Marine Endoperoxide Norterpenes

Subjects: Chemistry, Organic

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Organic extracts of marine invertebrates, mainly sponges, from seas all over the world are well known for their high in vitro anticancer and antibiotic activities which make them promising sources of compounds with potential use as pharmaceutical leads. Most of the structures discovered so far have a peculiar structural feature in common: a 1,2-dioxane ring. This is a highly reactive heterocycle that can be considered as an endoperoxide function. Together with other structural features, this group could be responsible for the strong biological activities of the substances present in the extracts. Numerous research programs have focused on their structural elucidation and total synthesis since the seventies. As a consequence, the number of established chiral centres and the similarity between different naturally occurring substances is increasingly higher. Most of these compounds have a terpenoid nature, mainly diterpene and sesterterpene, with several peculiar structural features, such as the loss of one carbon atom. Although there are many reviews dealing with the occurrence of marine peroxides, their activities, or potential pharmaceutical uses, no one has focused on those having a terpene origin and the endoperoxide function. We present here a comprehensive review of these compounds paying special attention to their structural features and their biological activity.

marine terpenoid endoperoxide norseterterpene

1. Introduction

Marine water covers a great proportion of the earth's surface and is proposed to contain a high percentage of the world's plant and animal species; although, ninety one percent of marine species remain undiscovered [1]. Organic extracts of these marine species often exhibit promising specialized biological activities, prompting the search for new marine metabolites [2]. Between these compounds, a huge number of peroxides have been isolated, mainly from marine invertebrates, particularly in sponges and soft corals.

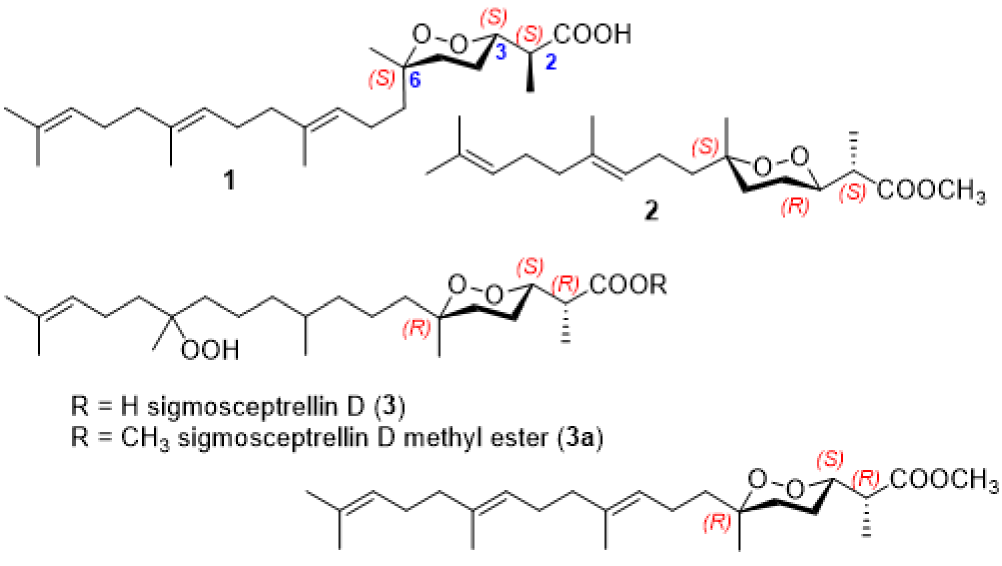
Numerous peroxides have shown confirmed activity in vitro against tumour cells and they are considered an important source of leads for drug discovery [3]. In fact, there are actually three approved marine drugs derived from sponges and several more have entered clinical trial [4]. On the other hand, terpenoids have a great chemical structural diversity and are also important secondary metabolites of marine species presenting diverse bioactivities [5].

This entry summarises marine endoperoxides of terpene origin and it is focused on their structure and the structural revision of newly-established stereochemistry, as well as in their biological activity. This entry is structured into two main sections: the first one summarises endoperoxides with a norterpene skeleton (norsesteterpenes and norditerpenes, principally) and the second one summarises endoperoxides with a terpene skeleton (sesquiterpenes and diterpenes). The first section is also subdivided for a better understanding, based on the type of cyclic skeleton. A final overview of all reported biological activities for these systems isalso included.

In all structural formulae, the stereocentres are depicted using the following convention: solid wedged bonds and hashed wedged bonds represent the known absolute configuration. In addition, *R* or *S* letters are written near the centre. When only the relative stereochemistry of the compound is known, it is represented with bold bonds and hashed bonds.

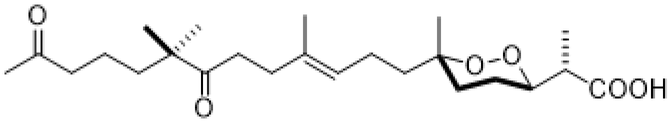
2. Marine Endoperoxide Norterpenes

2.1. Endoperoxide Norterpenes with an Acyclic Carbon Skeleton

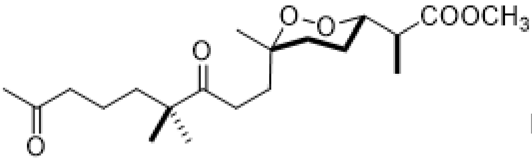


R = H sigmosceptrellin D (**3**)
R = CH_3 sigmosceptrellin D methyl ester (**3a**)

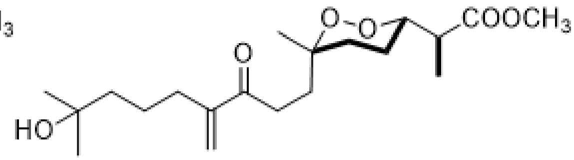
sigmosceptrellin E (**4**)



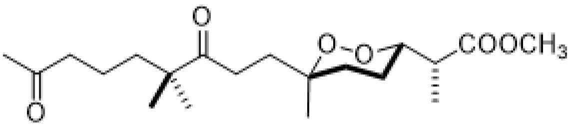
aikupikoxide A (**5**) or (+)-muqubilone



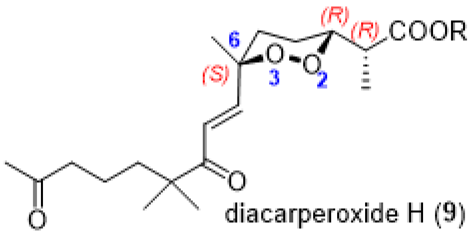
(+)-aikupikoxide C, (-)-diacarperoxide B (**6**)



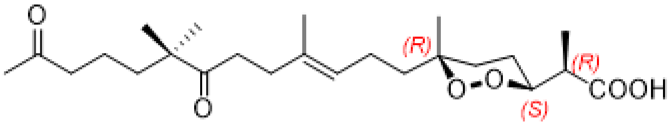
aikupikoxide D (**7**)



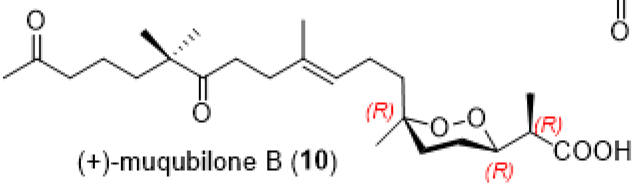
diacarperoxide C (**8**)



diacarperoxide H (**9**)

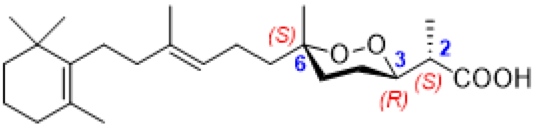


(-)-*ent*-muqubilone (**11**)

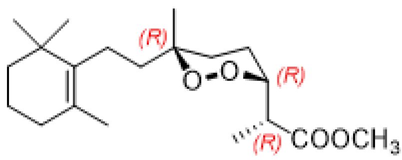


(+)-muqubilone B (**10**)

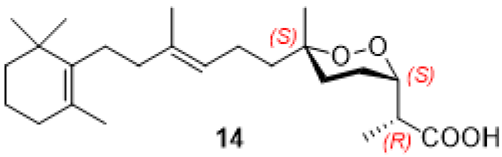
2.2. Endoperoxide Norterpenes with a Monocyclic Carbon Skeleton



muqubilin or prianicin A (**12**)



methyl nuapapuanoate or nuapapuin A (**13**)



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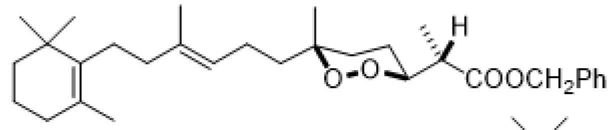
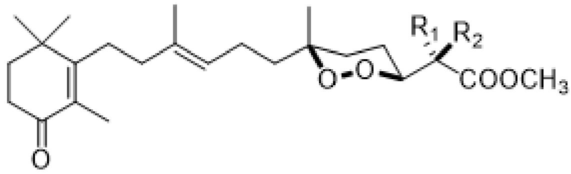
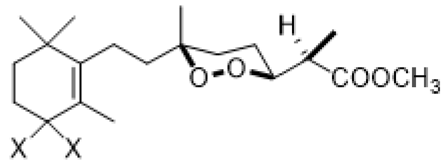


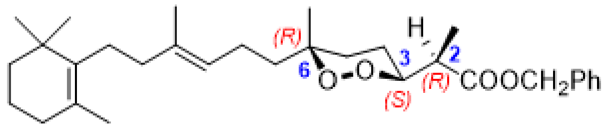
2-epimuqubilin benzyl ester (**15**)



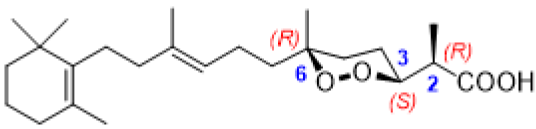
R_1= H R_2= CH_3 methyl prenyldiacarnoate A (**16**)
R_1= CH_3 R_2= H methyl 2-epiprenyldiacarnoate A (**17**)



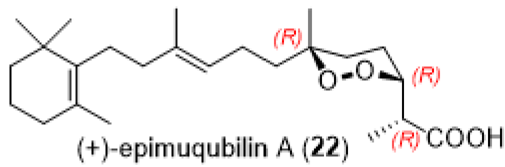
methyl 2-epinuapapuanoate (**18**) X=H
methyl diacarnoate A (**19**) X,X=O



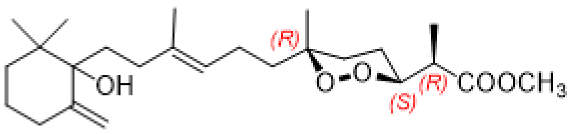
ent-muqubilin benzyl ester (**20**)



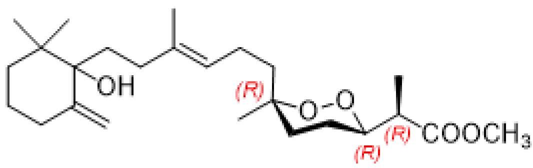
(-)-muqubilin or muqubilin A (**21**)



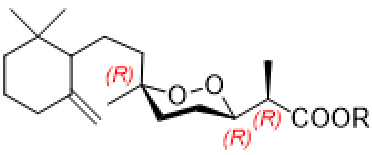
(+)-epimuqubilin A (**22**)



muqubilin B (**23**)

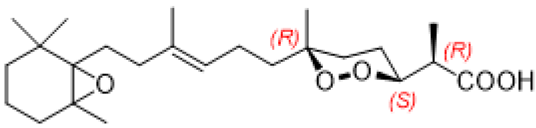


epimuqubilin B (**24**)

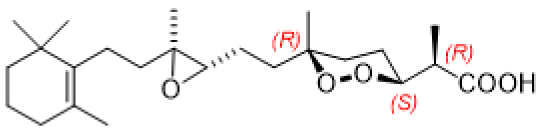


R = H nuapapuin B (**25**)
R = CH_3 nuapapuin B methyl ester (**25a**)

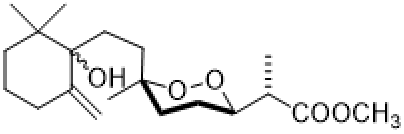
epinuapapuin B (**26**)



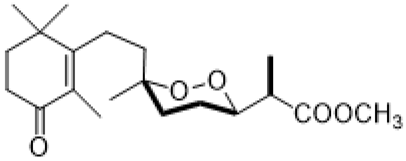
(-)-13,14-epoxymuqubilin A (**27**)



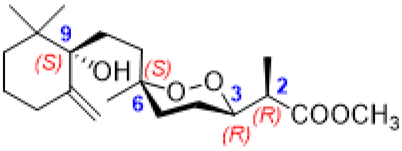
(-)-9,10-epoxymuqubilin A (**28**)



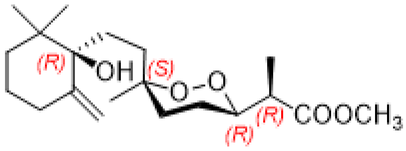
aikupikoxide B (**29**)



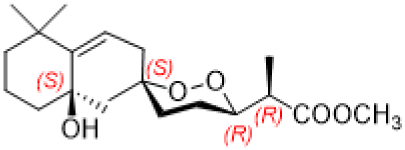
diacarperoxide A (**30**)



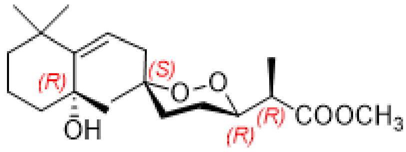
diacarperoxide I (**31**)



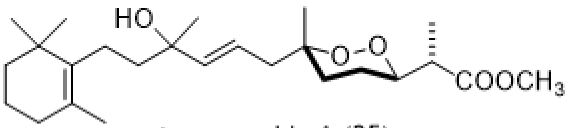
diacarperoxide J (**32**)



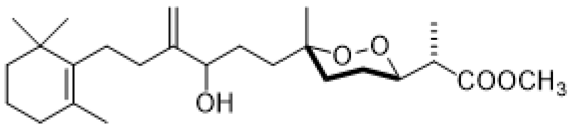
diacarperoxide K (**33**)



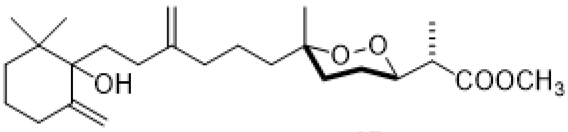
diacarperoxide L (**34**)



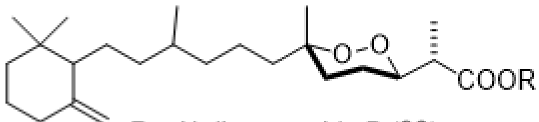
tasnemoxide A (**35**)



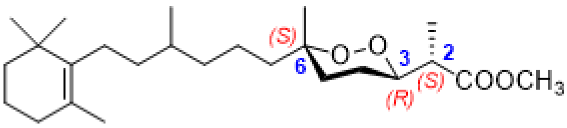
tasnemoxide B (**36**)



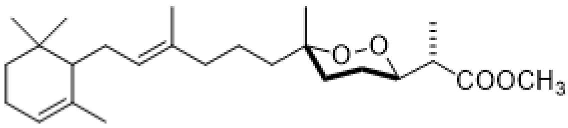
tasnemoxide C (**37**)



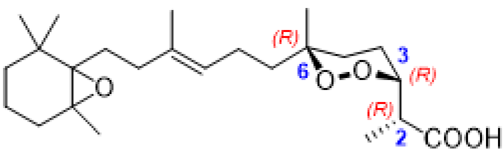
R = H diacarnoxide B (**38**)
R = CH_3 diacarnoxide A (**38a**)



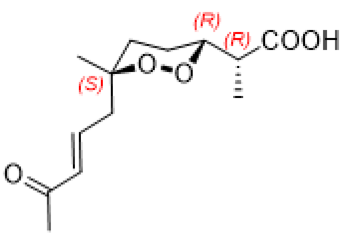
diacarnoxide C (**39**)



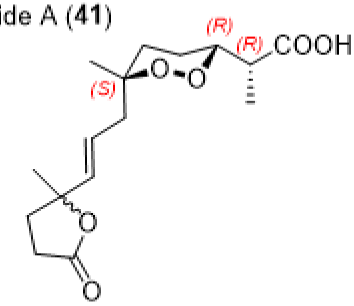
diacarnoxide D (**40**)



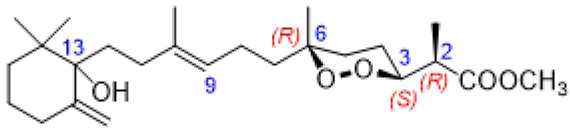
negombatoperoxide A (**41**)



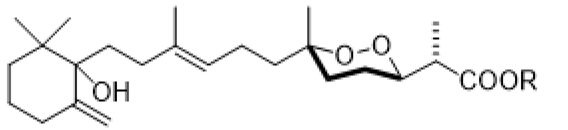
negombatoperoxide B (**42**)



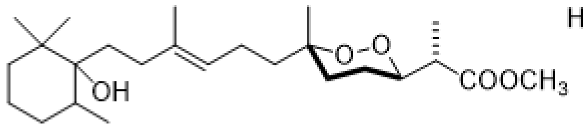
negombatoperoxides C/D (**43**)



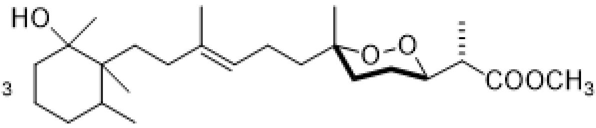
hurghaperoxide (**44**)



R = H (+)-2,3,6-epihurghaperoxide acid (**45**)
R = CH_3 (+)-2,3,6-epihurghaperoxide (**45a**)

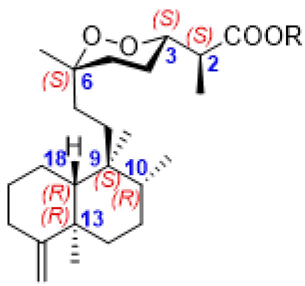


diacarnuperoxide M (**46**)

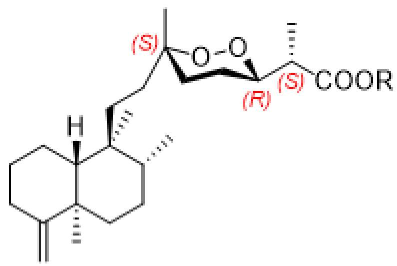


diacarnuperoxide N (**47**)

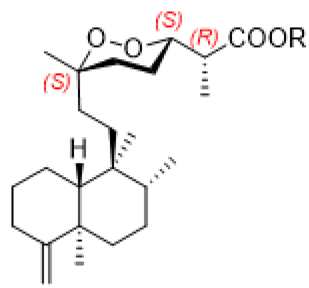
2.3. Endoperoxide Norterpenes with a Bicyclic Carbon Skeleton



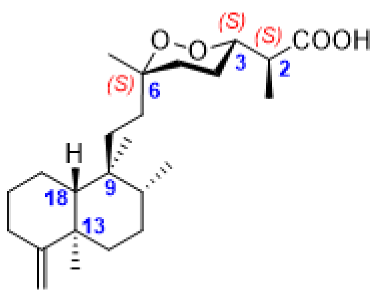
R= H sigmosceptrellin A
R= CH_3 sigmosceptrellin A methyl ester



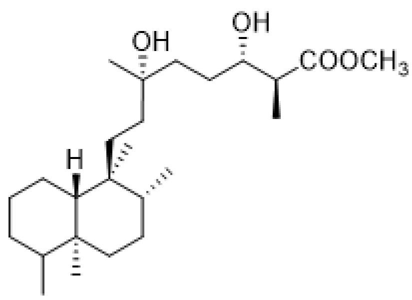
R= H sigmosceptrellin B
R= CH_3 sigmosceptrellin B methyl ester



R= H sigmosceptrellin C
R= CH_3 sigmosceptrellin C methyl ester



sigmosceptrellin A enantiomer (**48**)



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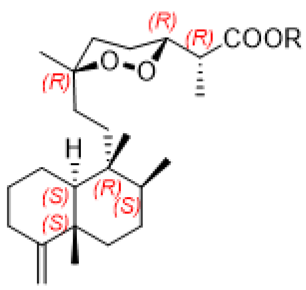
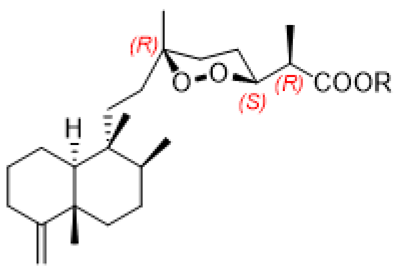
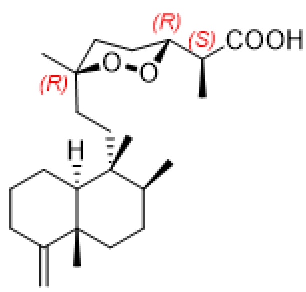


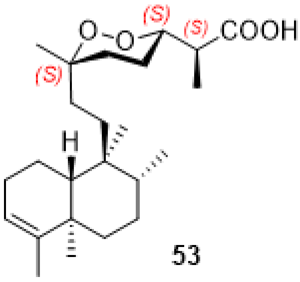
R= H sigmosceptrellin A (**50**)
R= CH_3 sigmosceptrellin A methyl ester (**50a**)



R= H sigmosceptrellin B (**51**)
R= CH_3 sigmosceptrellin B methyl ester (**51a**)



sigmosceptrellin C (**52**)



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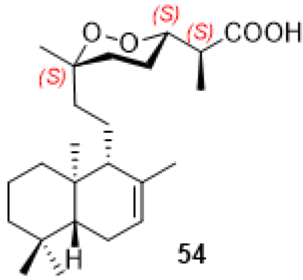

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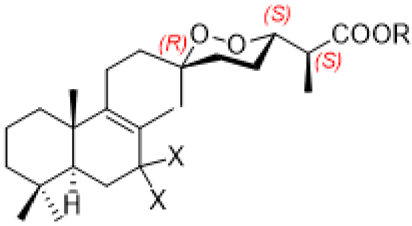
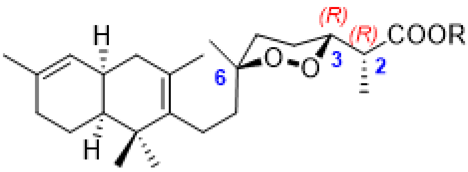
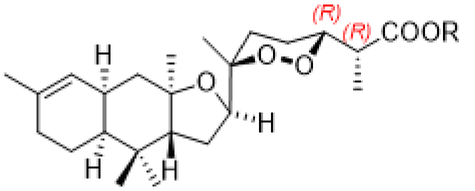


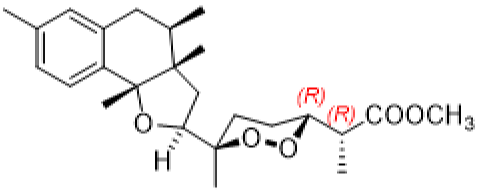
deoxydiacarnoate B benzyl ester (**55**) R= CH_2Ph, X= H
diacarnoate B methyl ester (**56**) R= Me, X,X= O



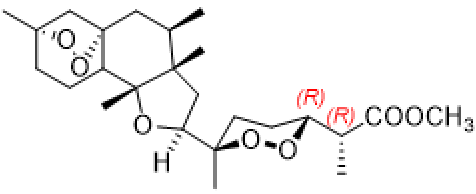
R = H trunculin A (**57**)
R = CH_3 trunculin A methyl ester (**57a**)



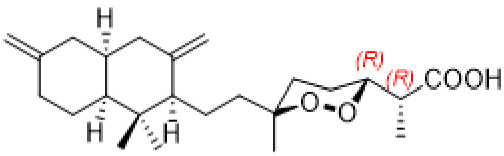
R =H trunculin B (**58**)
R = CH_3 trunculin B methyl ester (**58a**)



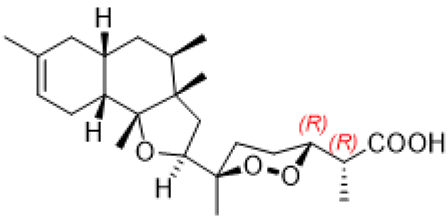
trunculin C (**59**)



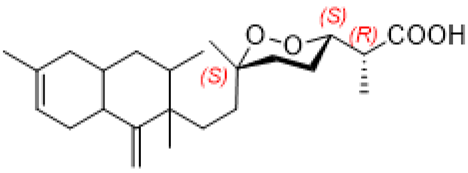
trunculin D (**60**)



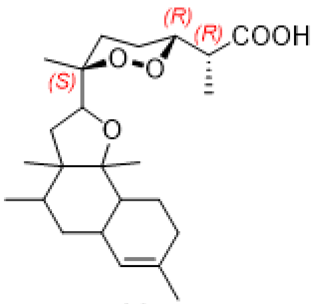
trunculin E (**61**)



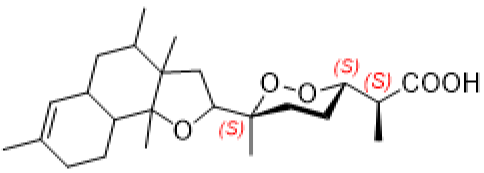
trunculin F (**62**)



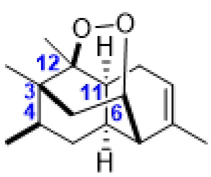
trunculin G (**63**)



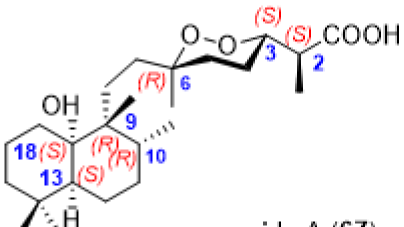
trunculin H (**64**)



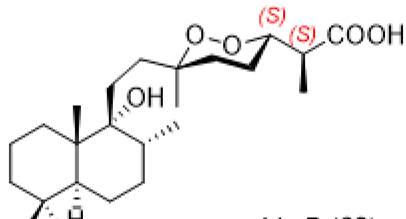
trunculin I (**65**)



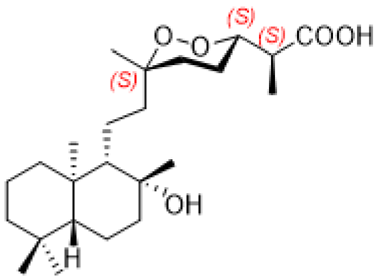
contrunculin B (**66**)



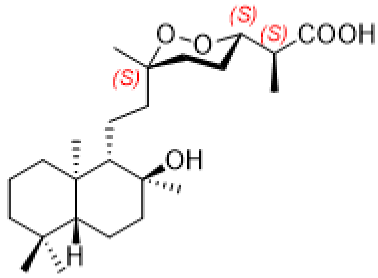
mycaperoxide A (**67**)



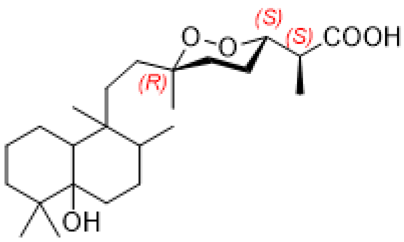
mycaperoxide B (**68**)



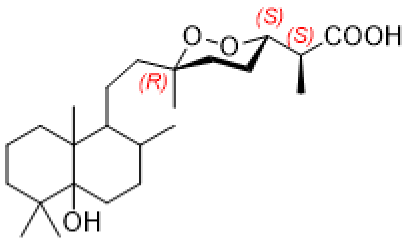
mycaperoxide C (**69**)



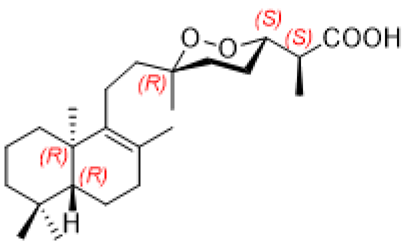
mycaperoxide D (**70**)



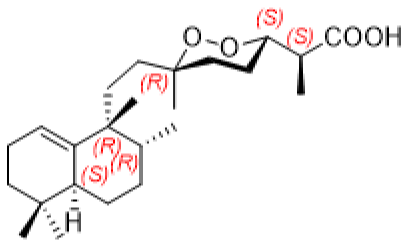
mycaperoxide E (**71**)



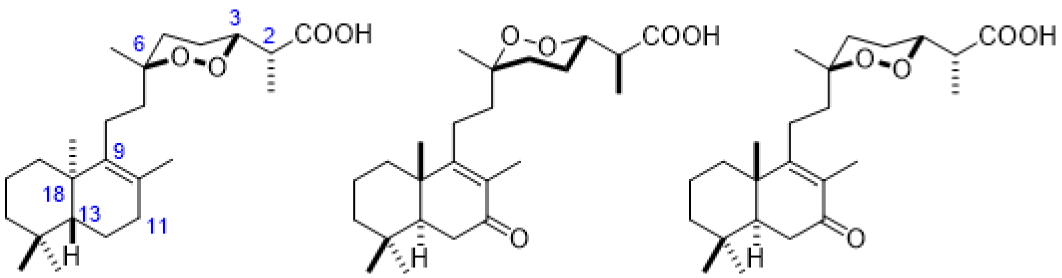
mycaperoxide F(**72**)



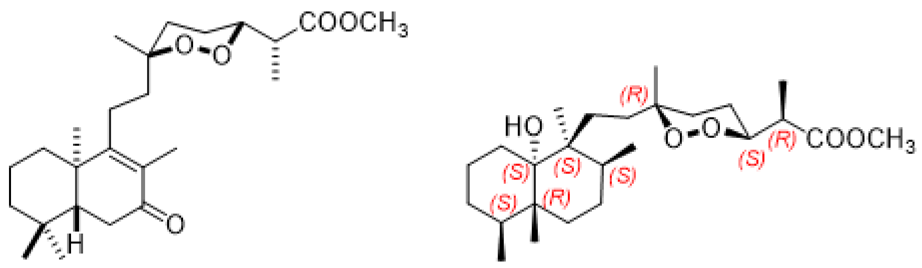
mycaperoxide G (**73**)



mycaperoxide H (**74**)



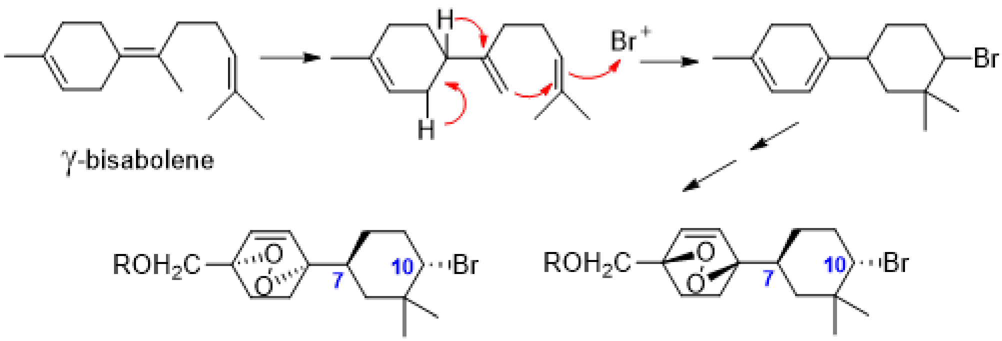
diacaperoxide D (**75**) diacaperoxide E (**76**) diacaperoxide F (**77**)



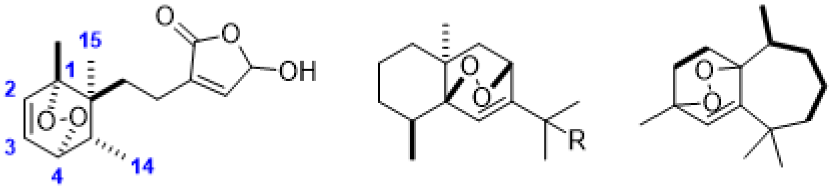
diacaperoxide G (**78**) diacaperoxide S or megaspinoxide A (**79**)

3. Marine Endoperoxide Terpenes

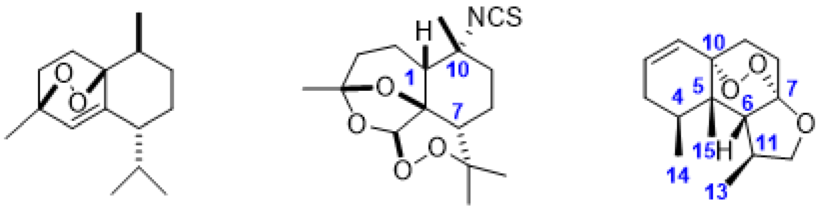
3.1. Endoperoxide Sesquiterpenes



R = H majapolene A (**80**)
R = Ac acetylmajapolene A (**81**)

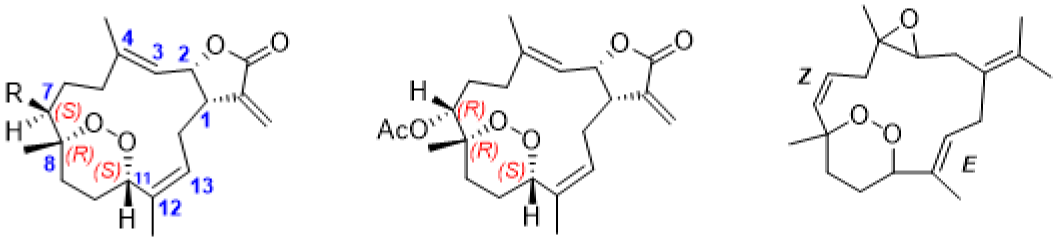


lingshuiperoxide (**82**) **83** R = OH **84** R = OOH **85**

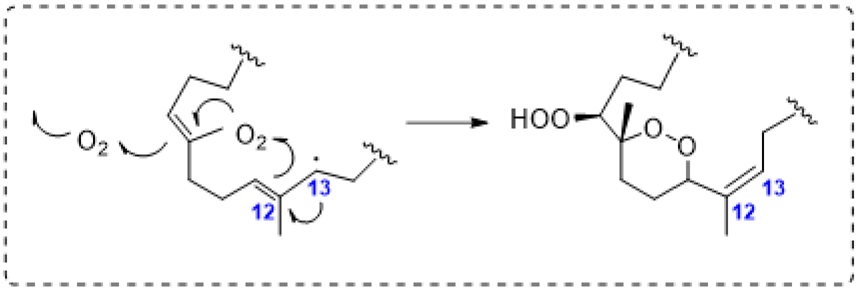


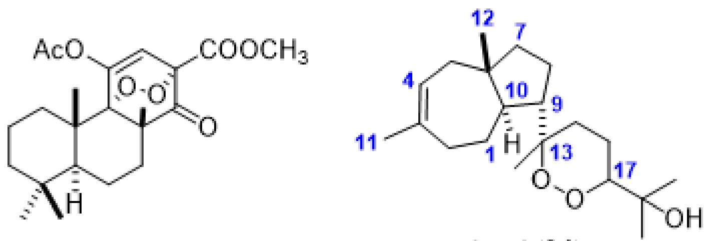
86 halichon B (**87**) xishaflavalin B (**88**)

3.2. Endoperoxide Diterpenes



R = OAc denticulatolide (**89**)
R = OCO_6H_4Br (**90**)
7-epidenticulatolide (**91**)
92





aplypallidioxone (**93**) peroxypolasol (**94**)

4. Biological Activity Overview

So far, more than 90 marine terpenic endoperoxides have been described, the vast majority being norsesterterpenes (59 compounds) and norditerpenes (17 compounds). Other terpenoids with an endoperoxidic moiety have also been isolated, although these are less frequent, like those having a sesqui- or diterpene structure (14 compounds).

There are many reports on the biological activity, possibly stimulated by the attractive endoperoxide moiety present in these substances. The studies have mainly focused on their activity against microorganisms, such as bacteria, yeasts, or viruses, as well as against protozoa that cause diseases, especially *Plasmodium*, which causes malaria, or *Trypanosoma* (**Table 1**). In addition, measurements of in vitro activity against different tumour cell lines are well documented (see table 1 for references). To a lesser extent, the anti-inflammatory activity has also been measured.

Both norsterterpenes and norditerpenes exhibit a remarkable range of bioactivities, although the number of studies with the first type is superior, possibly due to the fact that norsesterterpenes are more abundant. In all cases, the bioactive compounds are the free carboxylic acids, although sometimes natural methyl esters have been isolated. For example, although the acids **57** and **58** show activity against the bacteria and yeasts tested, their corresponding methyl esters, **57a** and **58a**, are inactive [6].

It is interesting to notice that the presence of the free acid form of these metabolites and the configuration of the methyl group in C6, may be critical for their growth of inhibitory activity in various cancer cell lines in vitro [7][8]. In the case of the NO inhibition related to inflammatory processes, both the presence of a free carboxylic acid and an equatorial orientation of the methyl group attached to C6 are critical for increased activity [9].

Of all the isolated compounds, the most tested and the one with the greatest range of activities is (+)-muqubilin (**12**) and its enantiomer **21**. This compound is active against *Plasmodium*, and this is the reason why it has been used as a prototype for the development of new antimalarial agents [10][11]. In addition, it is effective against *Troxoplasma gondii*. Moderate activity against the *Nicotiana tabacum* plant has also been described, as a result of a program devoted to the search of natural marine products as prototypes for agrochemical agents [12].

Finally, it is also worth mentioning that diterpene **89** and the acid fraction of *Sigmosceptrella laevis*, from which **50**, **51**, and **52** were isolated, also have ichthyotoxic properties as a defence method against predators [13].

Table 1. Biological activities of marine terpene endoperoxides.

Target	Norsesterterpenes			Norditerpenes [d]	Sesqui- and Diterpenes [e]
	Acyclics [a]	Monocyclics [b]	Bicyclics [c]		
Bacteria	**1** [14], **3a** [15], **4** [15]	**12** [16]	**57** [6], **58** [6], **61** [17], **67** [18], **68** [18], **79** [19]		**80** [20], **81** [20], **84** [21], **86** [22]
Yeasts	**1** [14]	**12** [16]	**57** [6], **58** [6], **61** [17], **79** [19]		

Target	Norsesterterpenes			Norditerpenes [d]	Sesqui- and Diterpenes [e]
	Acyclics [a]	Monocyclics [b]	Bicyclics [c]		
Viruses	**5** [23]	**12** [23]	**67** [18], **68** [18]		
Plasmodia		**12** [11], **15** [11][24], **20** [11][24], **21** [25], **45** [25], **45a** [25], **46** [25], **47** [25]	**50** [10], **55** [24]	**8** [11][24], **9** [26], **13** [25], **19** [11][24], **30** [25], **31** [26], **32** [26]	
Trypanosoma	**10** [27], **11** [27]	**22** [27]	**50** [27], **50a** [27], **51** [27]	**26** [27]	
Toxoplasma		**12** [23]	**51** [23]		
Inflammation		**22** [9][28]			**86** [22], **89** [29][30][31][32]
Citotoxicity	**5** [33][7]	**15** [34], **16** [34], **17** [34], **21** [8], **38** [35]	**50** [9], **51** [7], **51a** [7], **67** [18], **68** [18], **74** [36], **75** [37], **76** [37], **77** [37], **78** [37], **79** [19]	**6** [33], **7** [33], **13** [38], **18** [7], **25** [39]	**80** [40], **83** [21], **84** [41][21], **86** [22][42], **89** [13][43][29][30][31]

[a] 6 described structures, 6 bioactive. [b] 22 described structures, 11 bioactive. [c] 31 described structures, 14 bioactive. [d] 17 described structures, 12 bioactive. [e] 14 described structures, 6 bioactive.

a) 6 described structures, 6 bioactive. b) 22 described structures, 11 bioactive. c) 31 described structures, 14 bioactive. d) 17 described structures, 12 bioactive. e) 14 described structures, 6 bioactive.

5. Conclusions

Marine macro- and microorganisms, especially algae, soft corals, sponges and fungi, have a metabolism that produces a great diversity of bioactive compounds, many of them unparalleled in the terrestrial environment. The composition of many species of sponges from tropical and temperate waters has been investigated, with a wide diversity of compounds found in their extracts. Among them, a group of substances stands out: those with a norterpene skeleton, that is, terpenoids that have one carbon atom less than what would be produced through an ordinary biosynthesis, and that additionally incorporate an endoperoxide function. These substances not only have structures of moderate complexity, but they also present numerous asymmetric centres. The structural identification of these compounds is very complex, especially from the point of view of the stereochemical assignment of the chiral centres, that has required the development of remarkable special techniques. The group of substances presented in this review, originating from marine invertebrates, such as sponges, is exceptional due to the range of potential pharmacological applications. The antitumor activity of some of these substances stands out, some of which are capable of inhibiting the tumour cell growth in in vitro cultures at concentrations between 10 and 100 μg/mL. It is certainly a very promising field of research that will continue to provide exceptional developments in the near future.

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