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Natural peroxides. Chemistry and biological activity

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Abstract. This review is devoted to the chemistry of natural peroxides and their biologically active analogues. Data are presented on the natural sources of peroxy compounds and pathways of their formation. The structure, stereochemistry and chemical transformations of natural peroxides are considered; the problems of total synthesis of natural peroxy compounds and their structural analogues are also discussed. Data for the biological activity of peroxides are presented. The bibliography includes 134 references.

I. Introduction

The chemistry of peroxy compounds is a vast field which encompasses problems of organic synthesis, macromolecular chemistry, and free-radical processes. These problems have received much attention in the current literature. Lively discussions concern the involvement of peroxy intermediates in biochemical processes; much attention is given, in particular, to the role of peroxy compounds as biologically active metabolites in the synthesis of prostaglandins, thromboxanes, prostacyclins, leukotrienes, hepoxylins, and lipoxins as well as of a wide variety of unsaturated acids with oxygen-containing functions.[1–6]

Despite the apparently convincing evidence for a relatively high stability of ascaridol, which can be isolated by steam distillation of plant material,[7,8] further replenishment of the family of natural peroxides has long been considered problematic because of their high lability and short metabolic life.

In this regard, the history of isolation of prostaglandin endoperoxide, one of the key intermediates of prostanoid biosynthesis, commonly known as prostaglandin H_2 (PGH_2) appears to be very typical. This labile compound could be isolated only after isomerase has been blocked with mercury salts by rapid extraction of the culture medium.[6] However, among the wide variety of natural peroxides stable compounds have been found, which do not require any special precautions connected with their isolation. The formation of stable peroxides by photosensitised oxidation of terpenes and steroids stimulated the search for the peroxy compounds synthesised by animal and plant organisms.[9–11]

Beginning in 1970s, the opinion was repeatedly stated that peroxy metabolites can be present in marine organisms. Later, this assumption has often received experimental support. Thus, extracts of sea sponges were found to contain, in addition to the expected 6,9-endoperoxides of sterols, relatively stable 1,2-dioxane and 1,2-dioxolane derivatives and macrocyclic peroxides.

Studies of chemical transformations of natural peroxides revealed that the suggestions of their extreme lability are in many cases unwarranted. For example, some 1,2-dioxane derivatives retain the peroxy group even in the presence of such reagents as complex aluminium hydrides and OsO_4.

Biological assays of peroxides from marine organisms revealed highly active antibacterial, fungicidal, cytostatic, and anticarcinogenic agents.

An event, which changed dramatically many current notions of the natural peroxides, was the discovery by Chinese investigators[12] of a high antimalarial activity of a sesquiterpene peroxylactone artemisinin (qinghaosu) isolated from the wild plant *Artemisia annua* L (sweet wormwood). It is of note in this connection that in traditional Chinese medicine this plant had long been considered to be a highly effective antimalarial agent. The communication by Chinese authors[12] aroused considerable interest among chemists, pharmacologists, and practitioners. The studies performed in a number of laboratories have culminated in the preparation of a drug, which has a number of salient advantages over all currently known antimalarial agents, including the possibility of its application in pregnancy.[13] It is noteworthy that the discovery of therapeutic properties of artemisinin gave an impetus to the total synthesis of this sesquiterpene and its analogues. Data on the chemistry of artemisinin and other terpenoids isolated from *A. annua* have been reported.[12,14]

It is not inconceivable that medicinal drugs of peroxide nature will play a conspicuous role in the therapy of malaria, a disease which presently affects hundreds of millions of people all over the world.[15] It is not therefore surprising that the interest in elaborating the methods of synthesis and bioassay of peroxides has increased considerably during the past decade. Special mention should be made of the prime importance of the general approaches to the synthesis of cyclic peroxides.[10,11,16]

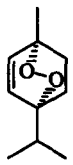
Nowadays, the chemistry of peroxides may be regarded as a new perspective in research in bioorganic chemistry and medicine.

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II. Naturally occurring peroxides and their biological activity

The first natural peroxy compound that has been isolated in an individual state is ascaridol **1**, which is present in the so-called chenopodium essential oil obtained by steam distillation of the plant *Chenopodium ambrosioides* L. This plant was cultivated in the USA and other countries specially for the purpose of obtaining an oil known as a potent anthelmintic agent. The peak of chenopodium oil production (up to 50 tons per year) was in 1930–1940.[17] The ascaridol content in this essential oil amounts to 60%. The essential oil of the plant *Chenopodium hircinum* contains 40% of ascaridol. The essential oils of the yarrow *Achillea micranta* M.B. and *Ajania fastigiata* contain 26%–51% of ascaridol.[8]

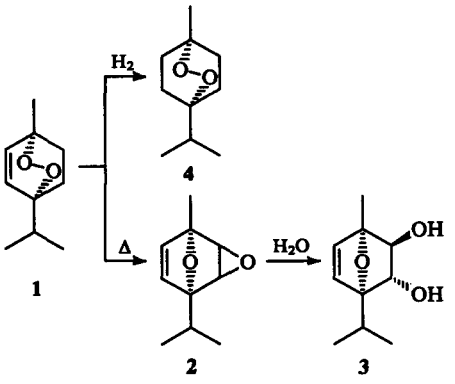


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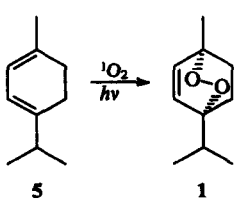
Apart from its potent anthelmintic action, ascaridol **1** is also active with respect to the central nervous system (CNS). It has been shown, in particular, that ascaridol displays a pronounced analgesic activity in the 'acetic convulsions' test and prolongs threefold the pentabarbital-induced anaesthesia. The ability of ascaridol at a dose of 100 mg kg^{-1} to reduce body temperature in experimental animals by 1.5 °C has been reported.

When heated above 150 °C, ascaridol explodes, which explains the cases of explosive decomposition of the chenopodium oil as a result of careless distillation. Boiling of ascaridole in a solution of *p*-cymene is accompanied by the rearrangement of the peroxy group, eventually resulting in the dioxide **2** being further hydrated into the glycol **3** (Scheme 1). At the same time, the peroxy group of ascaridol appeared to be resistant to catalytic hydrogenolysis. Thus, hydrogenation of ascaridol gives the dihydro derivative **4**.

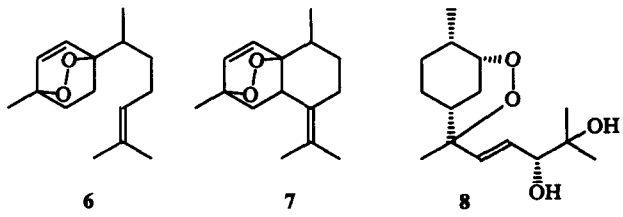
Scheme 1



Synthesis of ascaridol by photosensitised photooxidation of α-terpinene **5** occurs practically quantitatively.[18]



Many plants of the *Compositae* family produce sesquiterpene peroxides. For example, the sesquiterpene analogues of ascaridol **6** and **7** were detected in extracts of the plants *Rudbeckia laciniata* and *Senecio paludatinis*,[19] while the sesquiterpene peroxydiol qinghaosu-A **8** was isolated from the plant *Artobotrys hexapetalus* used in Chinese folk medicine as an antimalarial.[20] An opinion was expressed that qinghaosu is an artefact, since it had been isolated from the plant that underwent storage.



6 **7** **8**

The wild plant *A. annua* widely distributed throughout the Asian continent contains, apart from the steam-distilled essential oil, terpene extractives including 12 compounds of the cadinane series.

Unquestionably, the most remarkable of these compounds is lactone **9**, artemisinin, isolated and identified by Chinese investigators.[12,13] The artemisinin content in *A. annua* does not exceed 0.1%, reaching a maximum two weeks before the flowering of the plant.[21] A search for other natural sources of artemisinin led to its discovery in the extract of the wormwood *Artemisia apiaceae*.[21] The sweet wormwood growing in Middle Asian countries and Kazakhstan contains up to 0.05% artemisinin.[22] The artemisinin content in *A. annua* cultivated in Central Europe does not exceed 0.001%.[23] The interest in artemisinin can be inferred from the communication describing the introduction of the sweet wormwood in the USA.[24]

Artemisinin possesses rather high antimalarial activity; its use as a medicinal agent is due to its ability to suppress the proliferation of the plasmodium clones resistant to many modern antimalarial drugs.

It is reported that the antimalarial activity of the qinghaosu peroxydiol **8** is of the same order of magnitude as that of artemisinin.[25] The assay of all the sesquiterpene peroxylactones described above revealed their significantly lower antimalarial activity than that of artemisinin.[26]

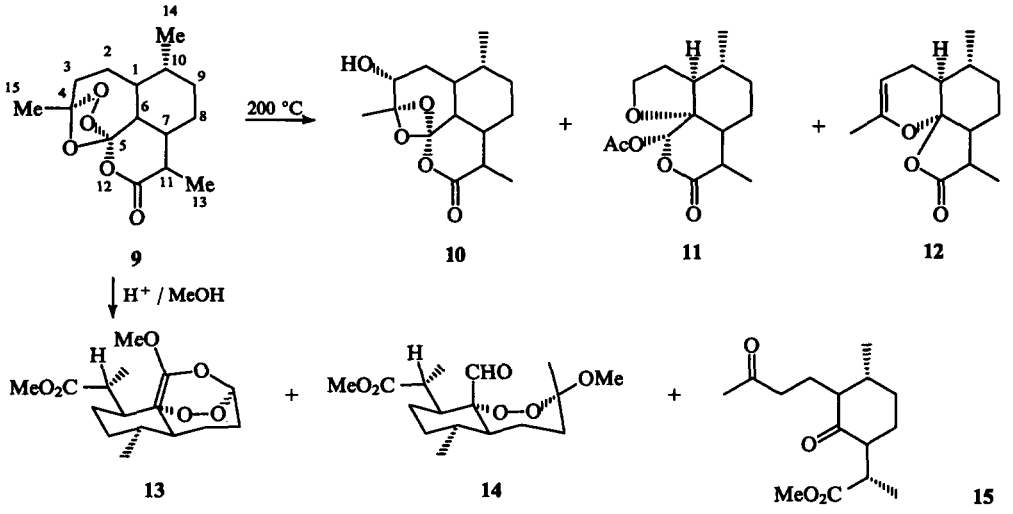
Artemisinin can regulate the plant growth. It has been shown that at a concentration of 5×10^{-6} M artemisinin inhibits the growth of the duckweed *Lemna minor*. Noteworthy, deoxyartemisinin devoid of the peroxy function does not display any inhibitory activity.[27]

Artemisinin is a sufficiently stable compound, which not only permits its isolation in a pure state, but also makes it possible to obtain a wide range of derivatives retaining the peroxide bridge.

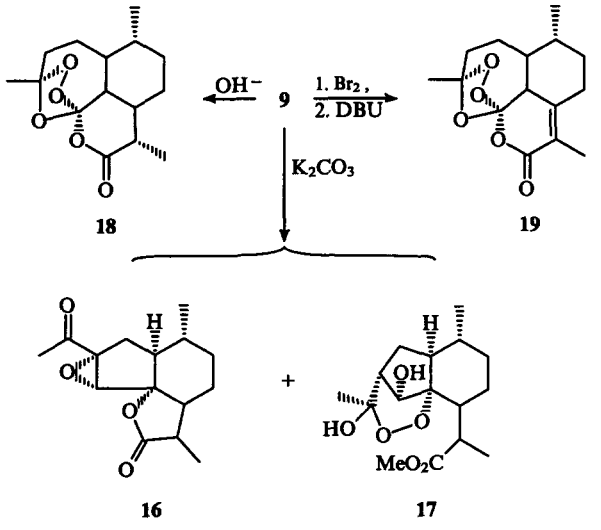
Thermal decomposition of artemisinin results in artemisinin D **10** and the products of more profound rearrangements of the molecule **11**, **12** (Scheme 2).[28] Upon treatment with a methanolic acid, artemisinin is converted into peroxy compounds **13** and **14** and the dioxo ester **15**.[29]

It should be noted that artemisinin, like compounds **13** and **14**, possess high antimalarial activity. Treatment of artemisinin with K_2CO_3 in methanol yields products of intramolecular rearrangement **16**, **17**.[30] The preparation of 11-epiartemisinin **18** under alkaline conditions and a two-step conversion of artemisinin into isoartemisitene **19** have been described (Scheme 3).[31]

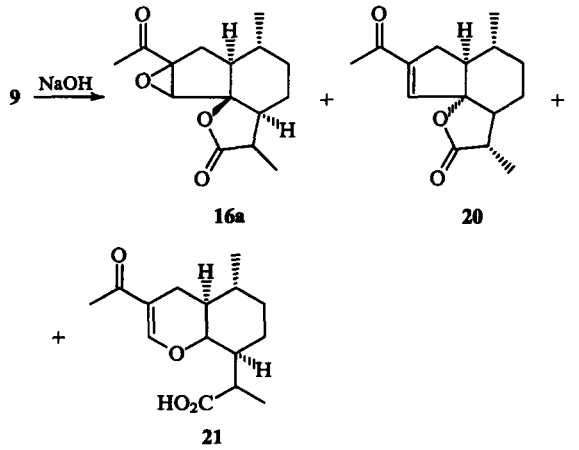
Scheme 2



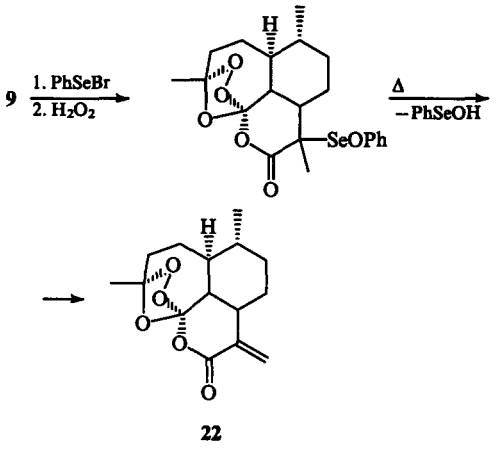
Scheme 3



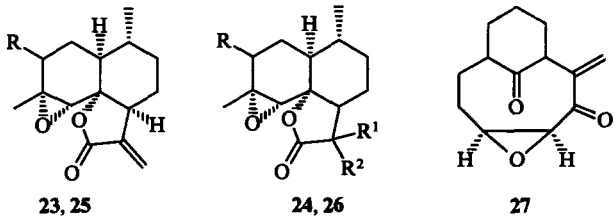
Treatment of artemisinin with alkali gives the epoxy ketone epimer **16a** and oxo compounds **20**, **21**.[32]



The peroxylactone **22**, artemisitene, has been found among the minor components of the extract of *A. annua*.[12,33] Its synthesis from artemisinin based on the use of a selenium-containing intermediate has been described.[34]



In the studies of the possibility of microbial transformations of artemisinin in the plant, it has been shown[35] that *Aspergillus flavipes* converts one of the components of *A. annua*, artemisinin B **23**, into the dihydro derivative **24**, while *Beauveria bassiana* transforms the compound **23** into the hydroxy lactones **25** and **26**.



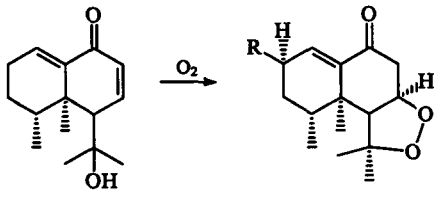
23: R = H,
25: R = OH.

24: R^1 = H, R^2 = Me;
26: R^1 = CH_2OH, R^2 = H.

UV irradiation of artemisinin B gives the product of profound skeletal rearrangement, lumiartemisinin B **27**.[36]

The plant *Nardostachys chinensis* Batalin of the Valerianaceae family is also extensively used in Oriental medicine. To the active extractives of this plant one can refer the oxo peroxides nardosinone **28** and canchone **29**.[37,38] Nardosinone is a cycloperoxy

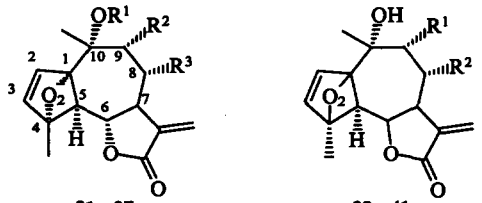
derivative of the hydroxyketone **30** (canchone A) and is present in the above plant together with the peroxides **28** and **29**.[39]



30 **28, 29**

28: R = H, **29**: R = OH.

The isolation of a series of 1,4-peroxy lactones **31**–**41** of the guaiane type differing in not only substituents, but also in the configuration of the peroxide cycle (Tables 1, 2)[40–45] has been described. Some of these compounds (e.g., the peroxy lactones **31**–**33** and **38**–**41**) manifest weak antimalarial activity.

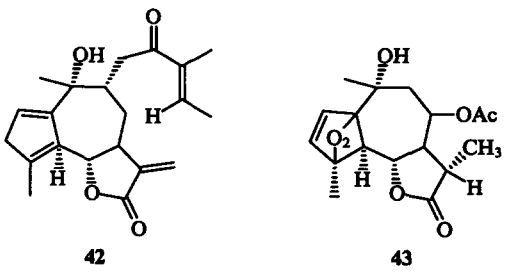


31–**37** **38**–**41**

It should be noted that isoachillofolidiene **42**,[46] the precursor of the peroxides **38**–**41**, was isolated from the leaves of the yarrow *Achillea millefolium*, while its dihydro derivative **43** was isolated, along with the esomontanine **41**, from the leaves of the yarrow *Artemisia montana* (Scheme 4).[45]

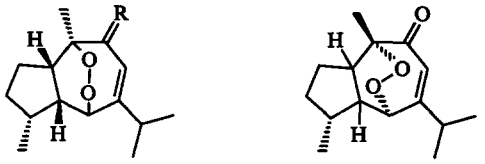
Some sesquiterpenes of the guaiane type contain a peroxide bridge in a 7-membered cycle. For example, the 6β,10β-peroxides,

Scheme 4



42 **43**

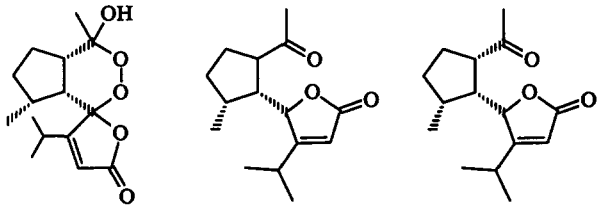
chanalpinol **44**, chanalpinone **45**, and isochanalpinone **46** were isolated from the plant *Alpinia japonica*.[47,48]



44, 45 **46**

R = C(OH)H (**44**), O (**45**).

One of the constituents of this plant is the peroxide alpinolide **47**. Its structure sheds more light on the biosynthetic pathways of the furopelargones A and B **48**, **49**, which are also present in this plant.



47 **48** **49**

Table 1. Some representatives of 1α,4α-peroxylactones of the guaiane type.

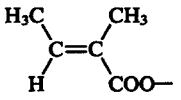
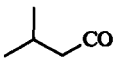
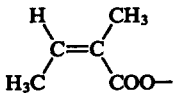
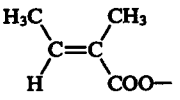
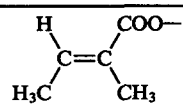
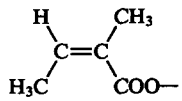
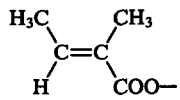
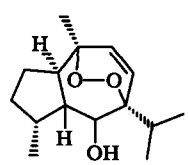
Compound	Name of the peroxide and its source	R^1	R^2	R^3	Ref.
31	Apressin, *Achillea depressa*	H	OAc	H	40, 41
32	Isoapressin, *Achillea ligustica*, *A. depressa*	Ac	H	H	40
33	Peroxyachifolide, *A. millefolium*		OH	H	42–44
34	*A. millefolium*	Ac	OH	H	44
35	*A. millefolium*		OH	H	44
36	*A. millefolium*		OH	H	44
37	*A. millefolium*	H	H		44

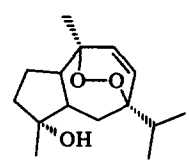
Table 2. Some representatives of 1β,4β-peroxylactones of the guaiane type.

Compound	Name of the peroxide and its source	R^1	R^2	Ref.
38	β-Peroxyisoachiofolide, *Achillea millefolium*		H	42–44
39	*Athunasia*		H	41
40	*Athunasia*		OH	41
41	Exomontanine, *Artemisia montana*	H	OAc	45

The Peruvian plant *Lialum floribundum* contains 7β,10β- and 1β,10β-peroxides, compounds **50** and **51**.[49]

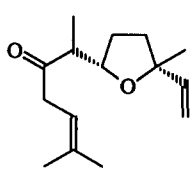


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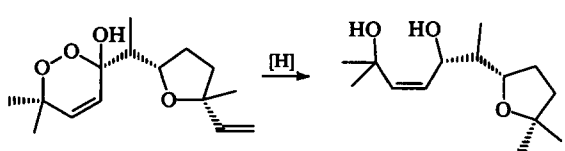
51

A group of peroxides structurally related to the sesquiterpene alcohol nerolidol has been described. Their precursor is davanone **52** isolated from the leaves of the tansy *Tanacetum vulgare*.[50]



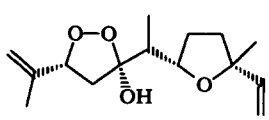
52

This plant also contains the peroxyketal **53**, whose structure was confirmed by its reduction into the diol **54**.

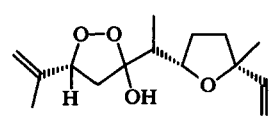


53 **54**

Peroxyketones of the davanone type **55** and **56** were isolated from the extracts of the yarrows *Artemisia maritima* and *A. abrotanum*.[51,52]



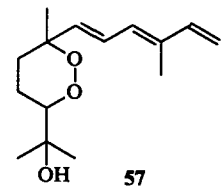
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56

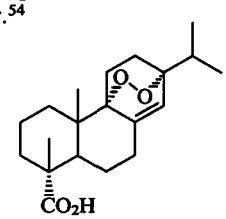
It is to be noted that compounds **53**–**56** possess a weak antimalarial activity.

The dark blotches formed on the apple peel on storage contain the triene peroxide **57**.[53]

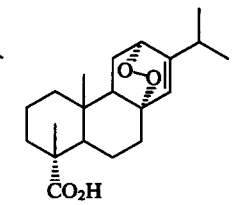


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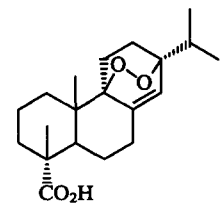
Peroxides of the diterpene type occur less frequently. Endoperoxides formed from resin acids are the most common representatives of this group. The endoperoxides of palustric **58** and levopimaric **59** acids were isolated from the needles of the Siberian fir.[54]



58



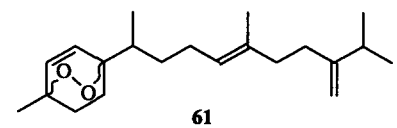
59



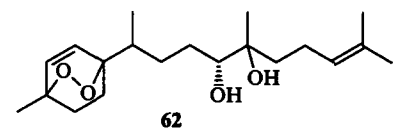
60

The peroxide **58** and its enantiomer **60** are the components of the plant *Elodea canadensis*.[55]

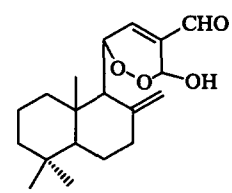
The diterpene analogues of ascaridol differing in the configuration of the peroxide cycle (**61**, **62**) are present in the wormwood *A. absintium*.[56] The monocyclic peroxydiol **62** was found in the plant *Helichrysum acutatum*.[57] The plant *Hedichium coronarium* used in Brazilian folk medicine as an antirheumatic agent contains, along with other terpenoids, coronarin B **63**, a peroxide of the labdane type.[58]



61

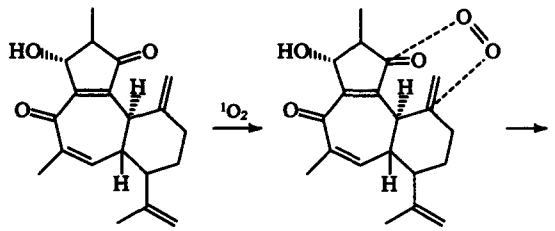


62

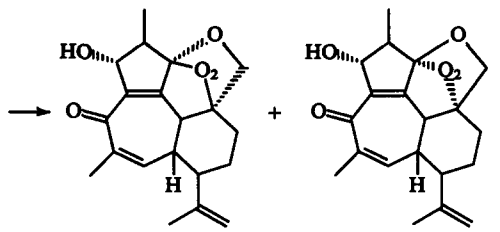


63

The bark of the tree *Jatropha grossidentata* is used by the Indian population of Paraguay as an antiparasitic means. The active principle of the bark extract are canioyan **64** and bisepicanioyan **65**. It has been suggested that both peroxides are formed as a result of an unusual attack of singlet oxygen at the diketone yatrogrossidione **66**, which has also been isolated from the extract of this plant.[59]

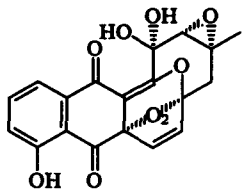


66



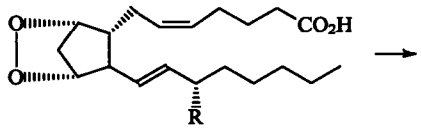
64 65

The peroxide **67** is of microbial origin; it is produced by *Streptomyces phaeochomogenes*.[60]

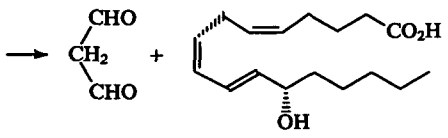


67

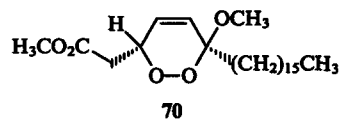
As already mentioned in the Introduction, prostaglandin endoperoxides **68** are formed from arachidonic acid under the action of prostaglandin cyclooxygenase.[1-6] The main pathways of their metabolism are as follows: synthesis of prostaglandins D_2, E_2, and $F_{2\alpha}$ by isomerases, synthesis of thromboxanes A_2 and B_2 by thromboxane synthetase and prostacyclin synthesis by prostacyclin synthetase; they also undergo degradation resulting in the formation of malonaldehyde and (12*R*)-hydroxyheptadeca-(5*Z*,8*Z*,10*E*)-trienoic acid.[5]



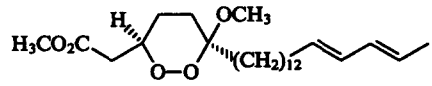
68, R = OH, OOH



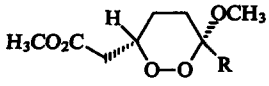
Peroxides isolated from marine organisms constitute a rather large group. Among them, the peroxides $MeCH(O_nH)OOEt$ **69** produced by the Ascidia, *Phallusia mamillata*, *Ascidia ahodori*, *Styela pricata*, and *Halocynthia roretri* have the most simple structure.[61] Of special interest are the 1,2-dioxane derivatives formed from linear unsaturated acids. For example, chondrillin **70** and xestins A and B **71**, **72** were isolated from the sponges *Xestospongia*[62] and *Chondriella*,[63] while peroxy esters **73**–**75** were isolated from the sponge *Plakortis lita*.[64] The compounds **69**–**74** possess a cytostatic activity.



70



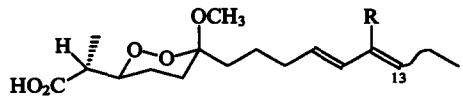
71



72–**75**

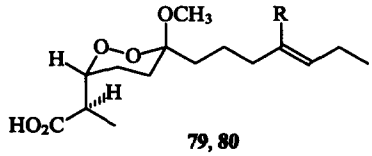
R = $(CH_2)_n$ [*n* = 12 (**72**), 9 (**73**), 7 (**74**)], $(CH_2)_{11}CH_3$ (**75**).

The sponges of the *Plakortis* genus produce a wide variety of peroxy acids, five of which [the peroxyplakoric acids A_1, A_2, A_3 (**76**–**78**), B_1 and B_3 (**79**, **80**)] have been isolated and identified.[65]



76 – **78**

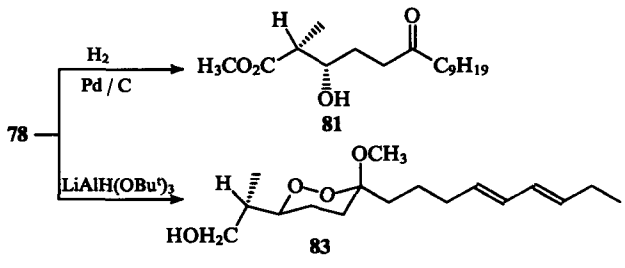
76: R = CH_3, 13*E*,
77: R = CH_3, 13*Z*,
78: R = H, 13*E*.



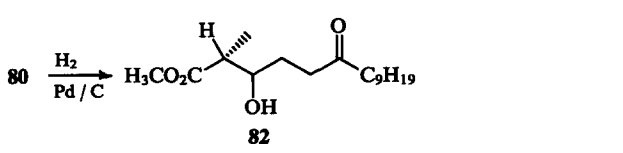
79, **80**

R = CH_3 (**79**), H (**80**).

The configuration of the peroxy acids **78** and **80** has been confirmed by their hydrogenation into the diastereoisomeric hydroxy oxo esters **81** and **82**, while the stability of the peroxide cycle is corroborated by the isolation of the compound **83** upon the reduction of the methyl ester of the acid **78** with $LiAlH(OBu^t)_3$.



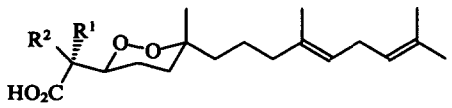
81



83

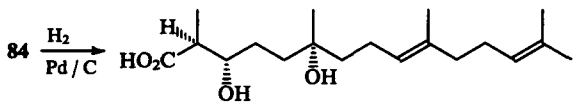
82

The diastereoisomeric isoprenoid peroxy acids **84** and **85** were isolated from the sponges *Latrunculata*.



84, 85

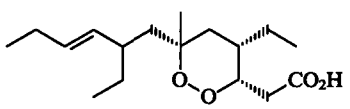
84: $R^1 = CH_3$, $R^2 = H$;
85: $R^1 = H$, $R^2 = CH_3$.



86

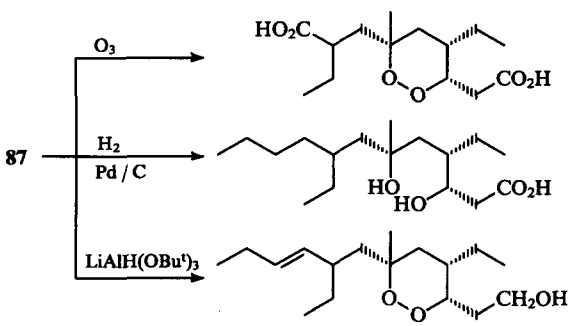
The configuration of the former peroxy acid has been confirmed by hydrogenation into the dihydroxy acid **86**.[66]

Branched-chain peroxides are produced by some species of marine sponges and, what is remarkable, at surprisingly high concentrations. For example, plakortin **87** was isolated from the reef sponges *Plakortis halihondrioides* with a 5.7% yield of the dry weight.[67]

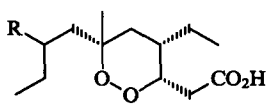


87

The transformations of this compound carried out in the course of structural analysis, testify to a high resistance of the peroxy group to reducing and oxidising reagents.

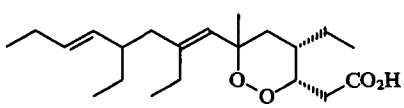


The sponges *Plakortis halihondrioides* contain a wide range of peroxides: 3-epiplakortin **88**, its dihydro derivative **89**, the unstable peroxides **90** and **91**, as well as the aryl-substituted peroxy acid **92**, its methyl ester, and lactone **93**.[68]

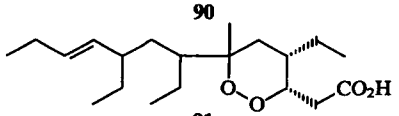


88, 89

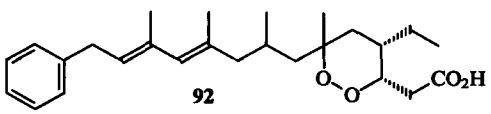
R = $(CH_2)_2CH{=}CHCH_3$ (**88**), C_4H_9 (**89**)



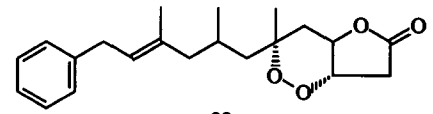
90



91

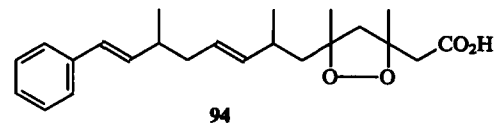


92

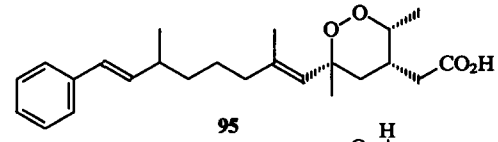


93

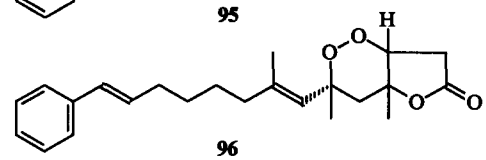
The sponges of the *Plakortis* genus contain plakininic acids A and B **94**, **95** and plakortolide **96**.[69,70]



94

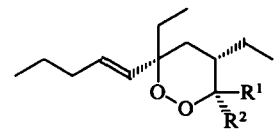


95



96

The Caribbean sponge *Chondrosia colletrix* produces the epimeric acids **97** and **98** and their methyl esters, whose content amounts to 6% of the dry weight.[71]

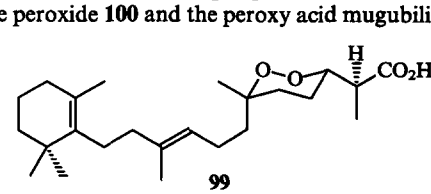


97, 98

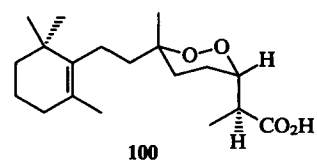
97: $R^1 = CO_2H$, $R^2 = H$;
98: $R^1 = H$, $R^2 = CO_2H$.

It is worth noting that the compounds **95**–**98** possess antimicrobial and antifungal activities.

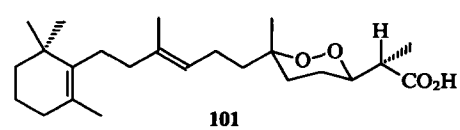
Mono- and bi-cyclic isoprenoid peroxy acids were first described in 1979. It was reported that the sponges *Prianos* dwelling in the Red Sea contain up to 1.5% of the peroxide **99**,[72] which was also found in the coral reef sponges together with the peroxy acid **100**.[73] The sponges of the *Latrunculata* genus contain the peroxide **100** and the peroxy acid mugubilin **101**.[66]



99

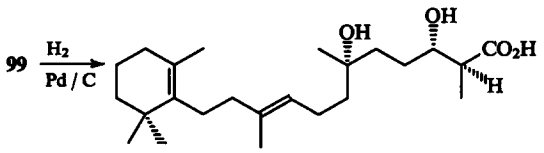


100



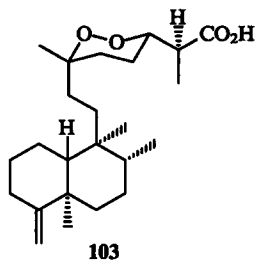
101

To confirm the configuration of the peroxy group in the compound **99**, the former was hydrogenated resulting in the dihydroxy acid **102**.



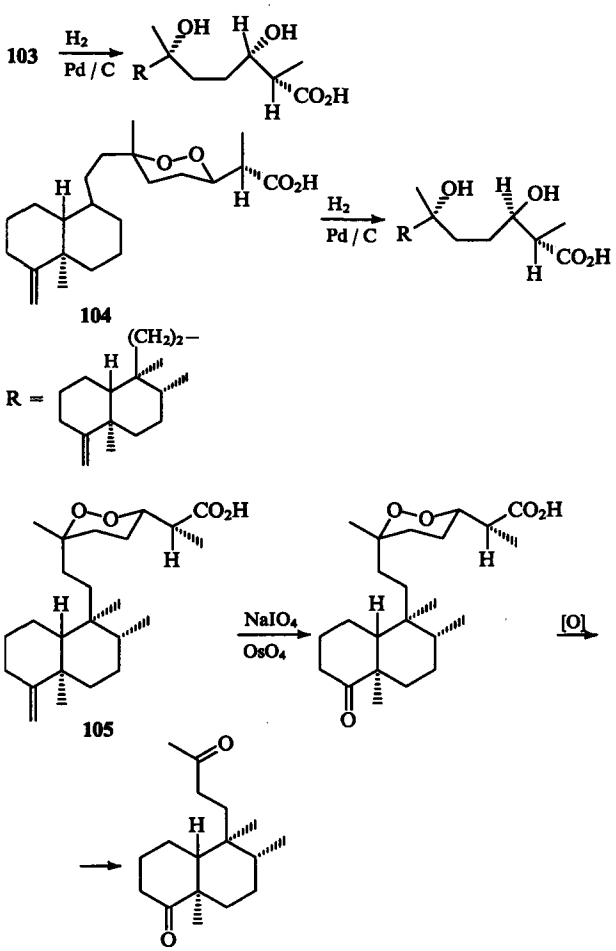
102

Sigmosceptrellin A **103**, whose structure was established by the X-ray analysis, was isolated from the extract of the sponges *Sigmosceptrella laevis*.[74]



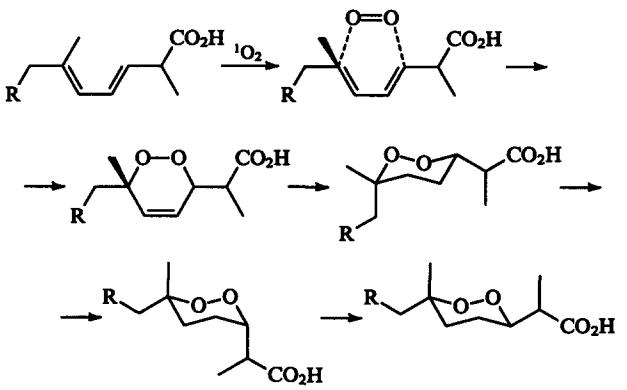
103

Later, the isolation of sigmoscentrellins B and C **104**, **105** and a series of transformations confirming their structure was reported.[75]

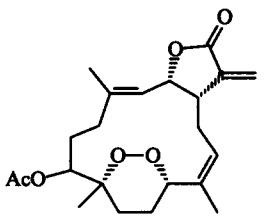


The compounds **99**–**101** have a cytostatic activity, whereas the compounds **102**–**105** manifest an ichtiostatic action.

The formation of peroxy acids occurs, most probably, with the participation of enzymes producing singlet oxygen as well as hydrogenases and isomerases.[66]

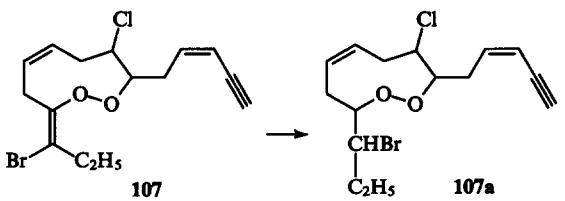


Among metabolites of marine organisms, compounds of a cembrane series were found, which possessed high cancerostatic, antimicrobial, and fungicidal activity.[76–83] For example, the ichthyotoxic coral *Lobophytum denticulatum* contains the cembranoid peroxide denticulatolide **106**, whose structure was established by X-ray analysis, while the correct conformations were calculated by using the molecular mechanics method.[84–87] The denticulatolide displays an antitumour activity.



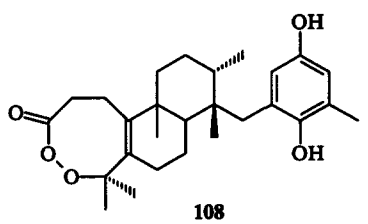
106

The halogen-containing peroxide rhodophytin **107** has been isolated from the algae of the *Laurencia* genus; it isomerises on storage in solution into the compound **107a**.[64, 88]



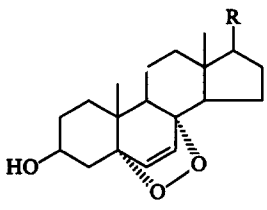
107 107a

The terpenoid peroxy ester **108** is produced by the brown algae *Taonia atomaria*.[87]

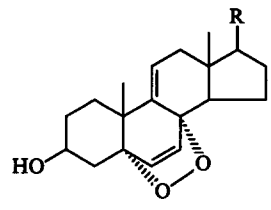


108

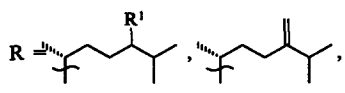
Steroid endoperoxides are distributed in marine organisms fairly widely. For example, the sponge *Tethya aurantia* contains four 6,9-endoperoxides of the type **109**;[87] 16 peroxides, whose structures resembled those of **109** and **110**, have been isolated from the extracts of the sponges *Ascidia nigru*, *Dendrogyra cylindrus*, *Thalysias juniperiana*, and *Aplysia dactiolomea*.[89]



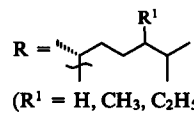
109



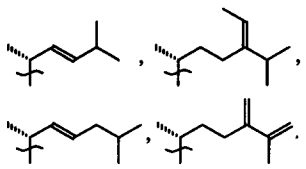
110

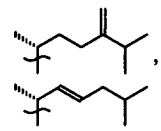


(R^1 = H, CH_3, C_2H_5),

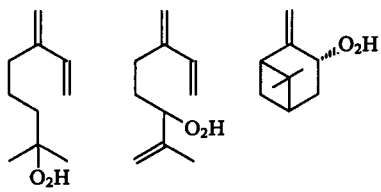


(R^1 = H, CH_3, C_2H_5),



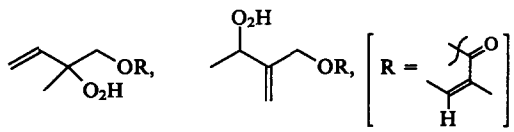


Hydroperoxides of terpene and steroid structures are produced by higher plants and marine organisms. For example, myrcene hydroperoxides **111**, **112** have been isolated from the extracts of the leaves of the wormwood *A. annua*,[90] while the *trans*-pinocarveyl hydroperoxide **113**, from the leaves of the plants *Anthemis nobilis*,[91] *Chenopodium ambrosioides*,[92] and *Achillea filipendulina*.[93]

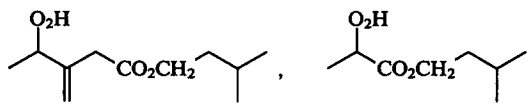


111 112 113

The plant *Anthemis nobilis* contains hydroperoxides, the derivatives of the esters of prenolic and aliphatic alcohols and the acids **114**–**117**.[91]

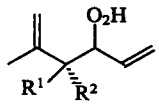


114 115



116 117

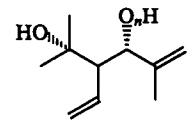
The medicinal plant *Achillea filipendulina* was used as a source of monoterpenes of a new structural type.[94] The extraction of the aerial parts of this plant results in four hydroperoxides of the achillene series.[88] Two of them, **118** and **119**, have also been found in the extract of the wormwood *A. lamcea*.[95]



118, 119

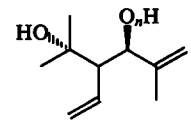
118: R^1 = H, R^2 = $CH{=}CH_2$;
119: R^1 = $CH{=}CH_2$, R^2 = H.

The structure of the hydroperoxides **120** and **121** was corroborated by X-ray analysis and by their reduction into the stereoisomeric diols **122** and **123**.[95]



120, 122

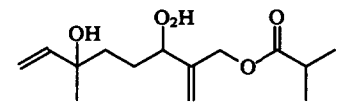
n = 2 (**120**), 1 (**122**).



121, 123

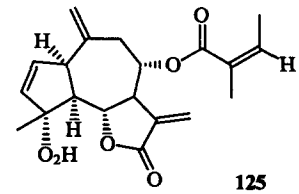
n = 2 (**121**), 1 (**123**).

The monoterpene hydroperoxide **124** structurally related to linalool has been isolated from the plant *Ferreanthus fruticosus*.[96]



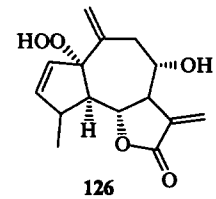
124

The isolation of several hydroperoxides of the guaiane type has been described. For example, the above-mentioned plant *Anthemis nobilis* contains the hydroxyperoxy lactone **125**.[91]

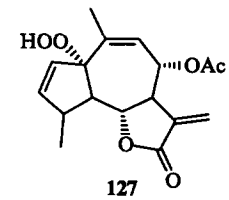


125

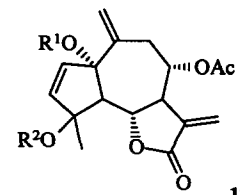
The plant *Cacosmia rugosa* produces the hydroperoxides **126** and **127**,[97] while the peroxy lactone hydroperoxides **130**, **131**[98] could be isolated from the plant *Bishophanthus solicers* together with the hydroperoxides **128** and **129**.



126

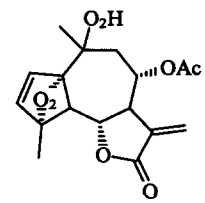


127

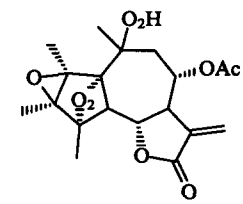


128, 129

128: R^1 = OH, R^2 = H;
129: R^1 = H, R^2 = OH.

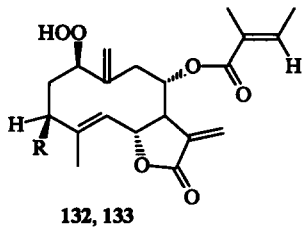


130



131

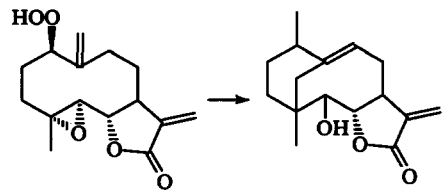
The hydroxyperoxy lactone of the germacrane series **132** has been isolated from the leaves of the plant *Anthemis nobilis*,[91,99] while its dihydroxy derivative **133** is present in the plant *Ferreanthus fruticosa*.[93]



132, 133

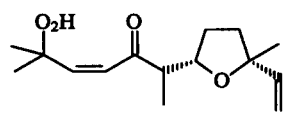
R = H (132), OH (133).

The tansy *Tanacetum vulgare* produces the cryspolide **134**. It has been postulated that the latter is formed in the plant from the peroxypartenolide **135**.[100]

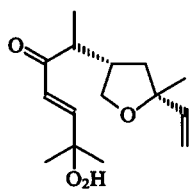


135 134

The hydroxyperoxide derivatives of davanone **50** have been isolated from the extracts of the tansy and some wormwood species. For example, flowers of the plant *Tanacetum vulgare* contain the *Z*-hydroperoxide **136**, while its leaves contain the *E*-isomer **137**.[50]

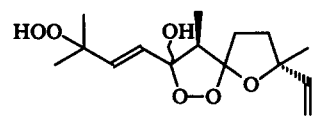


136



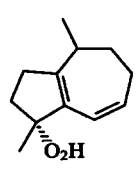
137

The latter has been isolated from the southernwood *Artemisia abrotanum*[52] as well as from the aerial parts of the wormwood *A. maritima*[51] and *A. inculta*.[101] The peroxyhydroperoxide **138** is produced by the plant *A. abrotanum*.[52]

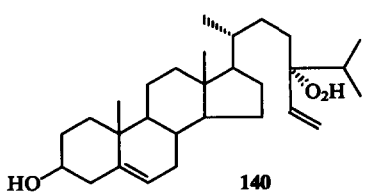


138

The hydroperoxide clavukerin C **139** has been isolated from the coral *Clavularia koellikeri*,[102] and the steroid **140** is present in the plankton *Phallusia mamillata*.[103]



139

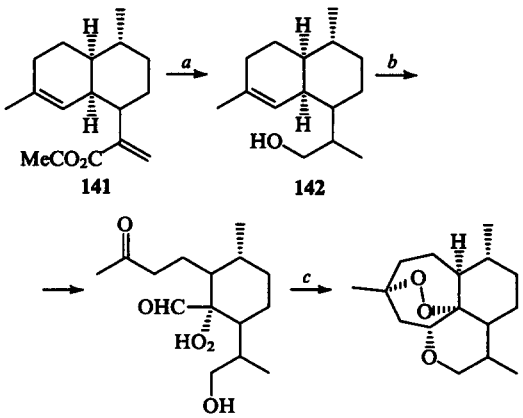


140

III. Synthesis of artemisinin, its derivatives and structural analogues

In the discussion of the pathways of synthesis of artemisinin and its structural analogues, we have deliberately excluded from the synthetic schemes those stages which have no principal significance, by omitting certain experimental details. The main attention was then focussed on the methods used in the synthesis of the peroxy fragments of the molecules. They involve the oxidation by singlet (photoexcited) oxygen, ozonisation, and the use of unique reagents, such as Et_3SiO_3H.

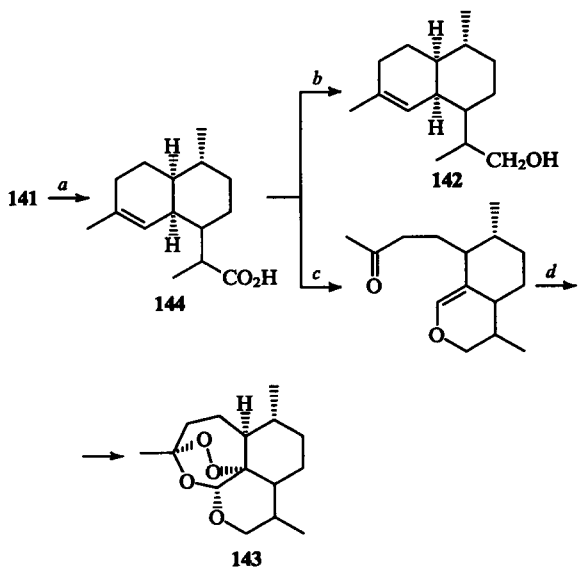
One of the most promising approaches to the synthesis of artemisinin is based on the use of artemisinic acid **141** as the starting compound. Its content in *Artemisia annua* exceeds by one order of magnitude that of artemisinin, and its isolation is much easier. The synthesis of (+)-deoxyartemisinin **143** can be carried out in only three stages via the hydroxy compound **142**.[104]



141 142

(*a*) $LiAlH_4$, $NiCl_2 \cdot 6H_2O$; (*b*) O_2, *hv*, Methylene Blue; (*c*) Dowex H^+.

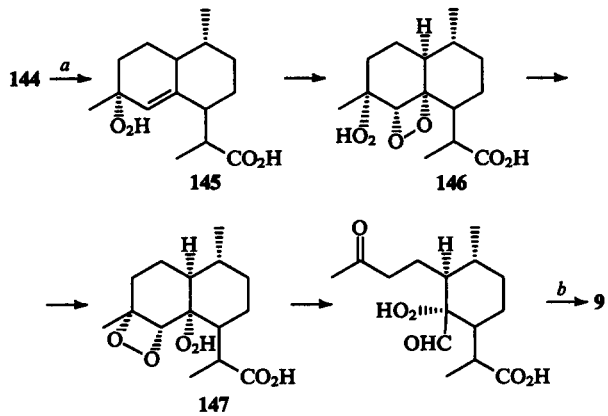
An alternative synthesis of the compound **143** has been described, which requires more steps and includes the formation of dihydroxyartemisic acid **144** at the first stage by reduction of the acid **141** with nickel boride.[105]



142 144 143

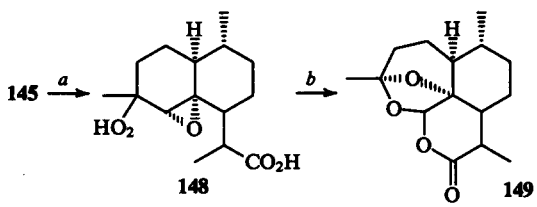
(*a*) $NaBH_4$, $NiCl_2 \cdot 6H_2O$; (*b*) $LiAlH_4$, Et_2O; (*c*) O_3, MeOH, Me_2S, *p*-TsOH, xylene; (*d*) O_2, *hv*, Methylene Blue, $CF_3SO_2OSiMe_3$.

The synthesis of artemisinin based on sensitised photooxidation of the dihydroxy acid **144** is initiated by the formation of the hydroperoxide **145** and further proceeds via the dioxetans **146** and **147**.[106]



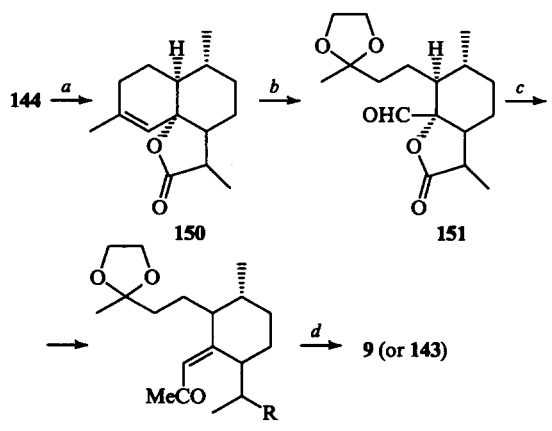
(*a*) O_2, *hv*, Methylene Blue; (*b*) Dowex H^+.

It has to be noted that the unstable epoxide **148** formed from the hydroxyperoxide **145** is converted into the deoxyartemisinin **149**.[107]

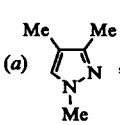


(*a*) *m*-$ClC_6H_4CO_3H$, $CHCl_3$; (*b*) *p*-TsOH.

An interesting conversion of dihydroxyartemisinic acid **144** into artemisinin **9** has been described.[108] Its key stage is the allylic oxidation of the acid **144** by the CrO_3–3,5-dimethylpyrazole complex into the lactone **150**, which after ozonolysis and ketalysation gives the aldehydo lactone **151**. This is followed by the synthesis of the enol ester **152** and the photooxidation sensitised with Bengal rose. This method can also be used to obtain deoxyartemisinin **143** by the reduction of the methoxycarbonyl group in the compound **152** and photooxidation of the compound **153**.

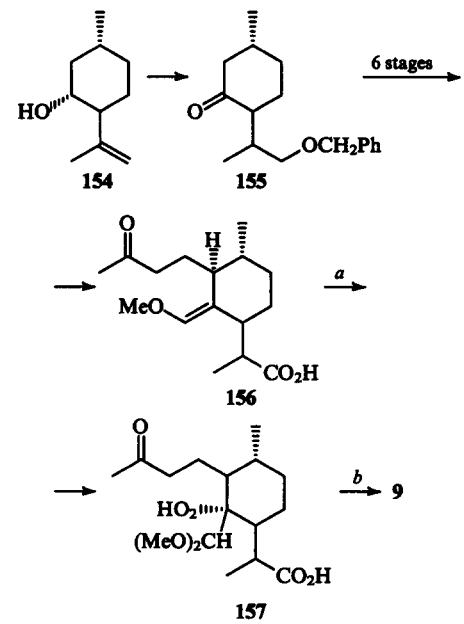


R = CO_2Me (**152**), CH_2OH (**153**)

(*a*) , CrO_3; (*b*) O_3, $[Me_3SiOCH_2]_2$, $CF_3SO_2OSiMe_3$;

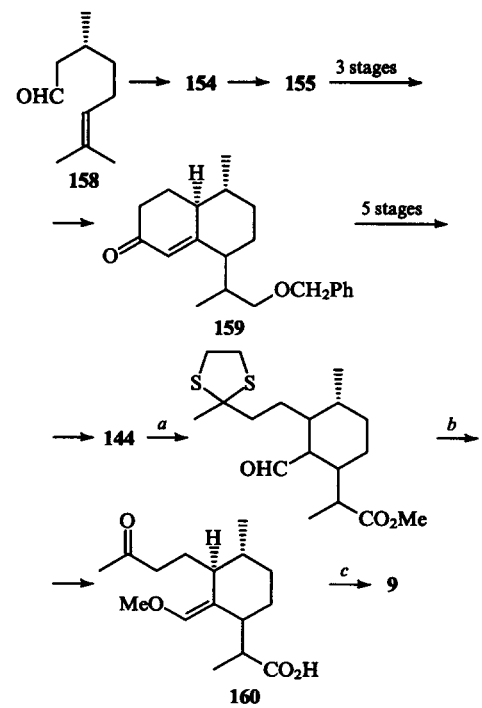
(*c*) Na–naphthalene, CH_3I; (*d*) O_2, *hv*, Bengal Rose, $HClO_4$.

The synthesis of artemisinin from more simple optically active precursors are multistep. For example, the use of isopulegol **154** entails its functionalisation to form 8-benzyloxymenthone **155** and the subsequent six-step conversion of the compound **155** into the oxo acid **156**. Photooxidation of the acid **156** in the presence of Methylene Blue gives the hydroperoxide **157**, which further cyclises into artemisinin.[109]



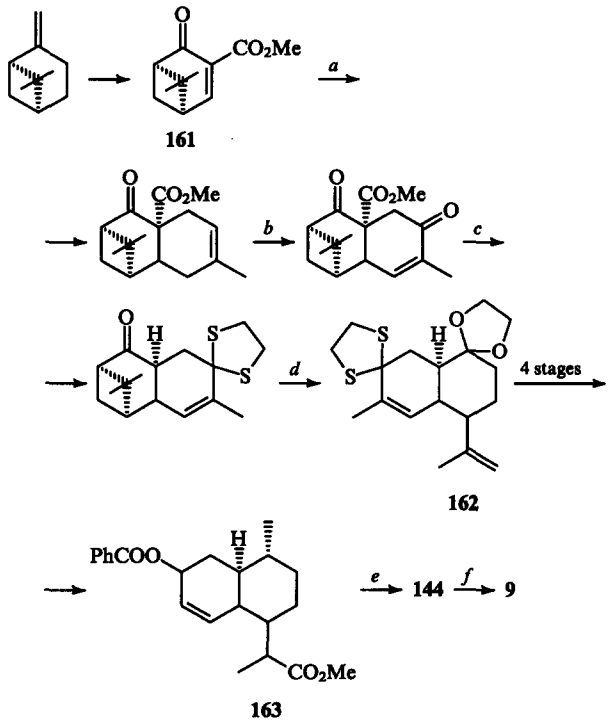
(*a*) O_2, *hv*, Methylene Blue; (*b*) HCO_2H, CH_2Cl_2.

The synthesis of artemisinin based on citronellal **158**, which is readily converted into isopulegol **154** and, further, into the ketone **155**, entails the annelation according to Robinson. The ketone **159** formed thereby is converted into dihydroartemisinic acid **144**, from which artemisinin is then obtained in three steps. Photooxidation of the artemisinin precursor, the compound **160**, was sensitised with Bengal Rose.[110]



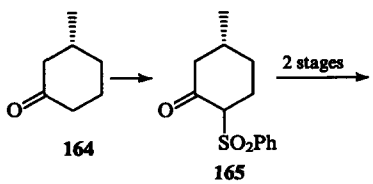
(*a*) O_3, Me_2S, $HS(CH_2)_2SH$, $BF_3 \cdot OEt_2$; (*b*) $HC(OMe)_3$, *p*-TsOH, $HgCl_2$; (*c*) O_2, *hv*, Bengal Rose, $HClO_4$.

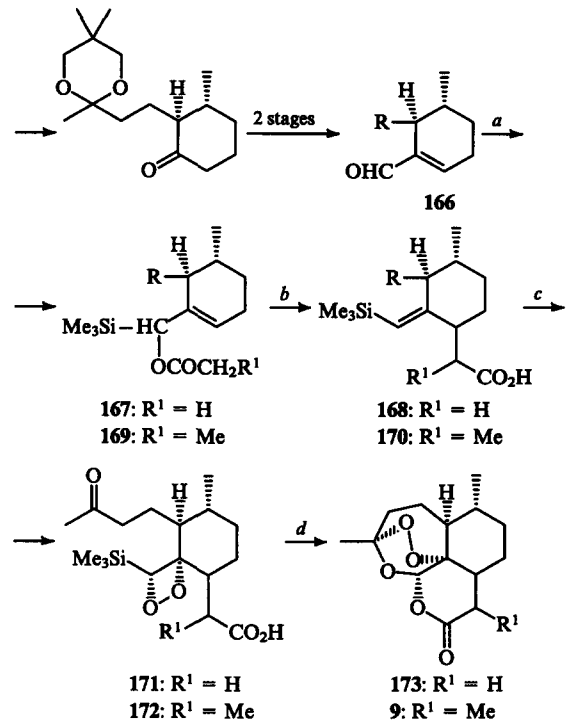
The synthesis of artemisinin based on the use of β-pinene is remarkable in that the specific rotation of the synthetic, optically active (+)-artemisinin did not practically differ from that of the natural sample.[111] The $ZnCl_2$-controlled interaction of dienophile **161** with isoprene, the scission of the picean bond resulting in the ketal **162**, and hydrogenolysis of the benzoyloxy group in the compound **163** by nickel boride giving the dihydroartemisinic acid **144**, are worth noting.



(*a*) $CH_2=CH-CMe=CH_2$, $ZnCl_2$; (*b*) O_2, *hv*, 5,10,15,20-tetraphenyl-21*H*,23*H*-porphyrin, Ac_2O, C_5H_5N, 4-dimethylaminopyridine; (*c*) $(CH_2SH)_2$, LiI, DMF; (*d*) $(CH_2OH)_2$, *p*-TsOH; (*e*) $NaBH_4$, $NiCl_2 \cdot 6H_2O$; (*f*) O_2, *hv*, Methylene Blue, CF_3CO_2H, O_2.

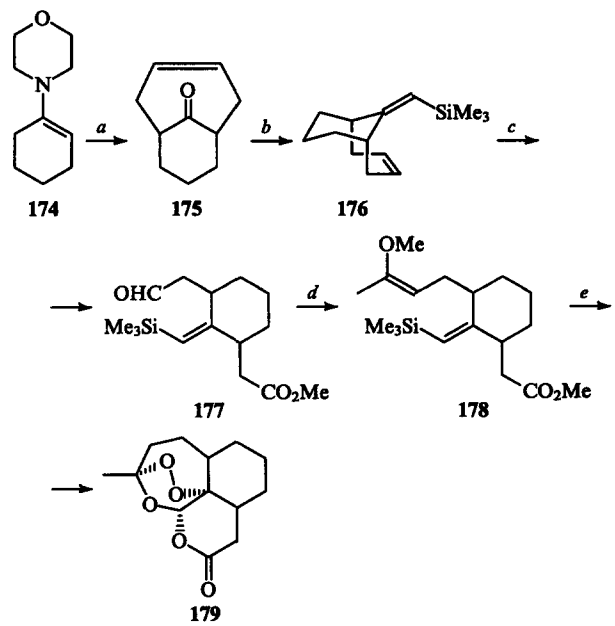
An approach based on the use of the optically active 3-methylcyclohexanone **164** is interesting in that the natural configuration on the C(10) atom in the artemisinin molecule is created initially.[112] The synthesis involves via the formation of the oxosulfoxide **165**, which is converted in several steps into the aldehyde **166**. This is followed by a remarkable transformation of the formyl group under the action of the organoaluminium reagent, $(Me_3Si)_3Al \cdot OEt_2$, with subsequent acetylation, resulting in the silyl acetate **167**. The Ireland rearrangement using lithium cyclohexylisopropylamide gives the unsaturated silane **168**. If the propionate **169** is employed instead of the acetate **167**, the rearrangement results in the silane **170**. Ozonisation of the compounds **168** and **170** occurs through the formation of the 1,2-dioxetanes **171** and **172**, which are further converted in the presence of CF_3CO_2H into demethylartemisinin **173** or artemisinin **9**.





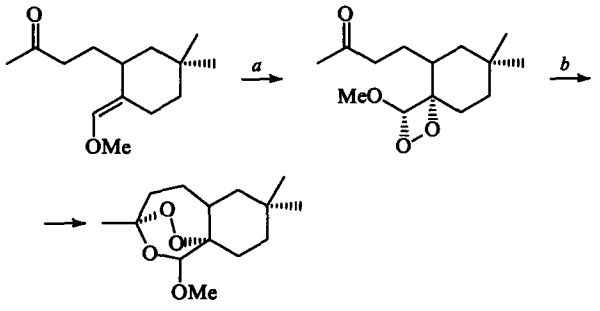
(*a*) $(Me_3Si)_3Al \cdot OEt_2$; (*b*) $C_6H_{11}Pr^iNLi$; (*c*) O_3, MeOH; (*d*) CF_3CO_2H, H_2O.

The total synthesis of 13,14-bisnorartemisinin **179** from non-chiral precursors begins with alkylation of the enamine **174** with (*Z*)-1,4-dichlorobutene.[113] This is followed by olefination of the ketone **175** to give silane **176** and ozonolysis of **176** to form the aldehydo ester **177**. This elegant synthesis is completed by olefination of the compound **177** and ozonolysis of the enolsilane **178**.



(*a*) *Z*-$ClCH_2CH=CHCH_2Cl$, H_2O; (*b*) $LiCH(SiMe_3)_2$; (*c*) O_3, Ac_2O, CH_2N_2; (*d*) $Ph_2P(O)=C(OMe)Me$; (*e*) O_3, CF_3CO_2H.

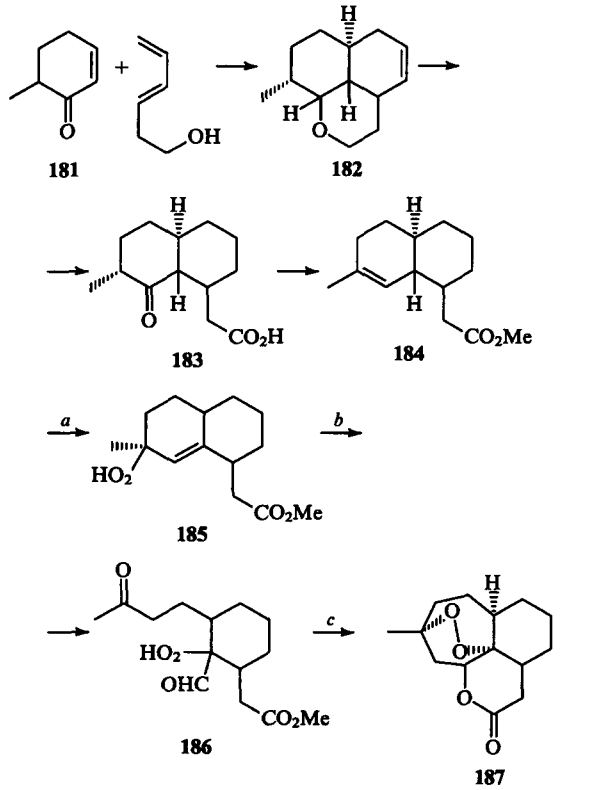
Singlet oxygen needed for the synthesis of dioxetans can be obtained from the hydrotrioxide, Et_3SiO_3H.[114] Thus, the synthesis of the model compound **180** exhibiting a high antimalarial activity is realised according to the following scheme:



180

(*a*) Et_3SiO_3H; (*b*) $CF_3SO_2SiMe_3$.

A structural analogue of artemisinin was synthesised on the basis of 6-methylcyclohex-2-enone **181**. The Diels–Alder synthesis of hexa-3,5-dien-1-ol with 6-methylcyclohex-2-enone gives the hemiketal **182**, whose oxidation and subsequent hydrogenation results in the oxo acid **183**. This is followed by the conversion of the acid **183** into the ester **184** and its photooxidation into the hydroperoxy ester **185** in the presence of Bengal Rose. The resulting ester **185** is subjected to oxidation in the presence of an iron–phenanthroline complex, $Fe(Phen)_3(PF_6)_3$, and copper triflate, resulting in the hydroperoxide **186** further cyclised in acid medium into the peroxylactone **187**.[115]

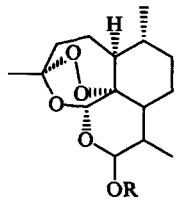


181 **182** **183** **184** **185** **186** **187**

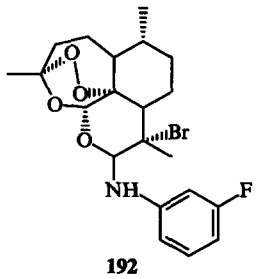
(*a*) O_2, *hv*, Bengal Rose; (*b*) O_2, $Fe(Phen)_3(PF_6)_3$, $(CF_3SO_3)_2Cu$; (*c*) *p*-TsOH.

The uniqueness of artemisinin as an antimalarial drug[116] posed the question as to the synthesis of artemisinin derivatives more active and convenient in application, of which dihydro esters and aminoacetals are becoming increasingly important. For example, the hydrogen succinate **188** in the form of sodium salt can be used for intravenous administration instead of the poorly water-soluble artemisinin.[117]

Prolonged activity was found in the glycoside **190**.[118] The esters **191**[119] and **192**[120] displayed a high activity against the plasmodia D-6 and W-2.



188–191

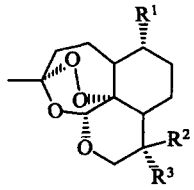


192

188: R = $CO(CH_2)_2CO_2Na$;
189: R = β-D-Glu(1→4)-β-D-Glu;
190: R = CH_2CO_2Me;
191: R = $CH_2C_6H_4CO_2Na$.

Among aminoacetals, the compound **192**[121] stands out as possessing a remarkably high activity.

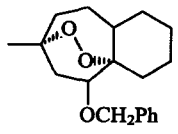
More than 70 artemisinin derivatives and analogues of the type **193** have been described;[122,123] 12-deoxoartemisinin (R^1 = Me, R^2 = R^3 = H) is very promising.



193

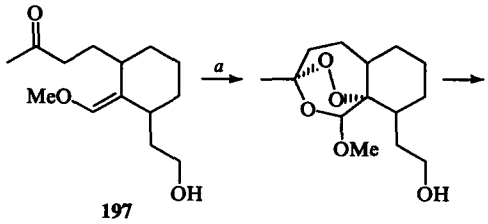
R^1 = H, Me;
R^2, R^3 = H, OMe, OCH_2Ph.

Extremely valuable artemisinin analogues have been synthesised. For example, the peroxyacetal **194** is not inferior to artemisinin as regards its activity towards *Plasmodium falciparum* (the Indo-Chinese clone W-2).[114]

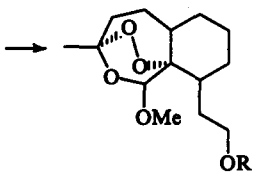


194

The ester **195** and the carbamate **196** obtained by photooxidation of the enol ester **197** or by its treatment with Et_3SiO_3H displayed, besides a high antiplasmodium activity, also a unique stability. These crystalline peroxides are now undergoing clinical trials.[124] It should be emphasised that the majority of artemisinin derivatives and analogues are active against those plasmodium clones that are resistant to potent antimalarial agents, such as plasmoquine.



197



195: R = $COC_6H_4CO_2Me$
196: R = $CONEt_2$.

(*a*) O_2, *hv*, Bengal Rose or Et_3SiO_3H.

The question of the activity of peroxy compounds against malarial pathogens is worth special discussion, since the search for antimalarial agents that can be obtained economically is a very urgent task. Structurally simple synthetic peroxides, which are promising as antiplasmodium agents, have been described.[125-131]

Recent publications deal with the synthesis of stable peroxides as promising drugs.[132-134] Terpene ozonides are the components of medicinal drugs endowed with antimicrobial and antiparasitic activities.[133]

* * *

The data presented herein attest to the fact that peroxy compounds are widely distributed in natural objects. Contrary to the earlier, common opinion about the lability of most natural peroxides, investigators encounter sufficiently stable substances more and more frequently. The literature data available on the biological activity of natural peroxides may be regarded as a pledge of future progress in the design of medicinal drugs and antipest agents in agroindustrial production. The example of artemisinin, where the investigations in the area of the chemistry of natural peroxides have acquired medical orientation, is very explicit. It is probable that in the near future the list of antiparasitic agents designed for clinical application will be supplemented with not only natural derivatives of artemisinin but also with synthetic peroxy compounds.

Attention should also be paid to such important properties of natural peroxides as their cytostatic, antitumour, and antimicrobial activity as well as the recently detected CNS activity.

Thus, the comprehensive bioassay of both natural and synthetic peroxy compounds is becoming a current problem.

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