial value in the flavour and perfumery industries as well as for pharmaceutical applications. Total synthesis of these compounds is often quite difficult, so alternative ways to produce them could be by chemical derivatization of natural compounds. This may require functionalization at non-activated carbon atoms. This type of transformation is often very difficult to achieve with reasonable yields and regioselectivity using classic chemical reactions.[1] For example quite interesting results have been described using Mazur's reagent, but only tertiary alcohols are obtained.[2] Similarly, the decomposition of lead alkoxides or hypohalogenities derived from sesquiterpenoid alcohols does not always yield the desired cyclic ethers. Oxidation at secondary carbon atoms may be achieved using Gif's reagent giving mixtures of hitherto unknown ketones, but only in very low yields.[3]

In this context bioconversion methods are of definite value. This technique makes it possible to hydroxylate substrate regioselectively in a single step which may be carried out by enzymic systems present in mammals or microorganisms.[4] In mammals, the process of hydroxylation takes place

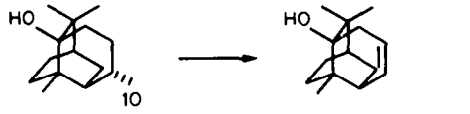
mainly in the liver microsomes. The enzymic systems involved are mono-oxygenases capable of providing one of the two atoms of the oxygen molecule. Among these mono-oxygenases, the key enzyme is P-450 cytochrome. These enzymic systems are also found in microorganisms. It has been possible to isolate such an enzyme in a crystalline state: the cytochrome P-450 mono-oxygenase of *Pseudomonas putida*-(+)-*camphor*.[5] In view of the similarity of the enzymic systems implied, one might expect to obtain the same metabolites from mammals and from microorganisms.

We have tried in this article to review the present state of knowledge concerning the biotransformations of sesquiterpenes. To facilitate possible future comparison of metabolites, we have arranged this bibliography according to sesquiterpenoid families. In view of the small number of studies carried out on sesquiterpene biohydroxylation we have extended the Report to include other biotransformations that we have encountered.

2. LITERATURE RESULTS

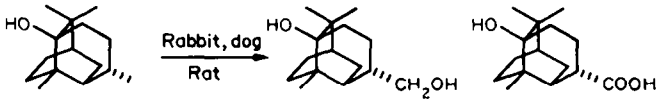
2.1. *Patchoulol*

Patchoulol is the main constituent of the essential oil of patchouli (35–40%) which is of considerable importance to the perfumery industry. The compound thought to be responsible for the olfactory properties of this essence is nor-patchoulenol (0.4%). Perfume manufacturers have therefore tried to transform patchoulol into nor-patchoulenol.



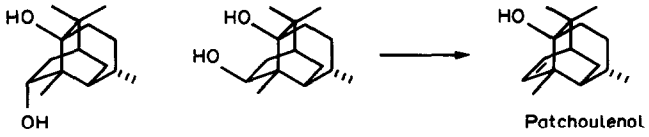
Patchoulol Nor - patchoulenol

This transformation is possible by hydroxylation of the C10 methyl group, so numerous studies have been carried out on mammals and microorganisms to try to obtain the diol which is the precursor of nor-patchoulenol. In 1975, Luu Bang and Ourisson studied the metabolism of patchoulol in the rabbit, the dog and the rat.[6] They obtained two products in identical proportions resulting from oxidation of the C10 methyl group. In the case of the rabbit, the yield was virtually quantitative.

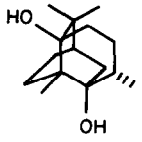


This transformation is unsuitable for exploitation on an industrial scale so studies were carried out with microorganisms. More than 850 strains were tested and a very large number of them resulted in the required diol. However, other hydroxylation products were also produced in yields varying according to the microorganism and the fermentation conditions.[6,7] Two strains of the genus *Pithomyces*, isolated from soil situated in the neighbourhood of Kamakura, *Pithomyces*

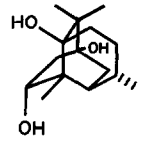
chartarum and *Pithomyces niger* produced 1,10-pathoulidiol (50–60%) in concentrations of up to 4 to 8 $g \cdot l^{-1}$ for the former.[8] With other fungi (*A. clavatus*, *A. ochraceus*, *C. lunata*, *F. lycopersici*, *M. aureocyanus*) it has been possible to obtain the following diols (50–55%). This mixture can be transformed into patchoulenol, with an odour very similar to that of nor-patchoulenol.



With *A. niger*, *C. circinana*, *G. roseum*, *R. niginana* and *M. parasiticus*, it has been possible to obtain the following bitertiary diol (50–86%).

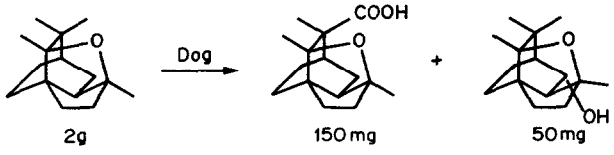


Depending on the fermentation conditions used, *C. circinana* can also produce the following major triol.



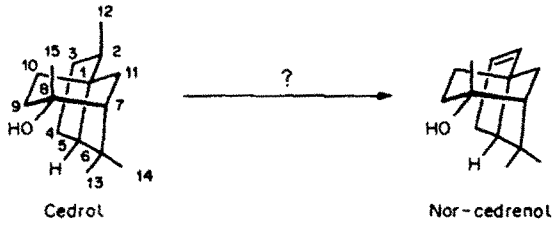
The example of patchoulol demonstrates the considerable value of biohydroxylation for compounds as complex as sesquiterpenoids and their derivatives.

In the patchoulol family, mention might be made of the transformation product of β-patchoulene epoxide, the bioconversion of which by dogs, studied by Ourisson *et al.*, gave the following products.[9]



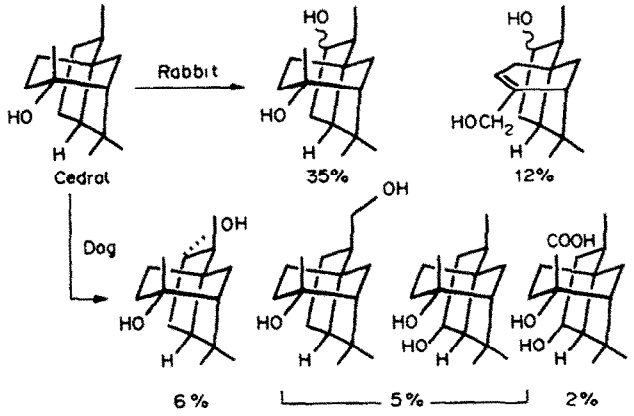
2.2. *Cedrol and α-cedrene*

Ourisson *et al.* have studied the biotransformation of cedrol and α-cedrene in the dog and the rabbit. One of the aims of this study was to determine whether the products obtained would provide access to nor-cedrenol, a compound that has not yet been isolated but which is suspected of having the same role in the essential oil of cedarwood as that of nor-patchoulenol in patchouli essence.

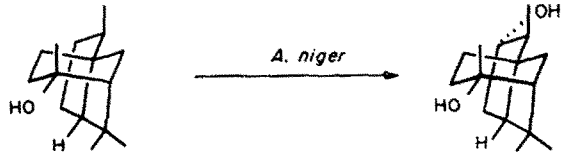


After hydrolysis of the metabolites and, in the case of the dog, acetylation and reduction of the acetates, the results shown in the next scheme[10-12] were obtained. Better regioselectivity may be noted in the rabbit than in the dog, with only the C3 carbon atom being hydroxylated. From the primary alcohol it was possible to obtain nor-cedrenol.

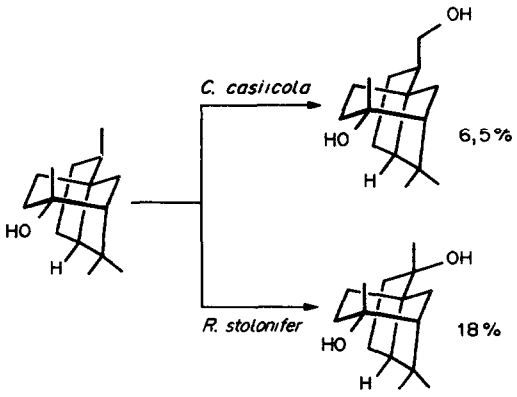
The results obtained with α-cedrene were inconclusive, both the dog and the rabbit yielding a complex mixture of products.[10]



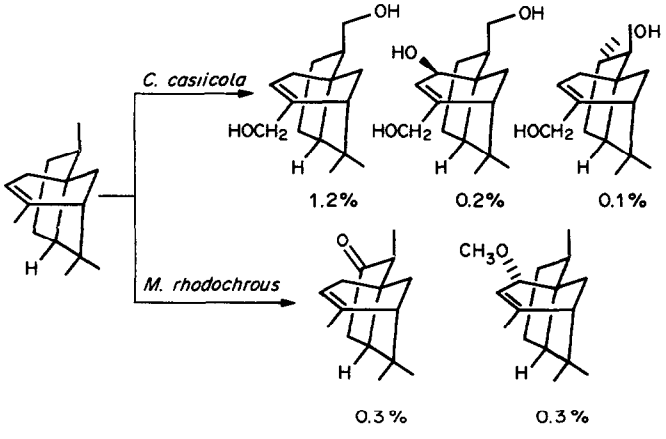
In 1972 Wang studied the effect of *Aspergillus niger* (ATCC 9142) on cedrol.[13] He obtained three metabolites, the major product being hydroxylated on the C3 carbon atom.



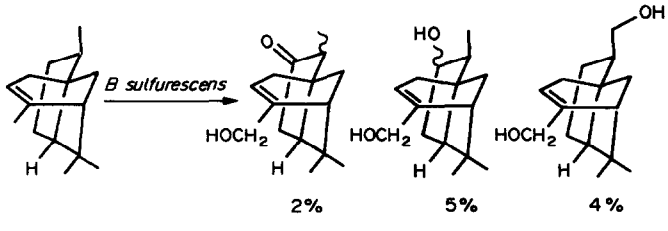
Abraham *et al.* have also studied the microbiological hydroxylation of α-cedrene and cedrol.[14] After screening 47 microorganisms, five strains were selected for a study of the metabolites of cedrol: *Corynespora casiicola* (DSM 62474), *Rhizopus stolonifer* (CBS 38252), *Streptomyces bikiniensis* (IFO 13350), *Verticillium tenerum* (DSM 63545) and *Streptoverticillium reticuli* (DSM 40776). Eight diols and a triol were obtained, the major products being metabolites hydroxylated on the C12 and C2 carbon atoms.

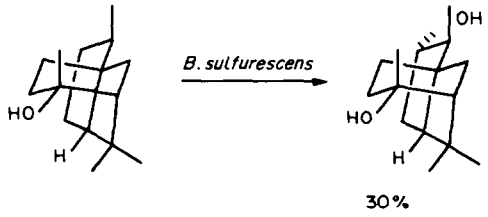


On the other hand, the use of α-cedrene gave results that were disappointing. Bioconversion of this hydrocarbon by *C. casiicola*[14] and *Mycobacterium rhodochrous* (ATCC 999)[15] produced various metabolites but in very low yields.



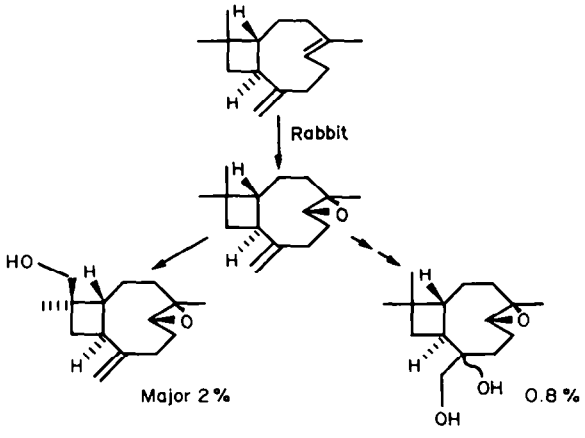
Similar results have been described recently by Furstoss *et al.* concerning bioconversions of α-cedrene and cedrol with the fungus *Beauveria sulfurescens* (ATCC 7159). The results obtained indicate that α-cedrene is only very slowly transformed giving low yields of diols. Interestingly, however, cedrol is hydroxylated with a regioselectivity different from that described by Abraham *et al.* with other fungi. The major diol, already obtained by Wang with *A. niger*, appears to be a very valuable synthon since it allows straightforward synthesis of cedrene-8-one-3, a minor constituent of Virginia Cedarwood oil, which displays odoriferous properties.[16]



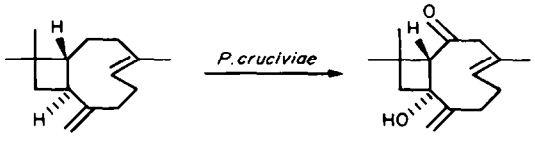


2.3. *Caryophyllene, caryolanol, caryophyllene oxide and humulene*

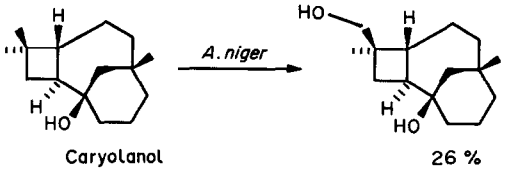
Asakawa *et al.* have studied the metabolism of caryophyllene and caryophyllene oxide in rabbit.[17] These two substrates yield the same major metabolite, which indicate that the biotransformation of caryophyllene by the rabbit starts with epoxidation of the endocyclic double bond. Caryophyllene produces a second trioxygenated metabolite which was not found among the mixture of secondary metabolites obtained by bioconversion of caryophyllene oxide. The scheme suggested for the metabolism of caryophyllene and caryophyllene oxide in the rabbit is as follows.



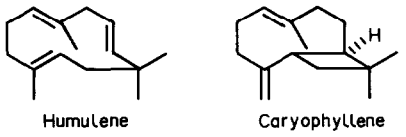
In 1979, Rama Devi isolated a strain of *Pseudomonas cruciviae* by enrichment culture on caryophyllene.[18] The major metabolite of this bioconversion is a product hydroxylated at the bridgehead and at the allylic positions. However, the yield is very low considering the number of other metabolites which are formed.



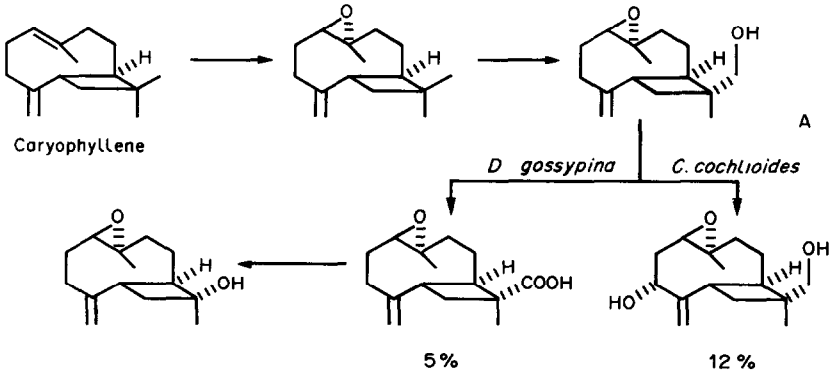
Quite recently, Furstoss *et al.* examined the biotransformation of caryolan-1-ol by the fungus *A. niger*.[19] This leads in fair yields (26%) to a single diol by regiospecific hydroxylation of the C14 methyl group. Interestingly, the regioselectivity of this hydroxylation is identical with the regioselectivity observed for the main metabolite of (−)-caryophyllene in rabbits.[17] ^{13}C-NMR assignments for the diol were deduced from the use of heteronuclear and homonuclear chemical shift correlation diagrams. This allowed full assignment of the NMR signals and modification of previous assignments to caryolan-1-ol.[20]



Abraham has studied the microbiological transformation of humulene, caryophyllene and their respective oxides by *Diplodia gossypina* (ATCC 10936) and two strains of *Chaetomium cochlioides* (DSM 63353 and ATCC 10195).[21]



Sixty-three products, including 49 that had never been described previously, were obtained and tested for their biological activity. The following scheme shows the main reaction pathway for the biotransformation of caryophyllene by these two fungi.

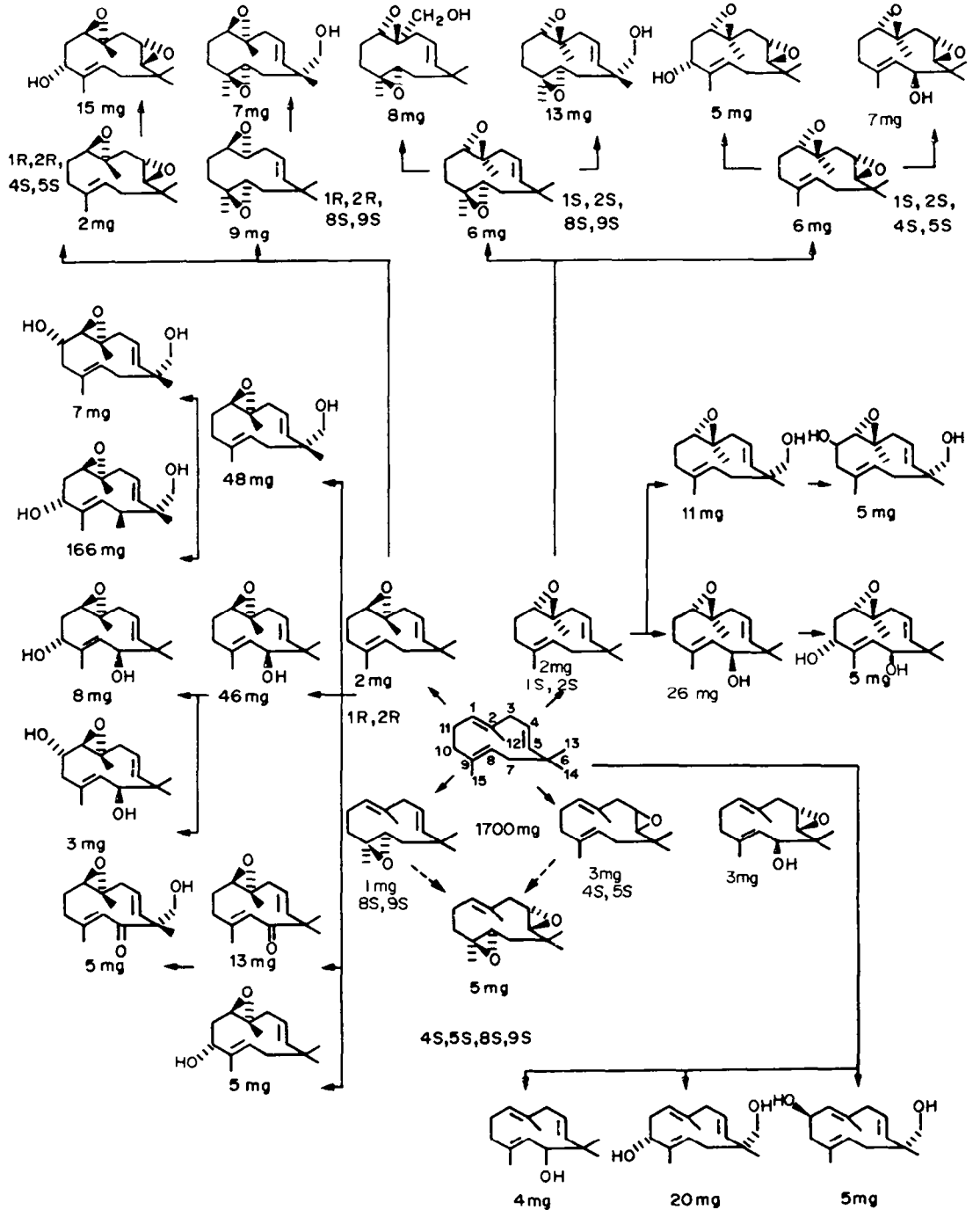


The last intermediate (A) common to these two bioconversions is also the major metabolite in the bioconversion of caryophyllene by the rabbit. This product has already been isolated from *Lactorius camphoratus*, a fungus found in Poland.[22] This suggests that very similar enzymic systems operate in mammals, microorganisms and in plants.

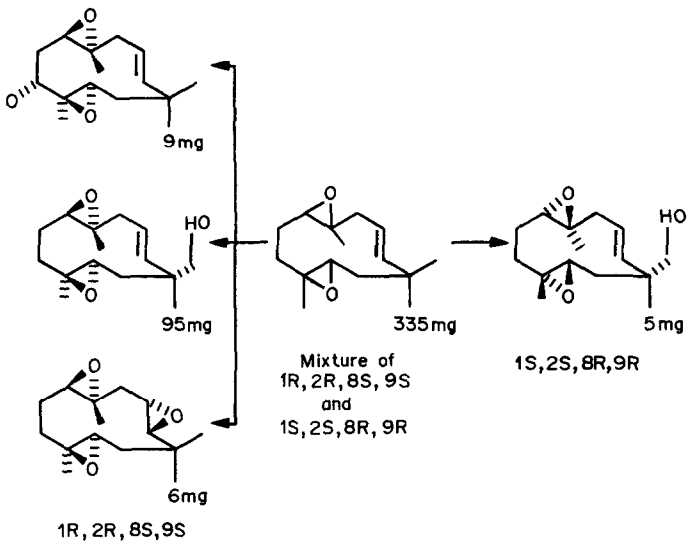
In the case of humulene, *Chaetomium cochlioides* (ATCC 10915) gives 32 different metabolites. The results of this bioconversion can be summed up by the following scheme.[15]

The major degradation pathway starts with epoxidation of the 1,2 double bond. The mono-epoxide obtained is racemic. Subsequent epoxidations yield 4(*S*), 5(*S*) and 8(*S*), 9(*S*) oxides in small quantities. These epoxides are then hydroxylated once or twice giving the alcohols 7(*S*), 10(*R*), 11 and 13. Hydroxylation on the C11 carbon atom is controlled by the configuration of the 1,2 epoxide. The 1(*S*) epoxide gives the 11(*R*) alcohol and the 1(*R*) epoxide gives the 11(*S*) alcohol. The major reaction product is the 1,2-epoxy-humulene 10,13-diol.

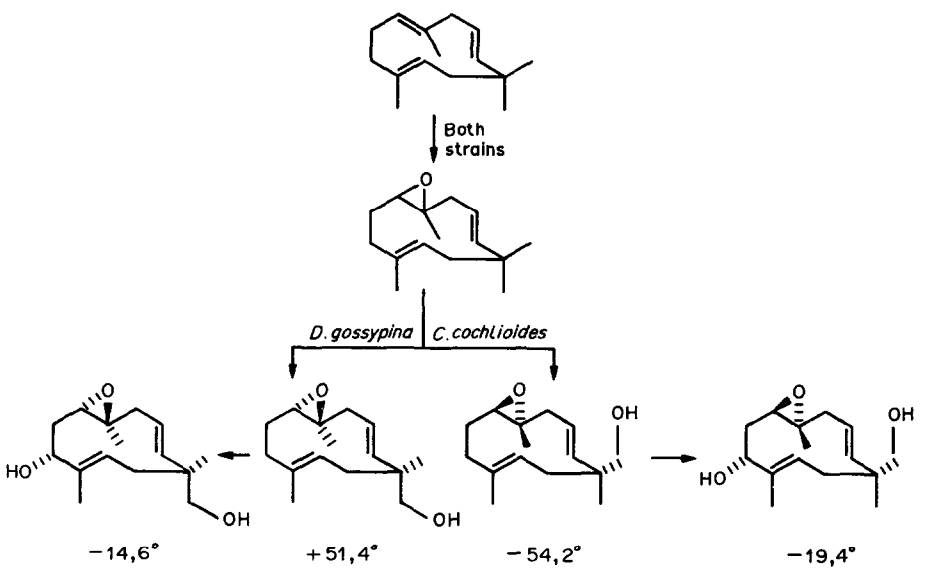
The mono- and di-epoxides of humulene have been synthesized and their biotransformation gave results similar to those obtained from the hydrocarbon. The mixture of the two diepoxides


15 mg
7mg
8mg
13 mg
5 mg
7mg
1R,2R,
4S,5S
2mg
9 mg
1R,2R,
8S,9S
6 mg
1S,2S,
8S,9S
6 mg
1S,2S,
4S,5S
7 mg
48 mg
166 mg
11 mg
5 mg
8 mg
46 mg
2 mg
1R,2R
2mg
1S,2S
26 mg
5 mg
3 mg
1700mg
1 mg
8S,9S
3mg
4S,5S
3mg
5 mg
13 mg
5 mg
4S,5S,8S,9S
4mg
20 mg
5mg

anti [I(*R*), 2(*R*), 8(*S*), 9(*S*)] and [1(*S*), 2(*S*), 8(*R*), 9(*R*)] gave the following results.



From the following scheme it is possible to compare the major products obtained from humulene by *C. cochlioides* and *D. gossypina*. It may be noted that, depending upon the microorganism used, the two intermediate dioxygenated enantiomers can be obtained.

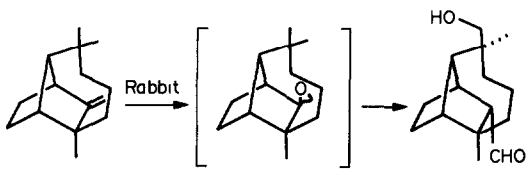


In 1962, Prema and Bhattacharyya studied the biotransformation of humulene by a strain of *Aspergillus niger*.[23] They isolated a diol, $C_{15}H_{24}O_2$ but this seems to bear no relation to the substrate of the bioconversion.

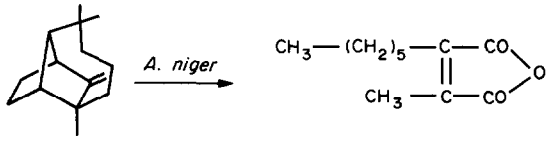
2.4. *Longifolene and isolongifolene*

Asakawa *et al.* have studied the bioconversion of longifolene by the rabbit.[17] The biotransformation takes place at two sites of the molecule, the methylene group and the *gem*-dimethyl

group. This gives the following major product, via an epoxide intermediate.

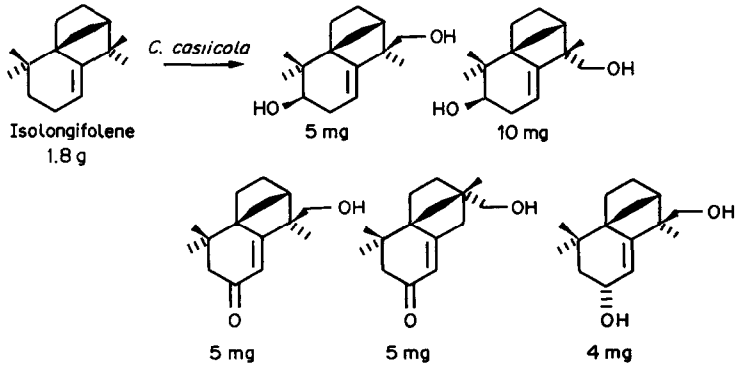


In 1963, Bhattacharyya studied the action of *Aspergillus niger* on longifolene, β-santalene and camphene.[24] They isolated an anhydride from all three substrates, but there is no evidence to prove that this product bears any relation to the substrates.



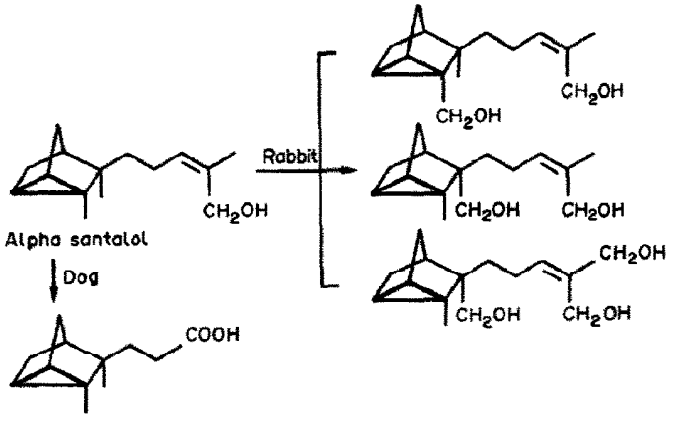
In 1968, Joglekar isolated strains capable of growth on terpene products as their sole source of carbon and energy. One of these products is longifolene. After incubation with two isolated microorganisms (*Escherichia coli* and *Pseudomonas pyrocyanus*), he recovered longifolene (90%). Only 2% of the substrate had been transformed by *E. coli* and 0.2% by *P. pyocyanus*. The metabolites are mainly acids and three hydroxyketones for which the exact structures are unknown.[25]

In 1984, Kieslich *et al.* studied the effect of *C. casiicola* (DSM 624747) on longifolene and isolongifolene (the transformation product of longifolene in acidic medium).[26] Longifolene was not transformed. On the other hand, biotransformation products were found for isolongifolene with *G. casiicola* and another fungus, *Metarrhyizium anisopliae* (IFO 5940).

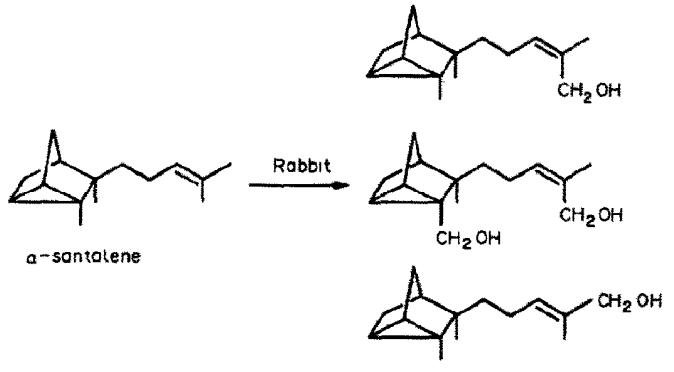


2.5. *α-Santalol and α-santalene*

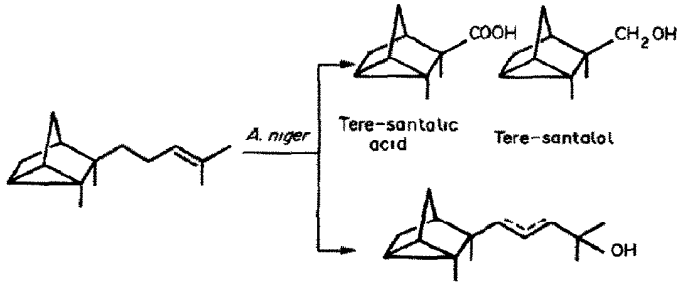
Zundel and Ourisson have studied the bioconversion of α-santalol and α-santalene by the rabbit and the dog.[27] This study led in the case of α-santalol to the following metabolites.



α-Santalene is hydroxylated by the rabbit giving α-santalol, an alcohol isomer of α-santolol and one of the metabolite diols of α-santolol.

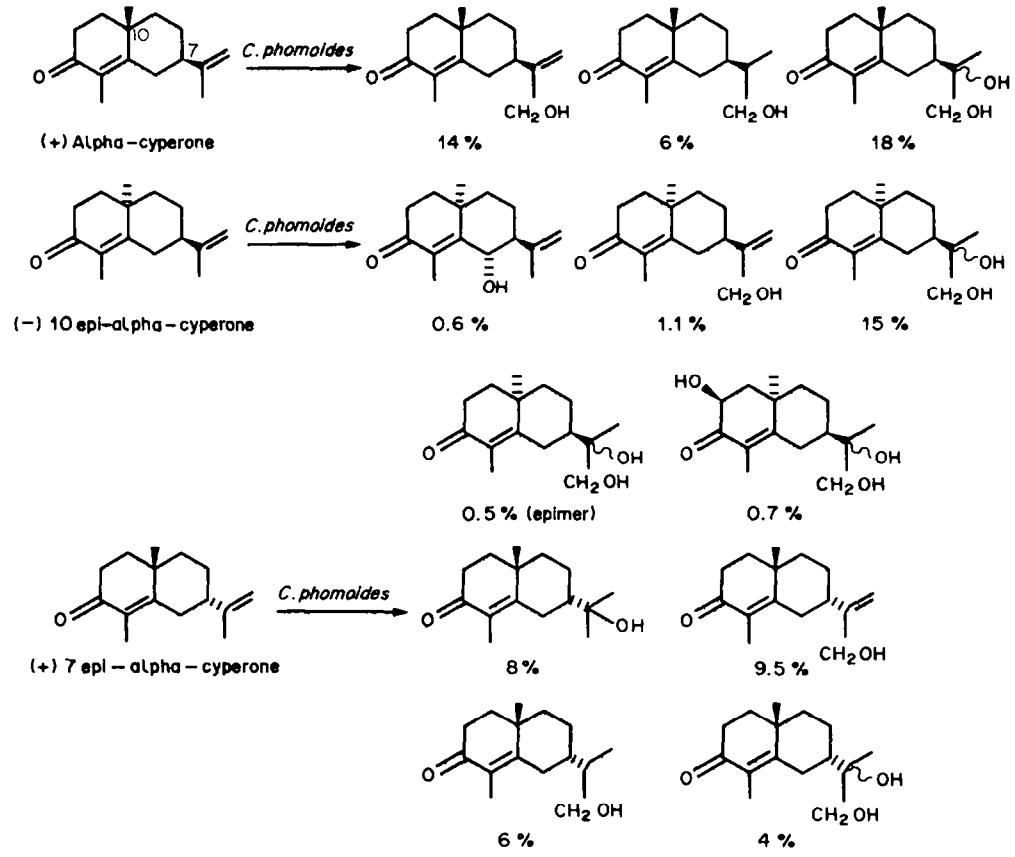


Prema and Bhattacharyya have also studied the bioconversion of this hydrocarbon by *Aspergillus niger*.[23] The major bioconversion product is tere-santalic acid. Two alcohols were also obtained: tere-santalol and an alcohol, $C_{15}H_{24}O$, which has not been identified.

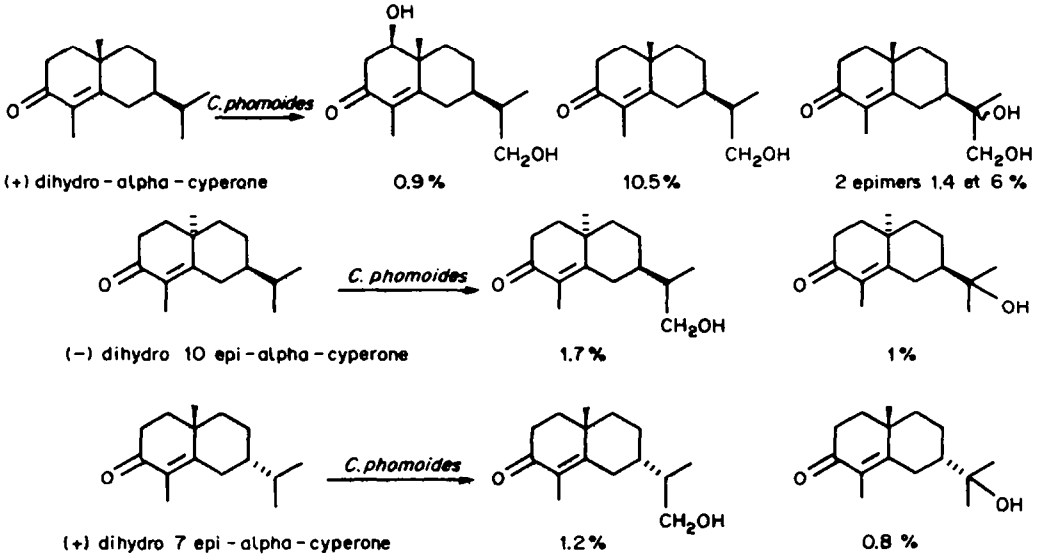


2.6. *α-Cyperone, dihydro-α-cyperone and their respective stereoisomers*

Hikino *et al.* have studied the microbiological transformation of α-cyperone and two of its isomers by *Collectotrichum phomoides* with a view to investigating the stereoselectivity of enzymic reactions in microorganisms.[128]



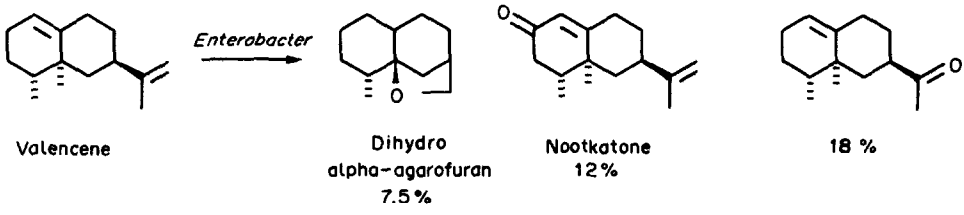
The metabolites obtained by bioconversion of these three stereoisomers of α-cyperone by *C. phomoides* show that the predominant transformation is modification of the side chain which includes a vinyl group. The authors continued to investigate these bioconversions by investigating the bio-oxidation of dihydro-α-cyperones obtained by hydrogenation of the terminal olefinic double bond.



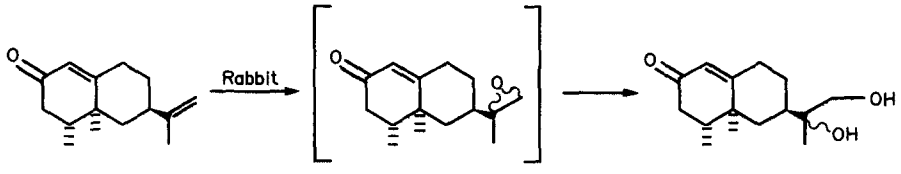
The results show that *C. phomoides* prefers to attack the side chain even in the absence of the terminal olefinic double bond. Hydroxylation of the ring is only observed in the case of (+)dihydro-α-cyperone.

2.7. *Valencene and nootkatone*

Dhavlikar and Albroscheit have studied the biotransformation of valencene by two bacteria of the genus *Enterobacter* isolated by enrichment cultures on valencene. One of these bacteria was isolated from a Dutch soil, the other from an infected local beer.[29] The authors identified three mono-oxogenated metabolites, an ether and two ketones, among the fifteen metabolites present in the crude product of the bioconversion. Their determination of the structure of the first metabolite was reexamined and corrected in a subsequent publication.[29b]

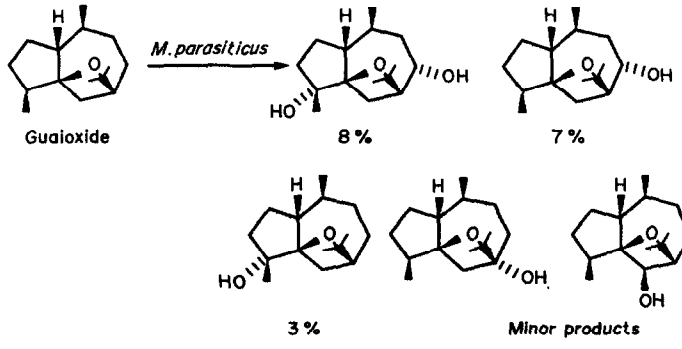


Nootkatone is a much sought-after aromatic substance and this is the main reason for work on valencene. The metabolism of nootkatone by the rabbit has been studied by Asakawa *et al.*[17] It involves epoxidation of the exocyclic double bond.

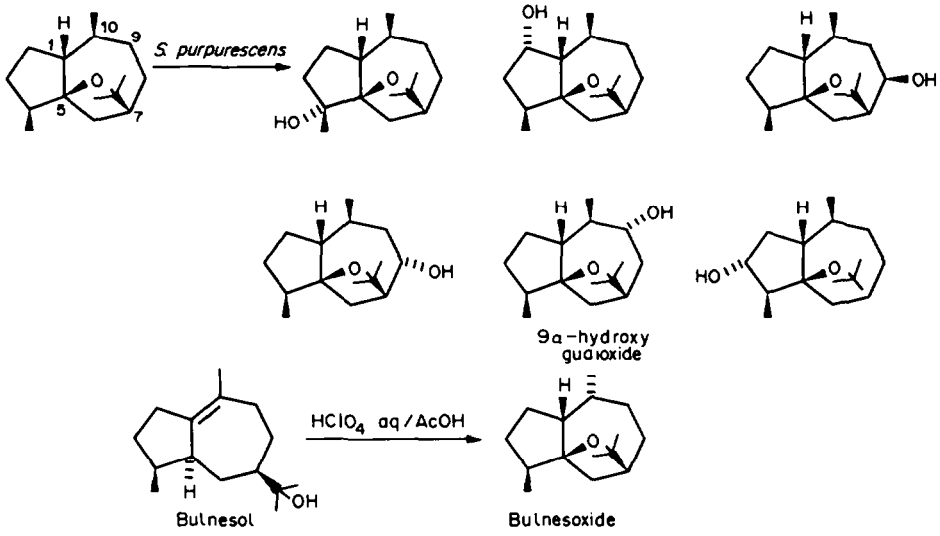


2.8. *Guaioxide and liguloxide*

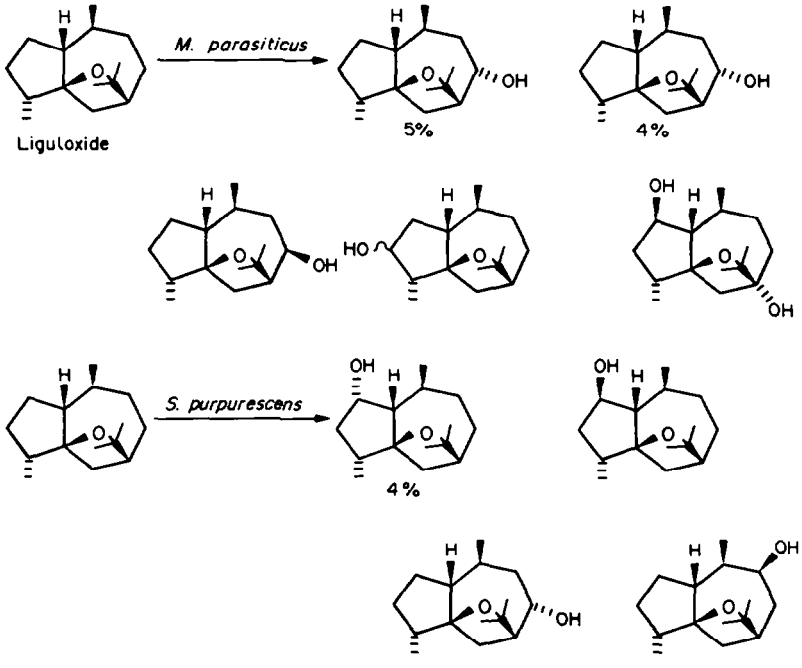
Guaioxide, a secondary constituent of guaiac wood oil, can be obtained by cyclization of guaiol by acid. To determine the structure of guaioxide, Ishii *et al.* studied its bioconversion by *Mucor parasiticus* (ATCC 6476).[30] Determination of the structure of the products of this bioconversion has made it possible to establish the stereochemistry of guaioxide and thence to deduce that of its epimer on the C4 carbon atom, liguloxide (isolated from *Ligularia fischeri* Turcz).



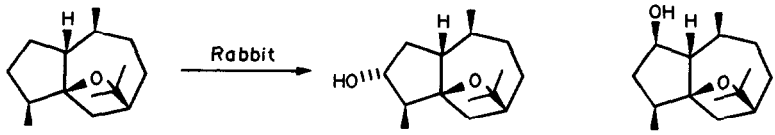
Ishii has also studied the bioconversion of guaioxide by *Streptomyces purpurescens*.[31] This yielded six monohydroxylated derivatives including 9α-hydroxy-guaioxide. Chemical transformation of this product made possible the preparation on the C10 carbon atom of the isomer of guaioxide, which is identical with bulnesoxide obtained by acid catalysed cyclization of bulnesol.



The same authors have also studied the bioconversion of liguloxide by *Mucor parastiticus*[32] and by *Streptomyces purpurescens*.[33]

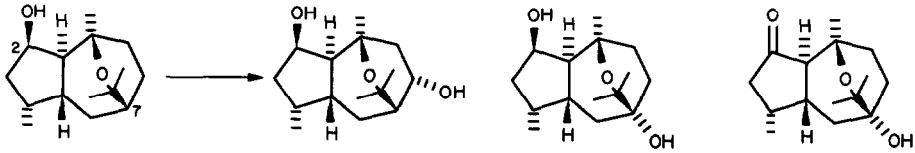


Ourisson *et al.* have studied the bioconversion of guaioxide by the rabbit.[9] This gave two monohydroxylated derivatives which were different from those obtained microbiologically.

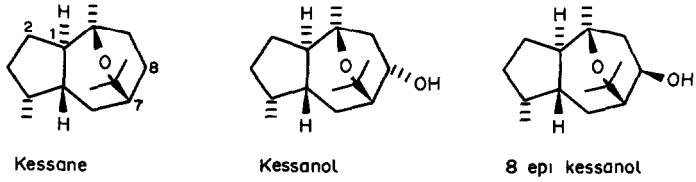


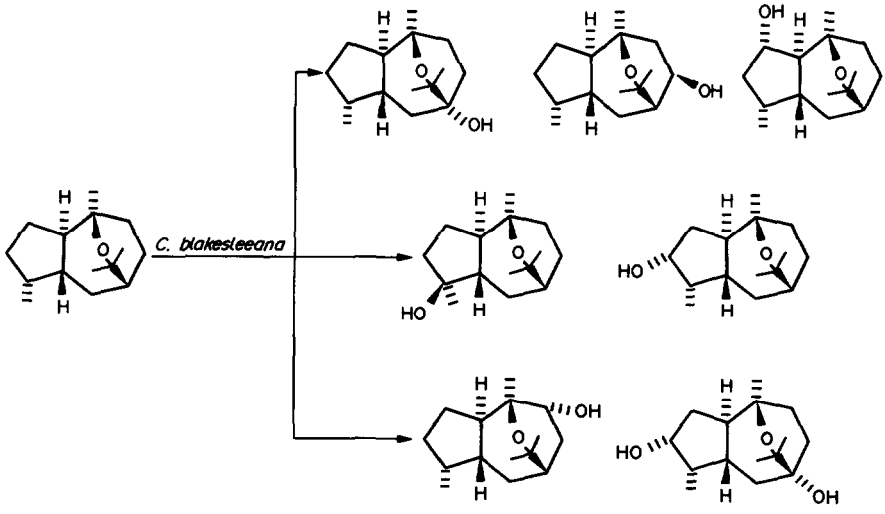
2.9. *α-Kessyl alcohol and kessane*

α-Kessyl alcohol and kessyl glycol are constituents of various species of Japanese valerians. Hikino *et al.* studied the transformation of α-kessyl alcohol in the hope of obtaining kessyl glycol by enzymatic hydroxylation, to prove that α-kessyl alcohol is the biosynthetic precursor of this glycol.[34] Four microorganisms were chosen for this transformation: *Cunninghamella blakesleeana, Corticium sasakii, Corticium centrifugum* and *Streptomyces aureofaciens*. They yield in differing proportions kessyl glycol and the 2β,7-kessane diol as major products and a ketol present as a trace element in the culture medium.



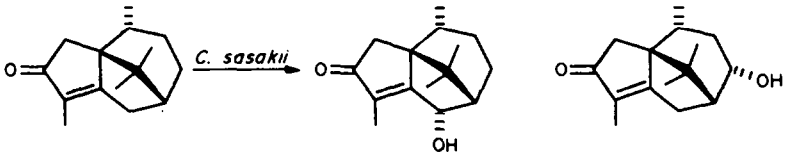
Two other derivatives of the kessane skeleton, kessanol and 8-*epi*-kessanol, exist in Nature.[35] Their biosynthetic origin is probably enzymic hydroxylation of kessane in plants. To check this hypothesis, the microbiological transformation of kessane by *C. blakesleeana* was studied.[36] This yielded the following seven products, including 8-*epi*-kessanol, which confirms the biogenetic hypothesis.





2.10. *Cyperotundone*

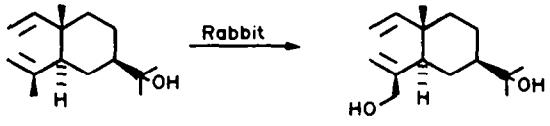
The study of the sesquiterpenoid constituents of *Cyperus rotundus* Linnaeus has made possible the isolation of cyperotundone and the keto alcohol sugeonol (6α-hydroxy-cyperotundone). The authors attempted the chemical transformation of cyperotundone in sugeonol to establish its structure. When this method proved unsuccessful, they studied the microbiological transformation of cyperotundone.[37] *Corticium sasakii* yielded a variety of metabolites of which it was possible to isolate and characterize two: sugeonol and isopatchoul-4-en-3-on-8α-ol.



Cyperotundone Sugeonol 14% 18%

2.11. *Elemol*

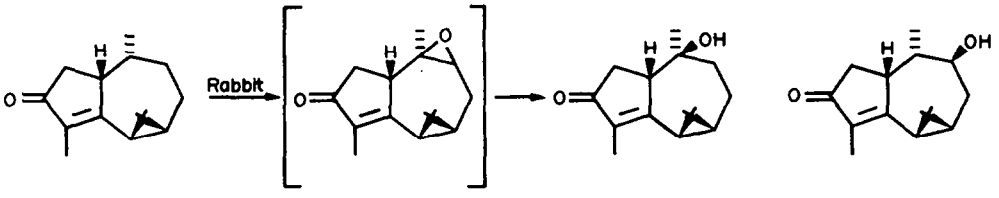
The bioconversion of elemol by the rabbit has proved difficult. 70% of the substrate is recovered and only a small fraction is hydroxylated. It was possible to characterize only one metabolite.[17]



Elemol

2.12. *Cyclocolorenone*

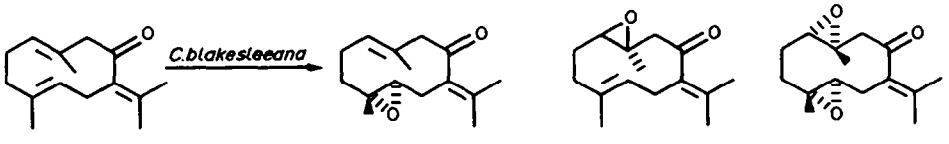
The bioconversion of cyclocolorenone by the rabbit gives two monohydroxylated metabolites.[17]



cyclocolorenone

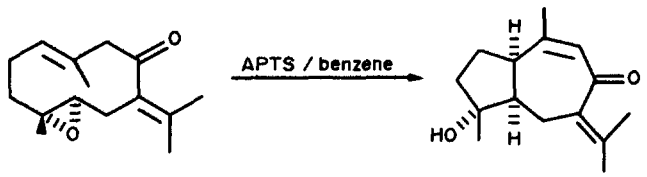
2.13. *Germacrone*

Hikino *et al.* have investigated by enzymic means the stereospecific epoxidation reactions of olefinic double bonds in the plant *Curcuma zedoaria* Roscoe. They studied the bioconversion of germacrone, a constituent of *C. zedoaria*, by microorganisms in the hope of obtaining stereoselective epoxidation as in the case of the plant.[38] *Cunninghamella blakesleeana* yielded three major products from germacrone:



germacrone

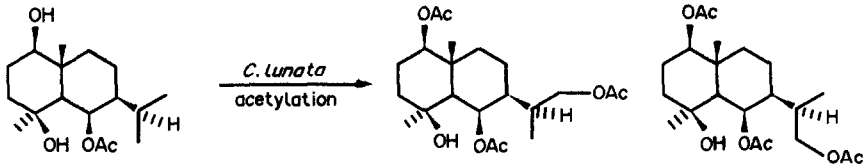
However, transformation of the 4,5-monoepoxide into procurcumenol showed that epoxidation by this microorganism was not entirely stereospecific. The optical purity of the product did not exceed 25%.



procurcumenol

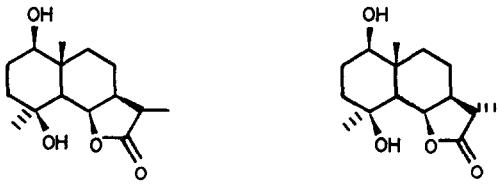
2.14. *6β-Acetoxyeudesmane*

Biohydroxylation of 6β-acetoxy-1β,4β-dihydroxy eudesmane, extracted from a labiate of the genus *Sideritis*, gave precursors of sesquiterpenoid lactones of the 6α-eudesmanolide type.[39] Bioconversion of this substrate by *Curvularia lunata* yielded two hydroxylated derivatives which it was possible to isolate in the form of triacetates (20%).



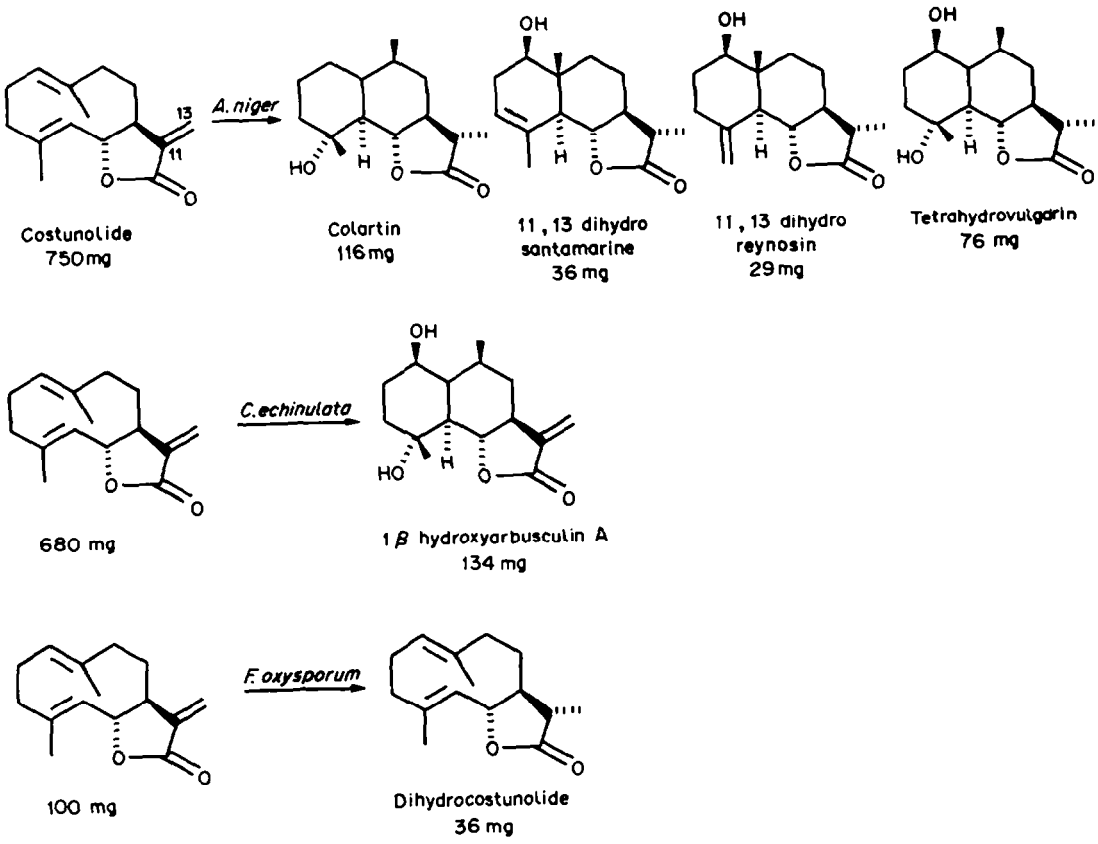
22% 20%

After reduction of the triacetates, oxidation of the products obtained by $RuH_2(PPh_3)_4$ yielded the following 6β-eudesmanolides.

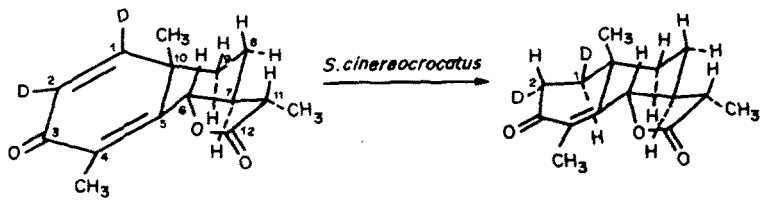


2.15. *Sesquiterpenoid lactones*

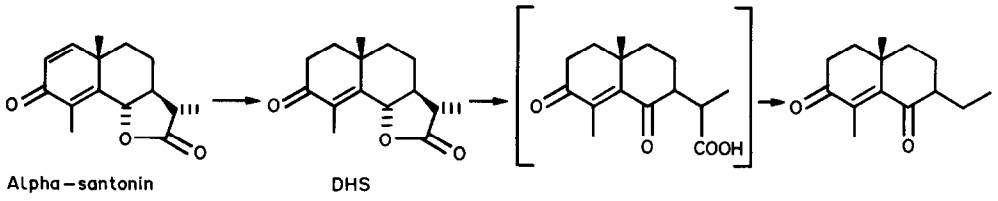
Sesquiterpenoid lactones are studied very extensively because of their biological activity. Costunolide has been subjected to bioconversions because, although it is not biologically active, hydroxylated derivatives of this type of compound could be.[40] Three microorganisms, *Aspergillus niger* (ATCC 16888), *Cunninghamella echinulata* (NRRL 3655) and *Fusarium oxysprum* (ATCC 7601) have yielded metabolites of costunolide including 1β-hydroxy-arbusculine A. This shows biological activity which was predictable because it has the α,β-unsaturated γ-lactone moiety necessary for cytotoxicity.



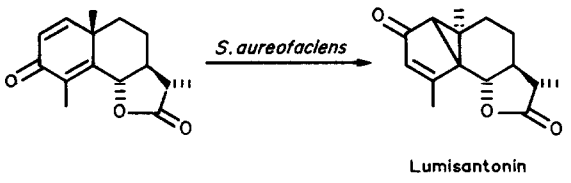
A number of authors have investigated the biological degradation of α-santonin. The first stage in the degradation process gives (+)-1,2-dihydro santonin (DHS). Thus *Cunninghamella blakesleeana* and *Streptomyces aureofaciens* transform α-santonin into DHS (5%) (41). Sato *et al.* have studied the stereochemistry of the hydrogenation of α-santonin into DHS by *Streptomyces cinereocrocatus* (NRRL 3443) by putting 1,2 deuterated α-santonin in contact with the microorganism.[42] The microbiological transformation of this substrate produced (+)-(1β, 2α-D) dihydro-(1,2) santonin (36%). This shows that the reaction is carried out by means of the *trans*-addition of two hydrogen atoms via an attack on the Si face of the 1,2 double bond.



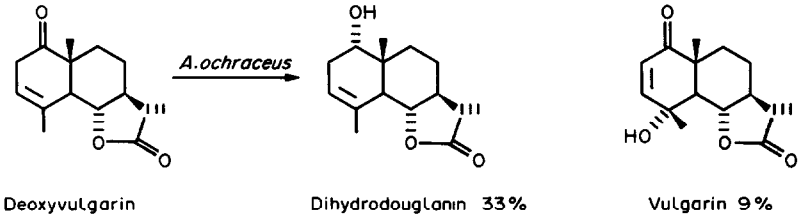
A second stage in the degradation process of α-santonin has been demonstrated with the strain *Pseudomonas S* (ATCC 43388). This leads to the diketone (0.1% in comparison with α-santonin).[43]

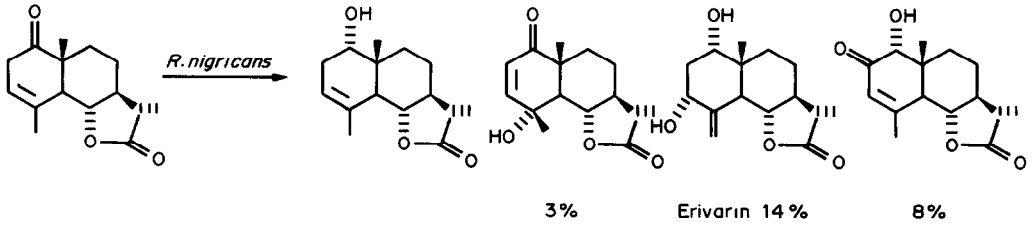


Using another strain of *Streptomyces aureofasciens* (KCC-S-0624), it is possible to achieve the transformation of α-santonin into lumisantonin (4%):[44]



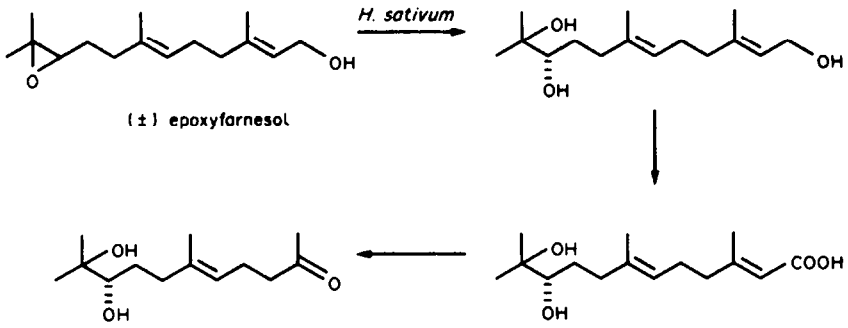
The biotransformation of deoxyvulgarine by *Aspergillus ochraceous* (CECT 2069) and *Rhizopus nigricans* (CECT 2072) gave the following metabolites.[45]



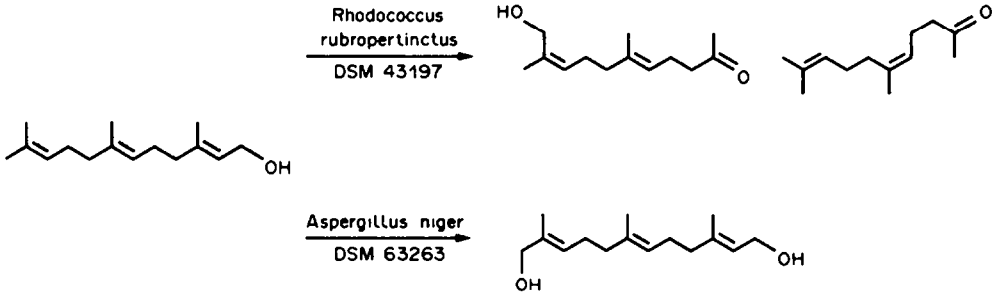


2.16. *Epoxyfarnesol, farnesol, cis and trans-nerolidol*

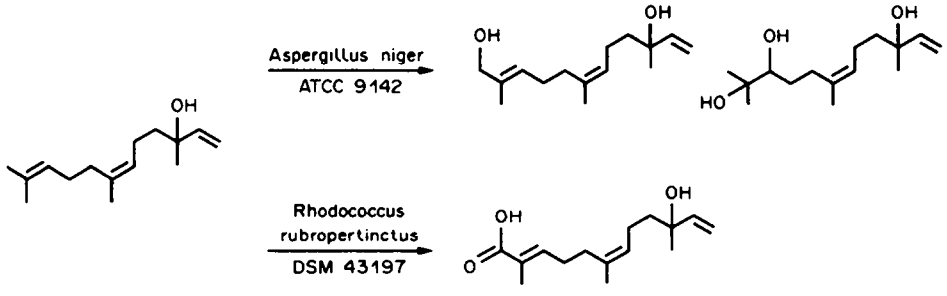
Suzuki and Marumo have studied the transformation of racemic epoxyfarnesol by *Helminthosporium sativum*.[46] They obtained three laevorotary products: (−)-10,11-dihydroxy-farnesol (12.4%); (−)-10,11-dihydroxyfarnesic acid and (−)-9,10-dihydroxygeranylacetone (6.6%). These results led them to postulate the following mechanism for this bioconversion.



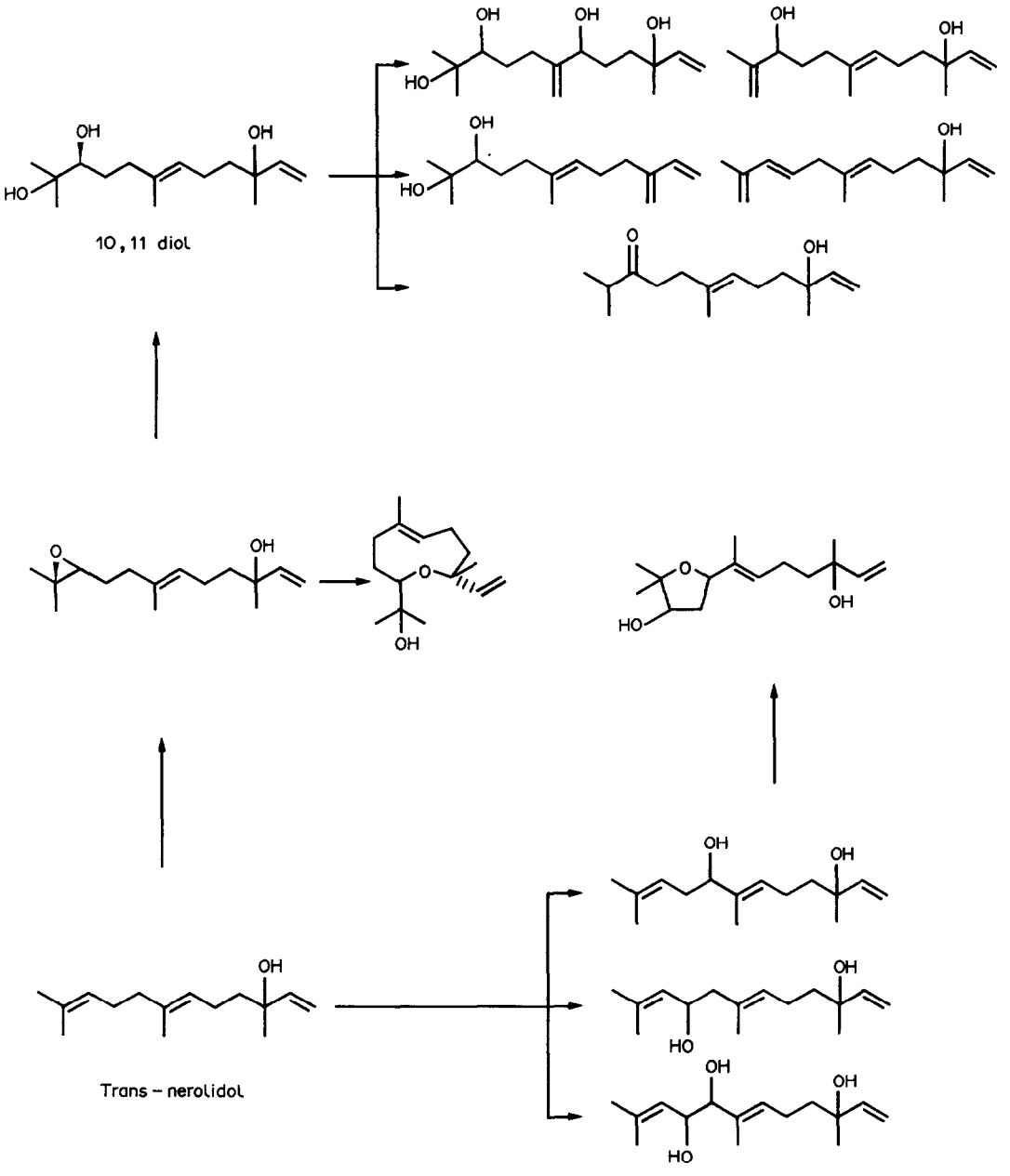
The biotransformation of a mixture of four farnesol isomers by *Rhodococcus rubropertinctus* (DSM 43197) yielded two products with the carbon chain reduced by two units. Under identical conditions, *Aspergillus niger* (DSM 63263) gave a single hydroxylation product (4.5%).[47]



Bioconversion of *cis*-nerolidol by *Aspergillus niger* (ATCC 9142) gave two hydroxylation products, the major metabolite being a triol (44%). *Rhodococcus rubropertinctus* (DSM 43197) transforms *cis*-nerolidol into one single product, a carboxylic acid (25%).[47]

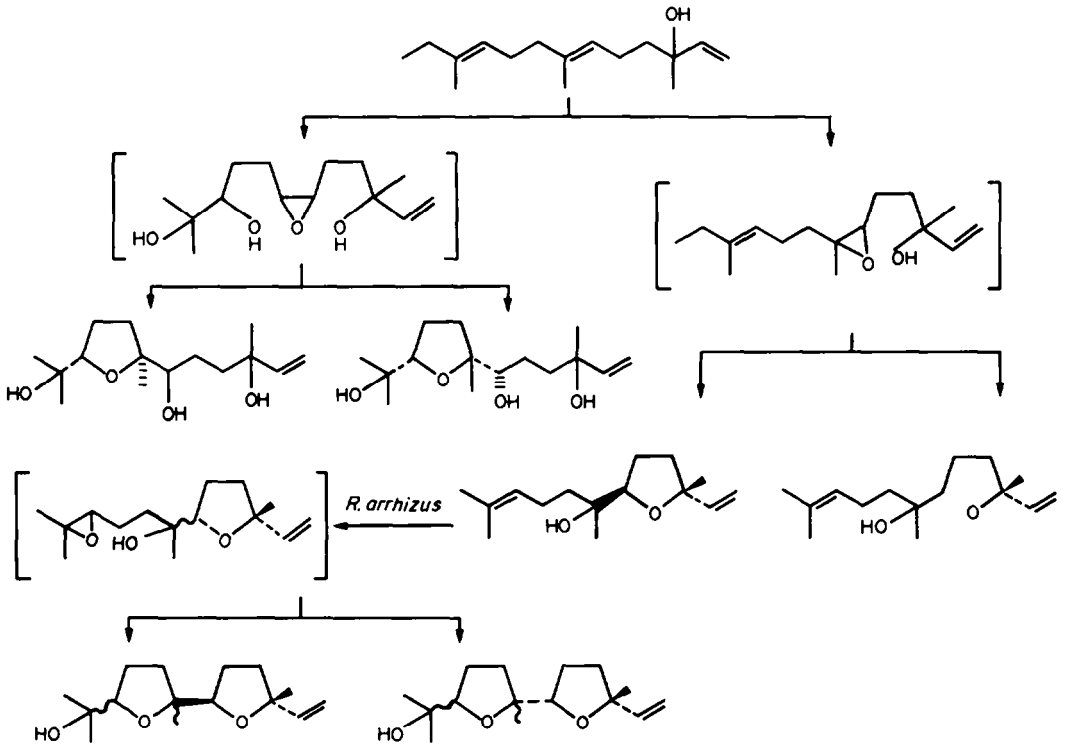


The microbiological transformation of *trans*-nerolidol has been studied by Kieslich *et al.* and yields, depending on the microorganisms used, either epoxidation products or products resulting from ω-hydroxylation. *Corynespora casiicola* (DSM 627), *Diplodia gossypina* (ATCC 10936) and *Gibberella cyanea* epoxidize the trisubstituted terminal olefinic double bond.[48,49] The epoxide obtained results in an intramolecular cyclization product or opens up giving a diol. This is obtained in a yield of 48% with *D. gossypina*.[50] It is then transformed into various dehydration and isomeration products (which may be artefacts produced during purification) and a tetraoxygenated compound.

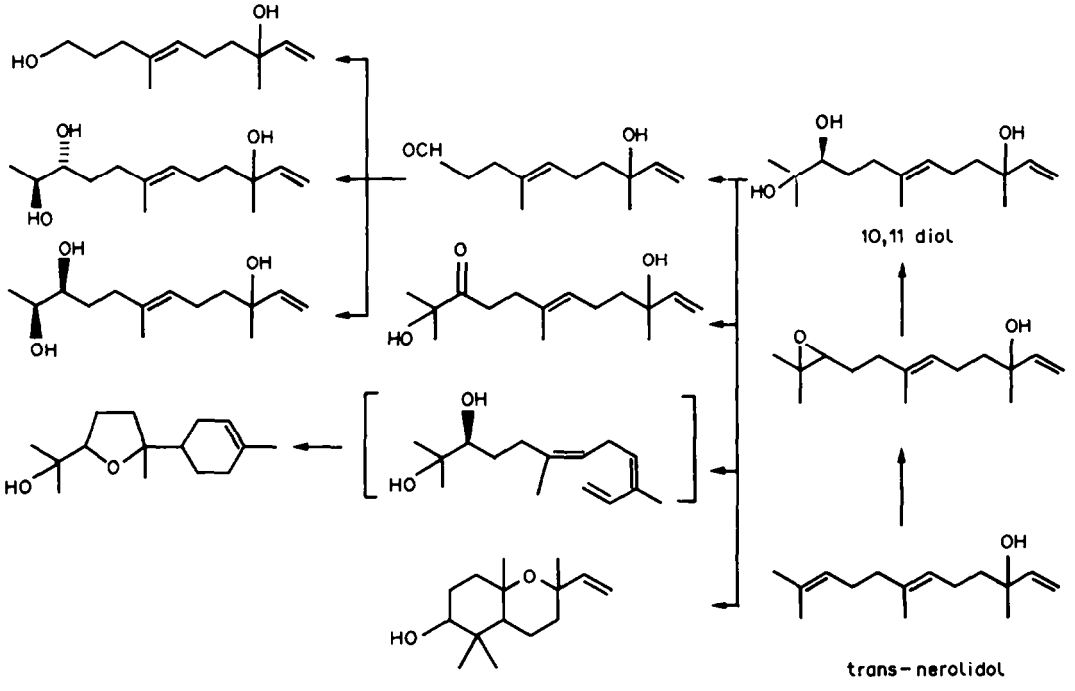


Absidia blakesleeana (ATCC 10148) and *Rhizopus arrhizus* (ATCC 11145) hydroxylate *trans*-nerolidol following a secondary reaction which does not involve the 10,11-glycol intermediate. Hydroxylation takes place at positions 8 and/or 9. The C8 alcohol, reacts with the 10,11-epoxide formed subsequently, giving a tetrahydrofuran derivative.

G. cyanea seems to be capable of epoxidizing the 6,7 double bond and forms tetrahydrofuran rings by means of attack on the epoxide by the hydroxyl group located on the C3 carbon atom or by the hydroxyl group on C10 of the 10,11-diol. *R. arrhizus* reacts in both directions, yielding ditetrahydrofuran structures. The formation of the tetrahydrofuran rings is not stereoselective and *cis*- and *trans*-isomers are obtained in each case.

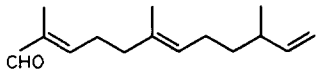


C. casiicola yields two glycols with the loss of one carbon atom and two cyclization products with six-membered rings.



Examples of the formation of carbon–carbon bonds by microbiological reaction are rather rare, so these intramolecular cyclizations are of some value.

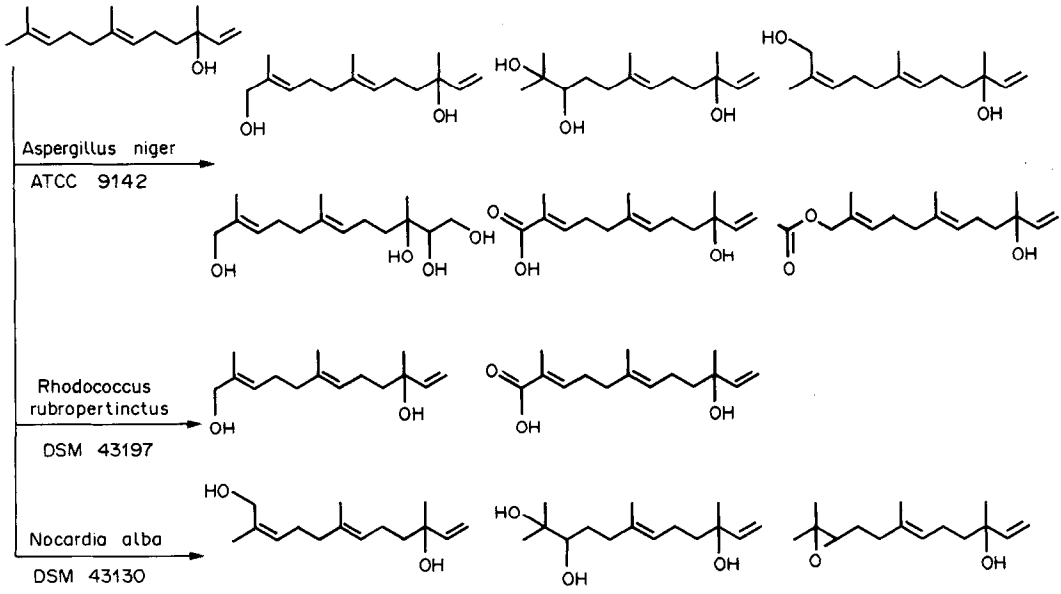
Arfmann *et al.* have looked for other microorganisms likely to perform ω-hydroxylation of *trans*-nerolidol. Using this reaction which gives low yields using chemical means, it is possible to obtain the precursor of α-sinensal which has the flavour of bitter orange.[47]



Aspergillus niger (ATCC 9142) yields the 12-hydroxy nerolidol as the major product. In analytical experiments, this is the only product (20%). However, when the experiment is carried out in a 10 l fermenter, other products are formed and the yield of the major product is no more than 5%.

Rhodococcus rubropertinctus (DSM 43197) leads to two metabolites including the hydroxy-acid (45%).

Nocardia alba (DSM 43130) did not give the desired metabolite. The major metabolite is the 10,11-epoxy-transnerolidol, (26%).



3. CONCLUSION

This bibliographical survey has shown how bioconversions can provide unequalled access to certain sesquiterpenoid derivatives which are of value to the perfumery and pharmaceutical industries, and make it possible to determine the structure of their precursors. Highly complex mixtures of products are often obtained from non-functionalized sesquiterpenes but pre-monoxygenated products such as the sesquiterpenoid alcohols are more suitable for bioconversions. They enable us to obtain hydroxylated metabolites with high regio- and stereo-selectivity in fair to good yields. Even if these reactions are not always suitable for exploitation on an industrial scale, they offer the possibility of obtaining in one single step products which can then be tested to determine their olfactory or biological properties. Bio-oxidation products could become worthwhile targets for organic synthesis.

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