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## The Bioactive Natural Products and Biological Activities of the Red Sea Soft Coral *Sarcophyton*: A Review.

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### ABSTRACT

Marine natural products are diverse in terms of chemical structures as well as biological activities. Soft corals are marine invertebrates possessing a vast range of terpenoid metabolites. These terpenes, mostly cembranoids, represent the main chemical defense for coral against natural predators. Soft corals of the genus *Sarcophyton* (family Alcyoniidae) are particularly rich in cembranoids diterpenes, Triterpenoids, Tetraterpenoids, Ceramide and Cerebrosides. Cembranoids contain a 14-membered macro cyclic skeleton and exhibit a wide range of biological activities including anti-tumor, neuro-protective, antimicrobial, calcium-antagonistic, and anti-inflammatory activity. The cembranoid diterpene sarcophine has been investigated since 1998 for its potential as a chemo-preventive agent, cytotoxic agent, anti-microbial agent, competitive cholinesterase inhibitor, noncompetitive phosphofructokinase inhibitor, and a Na<sup>+</sup>, K<sup>+</sup>-ATPase inhibitor.

**Keywords:** *Sarcophyton*, Soft coral, Terpenoids, Antitumor, Neuro-protective, Antimicrobial, Anti-inflammatory

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## INTRODUCTION

The marine environment may contain over 80% of world's plant and animal species [1]. Marine natural products are diverse in terms of chemical structures as well as biological activities. In recent years, many bioactive compounds have been extracted from various marine animals like tunicates, sponges, soft corals, sea hares, nudibranchs, bryozoans, sea slugs and marine organisms [2, 3]. Indeed of the 180 soft corals species identified world-wide, approximately 40% are native to the Red Sea [4]. The search for new metabolites from marine organisms has resulted in the isolation of more or less 10,000 metabolites [5], many of which are endowed with pharmacodynamic properties.

The knowledge of the physiological and biochemical features of marine organisms might contribute to the identification of natural products of biomedical importance. Insulin from fish such as cod exerts the same hormonal activity in mammals as does homologous insulin and insulin from tuna (which has a 40% difference in amino acid residue) that has been used to treat diabetic patients [6-8]. There is little doubt that marine biodiversity is a source of chemical and structural diversity. However, of over 14 000 compounds described [9], many of which display potent biological activity and have been utilized as bio-medical leads, few have proceeded to become approved pharmaceutical drugs [10, 11].

Compounds isolated from the marine environment are extraordinary for their complexity and connectivity, with substantial incorporation of heteroatom and halogen functionality. Faulkner suggested that marine organisms possess a greater prevalence of bioactive metabolites than do terrestrial organisms [12].

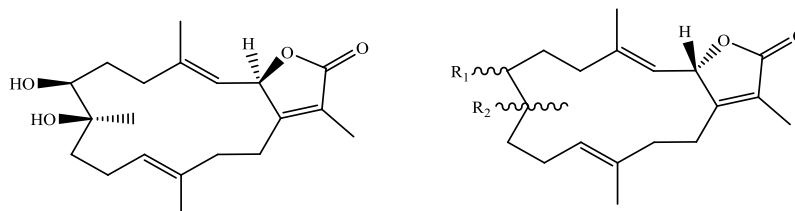
Secondary metabolites isolated from soft corals of the genus *Sarcophyton* are particularly rich in cembranoids diterpenes, Triterpenoids, Tetraterpenoids, Ceramide and Cerebrosides [14]. Published reviews clearly indicate the tremendous potential of taxonomically diverse marine possessing a wide range of pharmacological activities including antitumour, antibacterial, anti-inflammatory, antifungal and antiviral activities [10, 11, 13].

## CHEMICAL CONSTITUENTS OF SARCOPHYTON

Marine natural products are diverse in terms of chemical structures as well as biological activities. The Red Sea serves as an epicenter for marine bio-diversity with a high endemic biota. Indeed of the 180 soft corals species identified world-wide, approximately 40% are native to the Red Sea [4]. Soft corals are marine invertebrates possessing a vast range of terpenoid metabolites. These terpenes, mostly cembranoids, represent the main chemical defense for coral against natural predators [15]. Soft corals of the genus *Sarcophyton* (family Alcyoniidae) are particularly rich in cembranoids diterpene [16-31],[40], Lobane diterpenes [20], Triterpenes [22, 41, 42], Tetraterpenoids [22, 44, 33], Ceramide and Cerebrosides [41-47], [48].

### Diterpenes isolated from *Sarcophyton*

#### a- Cembranoids Diterpene



**1a**  $R_1 = 7\beta\text{-OH}$ ,  $R_2 = 8\alpha\text{-OH}$

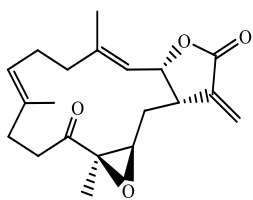
**2**  $R_1 = 7\alpha\text{-OH}$ ,  $R_2 = 8\beta\text{-OH}$

**3**  $R_1 = 7\beta\text{-OAc}$ ,  $R_2 = 8\alpha\text{-OH}$

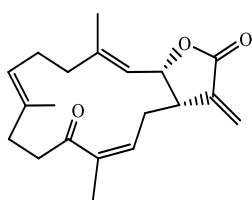
2*R*,7*R*,8*R*-dihydroxydeepoxy  
sarcophine (**1**) [16]

7 $\alpha$ ,8 $\beta$ -dihydroxy-deepoxy  
sarcophine (**2**) [16]

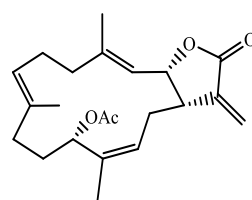
7 $\beta$ -acetoxy-8 $\alpha$ -hydroxydeepoxy  
sarcophine (**3**) [16]



1

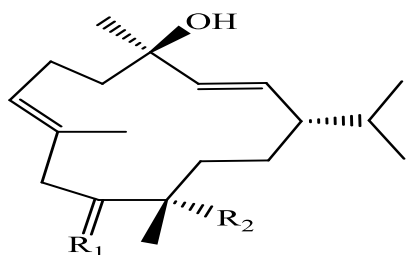


2



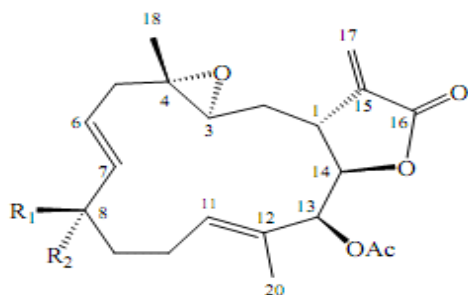
3

Cembranoids crassocolides N-P (1-3) [17]

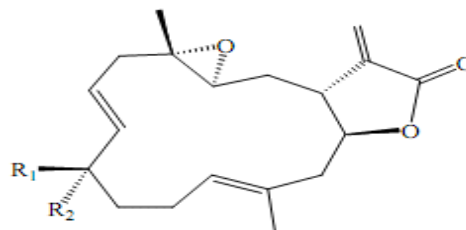


- 1- R<sub>1</sub> = O R<sub>2</sub> = CH<sub>2</sub>OH
- 2- R<sub>1</sub> = O R<sub>2</sub> = CH<sub>2</sub>OAc
- 3- R<sub>1</sub> = β-OAc R<sub>2</sub> = CHO

Sarcotol (1), sarcotol acetate (2), and sarcotol acetate (3) [18]

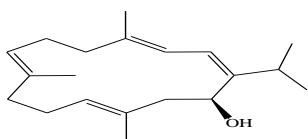


- 1: R<sub>1</sub>=CH<sub>3</sub> R<sub>2</sub>=OOH
- 2: R<sub>1</sub>=OOH R<sub>2</sub>=CH<sub>3</sub>
- 3: R<sub>1</sub>=CH<sub>3</sub> R<sub>2</sub>=OH
- 4: R<sub>1</sub>=OH R<sub>2</sub>=CH<sub>3</sub>

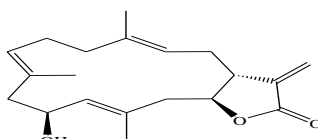


- 5: R<sub>1</sub>=CH<sub>3</sub> R<sub>2</sub>=OOH
- 6: R<sub>1</sub>=CH<sub>3</sub> R<sub>2</sub>=OH
- 7: R<sub>1</sub>=OH R<sub>2</sub>=CH<sub>3</sub>

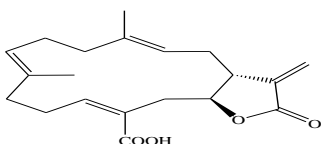
Cembranoids, sarcocrassocolides F-L (1-7) [19]



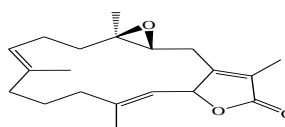
(+)-sarcophytol-A [20]



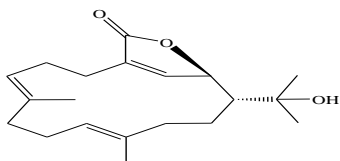
crassumolide A [20]



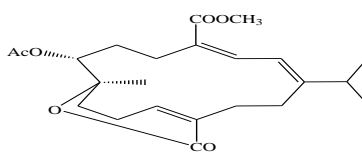
crassumolide [21]



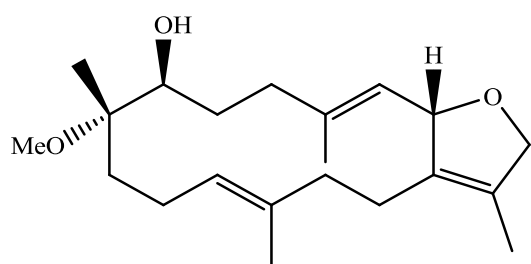
Sarcophytolide [21]



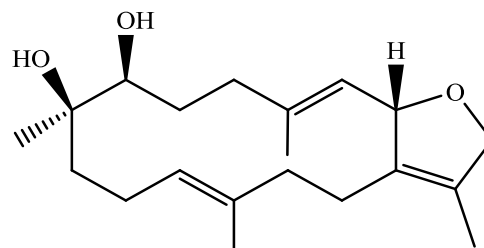
brassicolide [22]



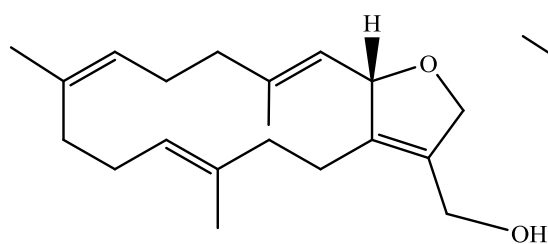
embilide [22]



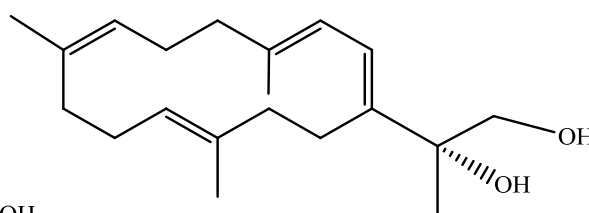
(-)-7 $\beta$ -hydroxy-8 $\alpha$ -methoxydeepoxy sarcophytoxide [23]



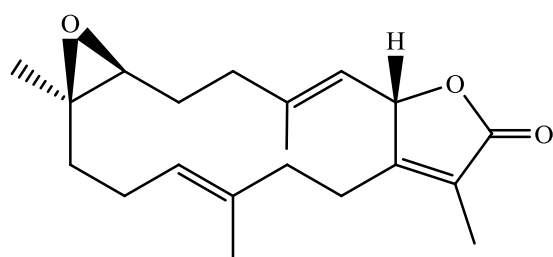
(+)-7 $\beta$ , 8 $\beta$ -dihydroxydeepoxy sarcophytoxide [23]



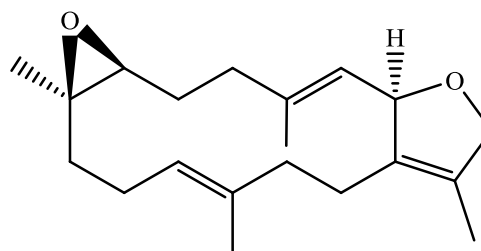
(-)-17-hydroxysarcophytonin A [23]



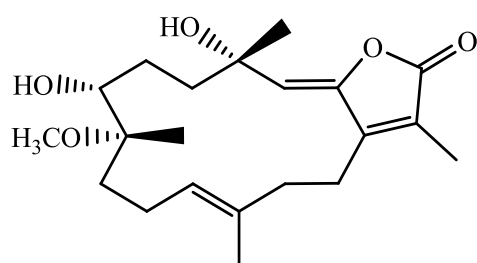
(-)-17-hydroxysarcophytol V [23]



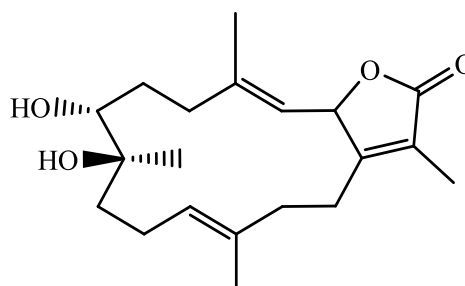
(+)-Sarcophine [23]



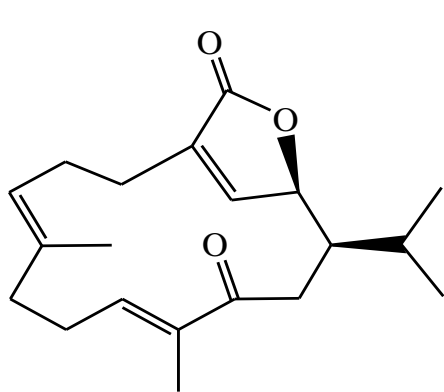
Sarcophytoxide [23]



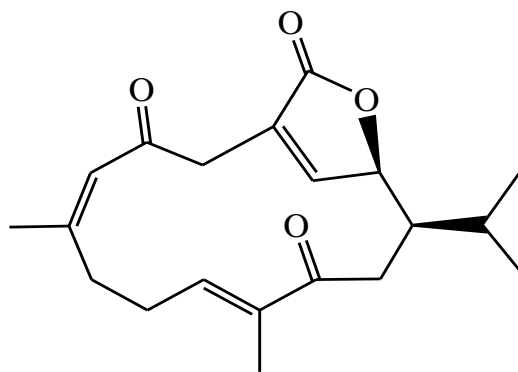
Sarcophylide A [24]



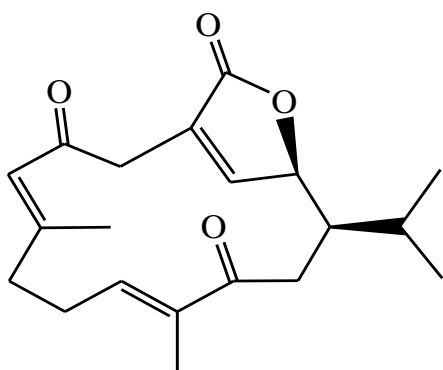
7 $\alpha$ , 8 $\beta$ -dihydroxydeepoxysarcophine [24]



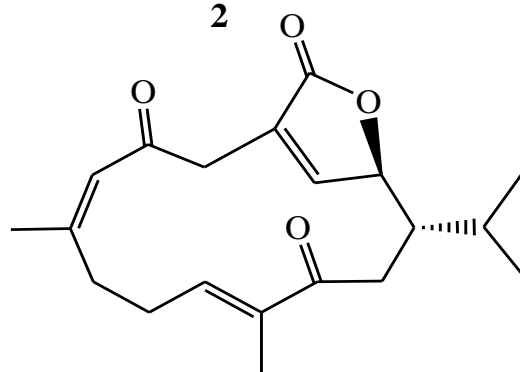
1



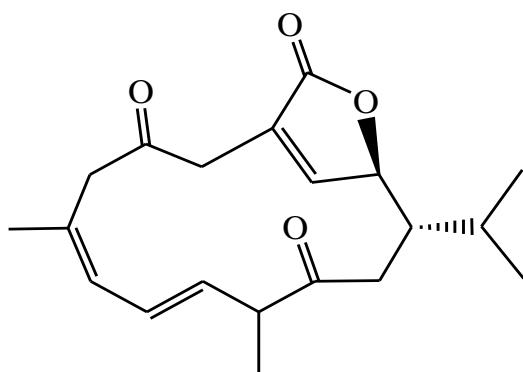
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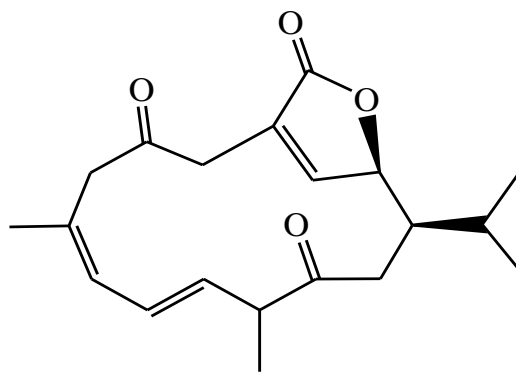
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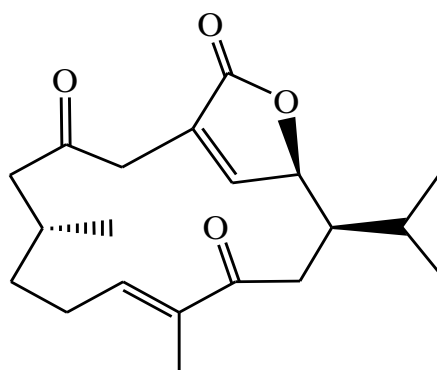
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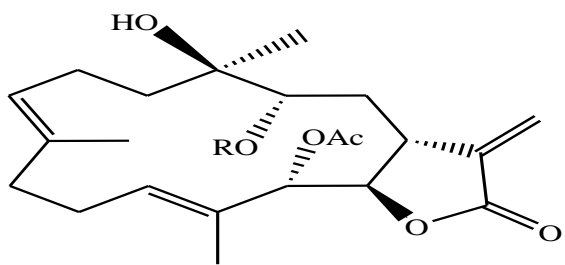


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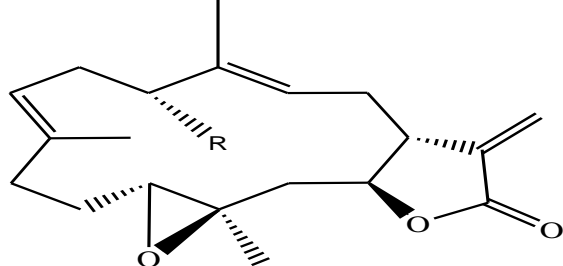


7

Sarcostolides A-G(1-7) [25]

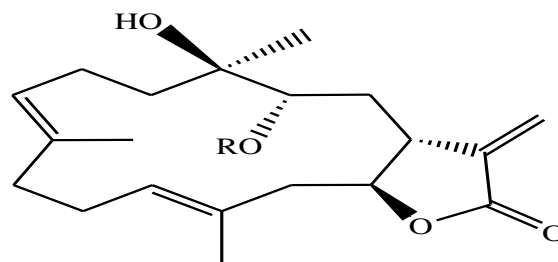


R = H  
R = Ac

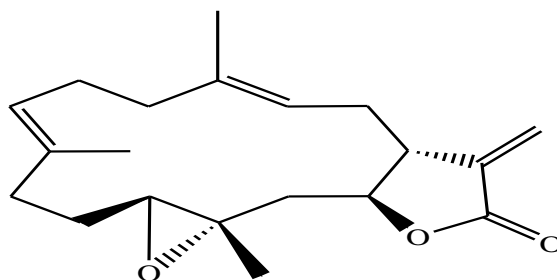


R = H  
R = OAc

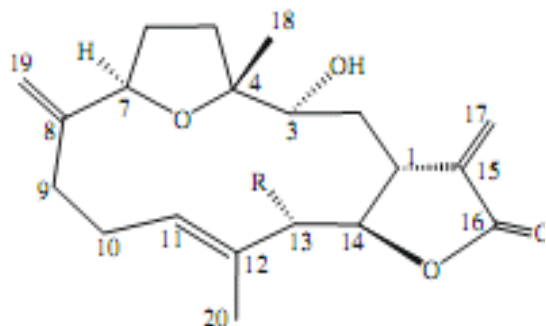
Crassocolides A-F [26]



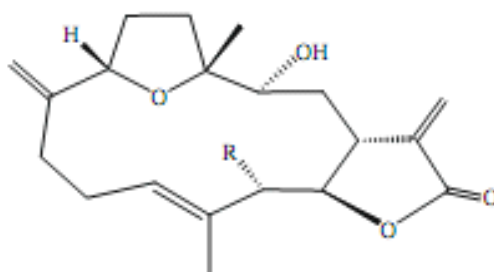
R = H  
R = Ac



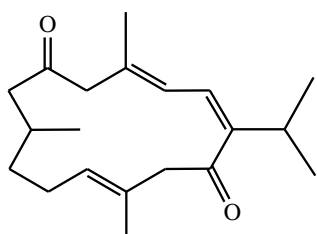
Lobophytolide [26]



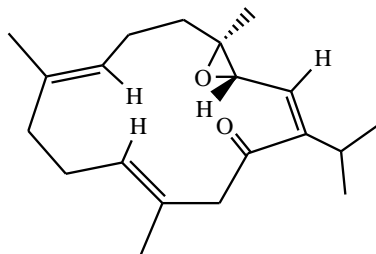
Sarcocrassocolides A-D (1-4) [32]



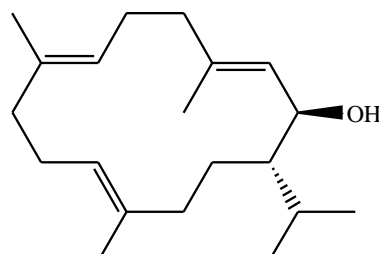
1 R =  
OAc  
2 R  
= H  
4 R = H



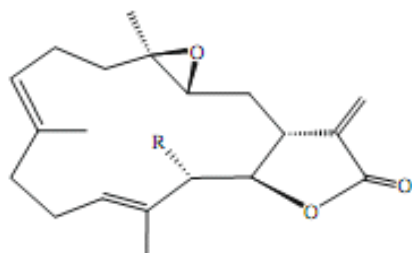
Flexusines A [27-29]



Flexusines B [27-29]



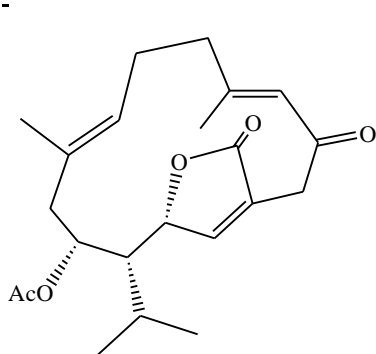
Epimukulol [27-29]



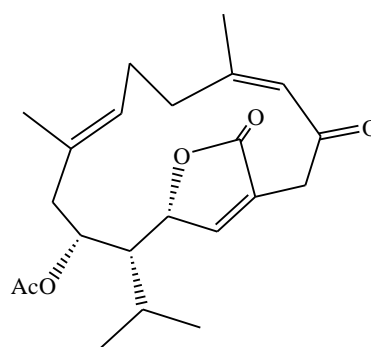
- 1 R = OCOEt
- 2 R = H
- 3 R = OH
- 4 R = OAc

Sarcocrassolides E (1) [32]

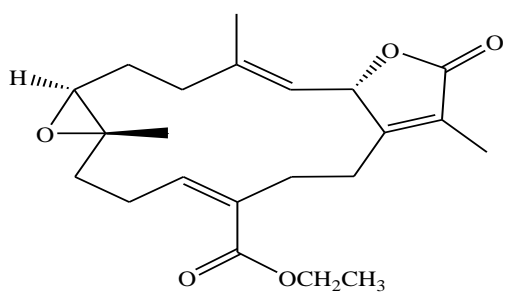
Sarcocrassolide (2), sinularolide (3) and 13-acetoxysarcocrassolide (4) [32].



Isosarcophytonolide D [33]

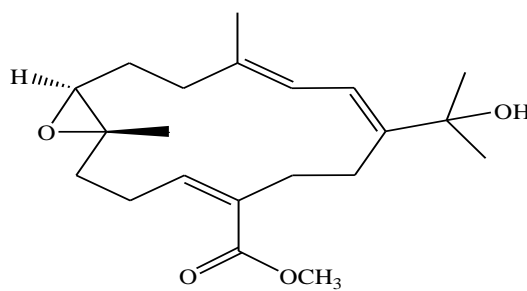


Sarcophytonolide D [33]



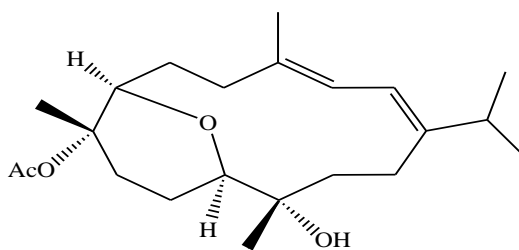
1

(+)-12-ethoxycarbonyl-11Z-sarcophine [34]



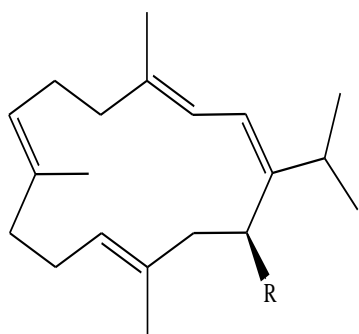
2

Ehrenbergol A [34]



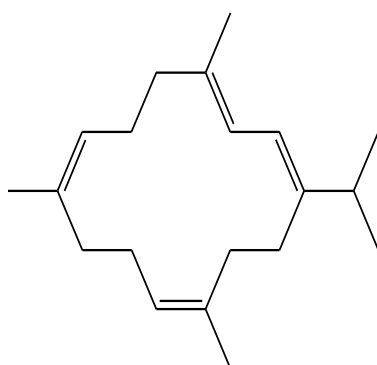
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Ehrenbergol B [34,35]



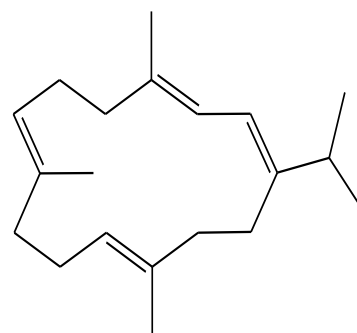
1 R = OH  
2 R = OAc

Sarcophytol-A (1) [36]  
Sarcophytol-A acetate (2) [36]



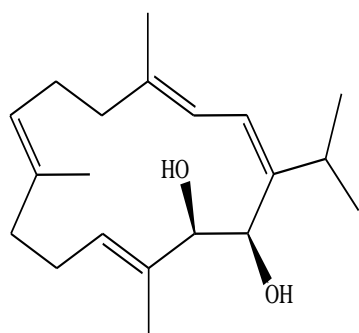
3

Istonecembrene A [36]



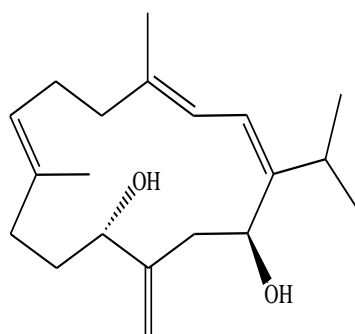
4

Cembrene C [36]



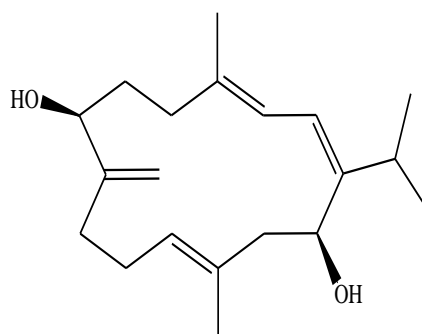
5

Sarcophytol-B [36]



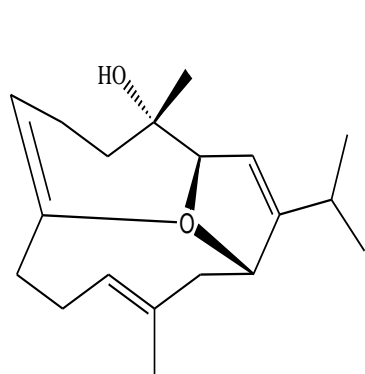
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Sarcophytol-E [36]



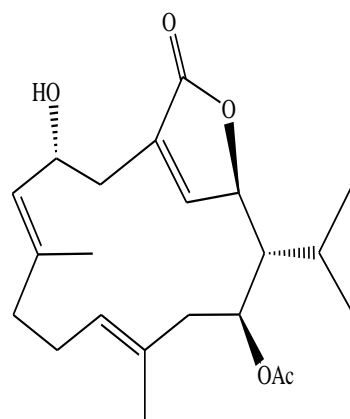
7

Sarcophytol-H [36]



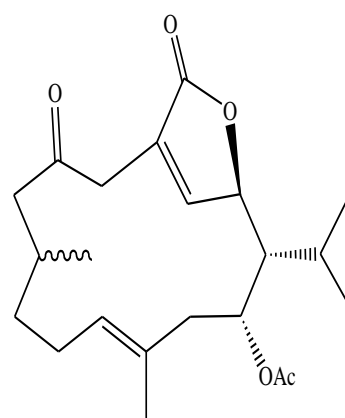
8

(-)-marasol [37]



9

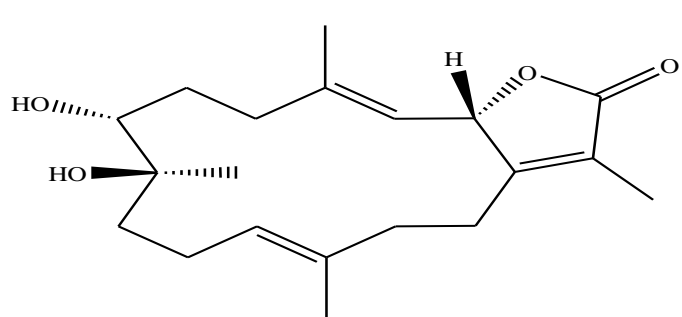
Sarcophytonolid-H [36]



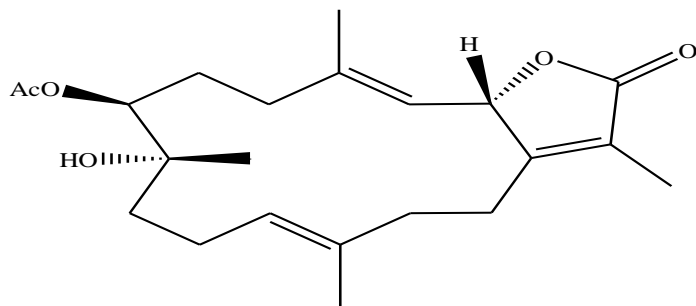
10

Sarcophytonolid-J [36]

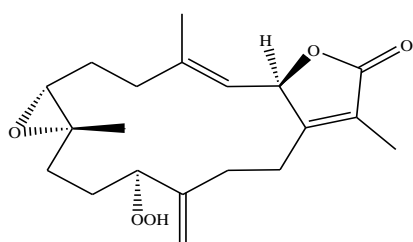




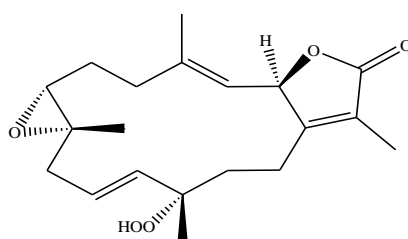
7 $\alpha$ ,8 $\beta$ -dihydroxydepoxy sarcophine [38]



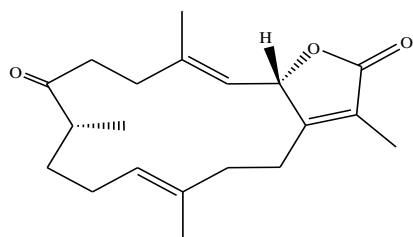
7 $\beta$ -acetoxy-8 $\alpha$ -hydroxydepoxy sarcophine [38]



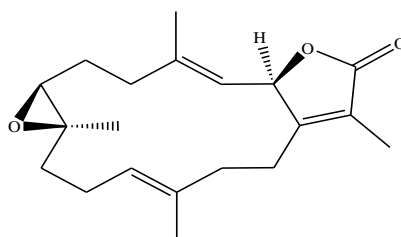
11(S)-hydroperoxy sarcoph-12(20) ene [38]



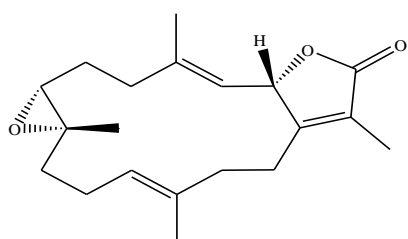
12-hydroperoxy sarcoph-10-ene [38]



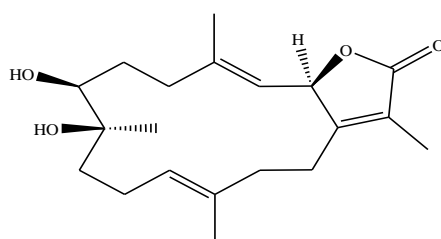
8-epi-sarcophinone [38]



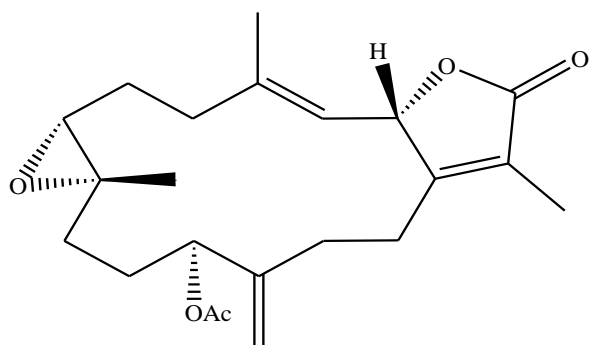
Ent-sarcophine [38]



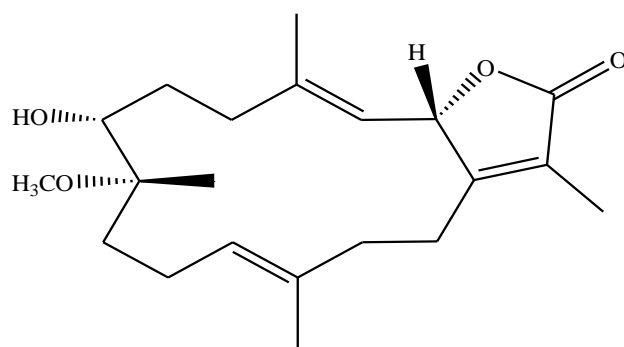
Sarcophine [38]



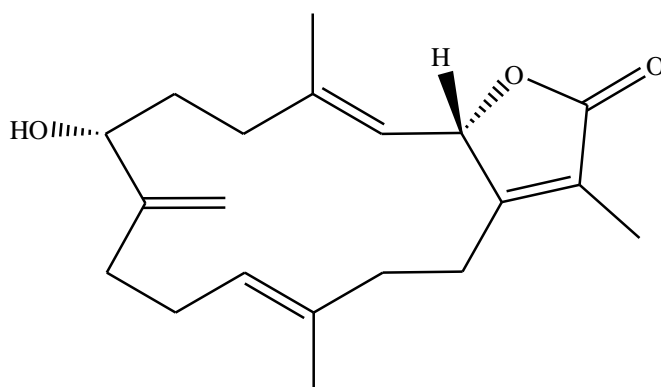
2R, 7R, 8R-dihydroxydepoxy sarcophine [38]



Trochelioid A [39]

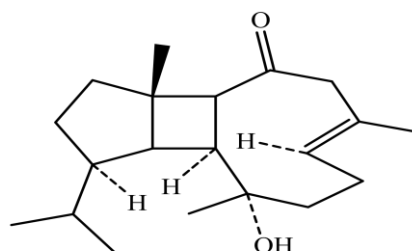


Trochelioid B [39]

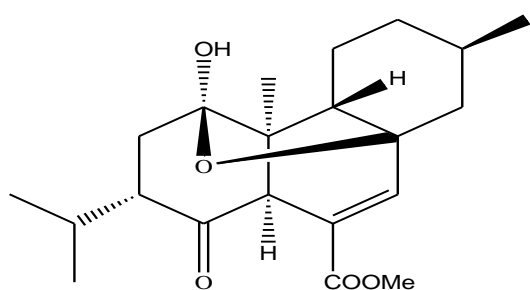


8-Epi sarcophinone [39]

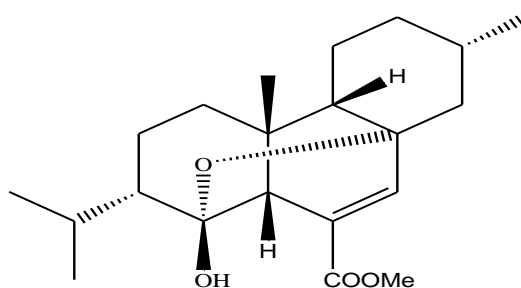
**b-Tricyclic diterpenoid**



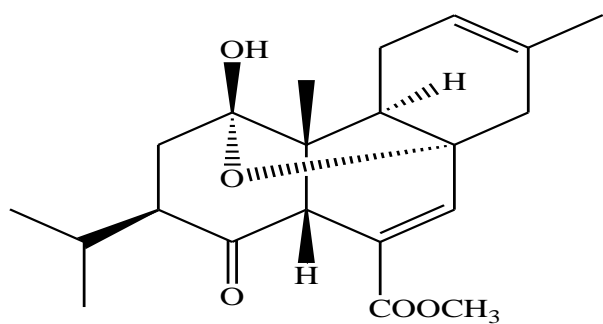
Sarcoglance [30]



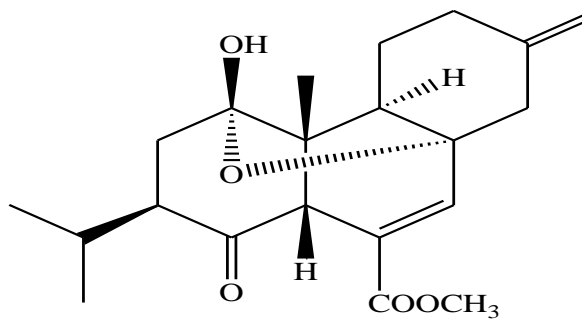
Sarcophytin [31]



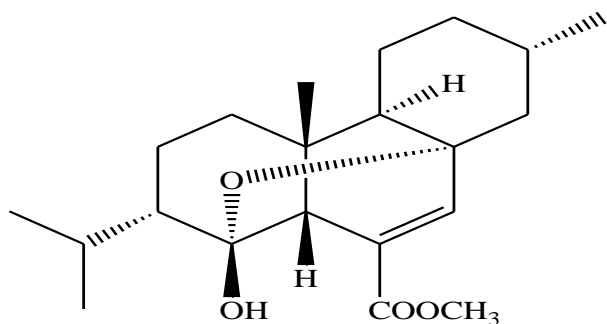
Chatancin [31]



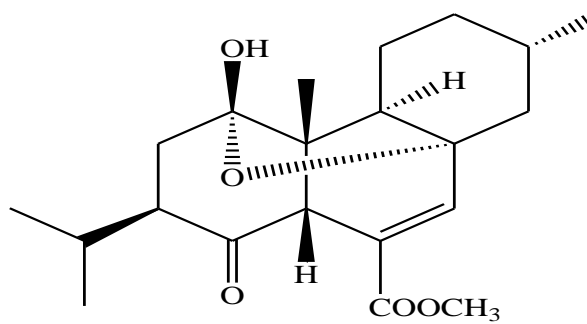
Sarcophytin B [40]



Sarcophytin C [40]

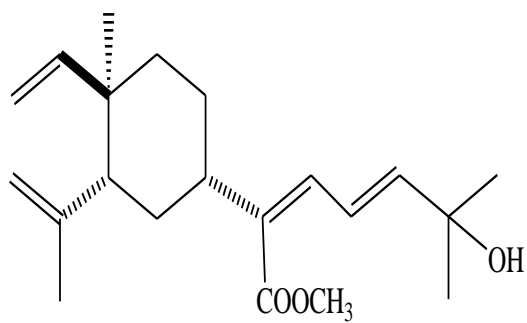


Sarcophytin [40]

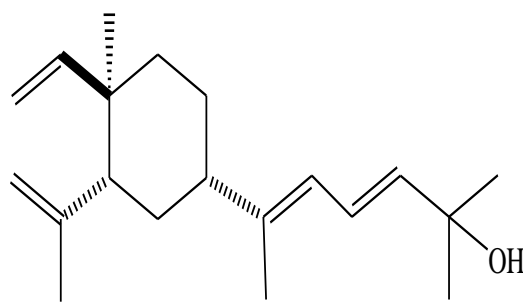


Sarcophytin [40]

**c- Lobane Diterpene**

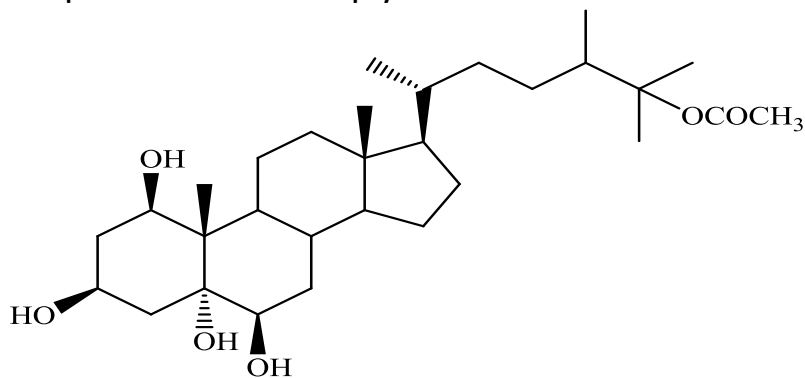


Carbomethoxyfuscol [20]

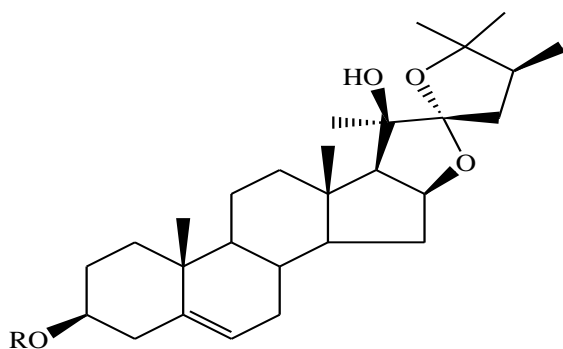


Fuscol [20]

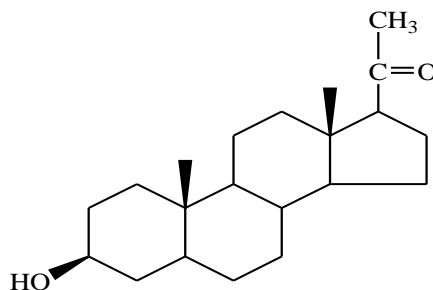
**Triterpenes isolated from Sarcophyton**



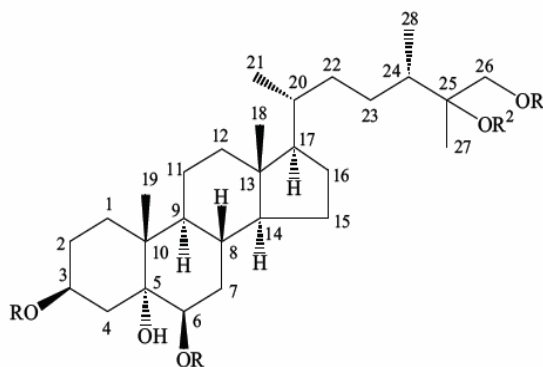
(24S)-24-methylcholestane-1, 3, 5, 6,  
25-pentol 25-monoacetate [22]



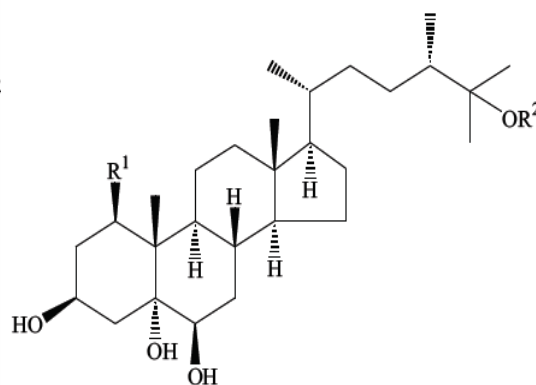
1 R = H  
2 R = OCOCH<sub>3</sub>  
Hippurins [41]



Pregnenolone [41]

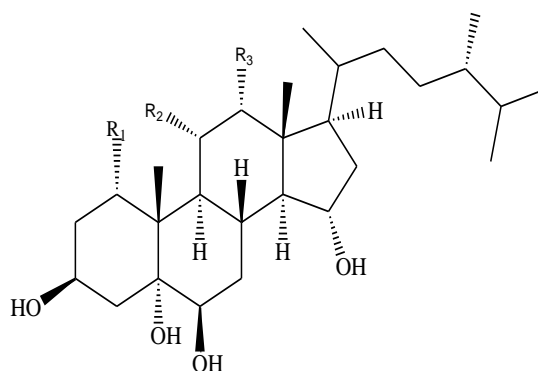
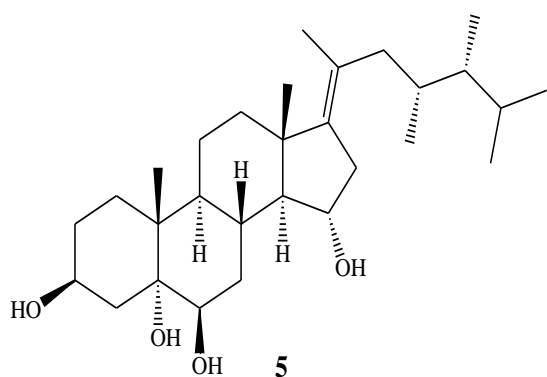
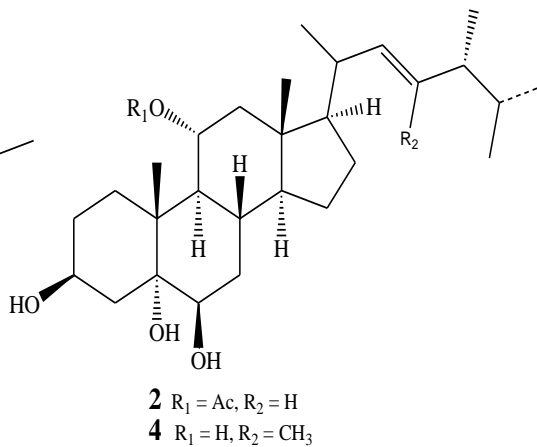
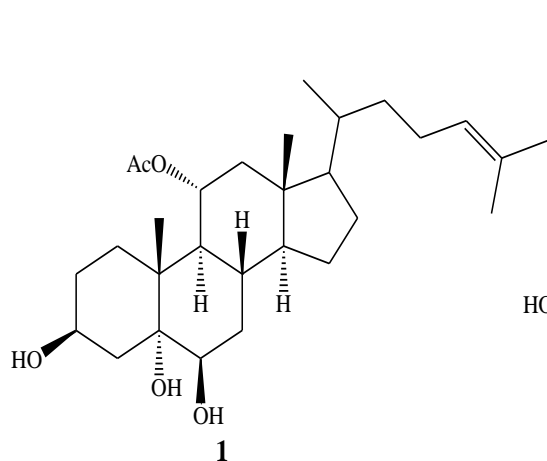


1 R = H, R<sup>1</sup> = CO(CH<sub>2</sub>)<sub>8</sub>CH<sub>3</sub>, R<sup>2</sup> = H  
2 R = H, R<sup>1</sup> = R<sup>2</sup> = Ac  
6 R = R<sup>1</sup> = R<sup>2</sup> = H  
7 R = R<sup>1</sup> = R<sup>2</sup> = Ac

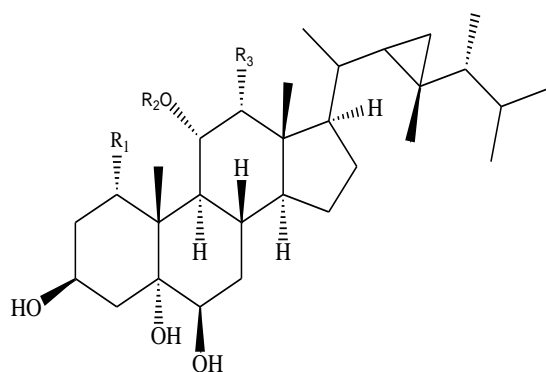


3 R<sup>1</sup> = H, R<sup>2</sup> = Ac  
4 R<sup>1</sup> = R<sup>2</sup> = H  
5 R<sup>1</sup> = OH, R<sup>2</sup> = Ac

Polyhydroxysteroids [42]

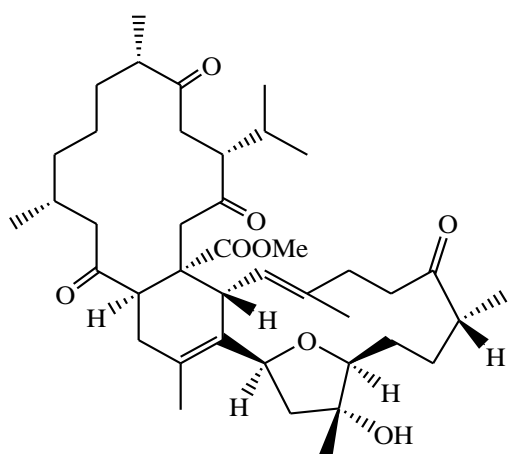


- 8**  $R_1 = R_3 = \text{H}, R_2 = \text{OAc}$   
**9**  $R_1 = R_2 = R_3 = \text{H}$   
**10**  $R_1 = R_3 = \text{H}, R_2 = \text{OH}$

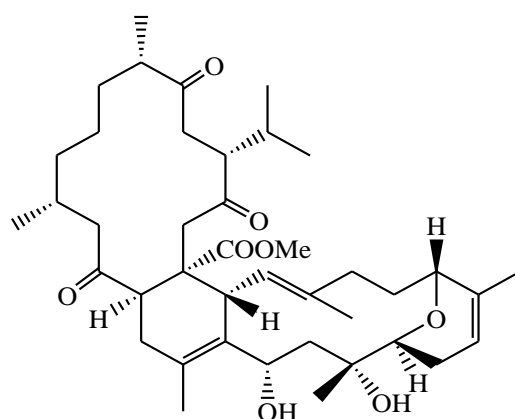


polyoxygenated steroids (1-7)  
 analogues (8-13) [43]

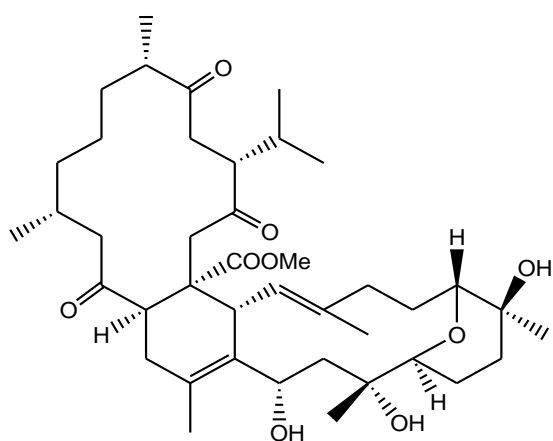
Tetraterpenoids isolated from *Sarcophyton*



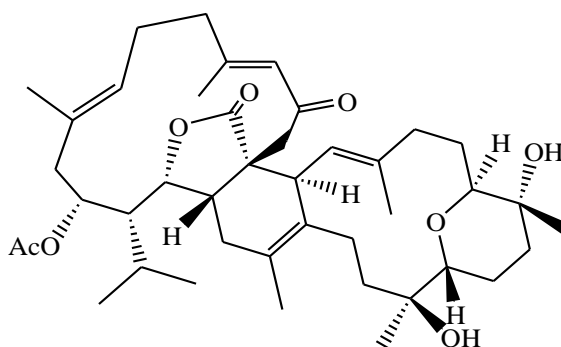
Methyl tortuoate A [22]



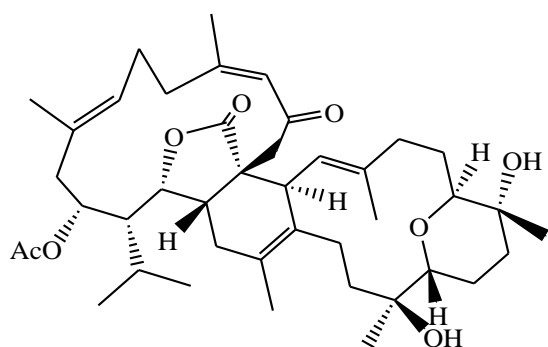
Methyl tortuoate B [22]



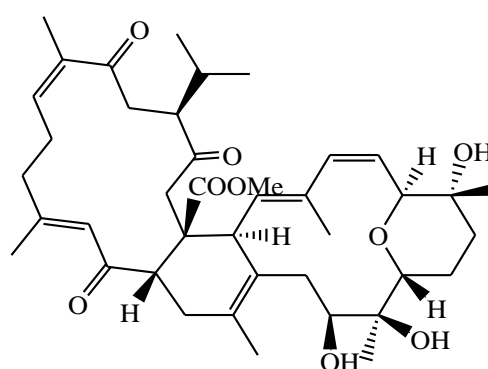
Methyl tortuoate D [44]



Bislatumlides A [33]

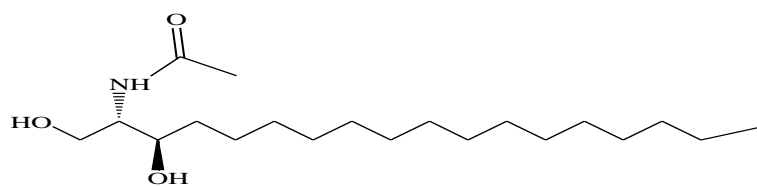


Bislatumlides B [33]



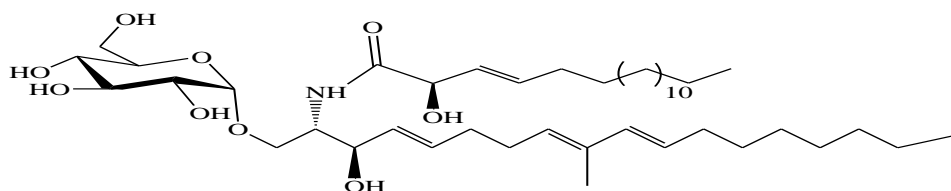
Bisglaucumlide A [33]

**Ceramides and Cerebrosides isolated from Sarcophyton**

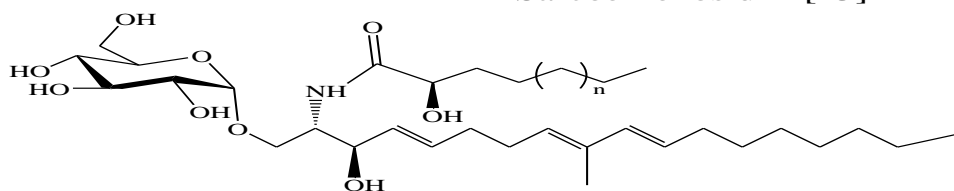


Ceramide [45]

**cerebrosides**

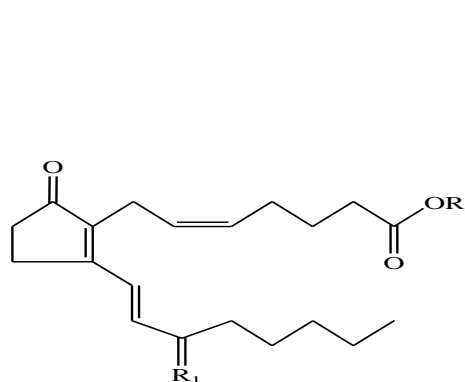


Sarcoehrenosid A [45]



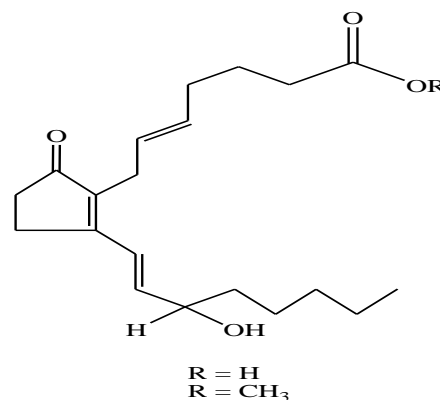
n = 16  
n = 15  
n = 14  
n = 10

**Sarcoehrenosid B [45]**



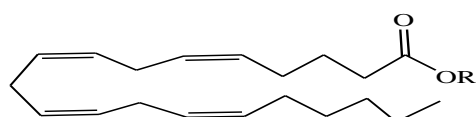
R = CH<sub>2</sub>CH<sub>3</sub>, R<sub>1</sub> = CH<sub>3</sub>CH<sub>2</sub>OH  
R = H, R<sub>1</sub> = CH<sub>3</sub>CH<sub>2</sub>OH  
R = CH<sub>3</sub>, R<sub>1</sub> = CH<sub>3</sub>CH<sub>2</sub>OH  
R = H, R<sub>1</sub> = =O  
R = CH<sub>3</sub>, R<sub>1</sub> = =O

Prostaglandins [41]



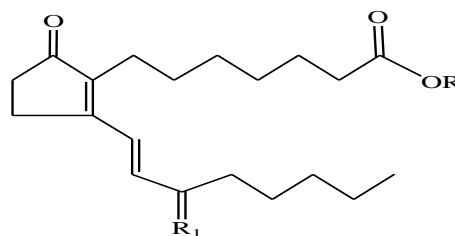
R = H  
R = CH<sub>3</sub>

Prostaglandins [41]



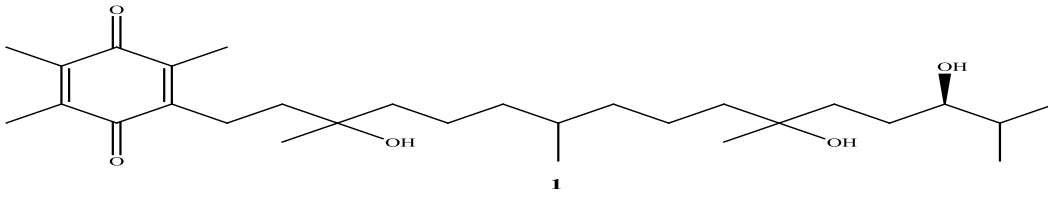
R = H  
R = CH<sub>2</sub>CH<sub>3</sub>

Pregnenolone [41]

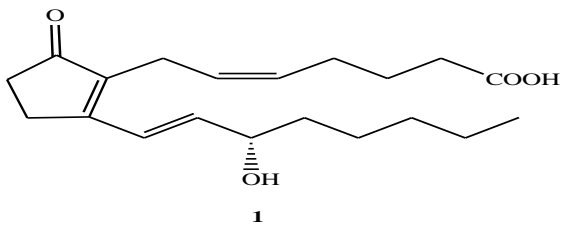


R = H, R<sub>1</sub> = CH<sub>3</sub>CH<sub>2</sub>OH  
R = CH<sub>3</sub>, R<sub>1</sub> = CH<sub>3</sub>CH<sub>2</sub>OH  
R = H, R<sub>1</sub> = =O  
R = CH<sub>3</sub>, R<sub>1</sub> = =O

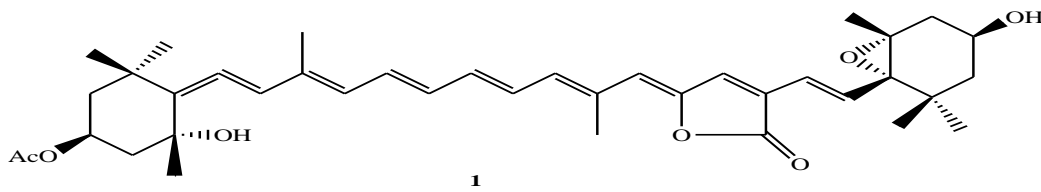
Prostaglandins [41]



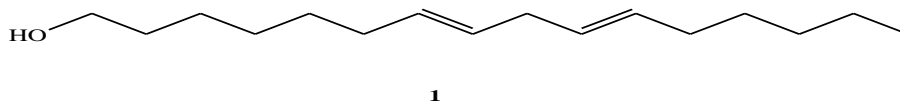
Tocopheryl quinone derivative [36]



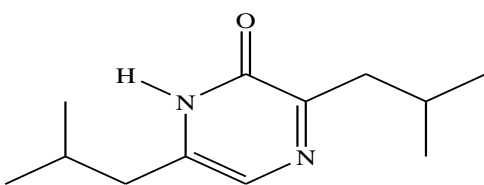
Prosta-glandin [36]



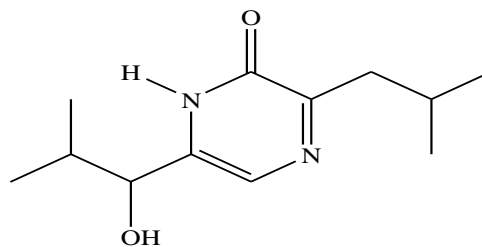
Carotenoid [36]



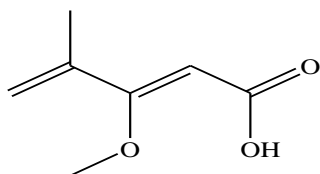
Lipid [36]



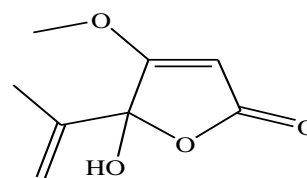
3,6-diisobutyl-2(1H)-pyrazinone [48]



3-isobutyl-6-(1-hydroxy-2-methylpropyl)-2(1H)-pyrazinone [48]

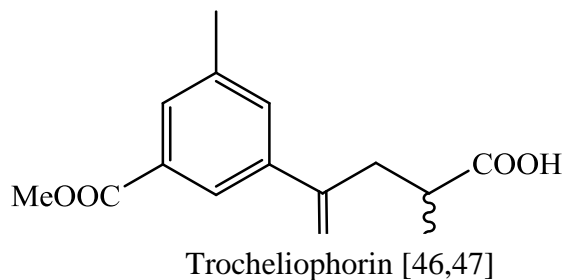


3-methoxy-4-methyl-2,4-dien-pentanoic acid [48]



Penicillic acid [48]





## BIOLOGICAL ACTIVITIES OF SARCOPHYTON

Cembranoids contain a 14-membered macro cyclic skeleton and exhibit a wide range of biological activities including anti-tumor, neuro-protective, antimicrobial, calcium-antagonistic, and anti-inflammatory activity [49–52]. The cembranoid diterpene sarcophine has been investigated since 1998 for its potential as a chemo-preventive agent [53], cytotoxic agent, anti-microbial agent [54], competitive cholinesterase inhibitor [55], noncompetitive phosphofructokinase inhibitor [56], and a Na<sup>+</sup>, K<sup>+</sup>-ATPase inhibitor [57]. Recent studies focusing on the treatment of human diseases have shown that sarcophine and sarcophine derivatives (e.g., hydroxylated sarcophine) are potent cancer chemo-preventive agents [53, 54, 58–60].

Cancer chemoprevention is based on chemical constituents that block, inhibit, or reverse the development of cancer in normal or pre-neoplastic tissue [61]. During the past 20 years, thousands of novel marine metabolites have been identified and assayed for anticancer activity [62]. Most of these drug leads are identified by high-throughput *in vitro* screening via a cost-effective testing of cancer cell lines derived from human and rodent sources. Indeed several marine-derived drug leads have reached phase II human clinical trials based on promising anticancer results, although toxicity testing has mostly screened out such candidate drugs. Sarcophine anti-tumor potency appears to at least in part involve inhibition of cell transformation that can be induced *in vitro* by 12-*O*-tetradecanoyl phor-13-bolacetate (TPA) with irreversible acquisition of tumorigenicity. In many cases, carcinogenesis is initiated by pro-carcinogens in combination with phase I enzymes such as cytochrome P450 1A and oxidative stress leading to DNA damage. This process can be mitigated at least in part by phase II detoxification enzymes such as glutathione *S*-transferases (GSTs), quinone reductase (QR), and epoxide -hydrolase (mEH) [52,58].

## CONCLUSION

Natural products have historically been a rich source of “lead compounds” for drug discovery. Although started only fifty years ago, the investigation of marine organisms aimed at searching new biologically active compounds has now gained a recognized role in this kind of studies.

The marine environment is yet to be extensively investigated; discoveries are being continually made of new sea life and unique ecosystems in the pelagic region. Advancement of modern scientific methods, especially bioassay-guided screening in conjunction with advanced spectroscopic techniques (2D-NMR, HPLC, LC/MS), have made it possible to detect, fractionate and elucidate the structure of natural products of low abundance and high structural complexity. These advances have resulted in the rapid and steady growth of marine natural product literature over the last thirty years. For example, in the period 2000 to 2003, 2450 new natural products of marine origin were reported. This compares to around 100 in the period 1965 to 1970.

Published reviews clearly indicate the tremendous potential of taxonomically diverse marine micro- and macro-organisms as a source of pharmaceuticals, possessing a wide range of pharmacological activities including antitumour, antibacterial, anti-inflammatory, antifungal and antiviral activities.

Marine organisms are a major reservoir of bioactive natural products with potential biomedical application; several marine natural products are regarded as potential therapeutic agents for the treatment of multiple disease categories. Many bioactive marine natural products and their derivatives are produced by invertebrates, such as sponges, soft corals, tunicates, mollusks or bryozoans, and are evaluated advancedly in preclinical and even clinical trials. Moreover, from 2005 to 2007, two of 13 natural products and natural products-derived drugs approved marketing worldwide are found from marine organisms.

These facts attract us to pay more efforts on the research of bioactive natural products from other marine invertebrates.

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