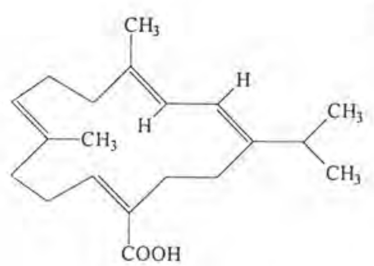
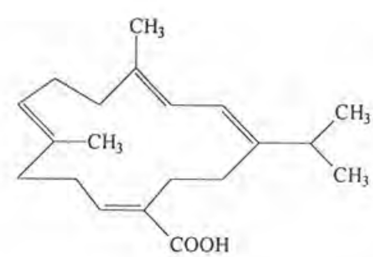
CHAPTER II

LITERATURE REVIEWS

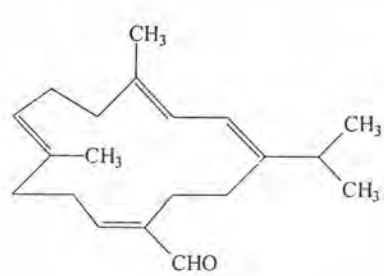
Previous studies in our research group established three new cembranoid diterpene compounds, namely, crotocembraneic acid (1), neocrotocembraneic acid (2) [14] and neocrotocembranal (3)[15], from stem bark of *C. oblongifolius* Roxb. in Thailand. The structure elucidations of these compounds were identified by spectral evidences as 14-membered ring compounds.



Crotocembraneic acid (1)



Neocrotocembraneic acid (2)

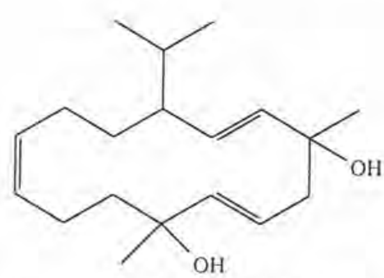


Neocrotocembranal (3)

2.1 Literature reviews of cembranoid diterpene compounds

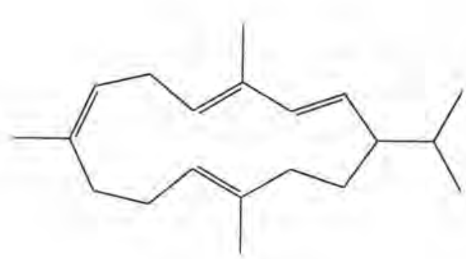
From literature surveys, cembranoid diterpene compounds have been isolated and studied from soft coral and tobacco since 1963. Many cembranoid compounds have biological activity as reported in the following examples.

In 1963, Rowland, R. L. and Roberts, D. L. [17] isolated two macrocyclic diterpenes, α- and β-3,8,13-duvatriene-1,5-diol, from tobacco. These compounds are shown to be diastereoisomer of 12-isopropyl-1,5,9-trimethyl-3,8,13-cyclotetradeca-triene-1,5-diol and provided two examples of the newly characterized naturally occurring diterpene series containing a fourteen-membered ring.



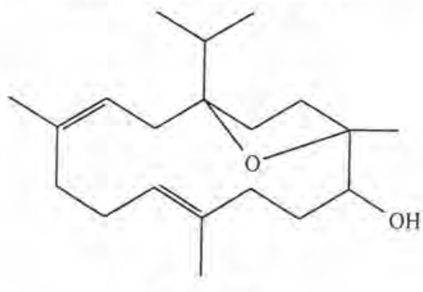
α-3,8,13-Duvatriene-1,5-diol and β-3,8,13-duvatriene-1,5-diol

In 1965, Dauben, W. G. and co-worker [18] found that cembrene is a monocyclic diterpene hydrocarbon which occurs in the oleoresin of many pine trees of the subgenus *Haploxylon*. Systematic degradation of the compound established the structure as 1-isopropyl-4,8,12-trimethyl-$\Delta^{1,3,7,11}$-cyclotetradecatetraene. Cembrene is the first 14-membered ring compound to be found in nature.



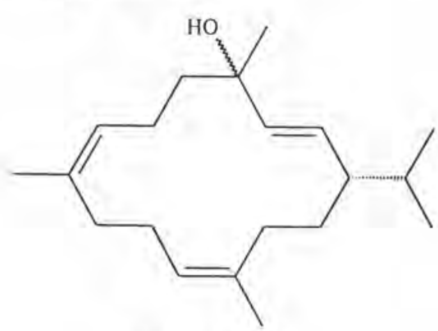
Cembrene

In 1967, Corsano, S. and Nioletti, R. [19] isolated a new diterpene alcohol, incensole from frankincense (*Boswellia carteri*) and it is related to cembrane. Chemical and physico-chemical data support the structure of 12-isopropyl-1,5,9-trimethyl-1,12-oxido-5,9-cyclotetradecadien-2-ol.



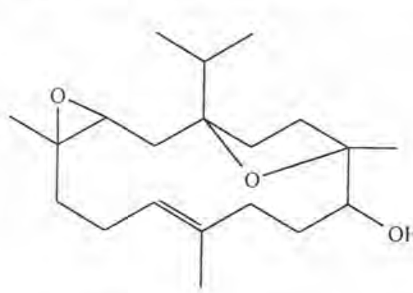
Incensole

In 1968, Kimland, B. and Norin, T. [20] established the structure of thunbergol which is a new member of the diterpene series containing a fourteen-membered ring from *Pseudotsuga menziesii* Mirb.



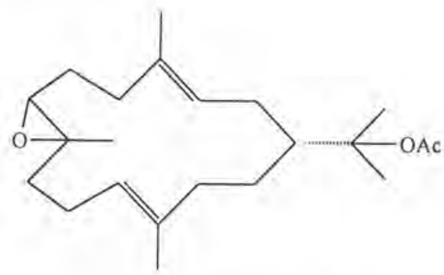
Thunbergol

In the same year, Nicoletti, R. and Forcellese, M. L. [21] isolated a new diterpenem incensole-oxide, closely related to incensole from frankincense (*Boswellia carteri*) in small amounts. The chemical and physico-chemical data indicated the position of the oxirane ring, thus supported the structure of incensole-oxide.

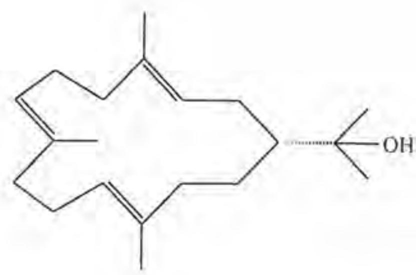


Incensole-oxide

In 1974, Schmitz, F. J., and co-worker [22] isolated two new cembrene derivatives, epoxynephthenol acetate and nephthenol from a Pacific soft coral (*Nephthea sp.*) and their structures have been established by spectroscopic analyses and chemical degradations.

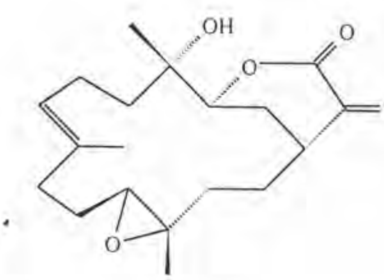


Epoxynephthenol

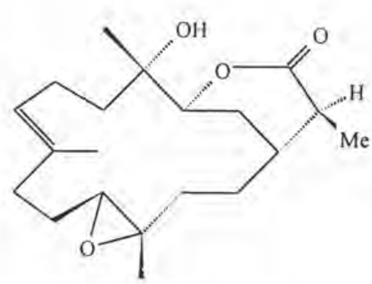


Nephthenol

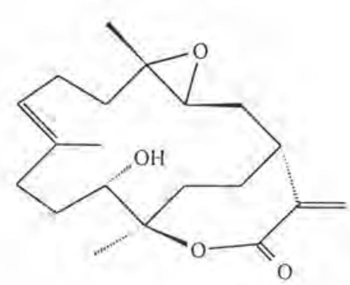
In 1977, Weinheimer, A. J. and co-worker [23] isolated two new cembranolides, sinularin and dihyodrosinularin from the soft coral, *Sinularia flexibilis*. The effective doses for 50 % inhibition (ED_{50}) of the *in vitro* KB and PS cell lines by sinularin (NSC 285706), dihydrosinularin (NSC 285707) and sinulariolide (NSC 285705) are 0.3 and 0.3, 1.6 and 1.1, and 20 and 7.0 μg/ml, respectively.



Sinularin

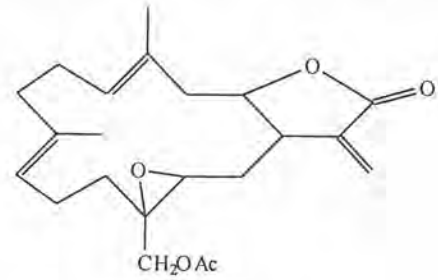


Dihydrosinularin



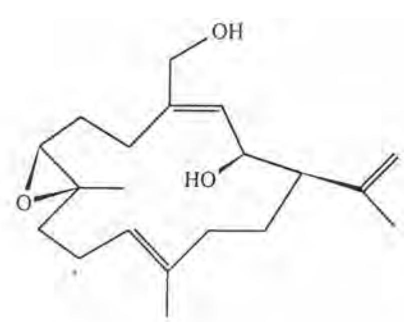
Sinulariolide

In the same year, Kashamn, Y and Groweiss, A. [24] reported a new cembranolide, lobolide, which was isolated from the petrol-ether extract of a freeze-dried *lobophytum sp.* collected in the soft coral of Eilat (Red Sea).



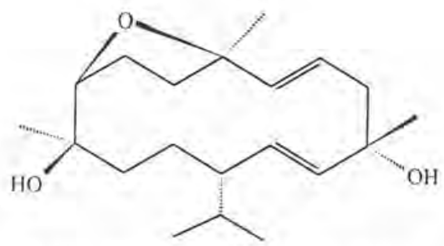
Lobolide

In the same year, Weiheimer, A. J. and coworker [25] isolated asperdiol from two gorgonian (*Eunicea asperula* and *E. tourneforti*) which shown to possess *in vivo* activity against the National Cancer Institute's P-388 cell line. Asperdiol is the first non-lactonic cembrane from gorgonians to display anticancer activity. Its effective doses for 50 % inhibition (ED_{50}) of the *in vitro* KB, PS and LE cell lines are 20, 6 and 6 μg/ml, respectively.

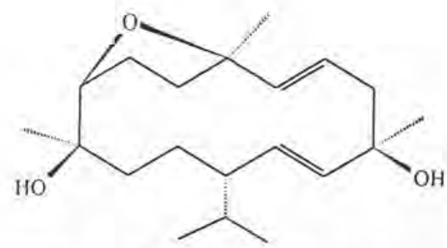


Asperdiol

In 1978, Behr, D. and co-worker [26] isolated two new diterpenoids from *Nicotiana tabacum* L. One of them was shown to be (*1S,2E,4S,6E,8R,11S,12R*)-8,11-epoxy-2,6-thunbergadiene-4,12-diol by synthesis and X-ray analysis, while the other was tentatively assigned as (*1S,2E,4R,6E,8R,11S,12R*)-8,11-epoxy-2,6-thunbergadiene-4,12-diol by spectroscopic means.

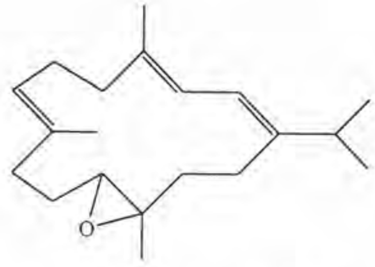


(*1S,2E,4S,6E,8R,11S,12R*)-8,11-epoxy-2,6-thunbergadiene-4,12-diol

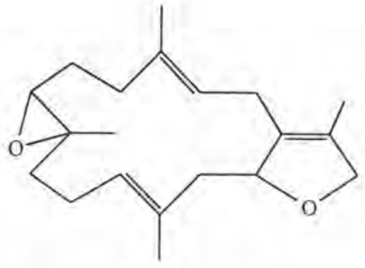


(*1S,2E,4R,6E,8R,11S,12R*)-8,11-epoxy-2,6-thunbergadiene-4,12-diol

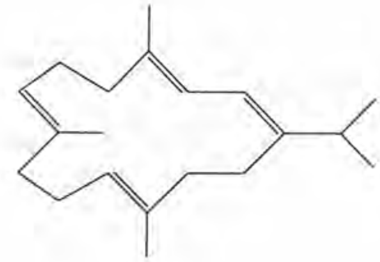
In the same year, Bowden, B. F. and co-worker [27] isolated an epoxyisoneocembrane-A [(*E,E,E*)-11,12-epoxy-1-isopropyl-4,8,12-trimethylcyclo-tetradeca-1,3,7-triene], from the soft coral *Sinularia grayi*. Its structure was established by chemical and spectroscopic means. The isolation of an isomer of the reported cembrene sarcophytotoxide and of isoneocembrene-A, an isomer of the termite trail pheromone neocembrane-A, from the soft coral Sarcophyton ehrenbergi was also reported. Chemical transformations enabled epoxyisoneocembrane-A [(*E,E,E*)-11,12-epoxy-1-isopropyl-4,8,12-trimethylcyclo-tetradeca-1,3,7-triene] to be converted into isoneocembrene-A.



Epoxyisoneocembrane A

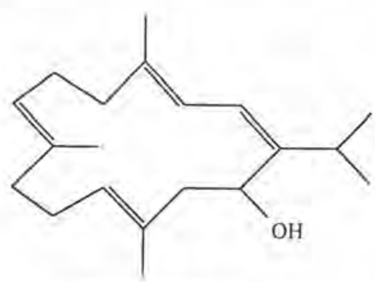


Sarcophytotoxide

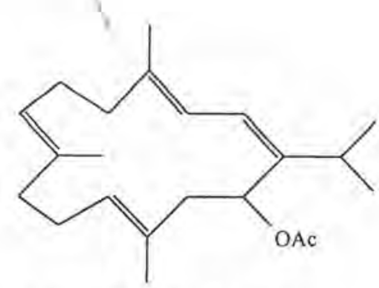


Isoneocembrane A

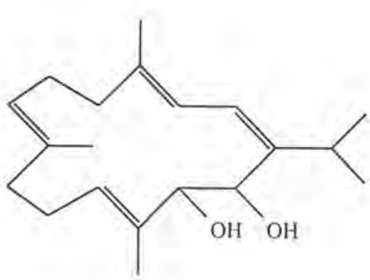
In 1979, Kobayashi, M. and co-worker [28] studied the lipid extracts of the soft coral, *Sarcophyton glaucum*, which was found to contain significant amounts of cembrane-type diterpenes. The structures of four major components, sarcophytol-A, sarcophytol A-acetate, sarcophytol-B, and sarcophytonin-A were characterized on the basis of spectral data and degradative studied by ozonolysis.



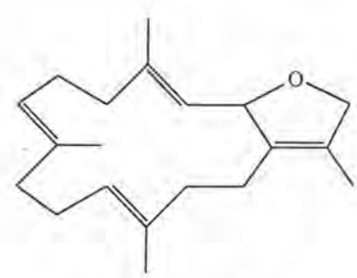
Sarcophytol A



Sarcophytol A acetate

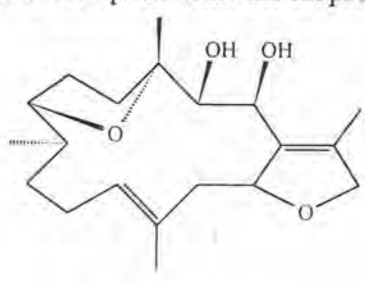


Sarcophytol B

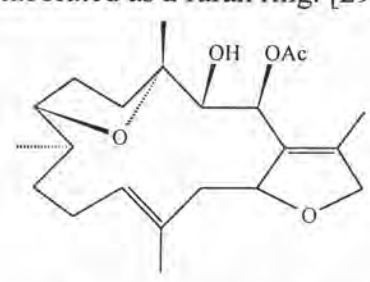


Sarcophytonin A

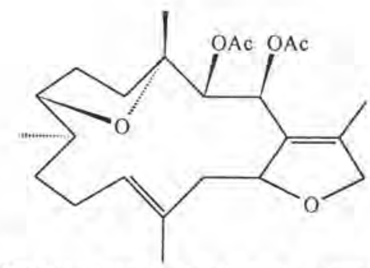
In the same year, Pachyclavulariadiol and its naturally occuring mono-and di-acetate derivatives were isolated from the soft coral *Pachyclavularia violacea*. Their structures were deduced spectroscopically and confirmed by a single-crystal X-ray diffraction study on the diol. Each compound was shown to be highly functionalized cembranoid diterpene with the isopropyl group elaborated as a furan ring. [29]



Pachyclavulariadiol

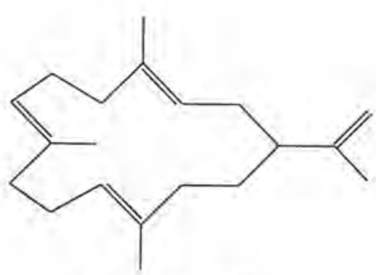


Pachyclavulariadiol acetate

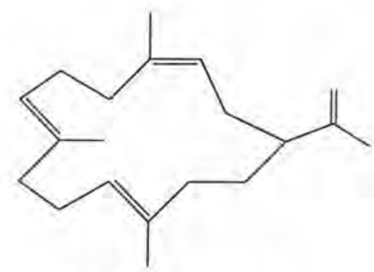


Pachyclavulariadiol diacetate

In the same year, Wiemer, D. F. and co-worker [30] isolated cembrene A and (3*Z*)-cembrene A from the hexane extract of *Cubitermes umbratus* Williams.

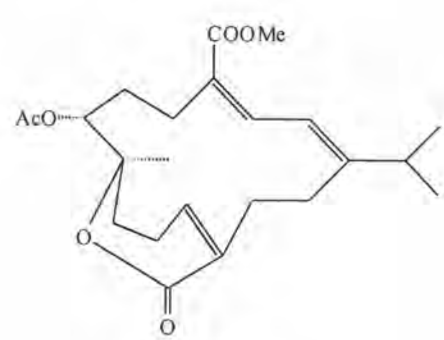


Cembrene A



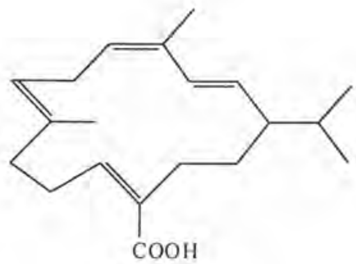
(3*Z*)-Cembrene A

In 1980 Toth, J. A. and co-worker [31] isolated emblide, a new cembrane diterpenoid which bears acetoxy, dienoic ester, and α,β-unsaturated ε-lactone function from the soft coral *Sarcophyton glaucum*. The structure of emblide was deduced from spectral and X-ray crystallographic data.



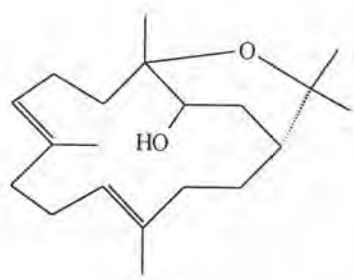
Emblide

In 1981, Sato, A. and co-worker [32] characterized poilaneic acid, a cembranoid diterpene, as (*1R**,*2E,4Z,7E,11Z*)-12-carboxyl-1-isopropyl-4,8-dimethyl-cyclotetradecatetraene from *Croton poilanei* Gagnep.

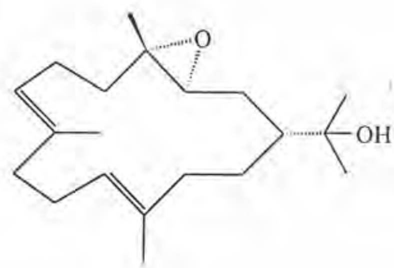


Poilaneic acid

In the same year, Carmely, S., Groweiss, A. and Kashman, Y. [33] studied the petroleum ether extract of the soft coral *Sarcophyton decaryi* to yield the cembrane-type diterpenes, thunbergol, decaryiol and 3,4-epoxynephthenol. Decaryiol and 3,4-epoxynephthenol were characterized by spectral data, degradative studies by ozonolysis, and chemical transformations.

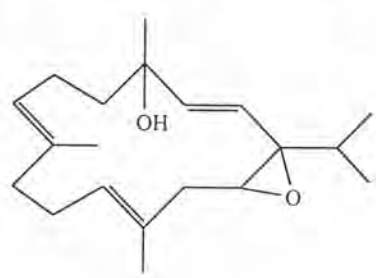


Decaryiol

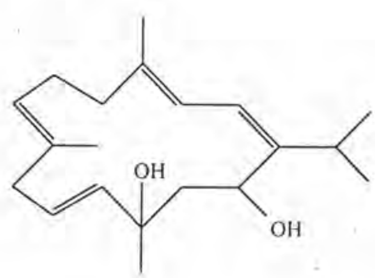


3,4-Epoxynephthenol

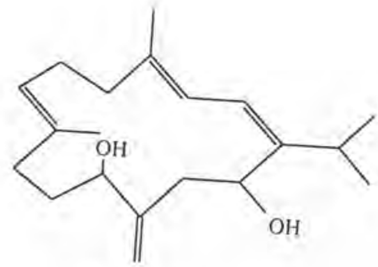
Nakagawa, T. and co-worker [34] found three new minor cembrane-type diterpenes, sarcophytol-C, sarcophytol-D, and sarcophytol-E



Sarcophytol-C

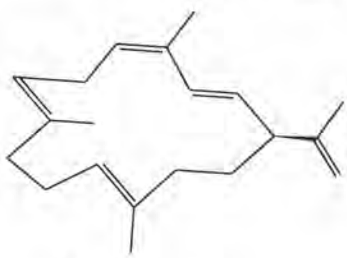


Sarcophytol-D

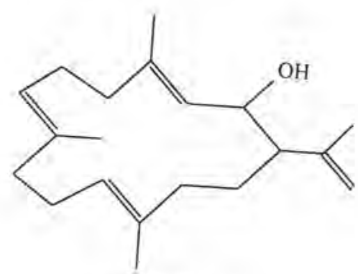


Sarcophytol-E

In the same year, Uchio, Y. and co-worker [36] isolated two new cembranoid diterpenes, cembrenene and mayol from *Sinularia mayi*, along with the first reported of cembrene from marine organism. The structures were determined from spectral data and chemical transformations.

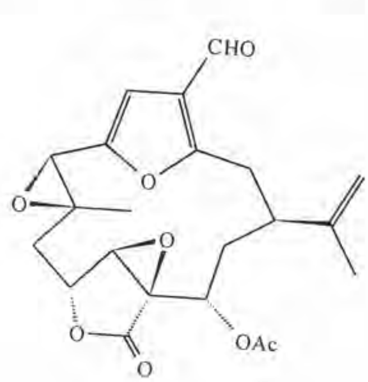


Cembrenene



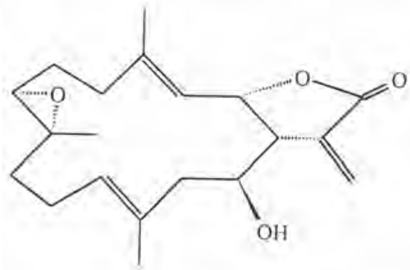
Mayol

In the same year, Fenical, W. and co-worker [36] isolated a new neuromuscular toxin, lophotoxin from several Pacific gorgonians of the genus *Lophogorgia*. The structure of lophotoxin was deduced by combined spectrochemical methods, and belongs to the well-known cembrene class of diterpenoid molecules. Lophotoxin contains furanoaldehyde and α,β-epoxy-γ-lactone functional groups, in sharp contrast to the cationic ammonium functional groups of the established neurotoxins.

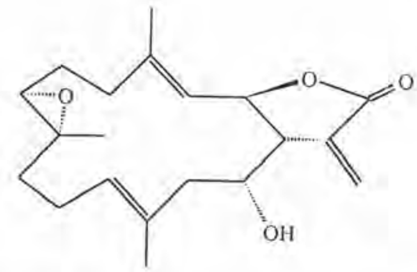


Lophotoxin

In 1982, Burns, K.P. and co-worker [37] isolated two new cembranolides (*1R,2S,3E,7R,8R,11E,14S*)-7,8-epoxy-14-hydroxycembra-3,11,15-triene-17,2-olide and (*1R,2R,3E,7R,8R,11E,14R*)-7,8-epoxy-14-hydroxycembra-3,11,15-triene-17,2-olide from different species of *Cespitularia* (soft coral).

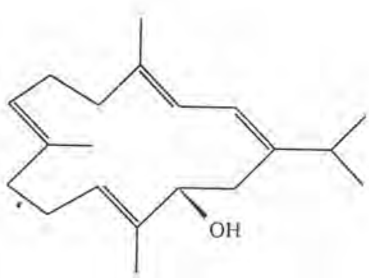


(*1R,2S,3E,7R,8R,11E,14S*)-7,8-epoxy-14-hydroxycembra-3,11,15-triene-17,2-olide

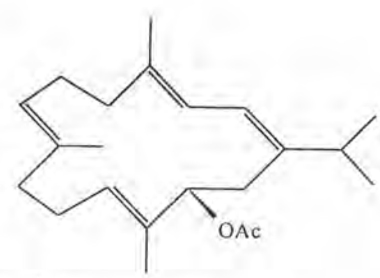


(*1R,2R,3E,7R,8R,11E,14R*)-7,8-epoxy-14-hydroxycembra-3,11,15-triene-17,2-olide

In the same year, Poet, S. and Ravi, B. N. [38] isolated two new cembranoid diterpenes and a non-cembranoid diterpene from a soft coral *Nephthea* species. The structures were determined from spectral data and chemical degradation sequences. The compounds were identified as (*1E,3E,7E,11E,13S*)-cembra-1,3,7,11-tetraen-13-ol, (*1E,3E,7E,11E,13S*)-cembra-1,3,7,11-tetraen-13-yl acetate.

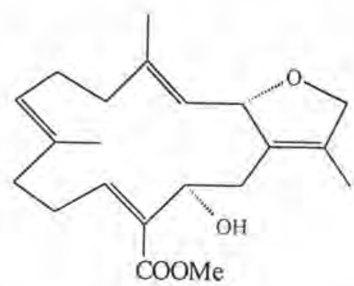


(*1E,3E,7E,11E,13S*)-cembra-1,3,7,11- tetraen-13-ol

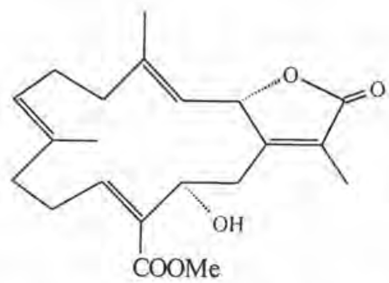


(*1E,3E,7E,11E,13S*)-cembra-1,3,7,11-tetraen-13-yl acetate

Kazlauskas, R. and co-worker [39] isolated two new cembrane diterpenes : methyl (*1Z,2S,3E,7E,11Z,13R*)-2,16-epoxy-13-hydroxycembra-1(15),3,7,11-tetraen-20-oate and methyl (*1Z,2S,3E,7E,11Z,13R*)-2,16-epoxy-13-hydroxy-16-oxocembra-1 (15),3,7,11-tetraen-20-oate, related to sarcophine, from a soft coral (*Sarcophyton* sp.). Methyl (*1Z,2S,3E,7E,11Z,13R*)-2,16-epoxy-13-hydroxy-16-oxocembra-1(15),3,7,11-tetraen-20-oate was the compound responsible for the effect on the central nervous system demonstrated by the crude extract.

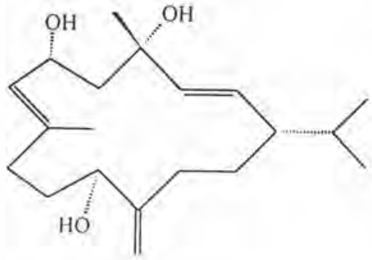


methyl (*1Z,2S,3E,7E,11Z,13R*)-2,16-epoxy-13-hydroxycembra-1(15),3,7,11-tetraen-20-oate

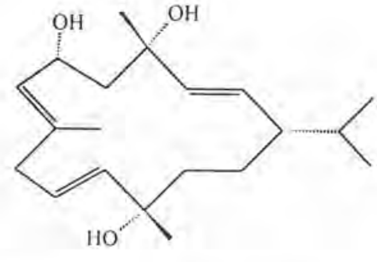


methyl (*1Z,2S,3E,7E,11Z,13R*)-2,16-epoxy-13-hydroxy-16-oxocembra-oxocembra-1(15),3,7,11-tetraen-20-oate

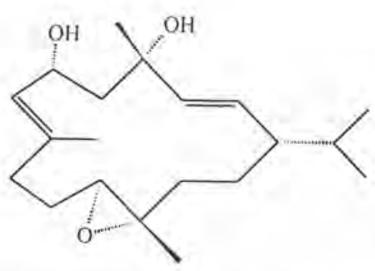
Wahlberg, I. and co-worker [40] isolated three new diterpenoids from tobacco. The first was shown to be (*1S,2E,4S,6R,7E,11S*)-2,7,12(20)-cembratriene-4,6,11-triol by X-ray analysis and chemical correlation, the second was formulated as (*1S,2E,4S,6R,7E,10E,12S*)-2,7,10-cembratriene-4,6,12-triol by spectral and chemical methods, while the third, (*1S,2E,4S,6R,7E,11S,12S*)-11,12-epoxy-2,7-cembradiene-4,6-diol, and latter, they isolated (*1S,2E,4S,6E,8S,11R,12S*)-8,11-epoxy-2,6-cembradiene-4,12-diol.



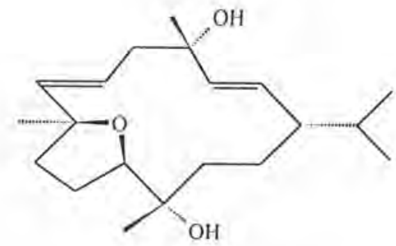
(*1S,2E,4S,6R,7E,11S*)-2,7,12(20)-cembratriene-4,6,11-triol



(*1S,2E,4S,6R,7E,10E,12S*)-2,7,10-cembratriene-4,6,12-triol

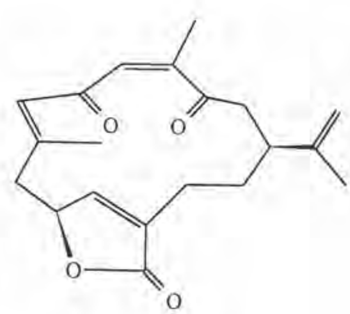


(*1S,2E,4S,6R,7E,11S,12S*)-11,12-epoxy-2,7-cembradiene-4,6-diol

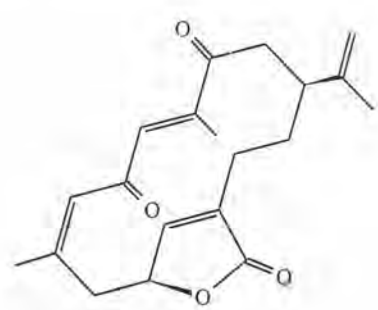


(*1S,2E,4S,6E,8S,11R,12S*)-8,11-epoxy-2,6-cembradiene-4,12-diol

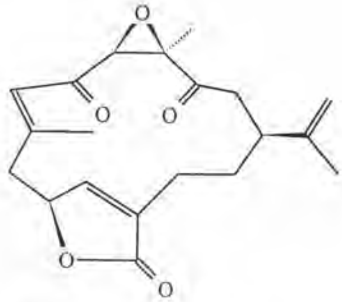
In the same year, Bandurraga, M. M. and co-worker [41] isolated three new diketone cembrenolides from the Pacific sea whip *Lophogorgia alba*. The structure of lophodione was assigned by X-ray crystallography, and isolophodione and epoxylophodione have been assigned based upon interconversion with lophodione and by proton difference decoupling and nOe experiments.



Lophodione

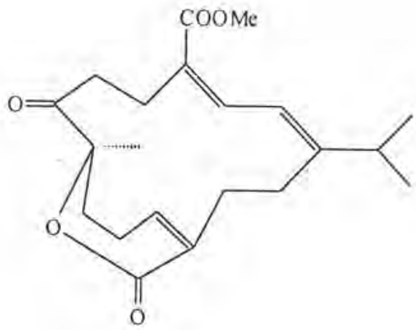


Isolophodione

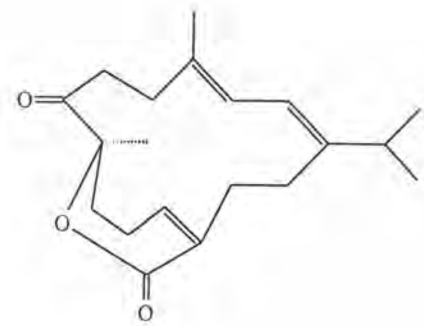


Epoxylophodione

In 1983, Uchio, Y. and co-worker [42] isolated two new cembranolides, ketoemblide and sarcophytolide, with ε-lactone function from the soft coral *Sarcophyta elegans*. The strucrures were elucidated on the basis of chemical correlation with emblide and spectral data.

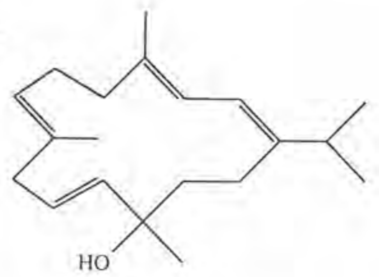


Ketoemblide

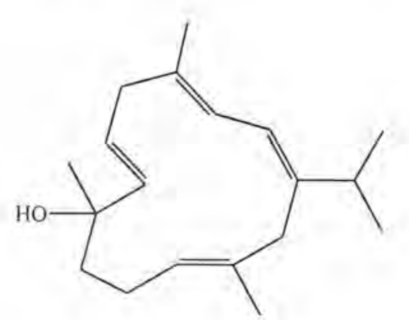


Sarcophytolide

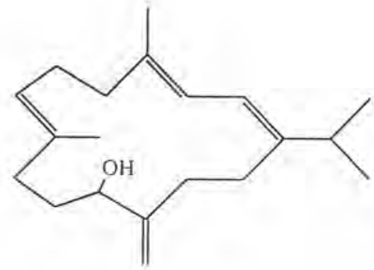
In the same year, Kinamoni, Z. and co-worker [43] isolated eight new diterpenoids from three soft corals, *Alcyonium utinomii*, *Lobophytum pauciflorum* and *Lobophytum crassum*. The compounds were shown to be 1,3,7,10-cembratetraen-12-ol; 1,3,6,11-cembratetraen-8-ol; 1,3,7,12(20)-cembratetraen-11-ol; 2,7,11-cembratrien-4,15-diol; 3,7,10-cembratrien-12,15-diol; and the lobolide related deacethyldeepoxy lobolide, deepoxy lobolide and deactyl-13-hydroxy lobolide, by spectral data and chemical studies (mainly ozonolysis).



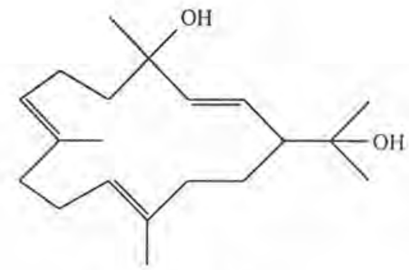
Alcyonol A



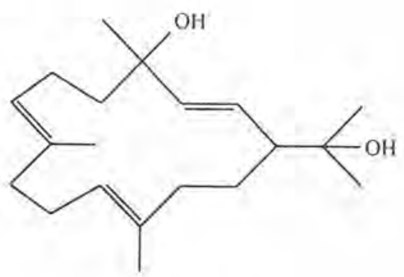
Alcyonol B



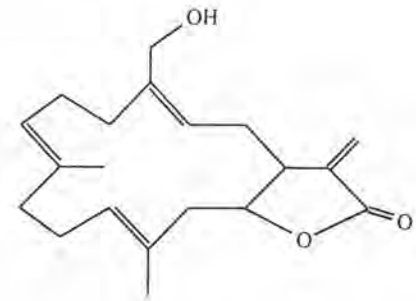
Alcyonol C



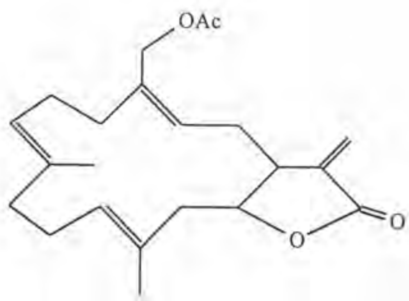
Pauciflorol A



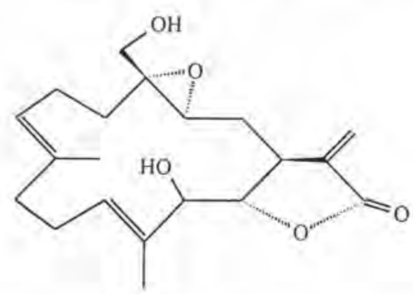
Pauciflorol B



Deacetyldeepoxy lobolide

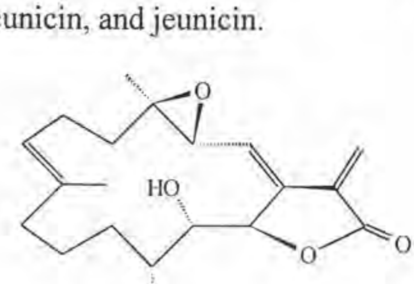


Deepoxy lobolide



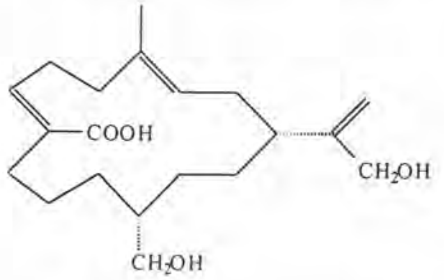
Deacetyl-13-hydroxy lobolide

In 1984, Gopichand, Y. and co-worker [44] studied the sesquiterpenoid and diterpenoid content of the gorgonian *Eunicea succinea* from different locations. A new cembranolide, 12,13-bisepieupalmerin, was isolated (the structure was elucidated by X-ray analysis) from specimens from St. Croix. U.S.V.I. 12,13-Bisepieupalmerin possessed the correct stereochemistry and believed to be a biosynthesis precursor of the related cembranolides, eunicin, and jeunicin.

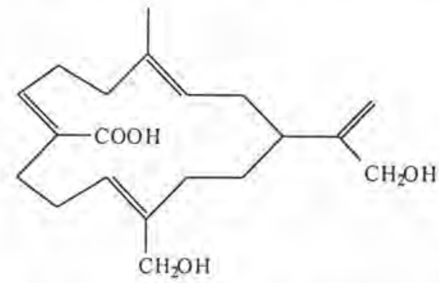


12,13-Bisepieupalmerin

In 1985, Kosela, S. and co-worker [45] isolated two new unsaturated cembrane acids from *Cleome viscosa* L. X-ray crystallographic methods showed one to be (*1R*,3E,7Z,12R**)-20-hydroxycembra-3,7,15-triene-19-oic acid. The structure of the second compound had been deduced from spectroscopic data to be (*3E,7Z,11Z*)-17,20-dihydroxycembra-3,7,11,15-tetraene-19-oic acid.

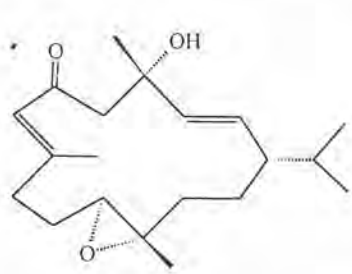


(*1R*,3E,7Z,12R**)-20-hydroxycembra-3,7,15-triene-19-oic acid

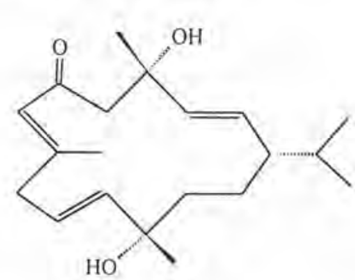


(*3E,7Z,11Z*)-17,20-dihydroxycembra-3,7,11,15-tetraene-19-oic acid

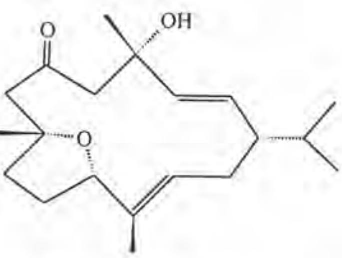
In the same year, Wahlberg, I. and co-worker [46] isolated five new cembranoids from Greek tobacco. They have been identified as (*1S,2E,4S,7E,11S,12S*)-11,12-epoxy-4-hydroxy-2,7-cembradien-6-one, (*1S,2E,4S,7E,11S,12S*)-4,12-dihydroxy-2,7,10-cembratrien-6-one, (*1S,2E,4S,8,11S,12S*)-8,11-epoxy-4-hydroxy-2,12-cembradien-6-one, (*1S,2E,4S,8R,11S*)-8,11-epoxy-4-hydroxy-2,12(20)-cembradien-6-one, and (*1S,2E,4S,8R,11S,12S*)-4,12-dihydroxy-8,11-epoxy-2-cembren-6-one by chemical and spectral methods and by X-ray analysis.



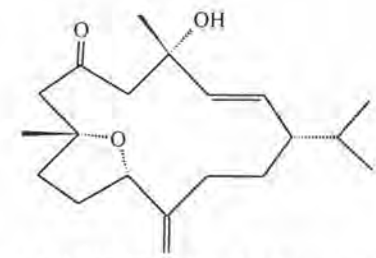
(*1S,2E,4S,7E,11S,12S*)-11,12-epoxy-4-hydroxy-2,7-cembradien-6-one



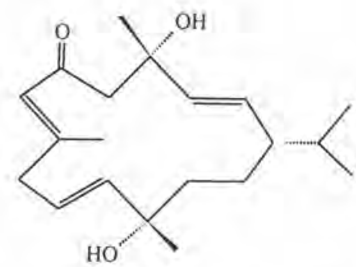
(*1S,2E,4S,7E,11S,12S*)-4,12-dihydroxy-2,7,10-cembratrien-6-one



(1S,2E,4S,8,11S,12S)-8,11-epoxy-4-hydroxy-2,12-cembradien-6-one

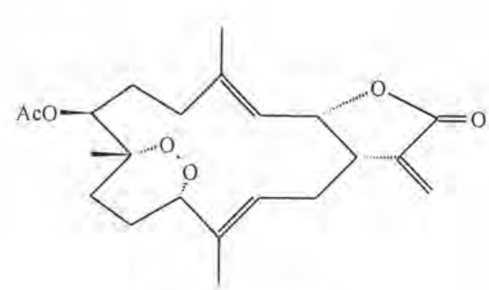


(1S,2E,4S,8R,11S)-8,11-epoxy-4-hydroxy-2,12(20)-cembradien-6-one



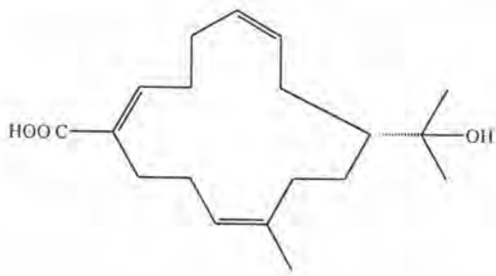
(1S,2E,4S,8R,11S,12S)-4,12-dihydroxy-8,11-epoxy-2-cembren-6-one

In the same year, Uchio, Y. and co-worker [47] isolated denticulatolide, an ichthyotoxic cembranoid diterpene bearing acetoxy, α-methylene, γ-lactone and cyclic peroxide functions from the soft coral *Lobophytum denticulatum*. A new cembranoid was toxic to the Medaka (*Oryzias latipes*) at a concentration of 5 μg/ml in laboratory test.

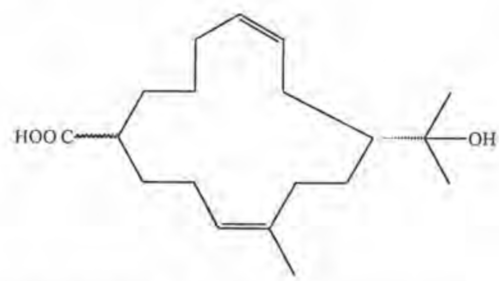


Denticulatolide

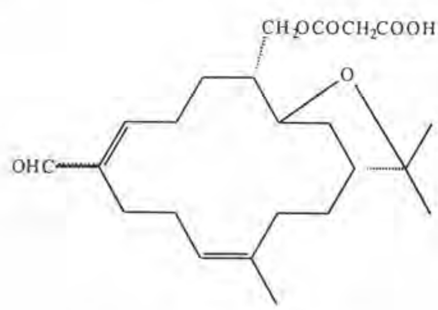
In 1986, Ghisalberti, E.L. and co-worker [48] reported three new cembrene diterpenes from Eremophila species. *(1R,3Z,7E,11Z)*-15-Hydroxycembra-3,7,11-triene-19-oic acid and *(1R,3S,8ξ,11Z)*-3,11 hydroxycembra-3,11-diene-19-oic acid were isolated from E. demprteri and *(1R,3S,4R,7E,11Z)*-3,15-epoxy-19-oxocembra-7,11-diene-18-ol as the malonate half ester derivative was isolated from *E. platycalyx* and a variety of *E. fraseri*. In addition the preparation of (*1R,3Z,7Z,11Z*)-cembra-3,7,11,15-tetraene (13; all-*cis*-cembrane-A) was reported.



(*1R,3Z,7E,11Z*)-15-Hydroxycembra-3,7,11-triene-19-oic acid

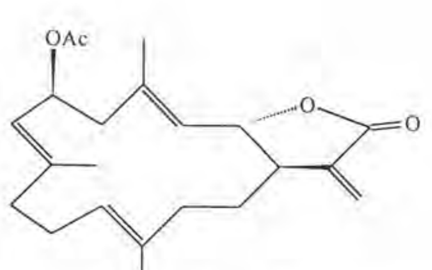


(*1R,3S,8ξ,11Z*)-3,11 hydroxycembra--3,11-diene-19-oic acid

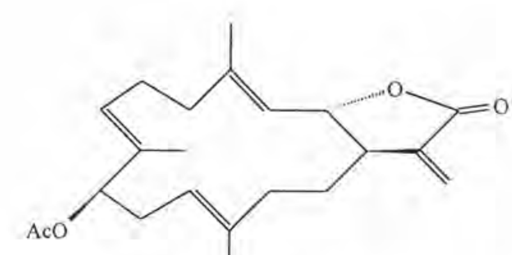


(*1R,3S,4R,7E,11Z*)-3,15-epoxy-19-oxocembra-7,11-diene-18-ol

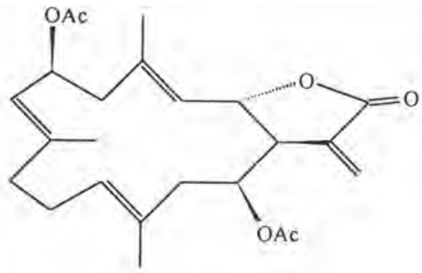
In the same year, Kobayashi, M. and co-worker [49] found five new cytotoxic cembrenolides, kericembrenolides A, B, C, D and E, having an α-methylene-γ-lactone moiety which were isolated together with neodolabelline and neodolabellenol from the Okinawan soft coral *Clavularia koellikeri*.



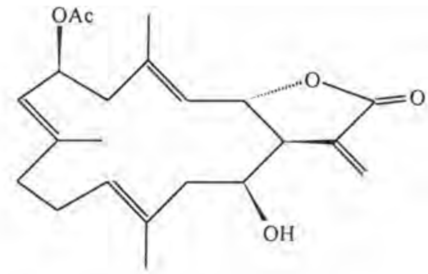
Kericembrenolides A



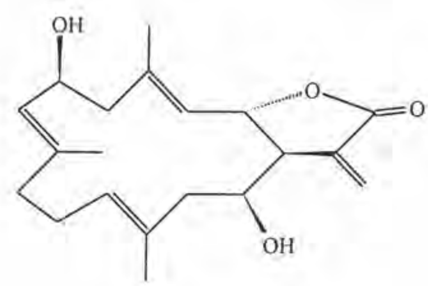
Kericembrenolides B



Kericembrenolides C

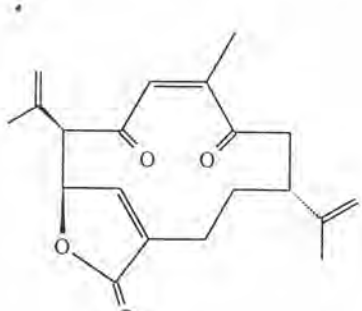


Kericembrenolides D

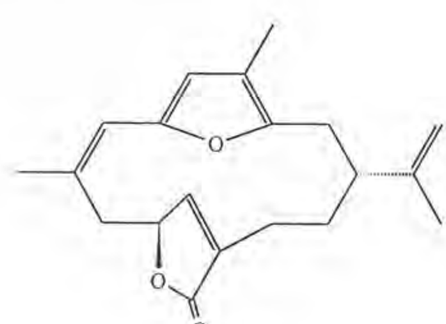


Kericembrenolides E

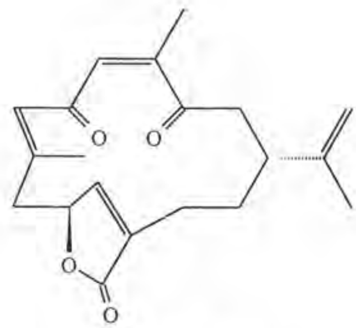
In 1987, Williams, D. and Andersen, R. J. [50] isolated three new diterpenes, gersemolide, rubifolide and epilophodione from the soft coral *Gersemia rubiformis*. The structure of gersemolide was solved by X-ray diffraction analysis and the structure of rubifolide and epilophodione were inferred from spectral data. Gersemolide has a pseudopterane skeleton, while rubifolide and epilophodione are cembranes.



Gersemolide

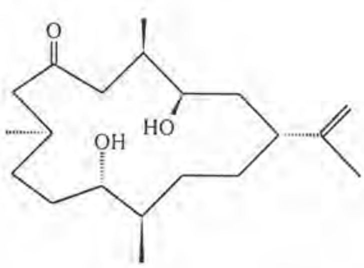


Rubifolide

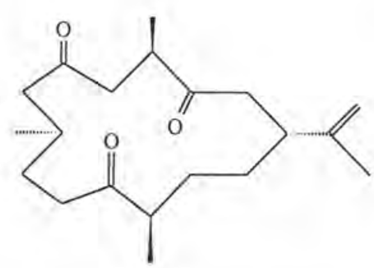


epilophodione

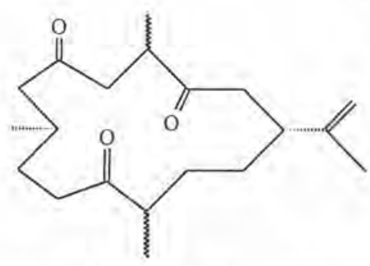
In 1989, Chan, W. R. and co-worker [51] isolated three new cembranoids, dihydroplexaurolone and two dehydroplexaurolones from the gorgonian *Plexaura A*. The structure of dihydroplexaurolone was established by X-ray crystallographic studies



Dihydroplexaurolone

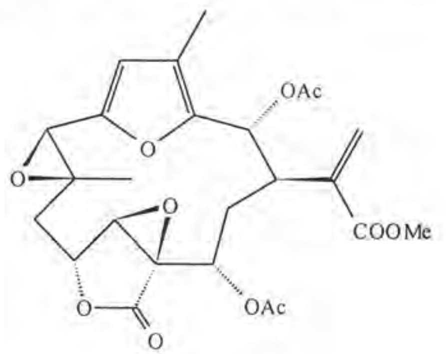


Dehydroplexaurolone

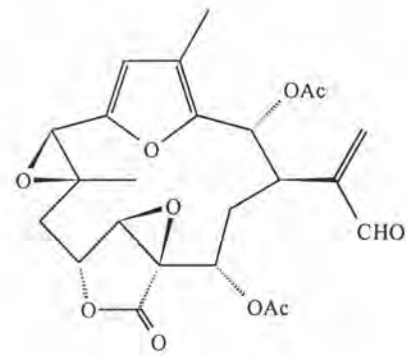


Isomeric dehydroplexaurolone

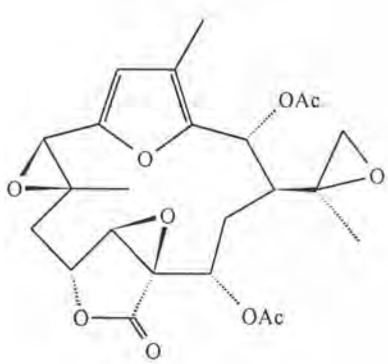
In the same year, Wright, A. E. and co-worker [52] isolated four new cytotoxic cembranoids, denoted as bipinnatins A-D from the gorgonian coral *Pseudopterogorgia bipinnata*. Their structures were determined through a combination of spectroscopic and X-ray crystallographic methods. Bipinnatins A, B, and D were active *in vitro* against the P388 murine tumor cell line with IC_{50}'s of 0.9, 3.2 and 1.5 μg/ml respectively. Bipinnatin C, which lacked the α,β-unsaturated carbonyl functionality at C15-C17, was much less active with an IC_{50} of 46.6 μg/ml suggesting that this functionality enhanced the activity of bipinnatins A, B and D. As both bipinnatin B and D showed similar activities, the epoxide found at C11,C12 was proposed not to be essential for activity.



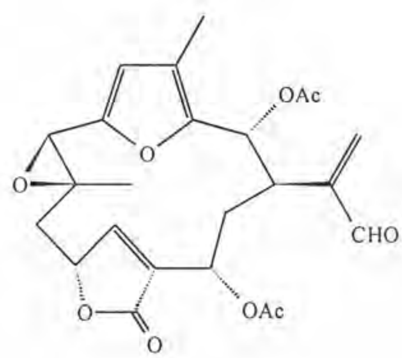
Bipinnatin A



Bipinnatin B

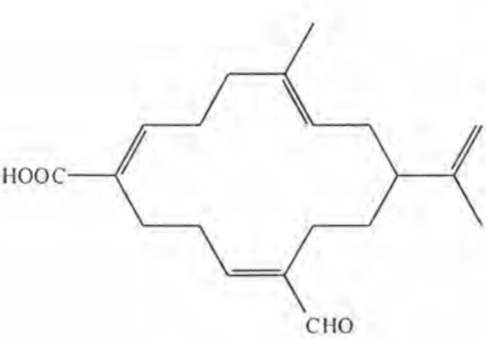


Bipinnatin C



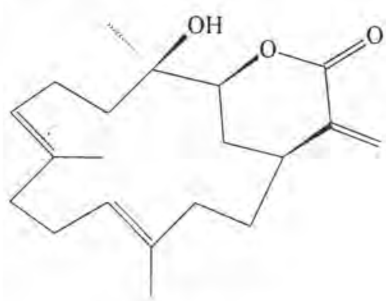
Bipinnatin D

In 1990, Jente, R. and co-worker [53] isolated a new macrocyclic diterpene (*3E,7E,11E*)-20-oxocembra-3,7,11,15-tetraen-19-oic acid (cleomaldeic acid) from *Cleome viscosa*.

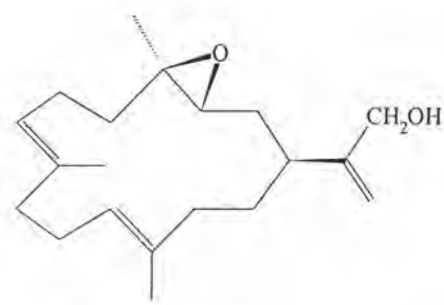


Cleomaldeic acid

In 1993, Shin, J. and co-worker [54] found 14-deoxycrassin and pseudoplexaurol from Caribbean gorgonian of genus *Eunicea*, which displayed potent antitumour property when screened against a panel of five human tumor cell lines. The cytotoxic activities of 14-deoxycrassin were established on the following cell lines: on human colon (HCT 116), IC_{50} = 2 μg/ml, on melanoma (SK5-MEL), IC_{50} = 0.5 μg/ml, and on kidney carcinoma (A 498), IC_{50} = 0.2 μg/ml. The cytotoxic activities of pseudoplexaurol were as follows: on human breast (MCF-7), IC_{50} = 20 μg/ml, on colon (HCT 116), IC_{50} = 10 μg/ml, and on T cell leukemia (CCRF-CEM), IC_{50} = 0.15 μg/ml.

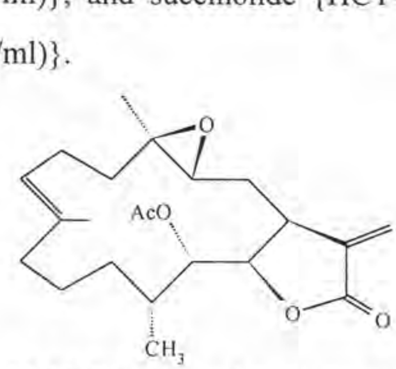


14-Deoxycrassin

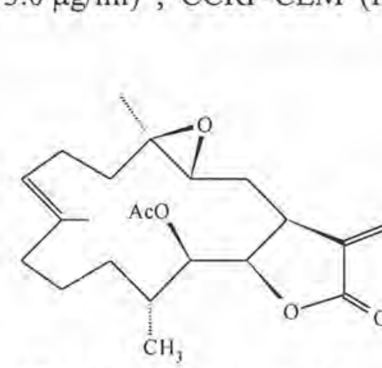


Pseudoplexaurol

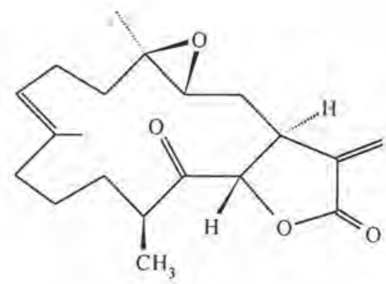
In the same year, Rodriguez, A. D., and Dhasmana, H. [55] studied the diterpenoid content of the Caribbean gorgonian *Eunicea succinea* and found three new cembranolide diterpenes, named 12,13-bisepieupalmarin acetate, 12-*epi*-eupalmarin acetate, and succinolide. The cytotoxic activities of the new compounds were as follows: 12,13-bisepieupalmarin acetate {HCT 116 (IC_{50} = 0.4 μg/ml) ; MCF-7 (IC_{50} = 6.0 μg/ml) ; SK5-MEL (IC_{50} = 5.0 μg/ml)}, 12-*epi*-eupalmarin acetate {HCT 116 (IC_{50} = 8.0 μg/ml) ; MCF-7 (IC_{50} = 8.0 μg/ml) ; CCRF-CEM (IC_{50} = > 50 μg/ml)}, and succinolide {HCT-7 (IC_{50} = 3.0 μg/ml) ; CCRF-CEM (IC_{50} = > 50 μg/ml)}.



12,13-Bisepieupalmarin acetate

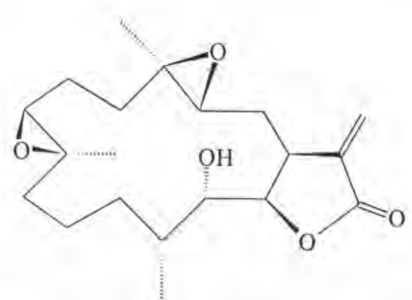


12-*epi*-Eupalmarin acetate

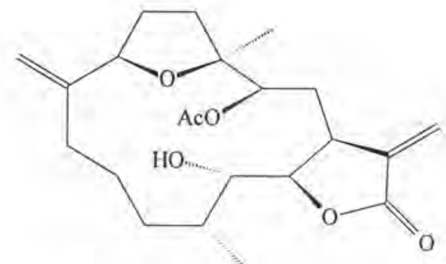


Succinolide

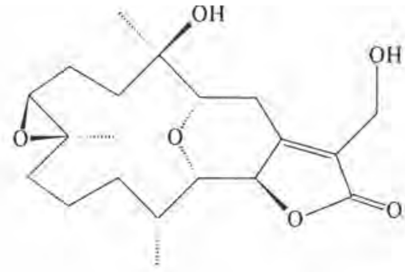
In 1998, Rodrignez A. D. and Acosta, A. L. [56], continued their search for new bioactive cembranolides from the Caribbian Sea. They had investigated a specimen of *Eunicea succinea* collected near Mona Island of the West Coast of Puerto Rico. Seven new cembranolides were found, which five of them belong to the "uprolide family" of Caribbean cembranolides. The NCI in vitro primary disease-oriented antitumor screen was used to ascertain the cytotoxic properties of three of the cembranolides. Of these compounds, 12, 13-bisepieupalmerine epoxide was the most promising, with concentrations of 10^{-6} M eliciting strong differential responses at LD_{50} level from nearly all the breast cancer cell lines and from several of the colon cancer cell lines. On the otherhand, eunicenolide was the least toxic, displaying moderate cytotoxicity against only one ovarian (IGROV1), one nonsmall cell lung (NCI-H522), and two leukemia (CCRF-CEM and RPMI-8226) cancer cell lines at concentrations of 10^{-5} M. Finally, at 10^{-6}–10^{-7} M. 12,13-Bisepiuprolide D acetate displayed strong nonselective cytotoxicity against almost all of the NCI panel cell lines.



12,13-Bisepieupalmerin epoxide

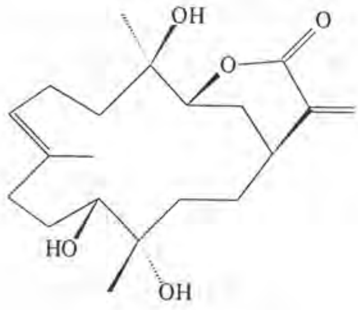


12,13-Bisepieuprolide D acetate

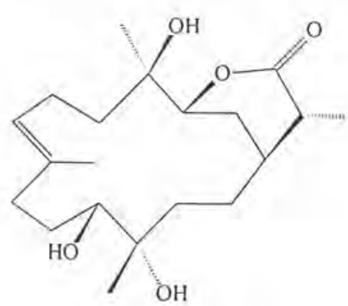


Eunicenolide

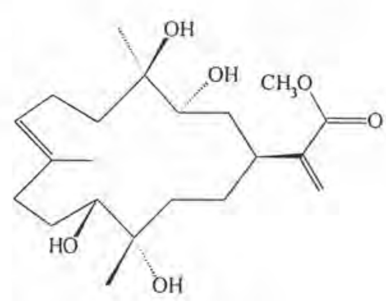
In the same year, Duh, C-Y. and co-worker [57] studied soft coral *Sinularia flexibilis* and found three new cytotoxic cembranoid diterpenes, sinuflexolide, dihydrosinuflexolide, and sinuflexibilin. Its CH_2Cl_2 extracts showed significant cytotoxicity in A549 (human lung adenocarcinoma), HT-29 (human colon adeno-carcinoma), KB (human epidermoid carcinoma), and P-388 (mouse lymphocytic leukemia) cell cultures.



Sinuflexolide

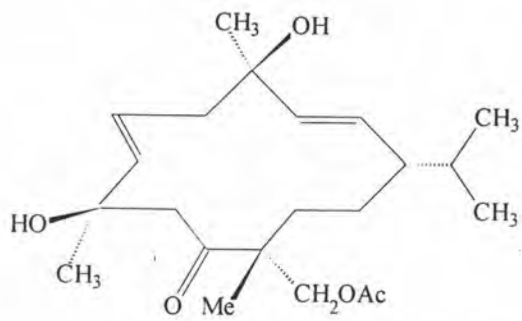


Dihydrosinuflexolide

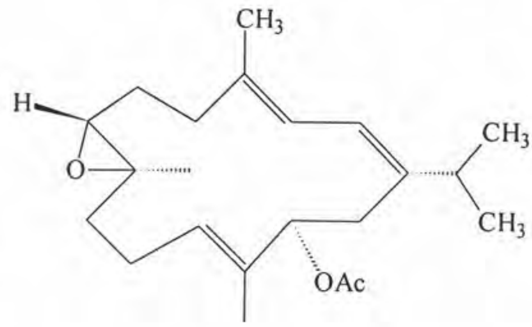


Sinuflexibilin

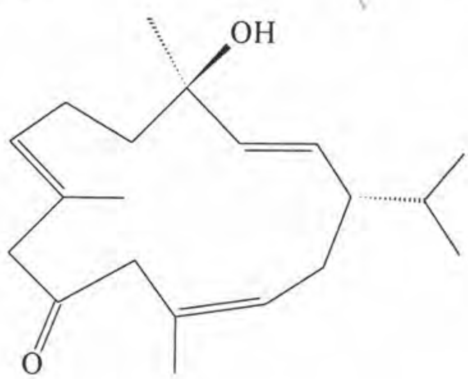
In 1999, Iwagawa, T. and co-worker [58] isolated three new cembranes, sartol acetate B, having a 13-membered carbocyclic ring; epoxysartone B, and sartone E, and three known cembranes, sartiones A and B and sarcotol acetate, from the soft coral *Sarcophyton* sp. Sartol acetate B and sartone E did not show ichthyotoxicity against killifish, *Oryzia latipes*, at a concentration of 20 μg/ml. The ichthyotoxicity test was not performed for epoxysartone B, because it decomposed.



Sartone acetate B



Epoxysartone B



Sartone E