CHAPTER-I

Introduction to five and ten membered lactone natural products

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Synthesis is a very important area to all parts of chemistry.[1] It encompasses the distinctive capability of chemists to develop new methods and to design molecules with a preferred set of properties. The practical and inventive nature of the 'chemical synthesis' is distinctive among all of the physical sciences. This is particularly true of research in the synthesis of natural products. Although various techniques are available to the natural product isolation chemists, it is not possible all the time to establish the complete structure and stereochemistry of natural product based on the spectroscopic techniques. Hence, chemical synthesis is very useful method and plays an important role in determination of structure.

The field of synthesis of natural products has been acknowledged with the Nobel Prize in chemistry with regular recurrence over the whole history of the award. These prizes have been awarded to E. Fischer (1902) for the syntheses of purine and sugar, H. Fischer (1930) for his research on the constitution of chlorophil, haemin and particularly for the haemin synthesis, R. Robinson (1947) for his explorations on biological importance of plant products, specifically the alkaloids, R. B. Woodward (1965) for the outstanding accomplishment on the art of organic synthesis and E. J. Corey (1990) for his theory and methodology development of organic synthesis. Recently, the field of organic synthesis comes into view as imperative as ever, and its prospect appears as

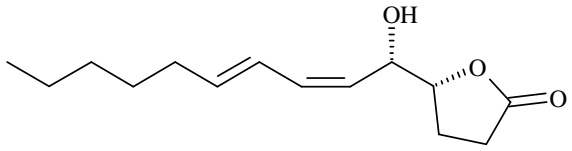
proficient as its history has been gratifying. There are several motivations why the synthesis of natural products endured the test of time as a rewarding and facilitating science and technology, its attractiveness as an inventive and intellectual effort offering possibilities for discovery. Even though the topic of synthesis of natural product is attracting a vigorous attention in research laboratories all over the world today, the causes for practicing it show a discrepancy. In general isolation of natural product is in small amount, however biologically interesting. Hence the synthesis of natural product in larger extent is important for further extensive evaluation of medicinal or biological properties. Furthermore the synthesis of a natural product still gives the absolute evidence of the assigned structure. Finally, there are those who will courageously and proudly declare that they enter campaign of total synthesis for the intellectual challenge and complete exhilaration of the endeavor. Due to this exciting information, we became involved in the synthesis of biologically active compounds as a part of our research work.

1.1. Five membered lactones:

Five membered lactone (γ-lactone) containing natural products are known to exhibit various of biological activities[2] such as cytotoxic,[3] antitumor,[4] cyclooxygenase or phospholipase A2 inhibition.[5] These are of fungal, bacterial or marine source. The natural products with γ-lactone

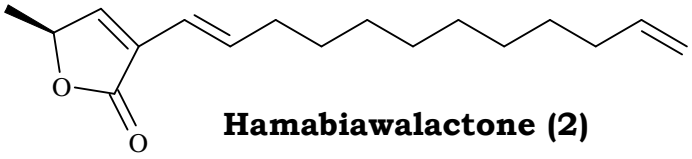
motif also showed valuable pharmacological properties. Biological properties, structural complexities of γ-lactone molecules, and challenges to synthesize in optically pure form, which are made them an attractive target for various total syntheses. Isolation and biological properties of some γ-lactone containing natural products are described below.

(R)-5-((S,2Z,4E)-1-hydroxydeca-2,4-dienyl)dihydrofuran-2(3H)-one (1):[6] It is a γ-lactone containing unsaturated side chain and hydroxy group. The compound **1** was isolated from *Lithophiton arboretum* by Tomas Rezanka *et al.* and it exhibits strong antibacterial activity against *Staphylococcus aureus* (MIC = 7.8 μg/ml). The structure of **1** was established by spectroscopic analysis and absolute configuration determined by Mosher's ester method.

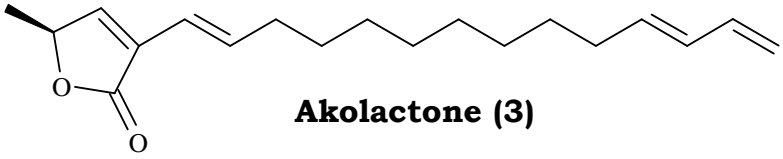


(R)-5-((S,2Z,4E)-1-hydroxydeca-2,4-dienyl)dihydrofuran-2(3H)-one (**1**)

Hamabiawalactone B (2) and akolactone B (3): Hyeong Kyu Lee *et al.* isolated Hamabiawalactone B (**2**) and Akolactone B (**3**) from the leaves of *Litsea japonica.*[7] The molecules **2** and **3** found to have potent anti-complement activity with IC_{50} values of 149 and 58 μg/ml respectively, when compared to rosmarinic acid (IC_{50}, 180 μg/ml), which was utilized as a positive control.

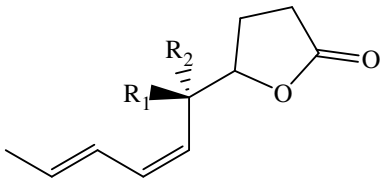


Hamabiawalactone (2)



Akolactone (3)

Sapinofuranones A and B (4 and 5): Two novel 5-substituted dihydrofuranones, apinofuranones A and B (**4** and **5**),[8] were isolated from liquid cultures of *Sphaeropsis sapinea*, which is a phytopathogenic fungus causing a variety of infection symptoms on conifers. They exhibit more phytotoxic activity on internal bark tissues than on peripheral ones. The structures of molecules were established by spectroscopic analysis and absolute configuration determined by Mosher's ester method.

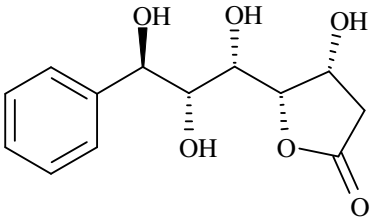


Apinofuranones A (4) R_1=OH, R_2=H

Apinofuranones B (5) R_1=H, R_2=OH

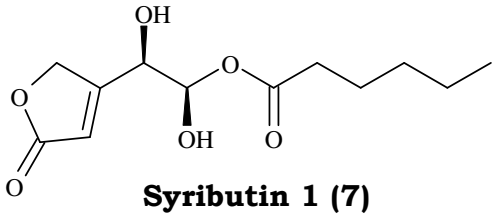
(+) Cardiobutanolide (6): The (+) cardiobutanolide[9] (**6**) was isolated from the stem bark of *Goniothalamus cardiopetalus*. The plant *Goniothalamus cardiopetalus* exhibits a variety of therapeutic actions in traditional

medicine to cure the edema, rheumatism, and as mosquito repellents. The structure of compound was established by spectroscopic methods.

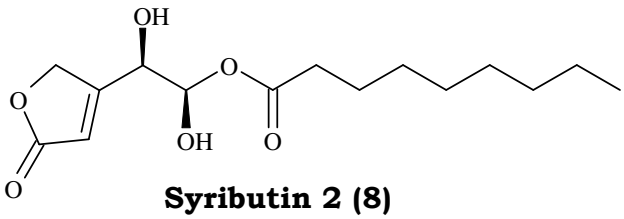


(+) Cardiobutanolide (6)

Syributin 1 (7) and Syributin 2 (8): Sims *et al.* isolated syributin 1 (**7**) and syributin 2 (**8**)[10] along with secosyrins, as co-isolates of syringolide from *Pseudomonas syringe*. The plant from which these compounds isolated, exhibited a variety of medicinal activities. The structures of compounds were established by spectral methods.

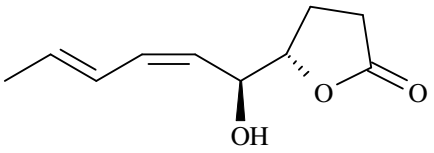


Syributin 1 (7)

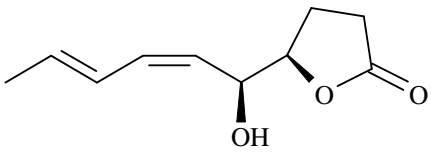


Syributin 2 (8)

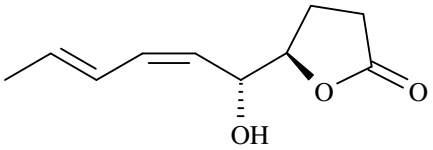
Sapinofuranones (9, 10 and 11): Simpson *et al.* isolated a novel metabolite sapinofuranone B[11] (**9**) from fermentation extracts of *Saphaeropsissapinae*. Subsequently, closely related lactones sapinofuranone A (**10**) and ent-sapinofuranone B (**11**) were isolated from *Saphaeropsissapinae* liquid cultures.



Sapinofuranone B (9)



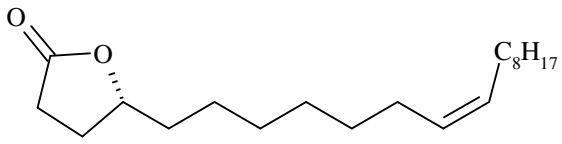
Sapinofuranone A (10)



ent-sapinofuranone B (11)

(4R,9Z)-9-Octadecen-4-olide (12):

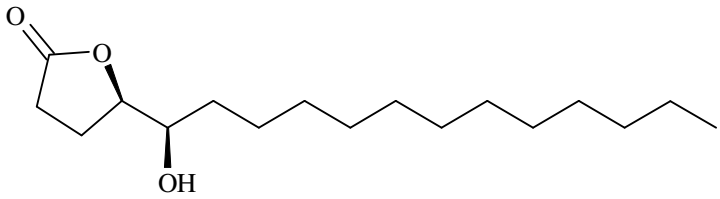
(4R,9Z)-9-Octadecen-4-olide (**12**) is the female sex pheromone of the female currant stem girdler, Janus integer, which is an occasional pest of red currant in North America and was isolated by Cosse *et al.* The compound **12** was isolated as a single enantiomer and its absolute configuration was proposed as *R*-configuration by a bioassay of synthetic samples.[12]



(4R,9Z)-9-Octadecen-4-olide (12)

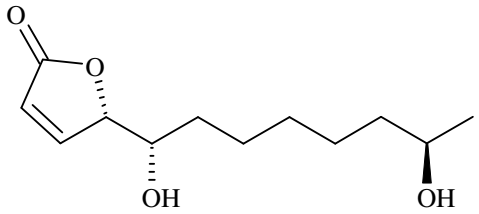
Muricatacin (13): J. L. McLaughlin *et al.* isolated muricatacin (**13**) as a novel metabolite from *Annona muricata.* The antitumor activities in addition to the patented pesticidal applications of the bark and seed

extracts from this family hold admirable prospective for development. The structure of **13** was established by spectral methods.[13]



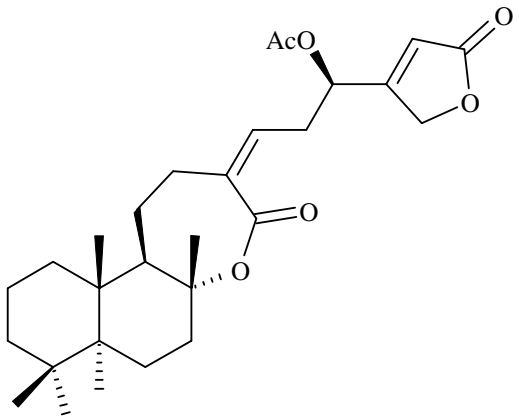
Muricatacin (13)

Iso-cladospolide-B (14): Ireland *et al.* isolated iso-cladospolide-B (**14**) [14] from a tissue sample of a marine sponge. The structure was determined by spectral methods and the absolute configuration was established by its total synthesis.



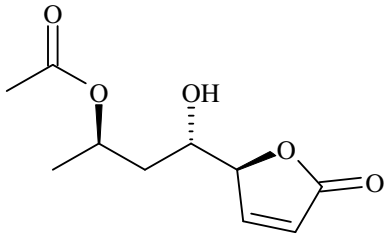
Iso- cladospolide B (14)

(+)-Luffalactone (15): De Silva *et al.* isolated (+)-luffalactone (**15**) from marine sponge *Luffariella variabilis*. It exhibits strong anti-inflammatory activity. The structure was determined by spectral studies and the absolute configuration at C-16 was established by Pilar Basabe *et al.* in 2009, by synthesis of the (+)-luffalactone.[15]



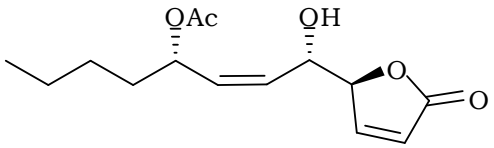
(+)-Luffalactone (15)

Botryolides E (16): James B. Gloer *et al*. isolated botryolide E (**16**) from the cultures of a fungicolous isolate of *Botryo trichum* sp. (NRRL 38180), in 2008.[16] The structure was determined by spectral data. The absolute configuration of **16** was determined by modified Mosher's method.



Botryolide E (16)

Pectinolide H (17): R. Perda-Miranda *et al*. isolated pectinolide H from the chloroform extract of the aerial parts of a Mexican terrestrial plant *Hyptis pectinata*. It displays strong antimicrobial activity against a panel of multidrug-resistant strains of *Staphylococcus aureus*. [17]



Pectinolide H (17)

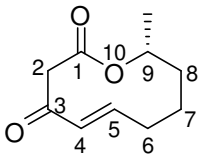
1.2. Ten membered ring containing macrolides

Natural products containing a macrolactone structure can be originated in bacteria, plants, insects and they may be of marine or terrestrial source. The valuable activities of macrolides vary from perfumery to medicinal and biological properties. The new results in the field of antibiotic and other antitumor active macrolides, accompanied by pheromones and plant growth regulators with macrolactone skeleton, are a motivation to chemists to study macrolides.

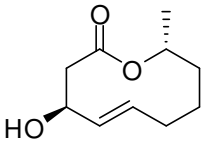
In relation to lactone structures and biosynthesis, these are classified into monocyclic oxylipins, monocyclic polyketides, aromatic bicyclic and aliphatic bicyclic lactones. In every subsection, these macrolides are explained in sequential order of their isolation.

1.2.1. Diplodialides:

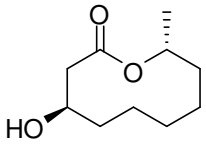
Diplodialides (**18-21**) are monocyclic ten-membered-ring containing lactones. In 1975, diplodialides A, B and C were isolated by Ishida and Wada, from the plant pathogenic fungus *Diplodia pinea.*[18] The isolation of diplodialide D (**21**)[19] and the structural elucidation of the metabolites,[20] were established by the same authors. (+) Diplodialide A (**18**) exhibited inhibitory activity against steroid 31674 hydroxylase.



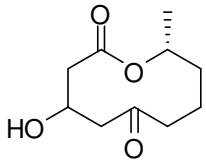
(+)-Diplodialide A (18)



(-)-Diplodialide B (19)

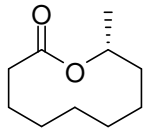


(+)-Diplodialide C (20)

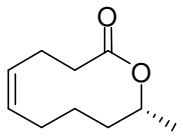


Diplodialide D (21)

1.2.2. Phoracanthonolides: The phoracanthonolides I (**22**) and J (**23**) were isolated from the secretion of the metasternal gland of eucalypt longicorn *Phoracantha synonyma* in 1976[21] and are structurally simple decalactones.

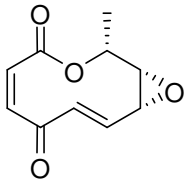


(-)-Phoracanthonolide I (22)

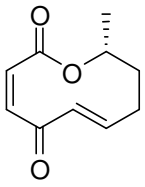


(-)-Phoracanthonolide J (23)

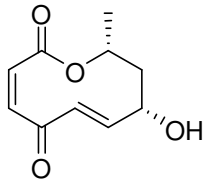
1.2.3. Pyrenolides: Pyrenolides A, B and C (**24–26**) were isolated by Nukina group, from the *Pyrenophora teres*[22,23] in 1980. Pyrenolide A also isolated from culture filtrates of *Ascochyta hyalospora*[24] in 1992. These show morphogenic and growth inhibition activities against fungi.



(-)-Pyrenolide A (24)



(-)-Pyrenolide B (25)



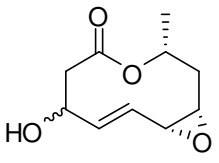
(-)-Pyrenolide C (26)

1.2.4. Decarestrictines: A series of metabolites were generated by various strains of *Penicillium* species were isolated in the early 1990s and called as decarestrictines. These lactones exhibited to be inhibitors of cholesterol biosynthesis and explained by both *in vivo* and *in vitro* studies.[25]

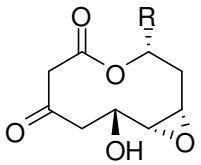
Most of the decarestrictines consist of ten-membered lactone moiety that varies in the oxygenation mold between C3 and C7. Five of them bear an epoxide function at C6–C7 such as A_1 (**27**), A_2 (**28**), B (**29**), E (**30**), and F (**34**), and eight of them A_1 (**27**), A_2 (**28**), C_1 (**31**), C_2 (**32**), D (**33**), F (**34**), H (**36**), K (**38**) contain a double bond, and seven of the decarestrictines B (**29**), E (**30**), F (**34**), G (**35**), H (**36**), J (**37**), K (**38**) are β-keto lactones.

The most biologically active decarestrictine D (**33**), was individually isolated from the Canadian Tuckahoe, the sclerotium of the *Polyporus tuberaster* fungus and called as tuckolide.[26]

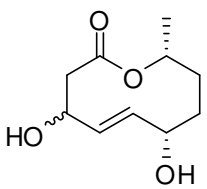
A C6-epimer of decarestrictine C_1 was obtained from the fungus *Cordyceps militaris*.[27] Multiplolides A and B, the lactones with epoxy ring (**40 and 41**) were isolated from *Xylaria multiplex*, and are closely correlated with the decarestrictine family.[28]



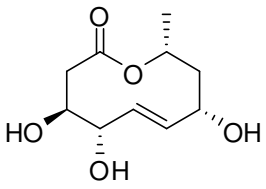
A_1 (a-OH) (27)
A_2 (b-OH) (28)



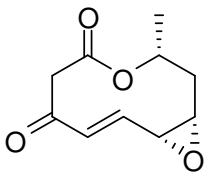
(+)-B R = H (29)
(-)-E R = CH_3 (30)



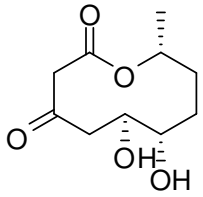
C_1 (b-OH) (31)
C_2 (a-OH) (32)



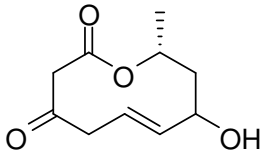
(-)-D (33)



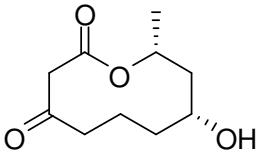
F (34)



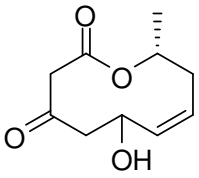
(-)-G (35)



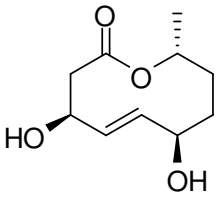
H (36)



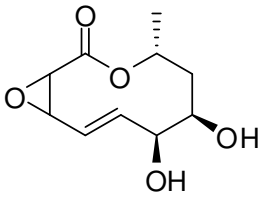
(-)-J (37)



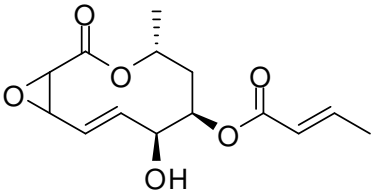
K (38)



6-epi -C_1 (39)



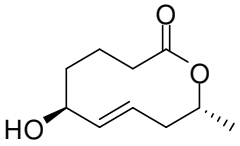
Multipolide A (40)



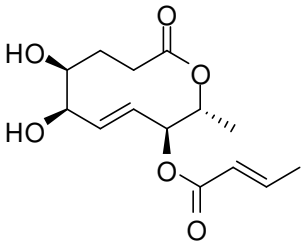
Multipolide B (41)

1.2.5. Aspinolides:

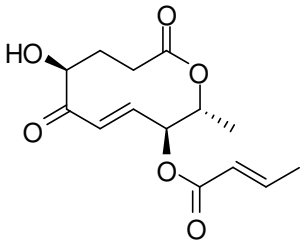
Aspinolides A–C (**42-44**) were isolated from the cultures of *Aspergillus ochraceus*, in 1997. The absolute configuration and structure elucidation evaluated by X-ray alalysis and Helmchen's method.[29]



Aspinolide A (42)



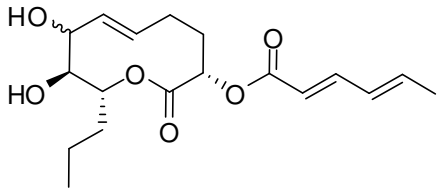
Aspinolide B (43)



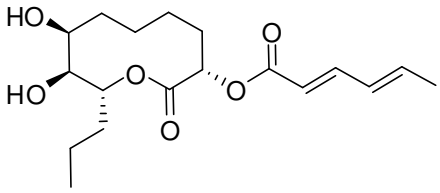
Aspinolide C (44)

Aspinolides are characterized by the occurrence of a methylcarbinol moiety in their structures and their C9-center is usually with the (*R*)-configuration, represents the starter unit in the polyketides biosynthesis.[30]

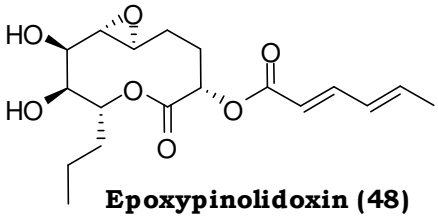
1.2.6. Pinolidoxins: Pinolidoxin (**45**), a decalactone isolated by evidente *et. al* from *Ascochyta pinoda* in 1993,[31] and also three similar macrolides, dihydropinolidoxin (**47**), epipinolidoxin (**46**) and epoxypinolidoxin (**48**) were isolated[32] and evaluated on bean and pea leaves, initial three molecules were exhibited to be highly toxic, but epoxypinolidoxin was inactive.



(+)-Pinolidoxin (b-OH) (45)
(+)-Epipinolidoxin (a-OH) (46)

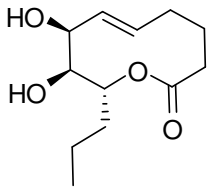


Dihydropinolidoxin (47)

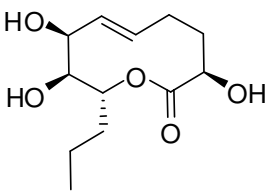


Epoxypinolidoxin (48)

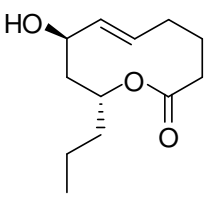
1.2.7. Herbarumins: Rivero-Cruz *et al.*[33,34] isolated three hexaketides from fungus *Phoma* (*P. herbarum*), and named as herbarumins I–III (**49-51**). These macrolides interact with the calmodulin of bovine brain and inhibit the cAMP phosphodiesterase enzyme activation.



(+)-Herburamin I (49)

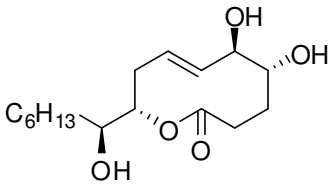


(+)-Herburamin II (50)

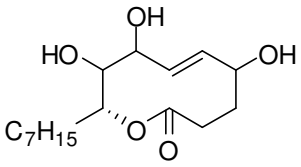


(+)-Herburamin III (51)

1.2.8. Microcarpalide: In 2001, Hemscheidt *et al.* isolated microcarpalide (**52**) from the fermentation broths of an unknown endophytic fungus.[35] This molecule works as a microfilament-disrupting agent, and it shows weak cytotoxic activity against mammalian cells. It molecular formula similar with achaetolide (**53**)[36], but differs in the position of the double bond and the hydroxy groups.

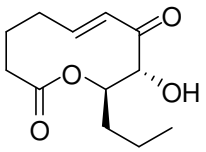


(-)-Microcarpalide (52)

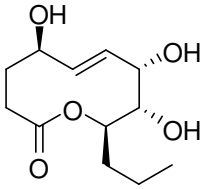


(-)-Achaetolide (53)

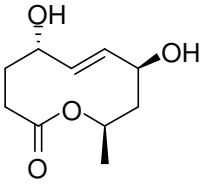
1.2.9. Stagonolides: Evidente[37,38] *et al.* isolated new phytotoxic metabolites from *Stagonospora cirsii*, which is a fungal pathogen isolated from *Cirsium arvense* and anticipated as a prospective mycoherbicide of this perennial toxic weed, generates phytotoxic metabolites in solid and liquid cultures. Stagonolides A-D (**54-57**), with remarkable phytotoxic activities were isolated from a liquid culture. The same fungus, grown-up in solid culture, showed an improved ability to produce five new nonenolides, called stagonolides E-I (**58-62**).



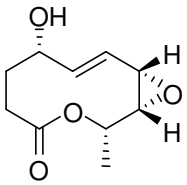
Stagonolide A (54)



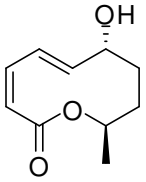
Stagonolide B (55)



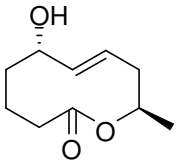
Stagonolide C (56)



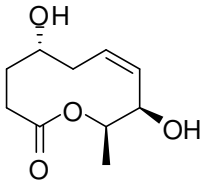
Stagonolide D (57)



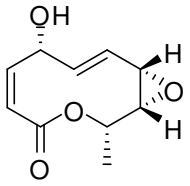
Stagonolide E (58)



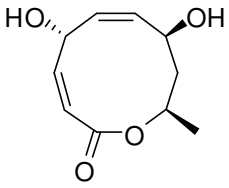
Stagonolide F (59)



Stagonolide G (60)



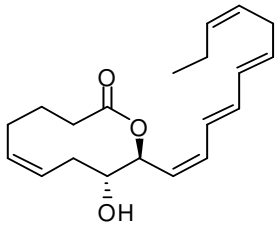
Stagonolide H (61)



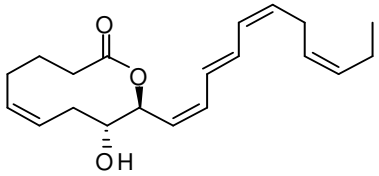
Stagonolide I (62)

1.2.10. Didemnilactones and Ascidiatrienolides:

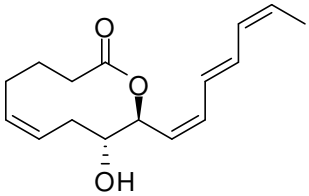
In the early 1990s, Niwa *et al.* isolated didemnilactones A and B (**63 and 64**), ascidiatrienolide A and neodidemnilactone (**65 and 66**). [39,40] These eicosanoid lactones were isolated from the marine tunicate *Didemnum moseleyi*, and exhibited modest inhibitory activity toward lipoxygenase.



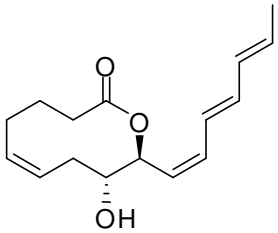
(-)-Didemnilactone A (63)



(-)-Didemnilactone B (64)



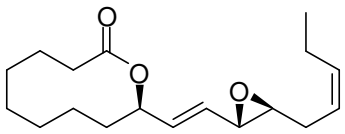
(-)-Ascidiatrienolide A (65)



(-)-Neodidemnilactone (66)

1.3. Mueggelone or Gloeolactone:

A lactone with 18-carbons and epoxy group (**67**) was isolated from the *Aphanizomenon flos-aquae,* a cyanobacterium in 1997, it was exhibited to be a fish development inhibitor, and called as mueggelone.[41] The same lactone was isolated from the blue-green algae *Gloeotrichia* sp., and was named as gloeolactone.[42]



(+)-Muggelone or gloeolactone(67)

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