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Bacterial transformation of terpenoids

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Data on the bacterial transformation of terpenoids published in the literature in the past decade are analyzed. Possible pathways for chemo-, regio- and stereoselective modifications of terpenoids are discussed. Considerable attention is given to new technological approaches to the synthesis of terpenoid derivatives suitable for the use in the perfume and food industry and promising as drugs and chiral intermediates for fine organic synthesis.
The bibliography includes 246 references.

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I. Introduction

Biocatalysis is one of the main tools in organic chemistry. As opposed to chemical methods of synthesis, biocatalysis technologies are suitable for performing transformations of molecules under mild conditions without the use of protecting groups with high chemo-, regio- and stereoselectivity.[1] Both individual enzymes and enzyme complexes of whole cells of microorganisms can be used as biological catalysts to modify complex molecules with the aim of preparing optically active compounds.

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Isoprene derivatives hold a special place among compounds extensively used in fine organic synthesis. Terpenes and their oxygen-containing derivatives, terpenoids, are typical representatives of isoprenes.[2] Terpenes are divided according to the number of isoprene units into mono- ($C_{10}H_{16}$), sesqui- ($C_{15}H_{24}$), di- ($C_{20}H_{32}$), triterpenes ($C_{30}H_{48}$) and so on. The classification of terpenes is based on the number of rings in the carbon skeleton (acyclic, mono-, bi-, tri-, tetra- and pentacyclic compounds). Resins, tissues and essential oils from higher plants are rich sources of terpenoids; in addition, these compounds are among end-products of bacteria, fungi, corals, marine algae and insects.[2–5] The structural and functional diversity of natural terpenoids provides the raw material base for the preparation of their semisynthetic derivatives exhibiting high biological activities, such as antitumour, antiviral, bactericidal, fungicidal, insecticidal, antispasmodic, hypotensive, hypoglycemic, anti-inflammatory, immunomodulatory and so on.[2, 6, 7]

Chemical methods of transformation of terpenoids can be employed to efficiently produce important products under controlled conditions independent of external factors. However, most of chemical modifications of difficult to access sites of terpenoid molecules are intricate processes, which involve many steps and require the selective protection of functional groups and the use of corrosive reagents.[8–10]

Studies of the biological transformation of terpenoids were performed using whole cells of bacteria, yeasts, mycelial fungi, microalgae, plants and purified enzymes of

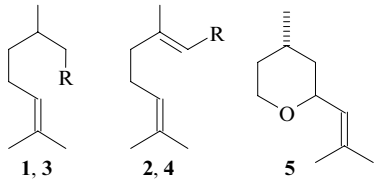
animal, plant and microbial origin.[5, 11–13] The percentage of research on transformations of terpenoids with the use of the mycelium of fungi and whole bacterial cells accounts for 33% and 41%, respectively.[14] However, it should be noted that the application of lower mycelial fungi in biotechnology is potentially dangerous due to their spore inoculum and the ability to synthesize mycotoxins with mutagenic and carcinogenic activities.[15] The high catalytic activity of fungi is usually achieved under cometabolic conditions in nutrient media.[16] Hence, the hydroxylation, redox transformations of oxygen-containing substituents, glycosylation, esterification and cyclization of terpenoids, as well as their isomerization and dehydrogenation catalyzed by bacteria are of great interest.

The improvement of known procedures and development of new methods of biotransformation of terpenoids in order to produce enantiomerically pure compounds, which are promising for the application in the perfume, food and medical industry, remain at the focus of attention from researchers in the areas of chemistry, microbiology, biochemistry and genetics. Microbiological transformations of acyclic and cyclic monoterpenoids,[12, 17] diterpenoids[5, 18] and triterpenoids[19, 20] are discussed in special reviews. The present work provides a more comprehensive overview of the results of research on the biotransformation of terpenoids, which were performed in the last decade employing the enzymatic activity of viable bacterial cells, as well as of purified complex enzyme preparations and individual bacterial enzymes.

II. Biotransformation of monoterpenoids

The oxidative biotransformation of acyclic monoterpenoids was studied in most detail using bacteria of the genus *Pseudomonas*, which metabolize these compounds, including in relatively high (5.0–7.5 g litre^{-1}) concentrations.[21] Pseudomonads were shown to be able to oxidize citronellol (**1**), *trans*-β-geraniol (**2**) and their derivatives to citronellic (**3**) and geranic acids (**4**)[17, 21–25] exhibiting insecticidal and fungicidal activities[26, 27] and to convert (+)-citronellol [(+)-**1**] into a mixture of *cis*- and *trans*-rose oxides (**5**) (2 : 1) used in the perfume industry.[28] It was found that the oxidative metabolism of alcohols **1** and **2** with cultures of *P. aeruginosa*, *P. citronellolis* and *P. mendocina* occurs in the presence of enzymes encoded by the specific *atu* (acyclic terpene utilization) gene cluster,[21, 23, 29, 30] as well as of nonspecific enzymes, such as the protein PA1535,[30] pyrroloquinoline quinone-dependent ethanol dehydrogenase (QEDH)[31] and enzymes encoded by the *liu* (leucine and isovalerate utilization) gene cluster.[17]

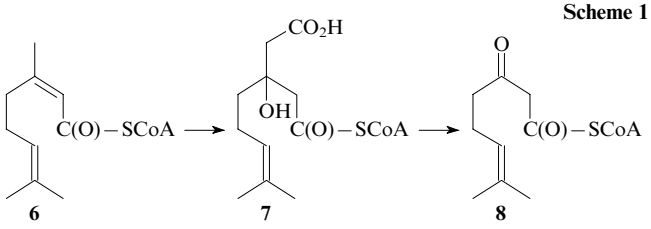
Structures 1–5



R = CH_2OH (**1**, **2**), CO_2H (**3**, **4**)

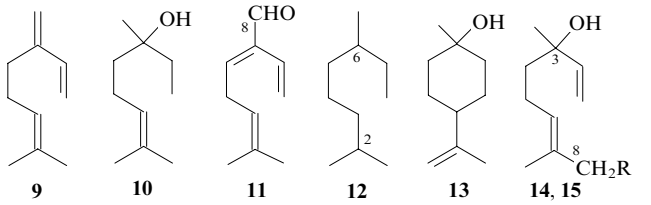
Enzymes encoded by the *liu* cluster show high (34%–64%) homology with key enzymes encoded by the *atu* cluster.[23–25] The mutation of genes of the Liu cluster leads to a decrease or loss of the ability of pseudomonads to perform the biotransformation of citronellol (**1**) and its derivatives.[32] It was found that the metabolic intermediate *cis*-geranoyl-CoA (**6**), which is formed in the course of the biotransformation of alcohols **1** and **2**, is oxidized to 3-hydroxy-γ-carboxygeranoyl-CoA (**7**) followed by the transformation of the latter into 7-methyl-3-oxooct-6-enoyl-CoA (**8**) (Scheme 1) catalyzed by 3-hydroxy-3-methylisohexylglutaryl-CoA lyase encoded by the *liu* cluster,[22, 24, 32, 33] analogues of which were not found in the *atu* cluster.[17] The cleavage products of alcohols **1** and **2** (in particular, acetyl-CoA) serve as inductors of enzymes involved in the glyoxylate cycle.[34, 35]

Scheme 1



The transformation of the acyclic hydrocarbon β-myrcene (**9**) by cells of *Pseudomonas* sp. M1 involves inducible catabolic enzymes (Myr cluster) of β-oxidation along with specialized proteins responsible for the bacterial cell penetration by terpene and facilitating an increase in the cell resistance to stress and toxic agents.[36] The oxidation of compound **9** using cells of *P. aeruginosa* gives rise to dihydrolinalool (**10**) as the major product (80%), whereas *P. putida* accumulates 8-oxo-*cis*-ocimene (**11**) (62%).[37, 38] The further incubation of pseudomonads with myrcene (**9**) leads to accumulation of 2,6-dimethyloctane (**12**) (90%) or monocyclic *cis*-β-terpineol (**13**) (68%) and linalool (**14**) (26%), respectively.[37, 38] Compound **14** exhibits diverse biological activities, including anti-inflammatory, analgesic, antibacterial and fungicidal.[39]

Structures 9–15



R = H (**14**), OH (**15**)

Examples of the biotransformation of acyclic monoterpenes using the following agents have been described in the literature: 1) actinobacterial *Rhodococcus erythropolis* strain MLT1 and *Rhodococcus* sp. strain GR3, which oxidize only ~2% of β-myrcene (**9**) to alcohol **2** (Ref. 40) and 50% of alcohol **2** to acid **4**,[41] respectively; 2) beta-proteobacterium 'Alcaligenes defragrans' (*Castellaniella defragrans*),† which catalyzes the oxidation of β-myrcene (**9**) to acid **4** (13%),[42] isomerization of geraniol (**2**) to

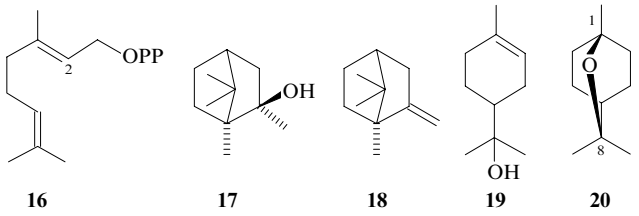
† Invalid generic names or obsolete names of the taxa of bacteria (according to the commonly accepted rules) are written in regular type and in quotation marks. The currently accepted names of taxa (if they are available) are given in parentheses.

linalool (**14**) or the dehydration of the latter to form compound **9**;[43] 3) the enzyme CYP111A2 from 'Novosphingobium aromaticivorans' (*Sphingomonas aromaticivorans*) ATCC 700278D-5, which selectively converts linalool (**14**) to 8-hydroxylinalool (**15**) exhibiting pronounced antimicrobial properties.[44, 45]

A special area of research on the biotransformation of terpenoids concerns the catalytic activity of bacterial monoterpene synthases. For example, linalool/nerolidol synthase catalyzing the transformation of geranyl pyrophosphate (**16**) into (3*R*)-linalool ((3*R*)-**14**) was found in the bacteria *Streptomyces* sp. (strain GWS-BW-H5), *S. clavuligerus* and *Stigmatella aurantiaca*. The gene expression of this enzyme in 'S. lividans' produces 8-hydroxy derivative **15** as an additional product.[46] Myxobacteria, cyanobacteria and streptomycetes were found to be able to perform the biosynthesis of bicyclic 2-methylisoborneol (**17**) from pyrophosphate **16** catalyzed by the enzymes *S*-adenosyl-L-methionine-dependent methyltransferase and 2-methylisoborneol synthase.[47 – 49] Synthases from *Micromonospora olivasterospora* KY11048 and *P. fluorescens* PfO-1 responsible for the biosynthesis of 2-methylenebornane (**18**) from 2-methyl-substituted pyrophosphate **16** were characterized.[49, 50] The gene encoding monoterpene synthase that catalyzes the sequential conversion of pyrophosphate **16** to α-terpineol (**19**) and then to 1,8-cineole (**20**) was found in cells of *S. clavuligerus* ATCC 27064.[39, 51] These cyclic derivatives have fungicidal activity and improve the bioavailability of drugs.

The naturally abundant monocyclic monoterpene limonene (**21**) is extensively applied as a substrate of the bacterial transformation, and its derivatives are widely used in the perfume industry and hold promise for pharmaceutics.[12, 39, 52] Low regiospecificity of homologous enzymes involved in the transformation of substrate **21** and its derivatives is often responsible for the formation of a mixture of biological oxidation products (Scheme 2).[12, 52 – 55] Representatives of *P. putida* were found to be able to perform the bioconversion of compound **21** giving perillyl alcohol (**22**), perillic acid (**23**), dihydrocarveol (**24**) or diol **25**.[12, 53 – 55] The cyanobacterium *Synechococcus* sp. PCC 7942 gives a mixture of carveols (4*R*,6*R*)-**26** and (4*R*,6*S*)-**26** in a ratio of 4.6 : 1.[56] Among numerous metabolites of limonene (**21**) produced by the marine bacteria *Vibrio cholerae* 11-114, *V. alginolyticus* 11-306 and 'Listonella damsela' (*Photobacterium damselae*) 11-213, 1,2-dihydroxy derivative **27** was identified as the major product.[57] Some cultures that catalyze the selective oxidation of limonene (**21**) were characterized. For instance, *P. fluorescens* accumulates alcohol **19** as the major product (up to 91%),[52] 'Alcaligenes defragrans' (*Castellaniella defragrans*) produces acid **4**,[42] the *Xanthobacter* sp. strain C20 quantitatively produces enantiomerically pure 8,9-epoxy-(4*R*,8*R*)-limonene (**28**).[58]

Structures 16 – 20



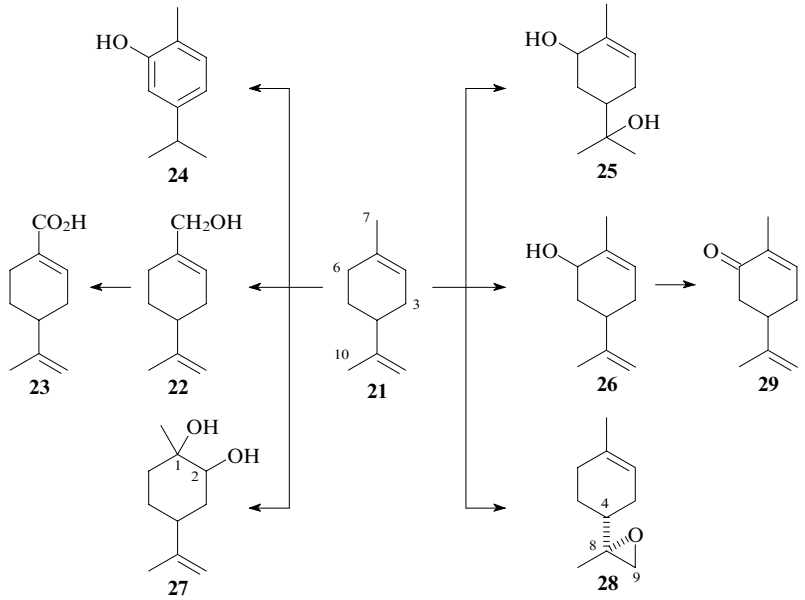
16 **17** **18** **19** **20**

PP is pyrophosphate

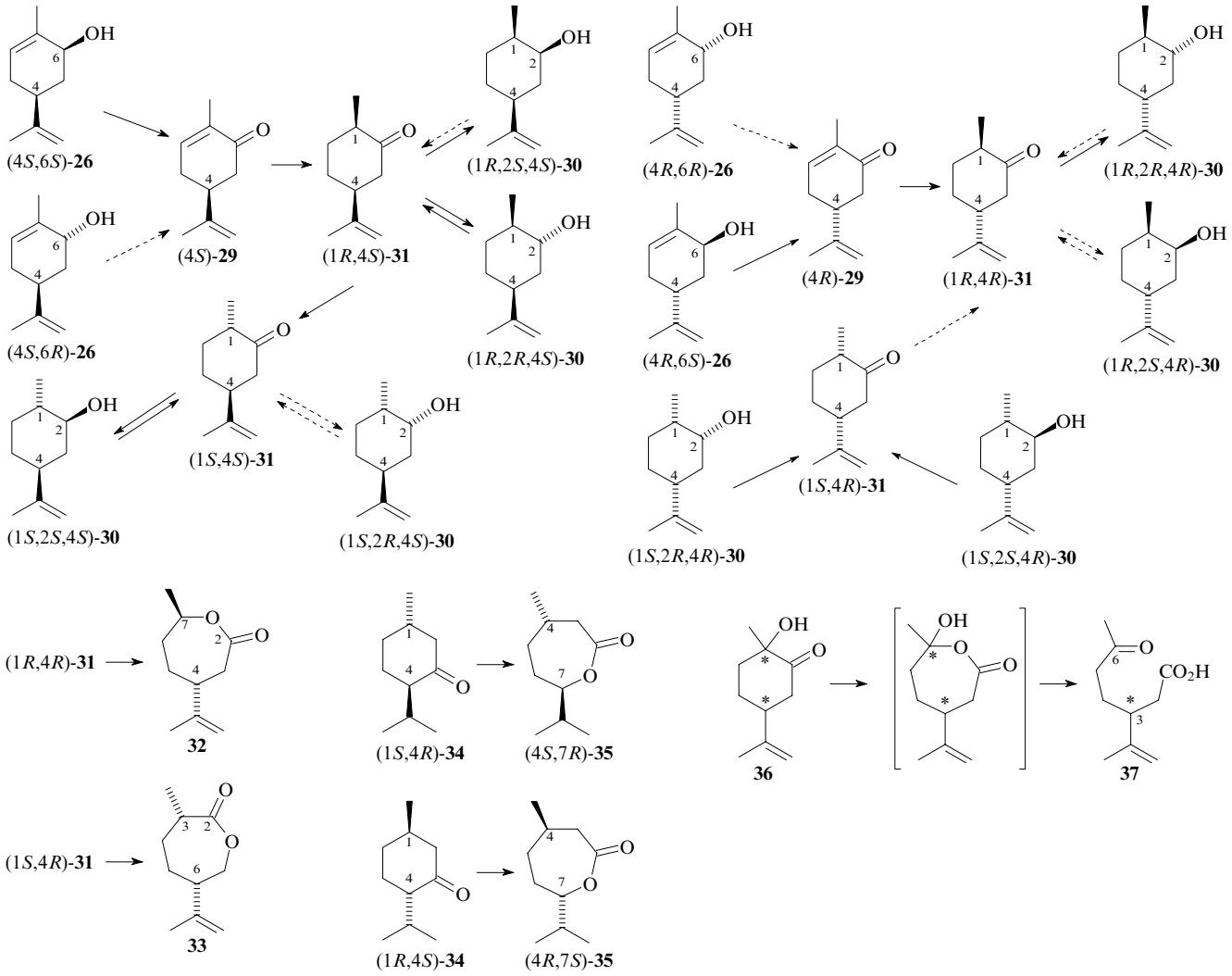
In most cases, the bacterial oxidation of substrate **21** is initiated by hydroxylation at the C(6) or C(7) atoms to form alcohols **26** and **22**, respectively, with anti-angiogenic and antitumour activities.[39, 59] Then carveol (**26**) is transformed into carvone (**29**), while perillyl alcohol (**22**) is oxidized to relevant acid **23**, which is further degraded *via* the β-oxidation pathway.[12, 53]

Whole cells of *R. erythropolis* DCL14, their extracts and individual enzymes were used to study in detail the transformation pathways and interconversions of limonene derivatives (**21**), in particular, mixtures of stereoisomeric carveols (4*S*,6*S*)-**26**/(4*S*,6*R*)-**26** and (4*R*,6*R*)-**26**/(4*R*,6*S*)-**26**, their individual dihydro derivatives (1*R*)-**30** or (1*S*)-**30**, as well as (4*S*)- and (4*R*)-carvones (**29**) and the relevant 1*S*- and 1*R*-stereoisomers of their dihydro derivatives **31** (Scheme 3, the pathways with low degree of conversion are

Scheme 2



Scheme 3



indicated by dashed arrows). The key enzymes of the redox transformation and isomerization of the starting compounds and products of their biotransformation were characterized.[60]

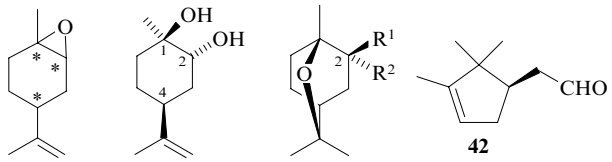
The experimental study of a mixture of compounds (1*R*,4*R*)-**31** and (1*S*,4*R*)-**31** showed that it is isomer (1*R*,4*R*)-**31** that mainly undergoes further oxidative biodegradation. This compound is transformed into (4*R*,7*R*)-4-isopropenyl-7-methyl-2-oxooxepane (**32**), which is a key intermediate of the limonene degradation pathway, in the presence of monocyclic monoterpene ketone 1,2-monooxygenase. Meanwhile, in the presence of this enzyme, isomer (1*S*,4*R*)-**31** is only partially converted to minor (3*S*,6*R*)-6-isopropenyl-3-methyl-2-oxooxepane (**33**), the hydrolysis of which is the dead-end metabolic pathway.[60, 61] It was found that this monooxygenase catalyzes also the oxidation of stereoisomers of menthone (1*S*,4*R*)-**34** and (1*R*,4*S*)-**34** to (4*S*,7*R*)- or (4*R*,7*S*)-7-isopropyl-4-methyl-2-oxooxepanes (**35**), respectively, whereas in the case of stereoisomers of 1-hydroxy-2-oxolimonene (**36**), unstable oxepanones are spontaneously rearranged into 3-isopropenyl-6-oxoheptanoic acids (**37**).[61]

The new metabolic pathway of limonene derivatives performed by the actinobacterium *R. erythropolis* DCL14 was theoretically substantiated based on the results of the study of 1,2-epoxylimonene (**38**). The regioselectivity of the attack on the carbon atoms of the epoxide ring in the latter compound by specific hydrolase from *R. erythropolis* DCL14 depends on the conformation of compound **38**, to be more precise, on the orientation of the isopropenyl substituent. The hydrolysis of mixtures of (1*R*,2*S*,4*S*)/(1*S*,2*R*,4*S*)- or (1*R*,2*S*,4*R*)/(1*S*,2*R*,4*R*)-stereoisomers **38** selectively affords (1*R*,2*R*,4*S*)- or (1*S*,2*S*,4*R*)-limonene-1,2-diols (**39**), respectively.[62] According to the results of the study,[56] in the transformation of a mixture of (1*R*,2*S*,4*R*)- and (1*S*,2*R*,4*R*)-stereoisomers **38**, the cyanobacterium *Synechococcus* sp. PCC 7942 had hydrolytic activity only towards the (1*S*,2*R*,4*R*)-stereoisomer. Diol (1*S*,2*S*,4*R*)-**39** (32%), the product of its oxidation, (1*S*,4*R*)-limonen-1-ol-2-one [(1*S*,4*R*)-**36**] (16%), and unchanged epoxide (1*R*,2*S*,4*R*)-**38** were found among the reaction products.

The study of the bacterial transformation of other monocyclic terpenoids showed that the conversion (98%) of 1,8-cineole (**20**) by rhodococcal species is characterized by a low degree of stereoselectivity and affords a mixture of (2 : 1) of 2-*endo*- [(2*S*)-**40**] and 2-*exo*-hydroxy [(2*R*)-**40**] derivatives along with their oxidation product **41**.[63] The lactic acid bacteria *Lactobacillus paracasei*, 'Streptococcus

macedonicus' (*Streptococcus gallolyticus* subsp. *macedonicus*) and *Lactococcus lactis* were found to be able to catalyze the reduction of the carbonyl group of α-campholenal (**42**) followed by its rearrangement to give the borneol isomer.[64]

Structures 38 – 41

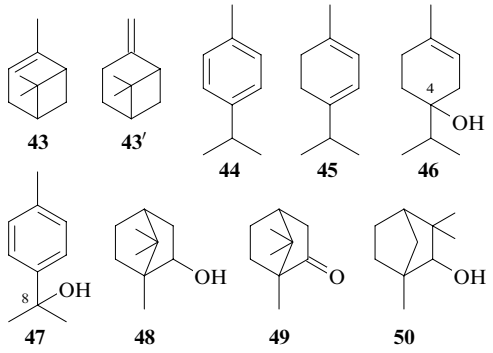


38 (1*R*,2*R*,4*S*)-**39** **40**, **41** **42**

R^1 = OH, R^2 = H [(2*S*)-**40**]; R^1 = H, R^2 = OH [(2*R*)-**40**]; $R^1 + R^2$ = O (**41**)

Examples of the bacterial transformation of pinane-type bicyclic monoterpenes have been documented. According to the chromatography/mass spectrometry data, the soil culture of *Pseudomonas* sp. PIN catalyzes the efficient (34% and 60%) bioconversion of α- (**43**) and β-pinenes (**43′**) to form complex mixtures, including *p*-cymene (**44**), limonene (**21**), α-terpinolene (α-terpinene) (**45**) and minor oxidation products [terpinen-4-ol (**46**), α-terpinenol (**19**), *p*-cymen-8-ol (**47**), borneol (**48**), camphor (**49**) and fenchol (**50**)].[65, 66]

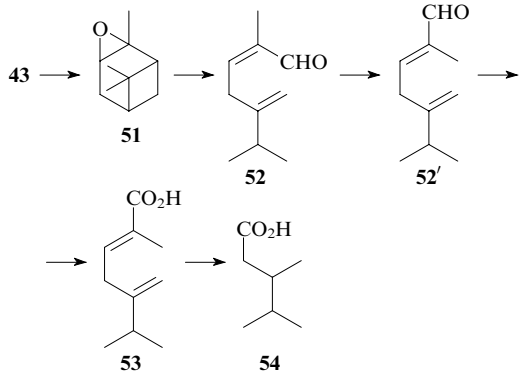
Structures 43 – 50



43 **43′** **44** **45** **46** **47** **48** **49** **50**

It was found that cultures of *P. fluorescens* and *P. rhodesiae* catalyze the sequential transformations α-pinene (**43**) → α-pinene epoxide (**51**) → isonovalal (**52**) → novalal (**52′**) → novalic acid (**53**) → 3,4-dimethylpentanoic acid (**54**) → β-oxidation products (Scheme 4), both cultures being able to perform the isomerization of β-pinene (**43′**) to α-derivative **43**.[52, 67]

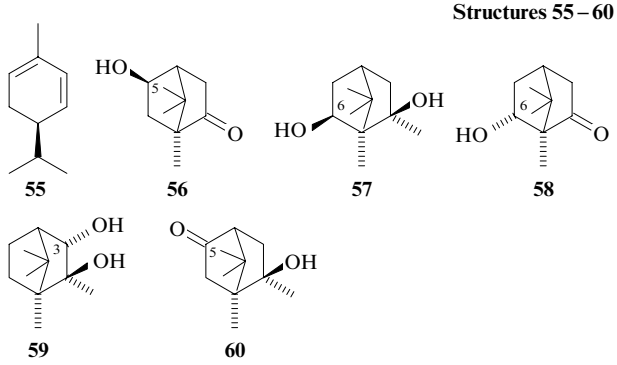
Scheme 4



43 **51** **52** **52′** **53** **54**

Under anaerobic conditions, 'Alcaligenes defragrans' (*Castellaniella defragrans*) was found to be able to convert α-phellandrene (**55**) and α-pinene (**43**) to geranic acid (**4**).[42] The redox transformations of camphor (**49**) into borneol (**48**) and(or) 5-*exo*-hydroxycamphor (**56**) using whole cells or individual enzymes P450 from *P. putida*[68] and 'Novosphingobium aromaticivorans' (*Sphingomonas aromaticivorans*) were described.[44] Meanwhile, 2-methylisoborneol (**17**) is transformed to 6-*exo*-hydroxy-2-methylisoborneol (**57**) in the presence of a culture of *P. putida* G1 adapted to compound **49**.[69] The selective 6-*endo*-hydroxylation of compound **49** giving metabolite **58** is catalyzed by *Rhodococcus* sp. NCIMB 9784.[70] The actinobacteria *R. ruber* T1 and *R. wratislaviensis* DLC-cam that perform the biodegradation of camphor were found to be able to catalyze the transformation of 2-methylisoborneol (**17**) to give derivatives oxidized at the positions C(3) (**59**) and C(5) (**60**), respectively.[69]

Structures 55 – 60

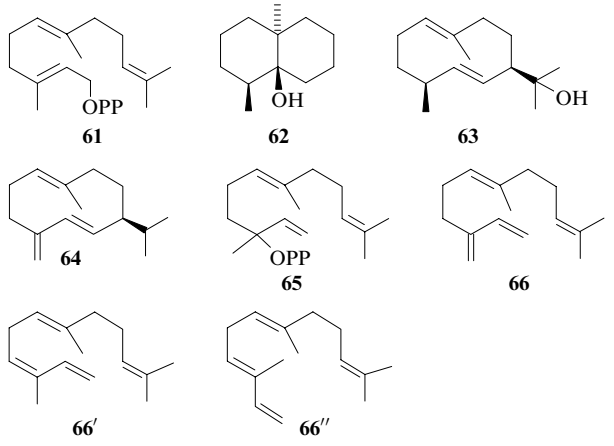


55 **56** **57** **58** **59** **60**

III. Biotransformation of sesquiterpenoids

Studies of the bacterial transformation of sesquiterpenoids dealt mainly with sesquiterpene synthases (cyclases) from the genus *Streptomyces*. The biotransformation of acyclic farnesyl pyrophosphate (**61**) catalyzed by these enzymes affords cyclic derivatives, in particular, geosmin (**62**), the presence of which in trace amounts in water, wine or fish is responsible for foul taste.[71 – 73] It was experimentally shown that germacradienol/geosmin synthases from *S. avermitilis* and *S. coelicolor* catalyzed the transformation of pyrophosphate **61** into geosmin (**62**) with accumulation of up to 86% of cyclic intermediate germacradienol **63** and 24% of (7*S*)-germacrene D (**64**),[71 – 74] whereas synthase from *S. peucetius*

Structures 61 – 66″



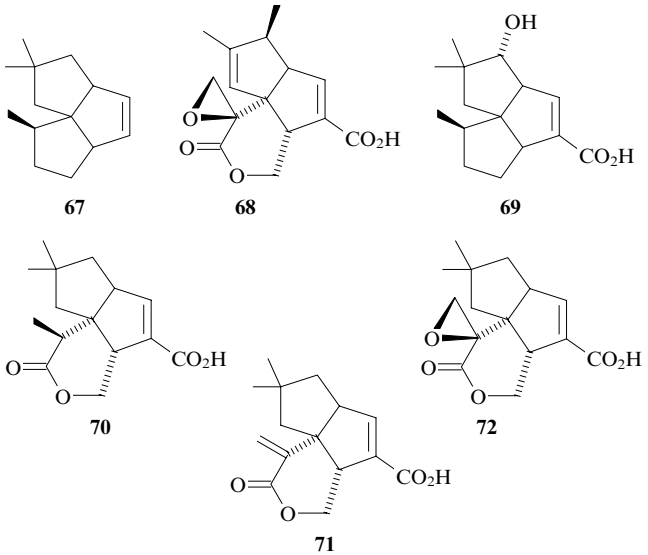
61 **62** **63** **64** **65** **66** **66′** **66″**

produced only alcohol **63**.[75] It was suggested that the N-terminal domain of germacradienol/geosmin synthase from *S. coelicolor* A3(2) is involved in the transformation of pyrophosphate **61** into compounds **63** and **64**, while the C-terminal domain is involved in the transformation of alcohol **63** into geosmin (**62**).[76] Meanwhile, there is evidence that the N-terminal domain of this synthase can by itself support the synthesis of geosmin (**62**), while the C-terminal domain is catalytically inactive. Other enzymes, such as cyclases, reductases and hydroxylases, are involved in the bacterial transformation of germacradienol **63** into geosmin **62**.[77, 78]

Germacradienol/geosmin synthases from *S. avermitilis* and *S. coelicolor* A3(2) were found to catalyze the transformation of nerolidyl pyrophosphate (**65**) into acyclic β-, (3*Z*)-α- and (3*E*)-α-farnesenes (**66**, **66′** and **66″**, respectively).[71]

Germacradienol/geosmin synthase shows considerable (>40%) homology with single-domain synthase from *Streptomyces* species that catalyzes the transformation of pyrophosphate **61** into pentalenene (**67**), which is a key intermediate in the synthesis of the antibiotic pentalenolactone (**68**).[77] Possible pathways of the biotransformation of compound **67** into pentalenolactone (**68**) through key intermediates, *viz*., pentalenic acid (**69**) and pentalenolactones D (**70**), E (**71**) and F (**72**), catalyzed by the bacteria *S. avermitilis*, *S. exfoliatus* and *S. arenae* were proposed.[79–82] Other bacterial synthases that catalyze the formation of various cyclic compounds from pyrophosphate **61** were also described (Table 1).

Structures 67–72



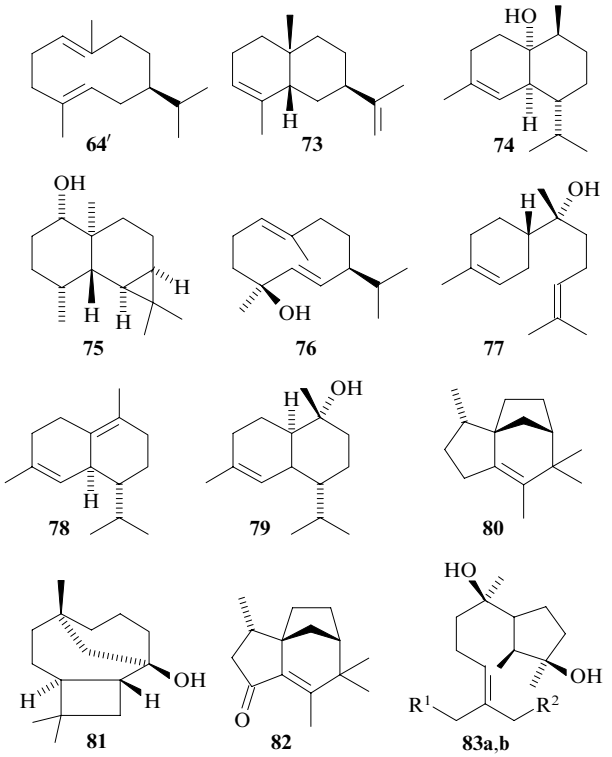
Cytochrome P450 monooxygenase (synthase) from *S. coelicolor* A3(2), which is involved in the transformation of epiisozizaene (**80**) into the antibiotic albaflavenone (**82**) and catalyzes the transformation of pyrophosphate **61** into β-farnesene (**66**) (61%) and compounds **66″** (26%) and **66′** (7%), was characterized.[90–92]

Examples of the efficient (up to 90%) biodegradation of geosmin (**62**) catalyzed by represnetatives of the class *Alphaproteobacteria*, bacteria of the family *Acidobacteriaceae*, representatives of the genera *Pseudomonas*, *Sphingomonas* and *Sphingopyxis*, and the culture of *R. wratislaviensis* DLC-cam have been reported.[93–95] The marine bacterium *Streptomyces* sp. MFAac67 was shown to be able to oxidize cyclonerodiol (**83a**) to form a mixture of cyclonerotriols (10*Z*)-**83b** and (10*E*)-**83b** (1 : 2 ratio). It was found that compound (10*Z*)-**83b** has cytotoxic activity against the HeLa cancer cell line.[96]

Table 1. Bacterial sesquiterpene synthases that catalyze the transformation of pyrophosphate **61**.

Bacterial cultures	Products	Ref.
'Nostoc sp.' PCC 7120	germacrene A (**64′**)	83
'N. punctiforme' PCC 73102	8a-*epi*-α-selinene (**73**), germacradienol (**63**)	83
Streptomyces sp. LL-B7	(+)-epicubenol (**74**)	84
S. avermitilis	avermitilol (**75**)	85
S. citricolor NBRC 13005	(−)-germacradien-4-ol (**76**), (−)-*epi*-α-bisabolol (**77**)	86
S. clavuligerus ATCC 27074	(−)-δ-cadinene (**78**), (+)-T-muurolol (**79**)	87
S. coelicolor A3(2)	(+)-epiisozizaene (**80**)	88
S. griseus IFO13350	(+)-caryolan-1-ol (**81**)	89

Structures 64′, 73–83



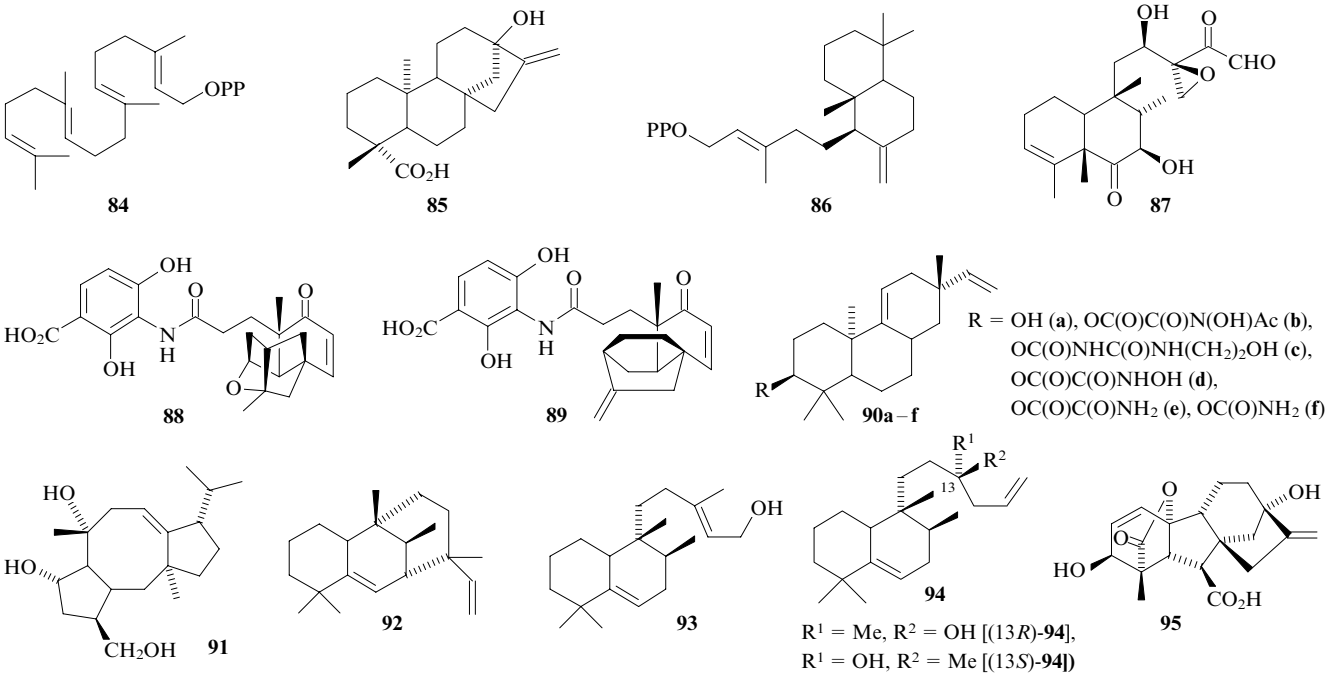
R^1 = H: R^2 = H (**83a**), OH [(10*E*)-**83b**]; R^1 = OH, R^2 = H [(10*Z*)-**83b**]

IV. Biotransformation of diterpenoids

Studies of the bacterial transformation of diterpenoids deal mainly with the detailed consideration of the pathways of cyclization of geranylgeranyl pyrophosphate (**84**) and the oxidative transformation of resin acids and steviol derivatives (**85**).

Diterpene cyclases from the genus *Streptomyces* have been characterized. These enzymes are involved in the transformation of pyrophosphate **84** or its cyclization product, copalyl pyrophoshate (**86**), into bi-, tri- and

Structures 84 – 95



84 **85** **86** **87** **88** **89** **90a – f** **91** **92** **93** **94** **95**

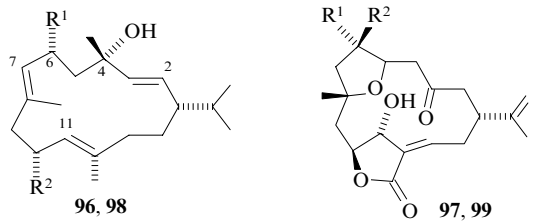
R^1 = Me, R^2 = OH [(13*R*)-**94**],
R^1 = OH, R^2 = Me [(13*S*)-**94**])

tetracyclic diterpene derivatives, including the cytotoxic antibiotic terpentecin (**87**),[97] compounds with antimicrobial and antidiabetic activities [platensimycin (**88**) and platencin (**89**)],[98] viguiepinol (**90a**),[99] oxaloterpin A (**90b**) exhibiting antibacterial activity, and oxaloterpins B (**90c**), C (**90d**), D (**90e**) and E (**90f**),[100] as well as cyclooctatin (**91**) serving as an inhibitor of lysophospholipase.[101] It was found that the cyclization of pyrophosphate **84** using the bacterial *Mycobacterium tuberculosis* strain H37Rv affords edaxadiene (**92**) crucial for the virulence of mycobacteria, as well as minor intermediates, such as tuberculosinol (**93**), (13*R*)- and (13*S*)-isotuberculosinols (**94**).[102 – 106] Synthases from the rhizobacteria *Bradyrhizobium japonicum*, *Bacillus pumilus* and *B. licheniformis* are involved in the biotransformation of pyrophosphate **84** into phytohormones [in particular, gibberellic acid (**95**)].[107 – 109]

Data on macrocyclic diterpenoids refer only to the oxidative bioconversion of 2,7,11-cembratriene-4,6-diol acetate (**96**) with the *B. megaterium* strain MO31 and of the norditerpenoid 5-episinuleptolide (**97**) with *S. lavendulae* ATCC 8664 cells to form compound **98** (30%) and a mixture of products **99** (7.5%) and **100** (0.5%), respectively.[110, 111] Very scarce data are available on the bacterial transformation of bicyclic diterpenoids. These data were published before 2000 and are not considered in the present review.

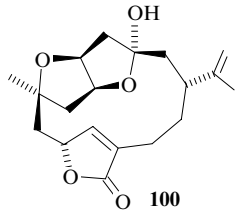
Cembrane derivatives are biogenetic precursors of taxane-type tricyclic diterpenoids, among which the anticancer agent taxol and its metabolic precursors baccatins are involved most often in the bacterial transformation.[112 – 116]

Structures 96 – 100



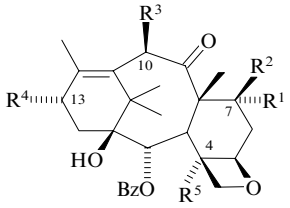
96, **98** **97**, **99**

R^1 = AcO, R^2 = H (**96**); R^1 = R^2 = OH (**98**);
R^1 + R^2 = O (**97**); R^1 = OH, R^2 = H (**99**)



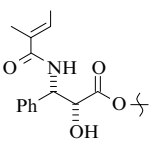
100

Structures 101



101a – j

Compounds **101**	R^1	R^2	R^3	R^4	R^5
a	H	OH	OAc	X	OAc
b	H	OH	OAc	OH	OAc
c	OH	H	OAc	OH	OAc
d	OH	H	OAc	X	OAc
e	H	OH	OH	X	OAc
f	H	OH	OH	OH	OAc
g	OH	H	see [a]	OH	OAc
h	OH	H	OH	X	OAc
i	OH	H	OH	OH	OAc
j	H	OH	OH	OH	OH

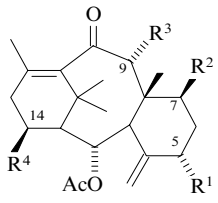
X =  ; [a] the oxo group at the C(10) atom.

Thus, representatives of the genus *Luteibacter* catalyze the epimerization of the 7β-hydroxy group and the hydrolysis of the side chain at the C(13) atom of cephalomannine (taxol B, **101a**) to form baccatin III (**101b**), baccatin V (**101c**), 7-*epi*-cephalomannine (**101d**) and deacetylated derivatives **101e**–**h** of the initial substrate and its products.[114] The *B. cereus* strain AS1.126, *B. megaterium* strain AS1.127, *B. mycoides* strain AS1.182, 'Nocardia corallina' (*Gordonia rubripertincta*) strain AS4.1037, *P. fluorescens* strain AS1.33, *P. oleovorans* strain AS1.1641 and *P. putida* strain AS1.1003 catalyze the inversion (by 20%–71%) of the asymmetric C(7) atom of 7-*epi*-10-deacetylbaccatin III (deacetylbaccatin V, **101i**) to form compound **101f**.[112] Cultures of *Rhodococcus* sp. ATCC 20191 and *Stenotrophomonas maltophilia* SC16447 catalyze the transformation (by more than 85%) of compound **101f** to the relevant 4-deacetylated derivative **101j**.[115]

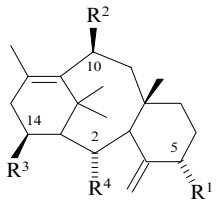
It was found that 'N. purpurea' CGMCC 4.1182 can selectively transform 2α,5α,14β-triacetoxy-10-oxotaxa-4(20),11(12)-diene (**102a**) into product **102b** deacetylated at the C(5) and C(14) atoms (in 81% yield), whereas the use of *S. griseus* CACC 200300 results in the 30% conversion of substrate **102a** to produce 7β-hydroxylated metabolite **102c** and minor (<1%) 5-deacetoxy (**102d**) and 9α-hydroxy (**102e**) derivatives.[116] The biotransformation of 2α,14β-diacetoxy-5α-hydroxy-10β-methoxytaxa-4(20),11(12)-diene (**103a**) using 'N. purpurea' CGMCC 4.1182 and *S. griseus* CACC 200300 affords complex mixtures of demethylated, acetylated and deacetylated metabolites **103b**–**e** and **103c**, **103f**–**h**, **104**, respectively, in yields varying from 5% to 31%.[116]

The bacterial transformation of tricyclic diterpenoids has attracted interest in relation to problems of detoxification and selective synthesis of pharmacologically active compounds. Among such diterpenoids, abietane- and pimarane-type resin acids [abietic (**105a**), dehydroabietic (**106a**) and isopimaric (**107**)] are most commonly used.

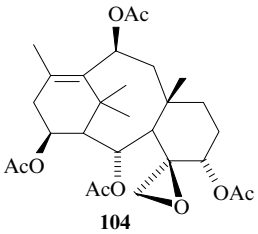
Structures 102–104



102a–e



103a–h



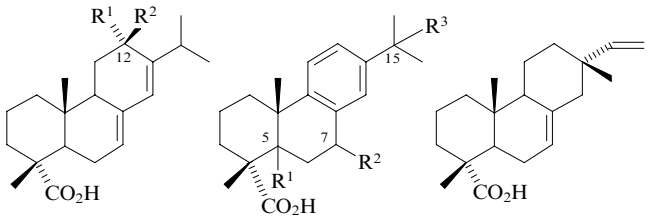
104

Compounds **102**	R^1	R^2	R^3	R^4
a	OAc	H	H	OAc
b	OH	H	H	OH
c	OAc	OH	H	OAc
d	OH	OH	H	OAc
e	OAc	H	OH	OAc

Compounds **103**	R^1	R^2	R^3	R^4
a	OH	OMe	OAc	OAc
b	OAc	OMe	OAc	OAc
c	OAc	OH	OAc	OAc
d	OH	OMe	OH	OH
e	OH	OH	OH	OAc
f	OH	OH	OAc	OAc
g	OH	see [a]	OAc	OAc
h	OAc	OAc	OAc	OAc

[a] The oxo group at the C(10) atom.

Structures 105–107



105a,b **106a–e** **107**

R^1 = H: R^2 = H (**105a**), OH [(12*R*)-**105b**];
R^2 = H, R^1 = OH [(12*S*)-**105b**]

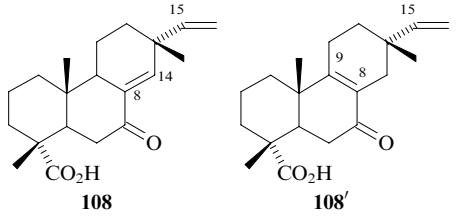
Compounds **106**	R^1	R^2	R^3	Compounds **106**	R^1	R^2	R^3
a	H	H	H	**d**	H	see [a]	H
b	OH	H	H	**e**	H	H	OH
c	H	OH	H				

[a] The oxo group at the C(7) atom.

Species of the genera *Alcaligenes*, *Arthrobacter*, *Bacillus*, *Burkholderia*, *Cupriavidus*, *Pseudomonas* and *Rhodococcus* were found to be able to perform the biotransformation of resin acids.[117–121] For most of the cultures, the initial step of the biotransformation of acid **106a** is catalyzed by P450 monooxygenases to form 5-hydroxy (**106b**), 7-hydroxy (**106c**) and 7-oxo derivatives (**106d**), although the use of the *Arthrobacter oxydans* cells or the enzyme from *Streptomyces griseolus* leads also to the hydroxylation of acids **105a** and **106a** at the C(15) atom, while monooxygenase from *B. megaterium* ATCC 13368 catalyzes the hydroxylation of acid **105a** at the C(12) atom to form a mixture of metabolites (12*S*)-**105b** and (12*R*)-**105b** in a 2:1 ratio.[119,121–124] Studies with the use of species of the genus *Rhodococcus* showed that there is a direct correlation between the specific type of rhodococci and the ability to perform the oxidative transformation of acid **106a**. It was found that under the cooxidative conditions in the presence of n-hexadecane, strains of *R. ruber* catalyzed the oxidation of acid **106a** at the C(7) atom to compound **106d** (12%–15%), whereas *R. erythropolis* species catalyzed mainly the hydroxylation of acid **106a** at the C(15) atom to form metabolite **106e** (24%).[125] A few examples of the bacterial transformation of pimarane-type acids were described in the literature. It was found that species of *R. ruber* catalyze the regioselective isomerization of acid **107** to isopimara-8(14),15-dien-7-on-

18-oate (**108**) or isopimara-8(9),15-dien-7-on-18-oate (**108′**).[117]

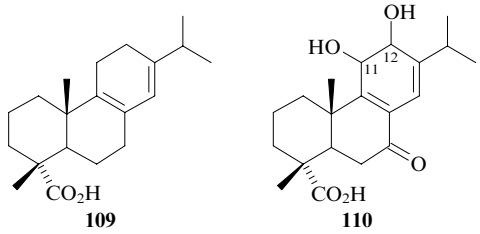
Structures 108, 108′



108 **108′**

It was suggested that, along with mono- and dioxygenases, dehydrogenases, permeases, hydrolases and CoA ligase of inducible or constitutive nature are involved in the oxidative biodegradation of compounds **105a** and **106a** and palustric acid (**109**).[118,121,126–128] The biotransformation of abietane-type resin acids most often affords the key intermediate, 7-oxodehydroabietic acid (**106d**), the biodegradation of which proceeds through 11,12-dihydroxy derivative **110**.[118,127–129]

Structures 109, 110



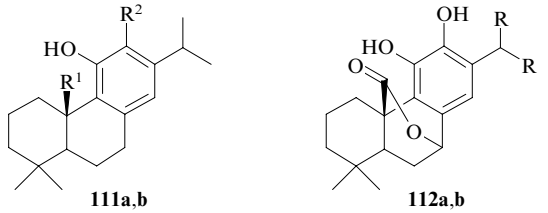
109 **110**

Along with individual resin acids, crude wastes of wood processing industry (extractive components from thermomechanical pulp, kraft cellulose waste, pine wood chips, *etc.*) containing a mixture of resin acids are often used as the starting substrates. The partial (from 20% to 45%) degradation of these compounds can be performed using pseudomonads, as well as *Burkholderia cepacia*, *P. fluorescens*, *Serratia marcescens* and *Xanthomonas campestris* species.[130,131] The most complete (up to 100%) biodegradation of resin acids in high (up to 200 μmol litre^{-1}) concentrations is catalyzed by cultures of *P. abietaniphila* BKME-9 and *Zoogloea resiniphila* DhA-35.[132–134]

A few examples of the biotransformation of abietane diterpenoids, which do not belong to resin acids, for example, of carnosic acid (**111a**) by cells of *Nocardia* sp. NRRL 5646 to form derivatives **111b** (10%), **112a** (38%) and **112b** (8%) having the antioxidant effect, were described in the literature.[135,136]

Studies of the biotransformation of tetracyclic diterpenoids are usually performed with the use of steviol-based

Structures 111, 112



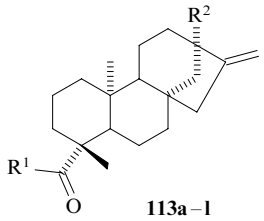
111a,b **112a,b**

$R^1 = CO_2H$, $R^2 = OH$ (**a**);
$R^1 = CH_2OH$, $R^2 = OMe$ (**b**)

R = Me (**a**), CH_2OH (**b**)

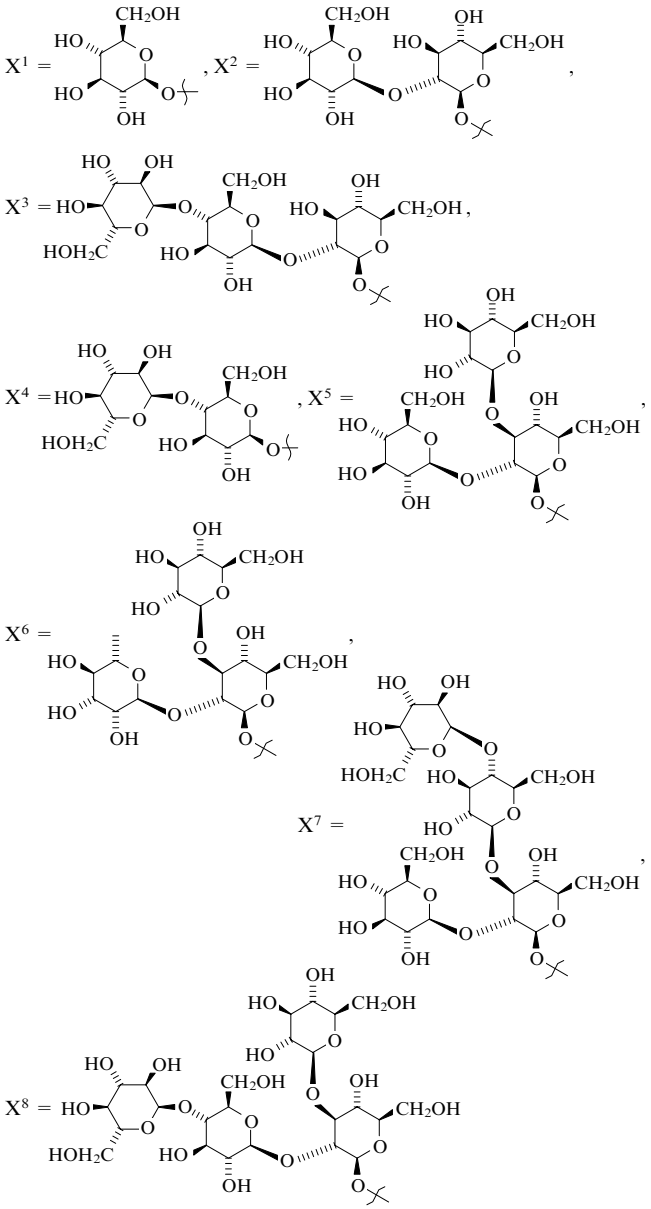
ent-kaurane glycosides (**85**) produced by perennial herbs *Stevia* of the family Composite. There are numerous examples of the bacterial hydrolysis of these compounds giving

Structures 113



113a–l

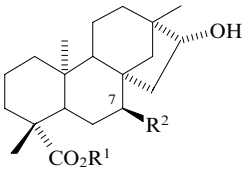
Compounds **113**	R^1	R^2	Compounds **113**	R^1	R^2
a	X^1	X^2	**g**	X^1	X^5
b	X^1	X^1	**h**	X^1	X^6
c	X^1	H	**i**	X^4	X^5
d	H	X^1	**j**	X^1	X^7
e	X^1	X^3	**k**	X^1	X^8
f	X^4	X^2	**l**	H	X^2



aglycone **85**, in particular, of stevioside (**113a**) by soil isolates of bacilli and cocci,[137] of rubusoside (**113b**), monoglucosylated steviol ester (**113c**) and steviol monoside **113d** by β-glucosidase from *Flavobacterium johnsonae*,[138] of glycoside **113a**, α-mono-glucosyl steviosides 1 (**113e**) and 2 (**113f**), rebaudiosides A (**113g**) and C (**113h**), α-monoglucosylated rebaudioside A derivatives (**113i–k**) by bacteria of intestinal microflora.[139–141] Some *Chryseobacterium* species and β-glucosidase from *Flavobacterium johnsonae* were found to be able to transform glycoside **113a** to form rubusoside (**113b**) and steviolbioside **113l**.[138, 142] It was found that intestinal microflora species almost completely (by 56%–100%) transform steviol glycosides used as sugar substitutes into aglycone **85**.[139–141] Numerous *in vitro* and *in vivo* studies did not confirm the expected genotoxic activity of high doses of steviol and provided evidence of its safety for humans.[143]

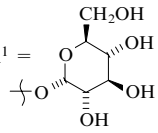
It was shown that *B. megaterium* ATCC 14581 can transform steviol (**85**) and 16β-hydroxy-*ent*-beyeran-19-oic acid (**114a**) into relevant 7β,11α-dihydroxy (**115a**) and 7β-hydroxy (**114b**) derivatives and 19α-D-glucopyranosyl esters (**115b**, **114c**,**d**);[144, 145] *S. griseus* was shown to transform steviol 16α,17-epoxide (**116**) into a mixture of hydroxylated products **117**, **118a–e** and **119**.[146]

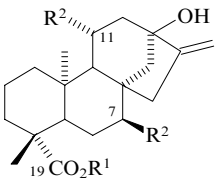
Structures 114–119



114a–d

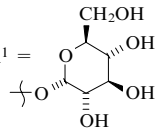
R^1 = H: R^2 = H (**a**), OH (**b**);

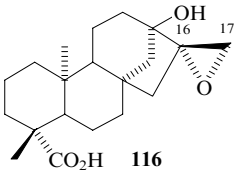
R^1 =  : R^2 = H (**c**), OH (**d**)



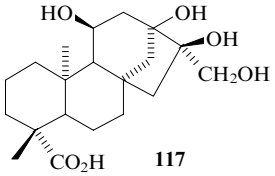
115a,b

R^1 = H: R^2 = OH (**a**);

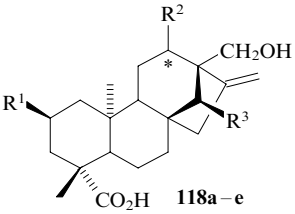
R^1 =  , R^2 = H (**b**)



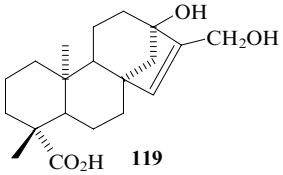
116



117



118a–e

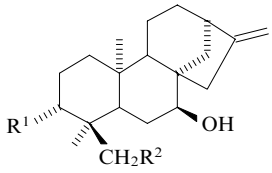


119

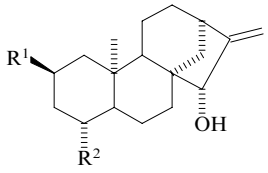
Compounds **118**	R^1	R^2	R^3
a	H	H	H
b	H	β-OH	H
c	H	α-OH	H
d	OH	H	H
e	H	H	OH

The biotransformation of other *ent*-kaurane-type diterpenoids, such as linearol (**120a**), atractyligenine (**121a**) and atractylitriol (**121c**), by *Pseudomonas* lipases was studied. The regioselective acetylation, deacetylation or acetyl group migration results in the formation of sidol (**120b**) (yield 65%) from compound **120a**, monoacetylated metabolite **121b** (up to 23%) from compound **121a** and a mixture of products **121d–f** from triol **121c**.[147]

Structures 120, 121



120a,b



121a–f

R^1 = OH, R^2 = OAc (**a**);
R^1 = OAc, R^2 = OH (**b**)

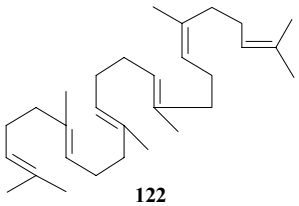
Compounds **121**	R^1	R^2	Compounds **121**	R^1	R^2
a	OH	CO_2H	**d**	OAc	CH_2OH
b	OAc	CO_2H	**e**	OH	CH_2OAc
c	OH	CH_2OH	**f**	OAc	CH_2OAc

V. Biotransformation of triterpenoids

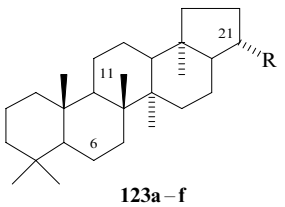
The biotransformation of sterols and steroids derived from triterpenoids as a result of the loss of some atoms of the carbon skeleton [2] is beyond the scope of the present review. Studies of biocatalysis of these compounds are covered in detail in reviews.[148–151]

In chemotaxonomy of bacteria, hopane-type pentacyclic triterpenoids are considered as biomarkers for differentiation between genera. It was found that the bacteria *Burkholderia* and *Desulfovibrio*, as well as *Rhodopseudomonas palustris*, 'Gluconacetobacter xylinus' (*Komagataeibacter xylinus*) and *Prochlorothrix hollandica* species, can perform the biosynthesis of such terpenoids from the acyclic triterpene squalene (**122**).[152–156] Various unsaturated and Δ^6-, Δ^{11}- and $\Delta^{6,11}$-dehydrated hopane derivatives, which differ

Structures 122, 123

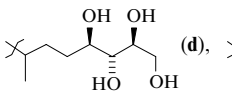


122

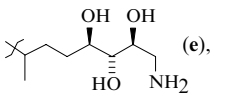


123a–f

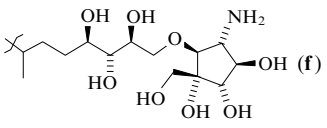
R = C(=CH_2)Me (**a**), CMe_2OH (**b**), $CMe(CH_2)_3OH$ (**c**),



(**d**),



(**e**),



(**f**)

in the structure of the side chain at the C(21) atom (in particular, compounds **123a–f**), were identified. The mechanism of the carbocation cyclization of squalene by squalene–hopene cyclase was proposed.[157]

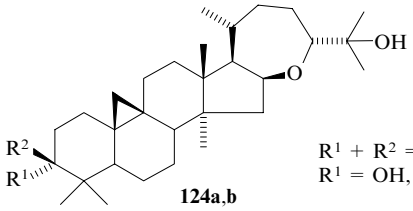
The possibility of the transformation of cycloartane-type tetracyclic triterpenoids was studied using cells of 'Nocardia corallina var. taoka' (*R. ruber*) ATCC 31338 and *Mycobacterium* sp. NRRL B3683, which catalyze the stereoselective reduction of argentatin B (**124a**) to form up to 10% of isoargentatin D (**124b**).[158] The β-glucosidase activity of the bacteria towards dammarane-type tetracyclic saponins (ginsenosides), which are glycosylated derivatives of protopanaxadiol (**125a**) and protopanaxatriol (**125b**) produced by the perennial plant of the genus *Ginseng*, was studied in detail.

It was found that cultures of *Microbacterium* sp. GS514,[159] 'Caulobacter leidyi' (*Sphingomonas leidyi*) GP45,[160] *Chryseobacterium ginsenosidimutans* THG 15^T,[161] *Terrabacter ginsenosidimutans* Gsoil 3082^T,[162] *Sphingobacterium multivorum* GIN723,[163] *Bifidobacterium* sp. Int57, SJ32 and SH5, *Lactobacillus delbrueckii* subsp. *delbrueckii* KCTC 1047 and 'Leuconostoc paramesenteroides' (*Weissella paramesenteroides*) PR[164] can catalyze the complete bioconversion of ginsenoside Rb1 (**125c**). Compound **125a**, ginsenosides Rg3 (**125d**), C-K (compoud K, **125e**), Rh2 (**125f**), Rd (**125g**), F2 (**125h**), XVII (**125i**) and LXXV (**125j**) were identified as key intermediates or final products.[159–164] Cultures of *Bifidobacterium* sp. Int57 and SJ32, as well as the *Mucilaginibacter composti* strain TR6-03(T), transform ginsenoside Re (**125k**) to produce compounds Rh1 (**125l**) and Rg2 (**125m**), respectively;[164,165] ginsenosides **125c** and **125g** are converted to compound **125e** by *Sphingomonas* sp. ZY-3 and *Lactobacillus pentosus* DC101;[166,167] the enzyme α-l-arabinofuranosidase from *Rhodanobacter ginsenosidimutans* Gsoil 3054^T catalyzes the transformation of ginsenoside Rc (**125n**) into derivative Rd (**125g**).[168] The enzymatic activity of human intestinal microflora against ginsenosides **125c**,**d**,**k**,**n**, Rb2 (**125o**) and Rg1 (**125p**) was examined in numerous studies, ginsenoside **125e** and(or) aglycones **125a**,**b** being found as characteristic products for most isolates.[169–176] The use of bacilli for the fermentation of a ginseng plant extract enriched with ginsenosides **125c**,**k**,**p** resulted in the formation of a product with high antioxidant activity containing ginsenosides Rb2 (**125o**), Rb3 (**125q**) and Rd (**125g**) as the major components.[177] It should be noted that the enzymatic hydrolysis of available ginsenosides catalyzed mainly by bacterial cultures is an efficient route to derivatives rarely occurring in nature,[178] including compounds with cytotoxic, anti-allergic and antibacterial activities, as well as to compounds inhibiting H^+/K^+-ATPase.[171,172]

Examples of the biotransformation of lupan-type pentacyclic triterpenoids have been reported in the literature. Bacteria of the genus *Rhodococcus* were found to be able to perform the regioselective biotransformation of betulin (**126a**) to betulone (**126b**) (the conversion is 40%–75%).[179,180] A method was developed for the 50% bioconversion of alcohol **126a** to betulinic acid (**126c**) using cells of *Mycobacterium*.[181] It was found that the *Nocardia* sp. strain NRRL 5646 efficiently catalyzes the methylation of betulinic (**126c**), 23-hydroxybetulinic (**126d**) and betulonic (**126e**) acids to produce relevant derivatives **126f–h**, as well as the 2α-hydroxylation and acylation of acid **126e** giving methyl 2α-acetoxy-3-oxolup-20(29)-en-28-oate (**126i**).[182,183] The *B. megaterium* strains ATCC 13368 and ATCC 14581 catalyze the oxidation of the 3β-hydroxy group, as well as the 1β-, 6α-, 7β-, 11α- and 15α-hydroxylation of acid **126c** to form oxidation products, including those with antimelanoma activity (compounds **126e** and **127a–e**).[184,185]

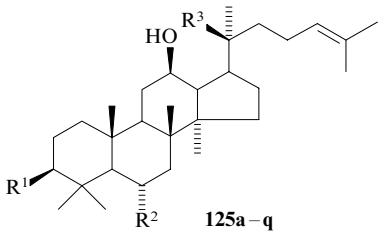
It was found that bacteria of intestinal microflora (in particular, *Eubacterium* sp. L-8) can perform the hydrolysis of glycyrrhizin (**128a**) to give the oleanane-type triterpenoid, 18βH-glycyrrhetinic acid (**128b**) exhibiting antitu-

Structures 124, 125



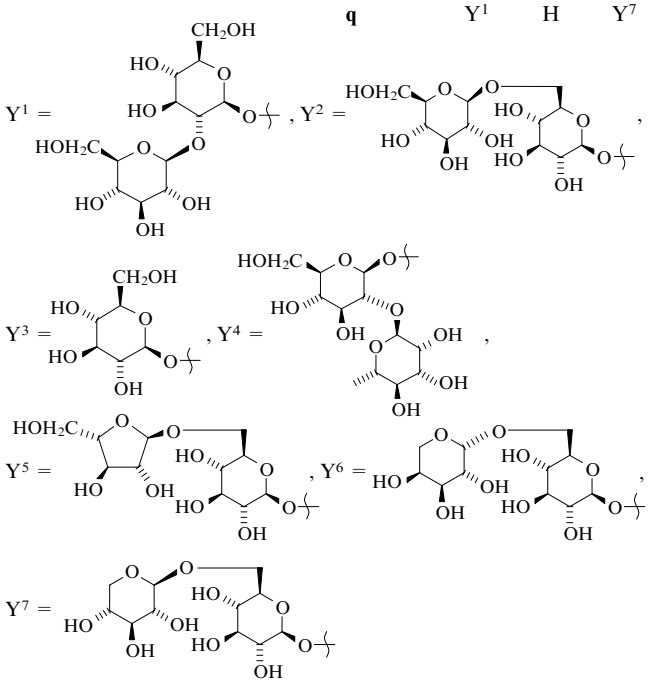
$R^1 + R^2 = O$ (**a**),
$R^1 = OH$, $R^2 = H$ (**b**)

124a,b

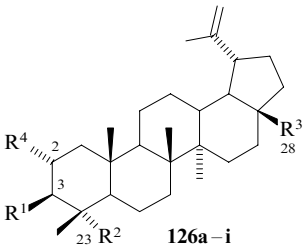


125a–q

Compounds **125**	R^1	R^2	R^3	Compounds **125**	R^1	R^2	R^3
a	OH	H	OH	**i**	Y^3	H	Y^2
b	OH	OH	OH	**j**	OH	H	Y^2
c	Y^1	H	Y^2	**k**	OH	Y^4	Y^3
d	Y^1	H	OH	**l**	OH	Y^3	OH
e	OH	H	Y^3	**m**	OH	Y^4	OH
f	Y^3	H	OH	**n**	Y^1	H	Y^5
g	Y^1	H	Y^3	**o**	Y^1	H	Y^6
h	Y^3	H	Y^3	**p**	H	Y^3	Y^3
				q	Y^1	H	Y^7



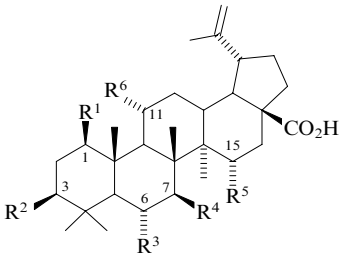
Structures 126 – 132



126a – i

Compounds **126**	R^1	R^2	R^3	R^4
a	OH	Me	CH_2OH	H
b	see [a]	Me	CH_2OH	H
c	OH	Me	CO_2H	H
d	OH	CH_2OH	CO_2H	H
e	see [a]	Me	CO_2H	H
f	OH	Me	CO_2Me	H
g	OH	CH_2OH	CO_2Me	H
h	see [a]	Me	CO_2Me	H
i	see [a]	Me	CO_2Me	OAc

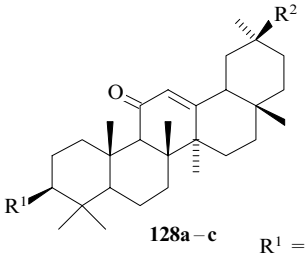
[a] The oxo group at the C(3) atom.



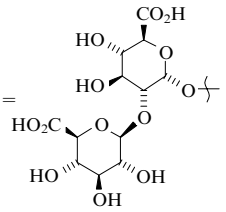
127a – e

Compounds **127**	R^1	R^2	R^3	R^4	R^5	R^6
a	H	see [a]	H	H	H	OH
b	OH	see [a]	H	H	H	H
c	H	OH	H	OH	OH	H
d	H	OH	H	OH	H	H
e	H	OH	OH	OH	H	H

[a] The oxo group at the C(3) atom.

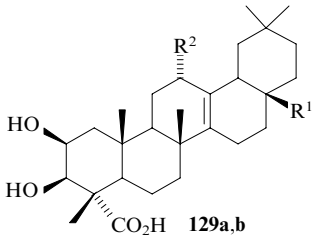


128a – c

R^1 = ,

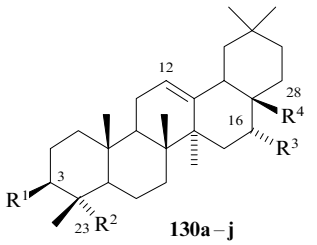
$R^2 = CO_2H$ (**a**);

R^1 = OH: $R^2 = CO_2H$ (**b**), CO_2Me (**c**)



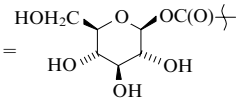
129a,b

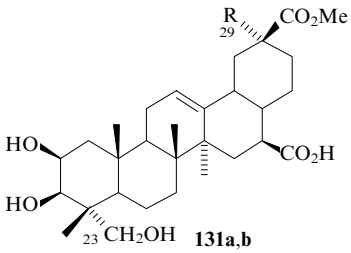
$R^1 = CO_2H$, $R^2 = CH_2Cl$ (**a**);
$R^1 = CO_2Me$, $R^2 = H$ (**b**)



130a – j

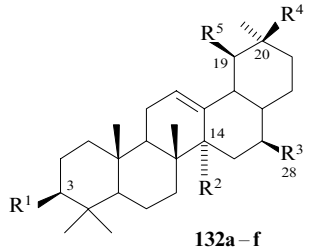
Compounds **130**	R^1	R^2	R^3	R^4
a	OH	Me	H	CO_2H
b	OH	Me	H	COMe
c	CO_2Me	Me	H	Me
d	OH	Me	H	Me
e	OH	CH_2OH	H	Me
f	OH	Me	H	CH_2OH
g	OH	Me	OH	CO_2H
h	see [a]	Me	OH	CO_2H
i	OH	Me	OH	Z
j	see [a]	Me	OH	Z

[a] The oxo group at the C(3) atom; Z = 



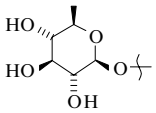
131a,b

R = Me (**a**), CH_2OH (**b**)



132a – f

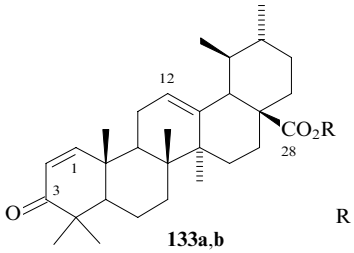
Compounds **132**	R^1	R^2	R^3	R^4	R^5
a	OH	Me	CO_2H	H	Me
b	OH	Me	CO_2Me	H	Me
c	X	CO_2H	CO_2H	H	Me
d	OH	CO_2H	CO_2H	Me	H
e	see [a]	Me	CO_2H	H	Me
f	see [a]	Me	CO_2Me	H	Me

[a] The oxo group at the C(3) atom; X = 

mour, antiviral and antibacterial activities.[174, 175, 186] The *Nocardia* sp. strain NRRL 5646 was found to catalyze the methylation of the carboxy group of compound **128b**, senegenin (**129a**) and oleanolic acid (**130a**) to form metabolites **128c**, **129b** and **130b**, respectively.[182] The proteobacteria *Rhodobacter sphaeroides* catalyze the hydrolysis and hydroxylation of β-amiryn acetate (**130c**) at the C(23) and C(28) atoms to form β-amiryn (**130d**), cytotoxic olean-12-ene-3,23-diol (**130e**) and 3β-erythrodiol (**130f**) in yields from 5% to 12%.[187] The ability of the culture of 'Nocardia corallina' (*Gordonia rubripertincta*) CGMCC4.1037 to transform 3β,16α-dihydroxyolean-12-en-28-oic acid (**130g**) was examined, 3-oxo derivative **130h** (23%) and glycosylated metabolites **130i**,**j** (< 1%) being isolated as bioconversion products.[188] The *S. griseus* strain ATCC 13273 catalyzes the directed hydroxylation of the C(29) methyl group of phytolaccagenine (**131a**) to form product **131b** (64%).[189]

Actinobacteria of the genus *Nocardia* can catalyze the methylation of the carboxy group [C(28)] and the C(19) → C(20) migration of the methyl group of ursolic acid (**132a**) to give methylated derivatives **132b**, **130b** and acid **130a**,[182] while glycosylated derivative **132c** containing the carboxy group at the C(14) atom is transformed to cincholic acid (**132d**) (20%).[190] It was also found that representatives of this group of bacteria can catalyze the transformation of acid **132a** into cytotoxic ursonic (**132e**) and 3-oxoursa-1,12-dien-28-oic (**133a**) acids and their methyl esters **132f** and **133b** in yields from 10% to 80%.[191]

Structures 133



133a,**b** R = H (**a**), Me (**b**)

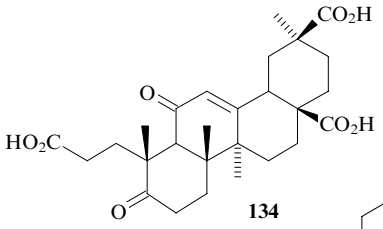
VI. Optimization of biotransformation of terpenoids

The search for ways to increase the efficiency of the biotransformation of terpenoids involves the examination of the effect of additional growth substrates, inducers and inhibitors of enzymatic reactions, studies of the conditions of the addition of the initial substrate to the fermentation medium, investigation of the applicability of two-phase systems for the cultivation of bacteria, the preparation of immobilized microbial cells, genetically modified biocatalysts and so on.

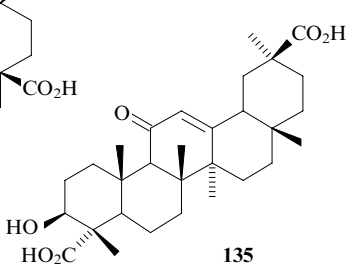
An increase in the regioselectivity of biocatalysts, which, as a rule, non-specifically transform limonene (**21**) to a mixture of oxidation products,[12] is facilitated by the induction of bacterial alkane monooxygenases and alkane hydroxylases by hydrocarbons (in particular, by n-octane).[192, 193] This leads to the allylic hydroxylation of substrate **21** at the C(7) atom to form perillyl alcohol (**22**) (up to 100%).[192] The latter compound has anticarcinogenic activity and is in the phase II of clinical trials. The more profound oxidation of substrate **21** to acid **23** (11 g litre^{-1}) with antimicrobial activity is achieved during growth of *P. putida* in the presence of glycerol.[55] The highest (31 g litre^{-1}) degree of production of acid **23** from limonene (**21**) is reached after the addition of Amberlite IRA 410 Cl as an adsorbent to an incubation medium for *P. putida*, which makes it possible to decrease the inhibitory effect of acid **23** on the biocatalyst.[194] The regioselective hydroxylation of substrate **21** at the C(6) atom to form (+)-*trans*-carveol [(4*S*,6*R*)-**26**] in a yield of up to 97% or of carvone (**29**), which is used as an aromatic and/or flavouring substance, can be performed under non-growth conditions using toluene or ethanol as an additional source of carbon for the preparation of the catalytically active biomass of *R. opacus* PWD4, *R. globerulus* PWD8 or *Cellulosimicrobium cellulans* EB-8-4.[195–197] A study with the use of the cyanobacteria *Synechococcus* sp. PCC 7942 showed that the immobilization of bacterial cells in calcium alginate results in a threefold increase in the level of formation of *cis*-carveol [(4*R*,6*R*)-**26**] from substrate **21** compared to free cells.[56] The chemical-enzymatic method was developed for the synthesis of novalal **52′** using non-growing cells of *P. fluorescens* NCIMB 11761, which convert α-pinene epoxide (**51**) to isonovalal (**52**), and the latter is partially (by 25%) isomerized to compound **52′** in the presence of the macroporous polystyrene adsorbent Lewatit OC 1064 and glycine as the amino group donor.[67]

The effect of oxygenase inhibitors on the biotransformation of 18βH-glycyrrhetinic acid (**128b**) to 3,4-seco-4,23,24-trinor-5,11-dioxoolean-12-ene-3,28,30-trioic acid (**134**) catalyzed by *Sphingomonas paucimobilis* G5 was studied. It was shown that, in the presence of inhibitors (1-aminobenzotriazole or metyrapone), the reaction products include the intermediate metabolite, 3β-hydroxy-11-oxoolean-12-ene-24,30-dioic acid (**135**).[198]

Structures 134, 135



134



135

The lipophilic nature of terpenoids is responsible for their low solubility (10^{-2}–10^{-3} g litre^{-1}) and, as a consequence, a low level of bioavailability to bacteria in an aqueous medium. Biological surfactants produced by many bacteria facilitate the suspension of hydrophobic substrates in a liquid cultivation medium, which, however, does not prevent the formation of solid particles of the substance that are poorly accessible to the biocatalyst. Individual bacterial species were shown to be able to transform terpenoids in two-phase systems (organic solvent–water) increasing the bioavailability of hydrophobic substrates. The extraction of a substrate or a product into an organic layer provides a decrease in the toxic effect on the cells and a shift of the reaction equilibrium towards the formation of the target products.[199–203]

Under anaerobic conditions, the enzymatic extract of *P. fluorescens* cells in n-hexadecane (40 g litre^{-1}) efficiently transforms substrate **21** (in a concentration of up to 20 g litre^{-1}) into α-terpineol (**19**) in 24 h (91% yield).[52] The more efficient transformation of the *R*-(+)-isomer of **21** (25 g litre^{-1}) into (*R*)-(+)-α-terpineol (**19**) in 30 h is achieved using a mixture of a concentrated suspension of

growing cells of *Sphingobium* sp. and sunflower oil (1 : 1).[204] In a two-phase system with isooctane, *R. opacus* PW4 cells, which were grown in a medium containing 0.125% of limonene (**21**) or 0.25% of toluene under increased aeration, transform substrate **21** (50 mmol litre^{-1}) into a mixture of *trans*-carveol (**26**) and carvone (**29**) (5 : 1) or *trans*- and *cis*-carveols (**26**) (~1 : 1), respectively.[196] The ability of *R. erythropolis* DCL14 to perform the 90% conversion of *trans*-carveol (4*R*,6*S*)-**26** to carvone (4*R*)-**29** is used in the highly efficient kinetic resolution of a racemic mixture of *trans*- and *cis*-carveols [(4*R*,6*S*)-**26** and (4*R*,6*R*)-**26**].[60, 200–203, 205, 206] In the n-dodecane–water system (1 : 5), whole cells of *Rhodococcus* bacteria efficiently oxidize isomer (4*R*,6*S*)-**26** (125 mmol litre^{-1}) to ketone (4*R*)-**29**,[205] whereas a buffered suspension of the cell extract is active only at 1 mmol litre^{-1} concentrations of isomers of alcohol **26**.[60] The scaling-up of the use of the system with n-dodecane under bioreactor conditions makes it possible to obtain the target product in this transformation in 92% yield at a 50 mmol litre^{-1} concentration of the substrate.[206] It was also found that the *R. erythropolis* strain DCL14 can selectively (97.5%) hydrolyze the *cis*-isomer (1*S*,2*R*,4*R*)-1,2-epoxylimonene (**38**) in its mixture with the (1*R*,2*S*,4*R*) isomer (50 mmol litre^{-1} substrate concentration) under conditions of a mechanical reactor in the presence of cyclohexane to form diol (1*S*,2*S*,4*R*)-**39**, a threefold increase in the initial rate of the transformation being observed compared to the aqueous phase.[207]

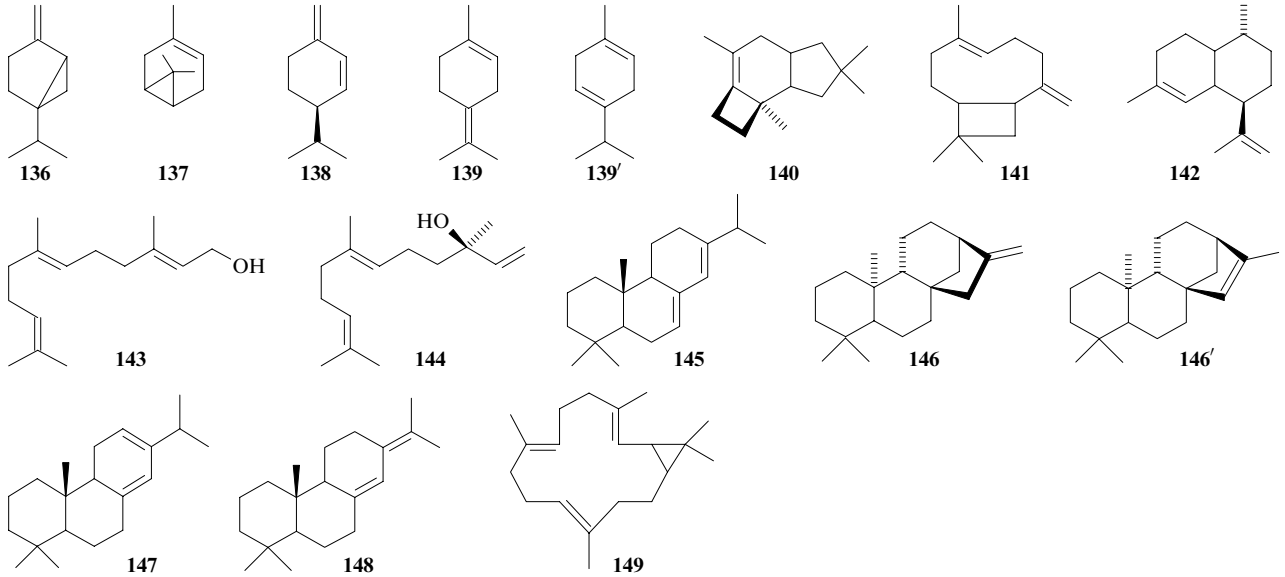
The use of two-phase systems for the biotransformation of triterpenoids was described only for the transformation of alcohol **126a** by the bacteria *Pseudomonas* sp. H-43. It was found that the maximum (38%) degree of conversion of the initial substrate is achieved using methyl ethyl ketone as the solvent.[208]

Genetic engineering techniques are extensively used to search for the optimal conditions of the biotransformation of terpenoids and production of new derivatives. This provides a deeper insight into the potential of bacterial metabolism. The insertion of genes encoding synthases from bacteria, fungi or plants into *Escherichia coli* cells, including these genes in a complex with genes encoding enzymes responsible for the synthesis of their acyclic precursors (pyrophosphates **16**, **61** or **84**), enables researchers to construct recombinant strains capable of synthesizing structurally diverse cyclic terpenoids (Table 2).

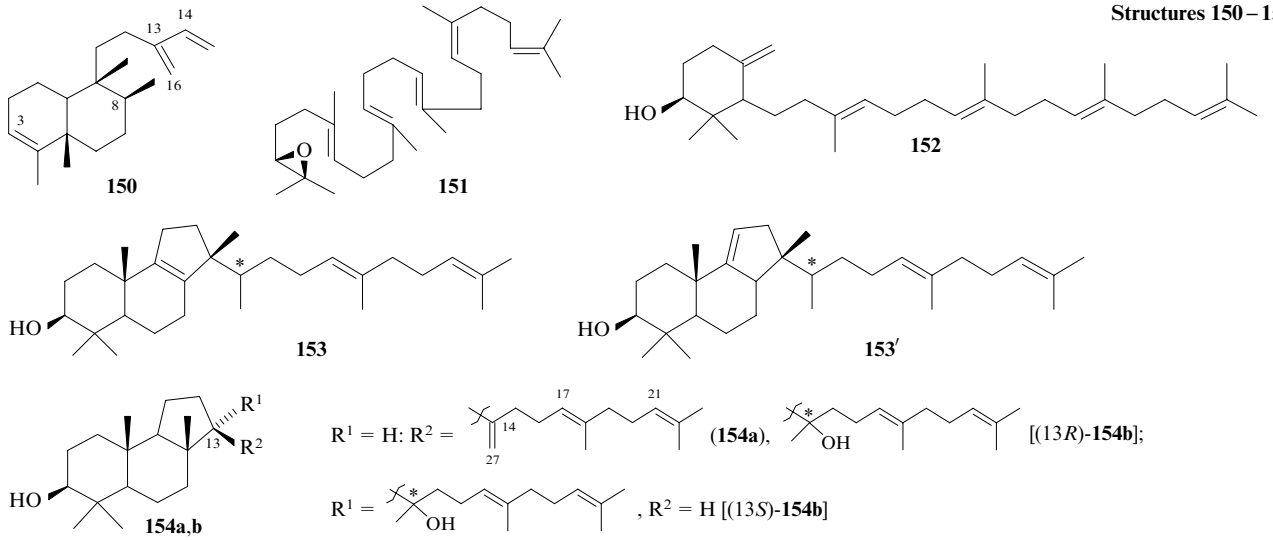
Table 2. Synthesis of mono-, sesqui- and diterpenoids from acyclic precursors **16**, **61** and **84** using recombinant *E. coli* strains.

Source	Products	Ref.
Monoterpenes (from pyrophosphate **16**)		
Picea abies	α-pinene (**43**), β-myrcene (**9**), sabinene (**136**), 3-carene (**137**), limonene (**21**), β-phellandrene (**138**), α-terpinene (**45**), terpinolene (δ-terpinene) (**139**)	209
S. coelicolor A3(2)	limonene (**21**), α- (**43**) and β-pinenes (**43′**), γ- (**139′**) and δ-terpinenes (**139**), α- (**19**), β- (**13**) and 4-terpineols (**46**)	210
Sesquiterpenes (from pyrophosphate **61**)		
Armillaria gallica	6-protoilludene (**140**)	211
Artemisia annua	β-caryophyllene (**141**), amorpha-4,11-diene (**142**)	212–215
S. avermitilis	(+)-epiisozizaene (**80**)	216
Zea mays	(*E*)-β-farnesene (**66**), (*E*,*E*)-farnesol (**143**) and (*E*)-nerolidol (**144**)	217
Zingiber officinale	germacrene D (**64**)	214
Diterpenes (from pyrophosphate **84**)		
Abies grandis	abietadiene (**145**)	218
Arabidopsis thaliana	*ent*-kaur-16-ene (**146**)	219
Ginkgo biloba	levopimaradiene (**147**)	220
Nicotiana sp.	abietadiene (**145**), levopimaradiene (**147**), neoabietadiene (**148**)	221
Ricinus communis L or *Phaeosphaeria* sp. L487	casbene (**149**) or a kaur-16-ene (**146**) + kaur-15-ene (**146′**) mixture	209

Structures 136–149



Structures 150 – 154



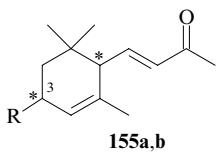
The gene expression of cyclases from *S. griseolosporeus* in 'S. lividans' resulted in the production of *ent*-clerod-3,13(16),14-triene (**150**) containing the β-oriented methyl group at the C(8) atom from pyrophosphate **61**, as opposed to α-epimeric terpenetriene produced by the initial streptomycetes.[97, 222] The Gly600-deletion mutant of bacterial squalene – hopene cyclase from *Alicyclobacillus acidocaldarius* acquires the ability to selectively transform only the 3*S* isomer of oxidosqualene (**151**) characteristic of the eukaryotic enzyme. The monocyclic compound achilleol (**152**), tricyclic triterpenoids with the podiodatriene skeleton **153** and **153′**, malabarica-14(27),17,21-trien-3β-ol (**154a**) and diastereomers of its hydroxylated derivative **154b** were identified as reaction products.[223]

The gene expression of P450 monooxygenases and hydroxylases from different sources produced genetically modified *E. coli* strains able to oxidize various substrates (Table 3). It should be noted that hydroxy derivatives **155b**

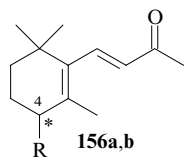
Table 3. Oxidation of various organic substrates by genetically modified *E. coli* strains.

Substrate	Products	Conversion (%)	Ref.
Limonene (**21**)	perillyl alcohol (**22**) + carvone (**29**) (3 : 1)	–	224
α-Pinene (**43**)	α-pinene epoxide (**51**)	63	225, 226
α-Ionone (*rac*-**155a**)	3-hydroxy-α-ionone (**155b**)	57	227
β-Ionone (*rac*-**156a**)	4-hydroxy-β-ionone (**156b**)	39	227
(+)-Valencene (**157a**)	nootkatone (**157b**) + *cis*- and *trans*-nootkatols (**157c**)	97	228
β-Eudesmol (**158a**)	5-hydroxy-β-eudesmol (**158b**)	–	229, 230
Cedrol (**159a**)	2-hydroxycedrol (**159b**) + 4-hydroxycedrol (**159c**) (3.2 : 1)	83	231
(−)-Aristolene (**160a**)	aristolone (**160b**)	–	231
Oleanolic acid (**130a**)	queretaroic acid (**161**)	–	232
11-Oxo-β-boswellic acid (**162a**)	15-hydroxy-11-oxo-β-boswellic acid (**162b**)	5	233

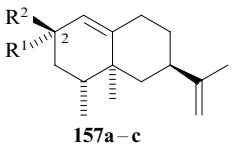
Structures 155 – 162



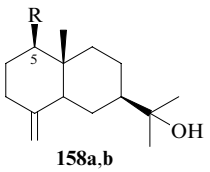
R = H (**a**), OH (**b**)



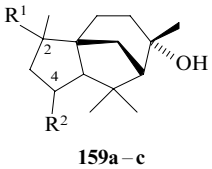
R = H (**a**), OH (**b**)



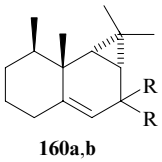
$R^1 = R^2 = H$ (**157a**);
$R^1 + R^2 = O$ (**157b**);
$R^1 = H$, $R^2 = OH$ [(2*R*)-**157c**];
$R^1 = OH$, $R^2 = H$ [(2*S*)-**157c**]



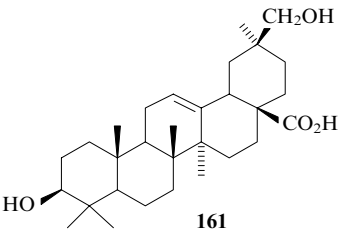
R = H (**a**), OH (**b**)

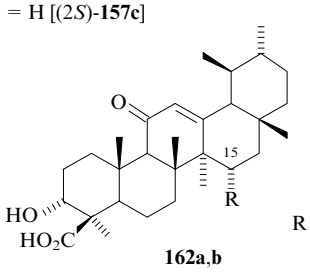


$R^1 = R^2 = H$ (**a**);
$R^1 = OH$, $R^2 = H$ (**b**);
$R^1 = H$, $R^2 = OH$ (**c**)



R = H (**a**),
2 R = O (**b**)



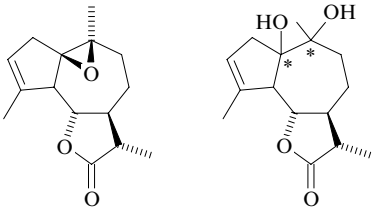


R = H (**a**), OH (**b**)

and **156b** hold promise for the use in the perfume industry and chemical synthesis.[227] It was shown that the replacement of amino acid residues in cytochrome P450 monooxygenase from mutant strains of *B. megaterium* results in a 300-fold increase in the hydroxylation [at the C(3) and C(4) atoms] activity of the enzyme towards α- (**155a**) and β-ionones (**156a**) compared to the native strain.[234, 235]

Recombinant cultures of *B. subtilis* 1K1, which transforms the sesquiterpene lactone arborescin (**163**) to form 12% of cytotoxic 1,10-dihydroxy-5,7α,6,11β(H)-guai-3-en-6,12-olide (**164**),[236] and *P. putida* GPo1, which catalyzes the oxidation of substrate **21** to perillyl alcohol (**22**),[193] were produced.

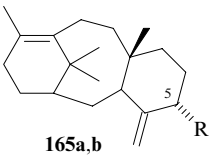
Structures 163, and 164



163 **164**

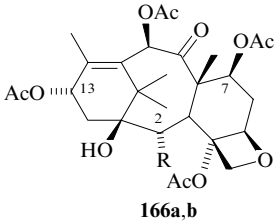
The expression of plant acyltransferases in *E. coli* made it possible to perform the directed (up to 90%) acylation of 10-deacetylbaccatine III (**101f**)[237] and taxa-4(20),11(12)-dien-5α-ol (**165a**)[238] to produce derivatives **101b** and **165b**, respectively, of 2-debenzoyl-7,13-diacetylbaccatine III (**166a**) to give 7,13-10-diacetylbaccatine III (**166b**),[239] and of compound **101f** to form 10-deacetyl-10-propionyl- (**167a**) and 10-deacetyl-10-butyrylbaccatines III (**167b**).[240, 241] The *E. coli* strains carrying overexpressed β-glucosidase from *Microbacterium esteraromaticum* KCTC 12040BP[242] and *Sphingomonas* sp. 2F2[243] were found to perform the partial hydrolysis of triterpenoid ginsenoside saponins Rb1 (**125c**), Rd (**125g**), Rc (**125n**) and Rb2 (**125o**). Recombinant glycosidase from *M. esteraromaticum* GS514 (KACC 16318), which catalyzes the 65% conversion of ginsenoside Rb2 (**125o**) to compound Rg3 (**125d**), was characterized.[244]

Structures 165–167



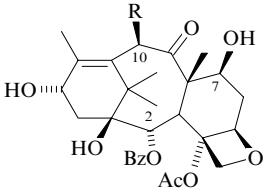
165a,b

R = OH (**a**), OAc (**b**)



166a,b

R = OH (**a**), OBz (**b**)



167a,b

R = OC(O)Et (**a**), C(O)Pr^n (**b**)

VII. Conclusion

Bacterial modifications of terpenoids have been extensively studied in recent years.[5, 12, 17–20, 245] Due to availability of terpenoids from natural sources, they are used as substrates of the biotransformation. Emphasis is given to investigations of the synthase and oxidative activities of bacteria. Terpene synthases from *Streptomyces* and diterpene synthases from *M. tuberculosis*, which catalyze the cyclization of pyrophosphates **16**, **61** and **84**, were characterized. The mechanisms of the oxidative biotransformation of monoterpenes were most comprehensively studied for acyclic and monocyclic compounds and their derivatives. Pseudomonads were shown to be efficient as biocatalysts for the oxidation of acyclic monoterpenes to biologically active derivatives and valuable products. Efficient methods were developed for the production of oxidized derivatives of limonene (**21**) by actinobacteria of the genus *Rhodococcus* with the use of additional growth substrates (in particular, hydrocarbons) or two-phase media for the cultivation of microorganisms proposed. Biotransformation methods for this compound and its derivatives developed under scaling-up conditions with the use of bioreactors are suitable for the efficient production of valuable derivatives (for example, alcohol **22**),[59] which are difficult to isolate from plant extracts.[193, 204, 206, 207] It should be noted that the efficient regioselective oxidation of limonene (**21**), for example, to perillyl alcohol (**22**) cannot be performed by means of chemical methods because of similar electronic properties of allylic methylene groups [C(3) and C(6) atoms] and methyl groups [C(7) and C(10) atoms] of compound **21**.[192]

Analysis of the published data on the biotransformation of mono- and sesquiterpene substrates using bacteria shows that studies in this area raised to a qualitatively new level based on a knowledge of the cell metabolic pathways and the possibility of their regulation by modern methods of genetic engineering. Investigations of the biotransformation of di- and triterpenoids are in the stage of accumulation of knowledge on the transformation ability of bacteria with respect to these substrates and refer mainly to the transformation of tricyclic resin acids or the hydrolytic cleavage of the glycosides of steviol (**85**), protopanaxadiol (**125a**) and protopanaxatriol (**125b**) by soil bacteria and mammalian intestinal microflora. Taking into account a high level of regioselectivity of the oxidative biotransformation of structurally complex polycyclic terpenoids, this method for the production of valuable compounds can be considered as a promising alternative to chemical synthesis. For instance, it was shown that actinobacteria of the genus *Rhodococcus* can catalyze the directed oxidation of alcohol **126a** and acid **106a** to form betulone (**126b**)[179] and 15-hydroxydehydroabietic acid (**106e**),[125] whereas the most efficient chemical methods for the synthesis of these compounds include three and seven steps, respectively.[246]

With the aim of increasing the regio- and stereoselectivity of methods of synthesis of target terpenoid derivatives, techniques of genetic modifications of microorganisms are extensively used along with the search for the optimal conditions of the transformation of the initial substrates. The goal of the production of recombinant bacterial cultures based on *E. coli* is generally to express genes encoding plant synthases, bacterial acyltransferases, β-glucosidases and monooxidases. This approach can be used to impart properties of individual enzymes to whole bacterial cells and

perform the biotransformation of terpenoids with high regio- and stereoselectivity under more accurate control over the reactions.

Analysis of the published data shows that, in spite of high selectivity and substrate specificity of the reactions catalyzed by individual enzymes, the transformations of terpenoids are most often performed using whole bacterial cells. Due to specificity of multipurpose enzyme systems, a high degree of adaptation to environmental factors and the possibility of the easy regeneration of cofactors, the use of whole bacterial cells in the biological transformation of terpenoids is feasible and economically advantageous.

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