

Pyrone-derived Marine Natural Products: A review on Isolation, Bio-activities and Synthesis

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Abstract:

Marine natural products (MNPs) containing pyrone rings have been isolated from numerous marine organisms, and also produced by marine fungi and bacteria, particularly, actinomycetes. They constitute a versatile structure unit of bioactive natural products that exhibited various biological activities such as antibiotic, antifungal, cytotoxic, neurotoxic, phytotoxic and anti-tyrosinase. The two structure isomer of pyrone ring is γ -pyrone and α -pyrone. In terms of chemical motif, γ -pyrone is the vinylogous form of α -pyrone which possess a lactone ring. Actinomycete bacteria are responsible for the production of several α -pyrone compounds such as elijopyrones A-D, salinipyrones and violapyrones etc. to name a few. A class of pyrone metabolites, polypropionates which has fascinating carbon skeleton are primarily produced by marine molluscs. Interestingly, some of the pyrone polyketides which are found in cone snails are actually synthesized by actinomycete bacteria. Several pyrone derivatives were obtained from marine fungi such as *Aspergillus flavus*, *Altenaria sp.*, etc. The γ -pyrone derivative namely, kojic acid obtained from *Aspergillus* fungus has high commercial demand and find various applications. Kojic acid and its derivative displayed inhibition of tyrosinase activity and, it is also extensively used as a ligand in coordination chemistry. Owing to their commercial and biological significant synthesis of pyrone containing compounds has been paid attention over the past years. Few reviews on the total synthesis of pyrone containing natural products namely polypropionate metabolites have been reported. However, these reviews skipped other marine pyrone metabolites and also omitted discussion on isolation and detailed biological activities. This review presents a brief account of the isolation of marine metabolites containing a pyrone ring and their reported bio-activities. Further, the review cover synthesis of marine pyrone metabolites such as cyercene-A, placidenes, onchitriol-I, onchitriol-II, crispatene, photodeoxytrichidione, (-) membrenone-C, lihualide-B, macrocyclic enol ethers and auriopyrones-A & B.

Keywords: Marine pyrones, Actinomycetes, Biological activities, Anti-tyrosinase, β -ketoester, Synthesis, Dess–Martin periodinane, Polypropionates.

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1. Introduction

The ocean not only supports/provides a livelihood to millions of people but also houses to several marine natural products that possess significant biological activities. Numerous marine natural products have been discovered from marine organisms such as soft corals, sponges, molluscs and microbes. There is steady increases in the number of secondary metabolites discovered from marine organisms as new molecules are being added. The major bioactive secondary metabolites isolated from the marine organisms include alkaloids [1], terpenes [2], peptide [3], sterols [4],etc. The chemicals and biological activities of these secondary metabolites have been presented in several published papers [5]. Recently, we have described the various pyrrole alkaloids with their biological activities [6] and also presented details on the marine natural products of oxazole, oxazoline, and isoxazoline [7].Marine natural products containing pyrone ring is found in various marine organisms. Particularly, 2-pyrone is often encountered in numerous marine organisms such as sponge, bacteria, and fungi. They exhibited several biological activities, including antibiotics, antifungal, cytotoxic, neurotoxic and phytotoxic [8].Structurally, pyrone has two isomers namely, α -pyrone and γ -pyrone (Figure 1).

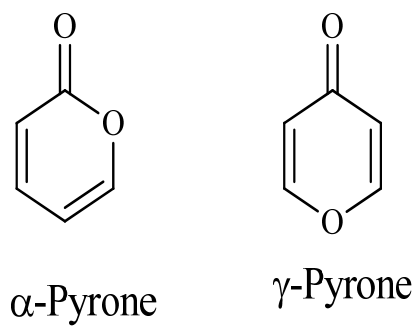


Figure 1. Chemical Structures of pyrones.

MNPs containing γ -pyrone are isolated from marine fungus, bacteria, mollusc and limited marine sponges and algae. The α -pyrone which possess a lactonic structure exhibited various biological properties and represent a highly valuable building block in synthetic chemistry [8]. This review presents an account of isolation and synthesis of pyrone-containing MNPs with their reported biological activities. The initial section of the review highlighted isolation and bioactivities and the subsequent section depicted the total synthesis of MNPs containing pyrone ring.

2. Marine natural products containing pyrone ring from Microbes:

Microbes are a source of several marine natural products including, those containing pyrone ring. Numerous compounds of natural products with pyrone ring have been reported from fungus, bacteria

and pure strains. The compounds obtained from these microbes along with their bioactivities are described in the following sub-headings.

2.1. Derived from Fungi

Marine fungi are well-known for the production of several natural products containing pyrone ring. Among the pyrone containing metabolites isolated from marine fungus, kojic acid (**1**) is one of the most prominent compounds. Kojic acid was first isolated by Saito in 1907 from the culture of *Aspergillus oryzae* and the name was given by Yabuta [9]. Kojic acid is mainly produced by *Aspergillus flavus* [10], *Aspergillusoryzae* [11], *Aspergillustamari* [12] and *Aspergillusparasiticus* [13] which were known to produce a large amount of kojic acid. Enormous interest has been paid on kojic acid in industries especially in cosmetic industries [14]. Indeed, kojic acid has several applications not only in cosmetic and pharmacology [15] but also have been used as a ligand in coordination chemistry such as Zn(II) [16] and Ru(II) [17] complexes to name a few. Further, it is well understood that several marine fungi derived compounds including pyrone-derivatives have a lot of scope in the future as cosmeceutical products [18].

In 2008 Lin *et al.* isolated two new α -pyrone compounds namely, 4-(hydroxymethyl)-5-hydroxy-2H-pyran-2-one (**2**) and (5-hydroxy-2-oxo-2Hpyran-4-yl) methyl acetate (**3**) from a marine-derived fungus *Aspergillus flavus* (Figure 2) [19]. The compounds **2** & **3** were tested for the cAMP assay on GPR12-transfected cells and their vector-transfected controls, namely human embryonic kidney cells (HEK293) and Chinese hamster ovary cells (CHO). The compound **2** was found to promote a significant cAMP increase in both GPR12-HEK293 cells and GPR12-CHO cells but no significant difference was observed on their vector controls. However, compound **3** did not show any activity at the specified concentration, 100 μ M and neither of the compounds **2** & **3** showed cytotoxicity at the concentration of 100 μ M.

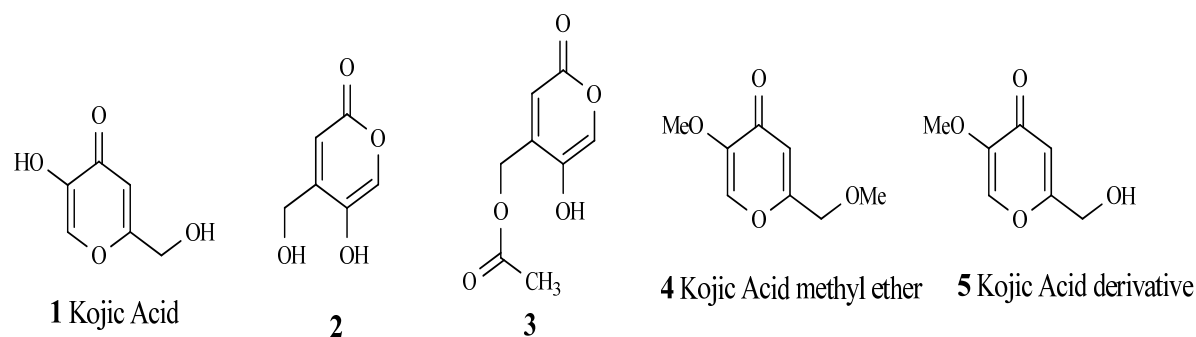


Figure 2. Chemical structures of kojic acid (**1**) and pyrone metabolites (**2-5**) isolated from marine-derived fungi *Aspergillus* and *Altenaria sp.*

Kojic acid (**1**) and two related γ -pyrone derivatives namely kojic acid methyl ethers (**4** & **5**) were isolated from marine the derived fungus *Altenaria sp.*(Figure 2) [20]. The compounds **4** and **5** did not show antityrosinase activity whereas, kojic acid showed significant activity with IC₅₀value of 12.0 μ M. Anti-tyrosinase action of kojic acid is well-understood. It is believed that kojic acid chelated copper ion contain in the active site of enzyme, thus preventing copper from activating tyrosinase which in turn prevent creating melanin.

Trisuwan *et al.* isolated three α -pyrone metabolites from the marine-derived fungus *Nigrospora sp.* PSU-F5 (**6-8**)(Figure 3)[21]. All these compounds showed insignificant antibacterial activities against both the tested strains, *Staphylococcus aureus* ATCC 25923 and MRSA SK1. A new γ -pyrone derivative, carbonaronesA(**9**) was isolated from a marine-derived fungus *Aspergillus carbonarius*[22]. Cytotoxicity screening of carbonaronesA (**9**) showed a moderate activity against K562 cells (IC₅₀, 56.0 μ g/mL).

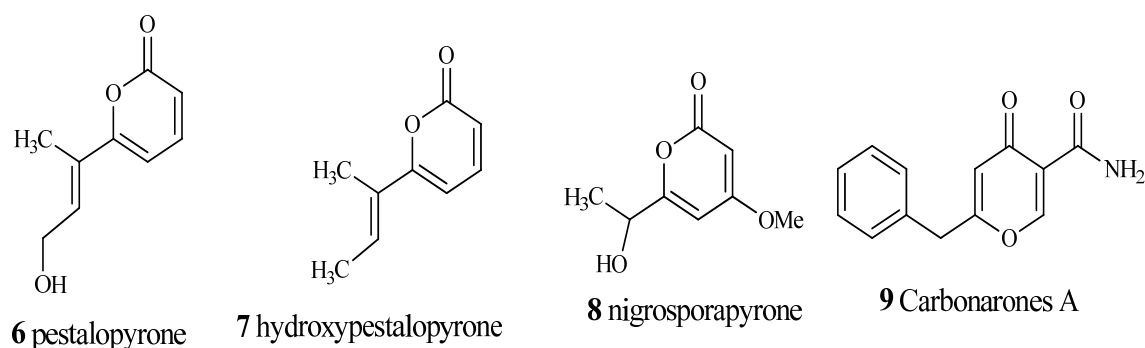


Figure 3. Chemical structures of pyrone metabolites (**6-8**) from the marine derived fungus *Nigrospora sp.* PSU-F5.

It is well-known that several fungal naphtho- γ -pyrones have potent antibiotics towards drug-resistance microbial pathogens [23] and possess a broad range of biological activities including cytotoxicity, antitumor and anti-HIV [24]. Zhu and co-workers isolated a series of naphtho- γ -pyrones compounds (**10-18**) from the marine-derived fungus *Aspergillus carbonarius*(Figure 4) [25]. The antimycobacterial activities of naphtho- γ -pyrones compounds **10**&**11** against *Mycobacterium tuberculosis*H37Rv displayed weak activity with MIC values of 43.0 and 21.5 μ m, respectively. In the subsequent year, several naphtho- γ -pyrones(**19-23**) along with pyrophen (**24**) and fonsedin(**25**) were isolated from the other marine-derived fungus namely, *Alternaria alternate* (Figure 5)[26]. Antibiotic screening of the compounds showed pyrophen (**24**) and rubrofusarin B (**19**) exhibited high and moderate activity against *C. albicans* while aurosperone A (**20**) showed activity against the plant pathogenic fungi, *Rhizoctonia solani*.

Three new naphtho- γ -pyrones, peninaphones A-C (**26-28**) along with the known bis-naphthopyrones (**29 & 30**) was just reported by Zheng *et al.* from a mangroverhizosphere soil-derived fungus *Penicillium sp.* HK1-22 (Figure 6)[27]. Screening of antibacterial activity of these compounds revealed that peninaphones A-C (**26-28**) showed only moderate activity against *Staphylococcus aureus* ATCC 43300 and 33591 with the MIC values of 12.5 and 25 $\mu\text{g/mL}$, respectively. However, neither of the two dimers (**29 & 30**) showed activity against the tested strains. Further, compound **28** showed significant antifungal activity against the crop pathogens namely, *Rhizoctonia cerealis*, *Rhizoctonia solani*, *Gaeumannomyces graminis*, and *Alternaria alternata*.

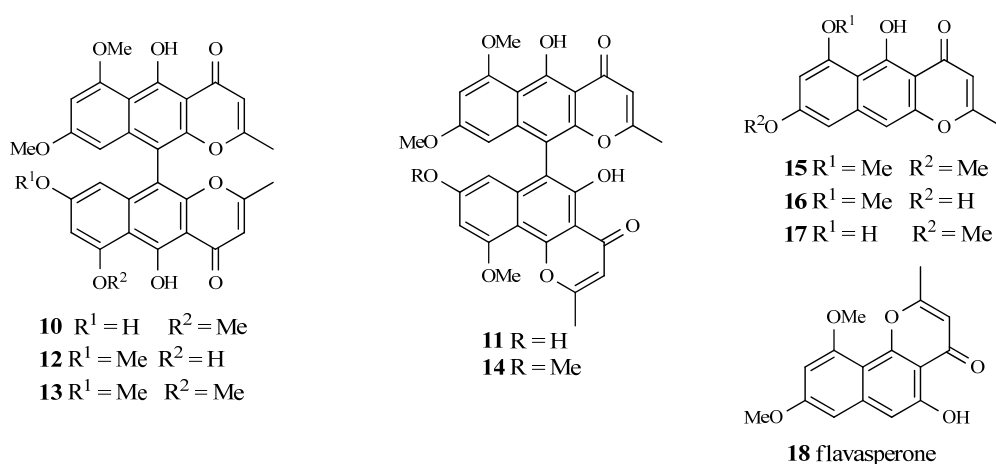


Figure 4. Structures of naphtho- γ -pyrones compounds (10-18) isolated from from the marine-derived fungus *Aspergillus carbonarius*.

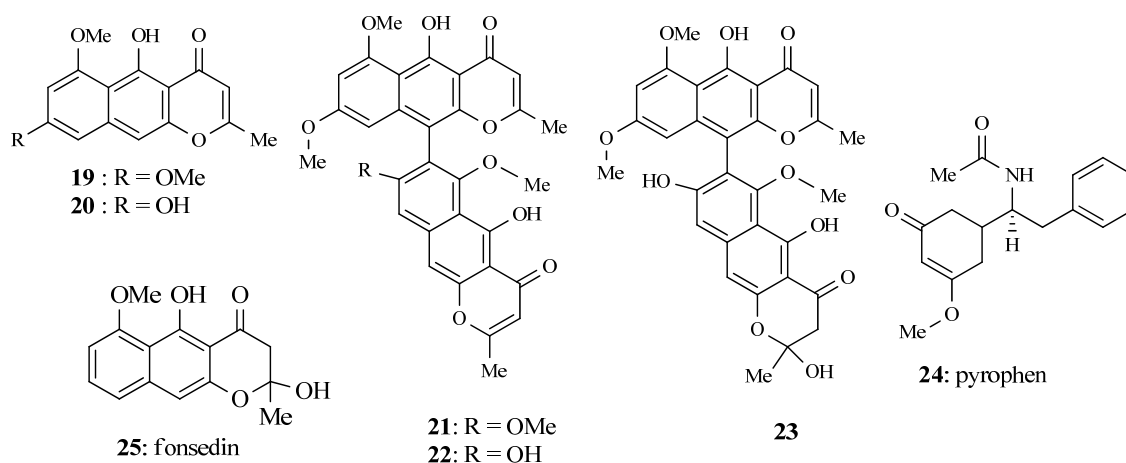


Figure 5. Naphtho- γ -pyrones (**19-23**) and pyrophen (**24**) and fonsedin (**25**) from the marine fungus *Alternaria alternata*.

Previously, Li and co-workers isolated the known naphtho- γ -pyrone derivatives, isochaetochromin-B₂(**30**) and ustilaginoidin D (**31**)(Figure 6) from the sponge-derived fungus *Metarhizium anisopliaemxh-99*[28]. Compounds **30** and **31** exhibited antitubercular activity against *Mycobacterium phlei* with the MIC value of 50 μ g/mL.

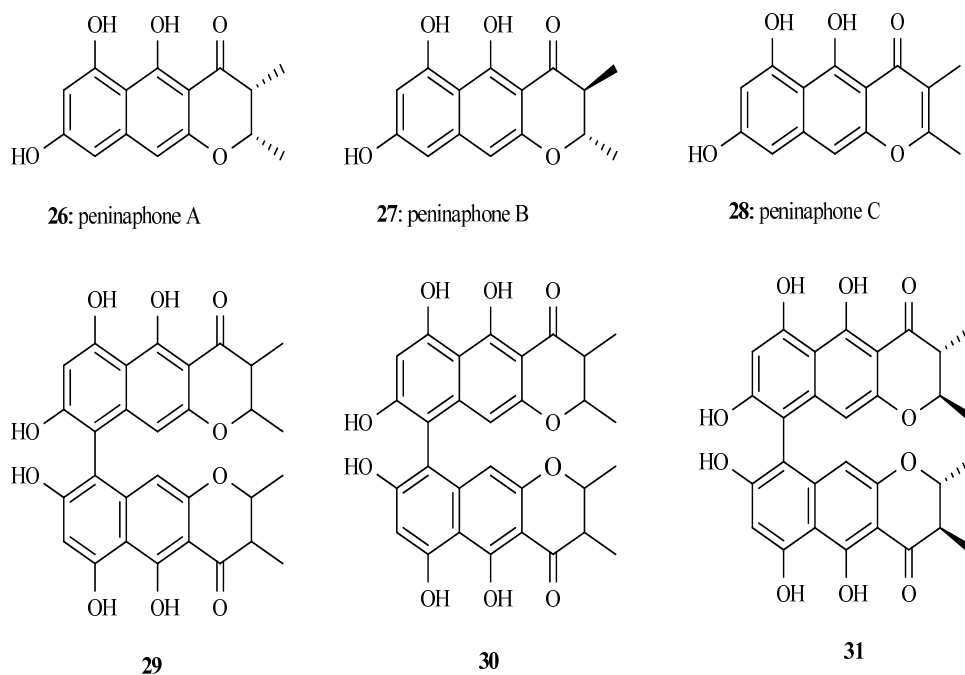


Figure 6. Chemical structures of naphtho- γ -pyrones, peninaphones A-C (**26-28**) and bis-naphthopyrones (**29-31**).

Very recently, new γ -pyrone containing polyketides, fusaresters A–E (**32-36**) were reported from the fungus *Fusarium sp.*(Figure 7) [29]. Cytotoxicity screening of the compounds **32-36** against the seven human cancer cell lines, namely SW480, HL-60, A549, MCF-7, HepG2, HeLa and SMMC-7721 as well as the inhibitory activity against protein tyrosine phosphatase 1B (PTP1B) showed that only the compound **33** exhibited a weak activity with inhibition rate of 56% at 40 μ M while rest were inactive.

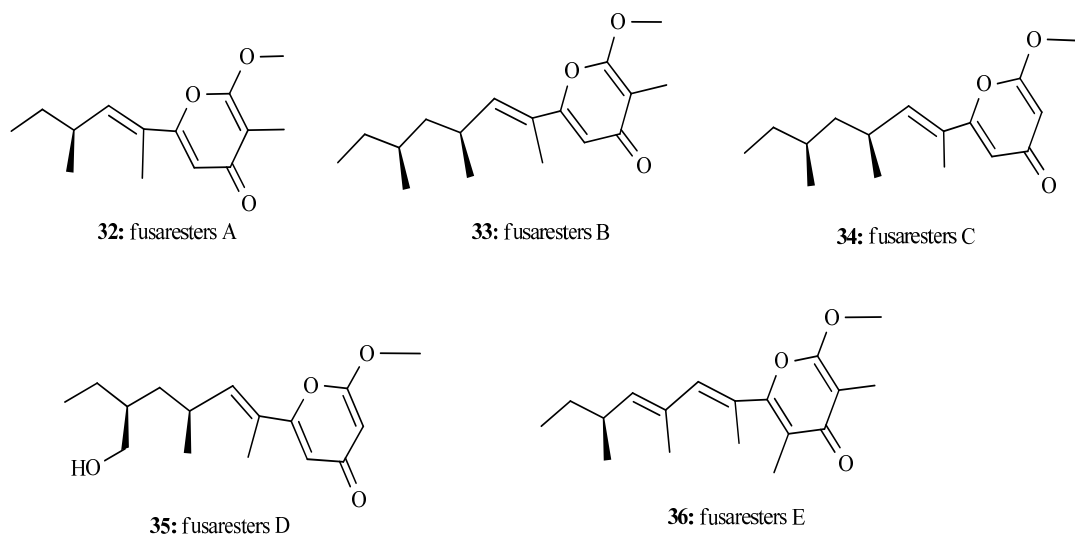


Figure 7. Chemical structures of fusaresters A–E (32–36).

In 2003, Jung and co-workers isolated five α -pyrone derivatives (37–41) along with the known kojic acid (1), of which two were new α -pyrone derivatives (37&38) from the sponge derived-fungus *Paecilomyces lilacinus* [30] whereas, the compounds (39 and 40) were previously reported from blackleg fungus [31] and *Helichrysum italicum* [32] (Figure 8). Four new pyrone derivatives, nigrosporapyrones A–D (42–45) along with the known pyrone derivatives (46) and (47) were isolated by Trisuwan *et al.* from the marine-derived fungus *Nigrospora sp.* PSU-F18 [33] (Figure 9). Antibacterial screening of the isolated compounds against *Staphylococcus aureus* ATCC 25923 (SA) and MRSA revealed that the compound 42 exhibited the best activity (MIC = 128 $\mu\text{g/mL}$), but the activity of the other compounds was not significant against both the strains.

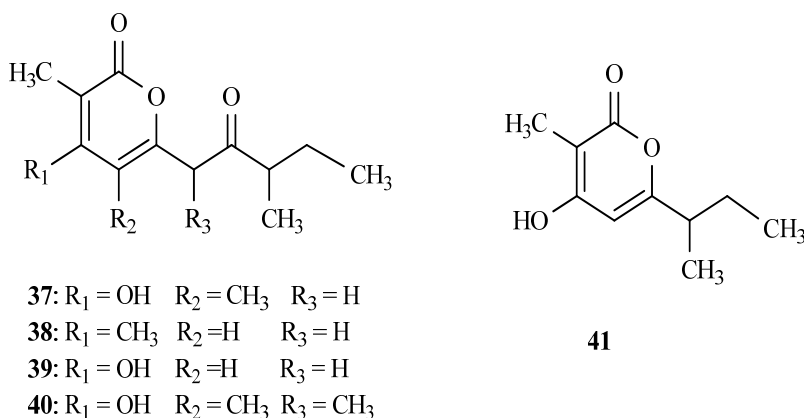


Figure 8. Chemical structures of α -pyrone derivatives (37–41).

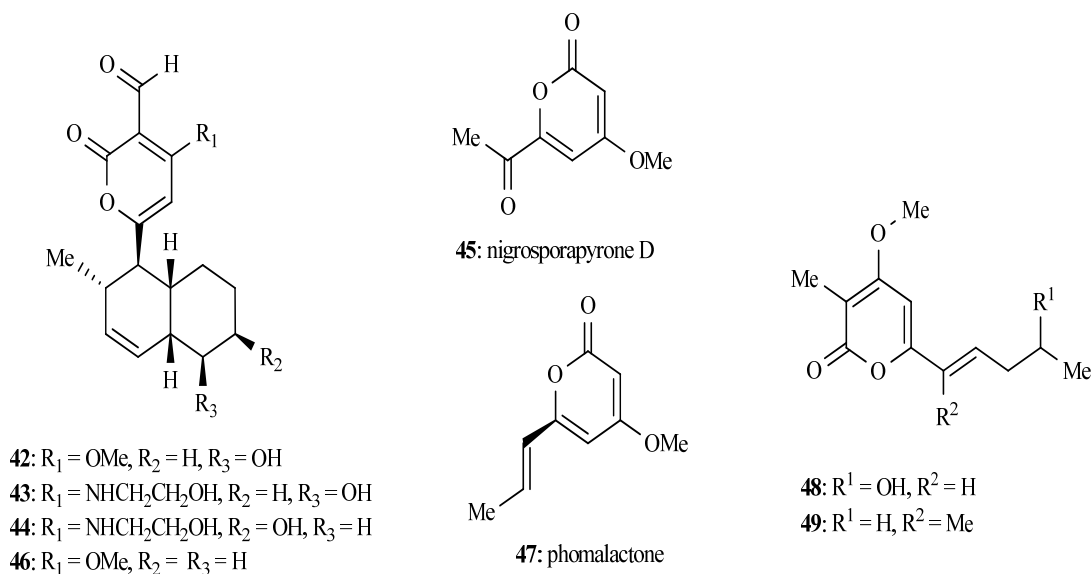


Figure 9. Chemical structures of nigrasporapyrones A-D (**42-45**) and α -pyrone derivatives 46-49.

It is noteworthy that fungi belonging to *Trichoderma sp.* are widespread in both terrestrial and marine environment e.g., soil, and association with higher plants and sponges. Wright's research group isolated pyrone derivatives, trichopyrone (**48**) and trichodermanone (**49**) from this marine-derived fungus (Figure 9)[34]. Bioassay of trichopyrone (**48**) including radical scavenging, antioxidant, antimicrobial, and inhibition of HIV-1 either showed weak or no significant effect.

A series of new pyrone derivatives verrucosidinol (**50**), verrucosidinol acetate (**51**), norverrucosidin (**52**) and verrucosidin (**53**) were isolated from the marine-derived fungus *Penicillium aurantiigriseum*(Figure 10)[35]. The structures of these compounds were established by NMR studies and the relative configuration of verrucosidinol acetate (**51**) was assigned to be the same as that of verrucosidin (**53**) [36]. The biological activity of these pyrone derivatives against the antimicrobial strain methicillin-resistant *Pseudomonas aeruginosa*, *Candida albicans* SC5314, *Staphylococcus aureus*, and synergistic antifungal activity with ketoconazole showed no significant activity.

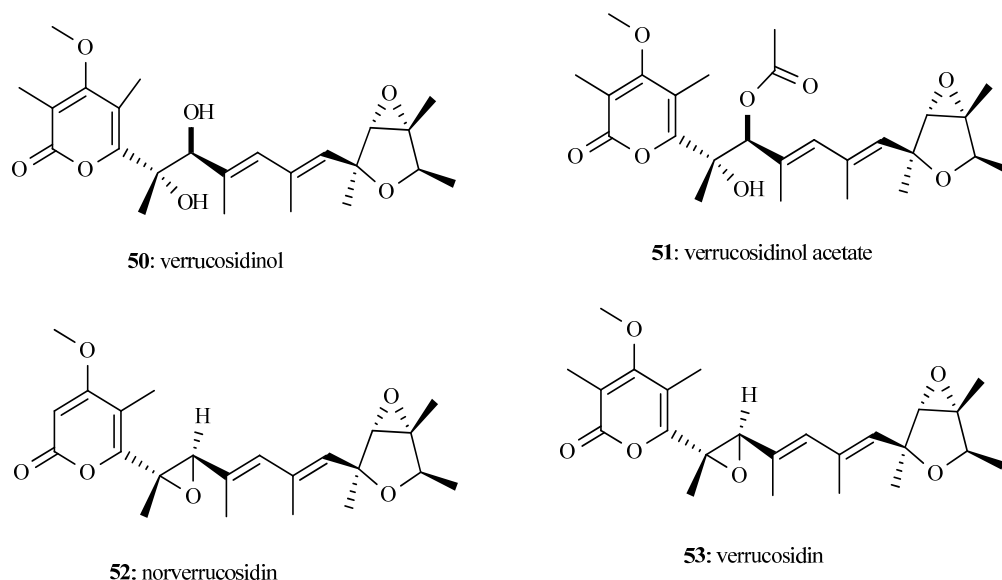


Figure 10. Chemical structures of verrucosidinol (**50**) and related pyrones (**51-53**).

In 2010, Ding *et al.* isolated four 4-hydroxy- α -pyrones, nipyrones A-C (**54-56**) from a marine sponge-derived fungus *aspergillus niger* (Figure 11)[37]. The compounds were tested for antibacterial activities, however, only nipyrene-C (**56**) exhibited significant activity against *S. aureus* and *B. subtilis*, (MIC = 8.0 and 16 $\mu\text{g/mL}$). Further, the compound (**56**) was found to exhibit weak antitubercular activity against *M. tuberculosis* (MIC = 64 $\mu\text{g/mL}$). The other two compounds, nipyrones-C & D (**54**&**55**) showed a moderate antibacterial activity against the four pathogenic bacteria with the MIC values ranging from 32–64 $\mu\text{g/mL}$. A new compound, penichrypyrone A (**57**) featuring γ -pyrone ring was just reported by He *et al.* from *penicillium chrysogenum* LS18 (Figure 11)[38]. The compound was evaluated for antioxidant activity but did not show any significant activity.

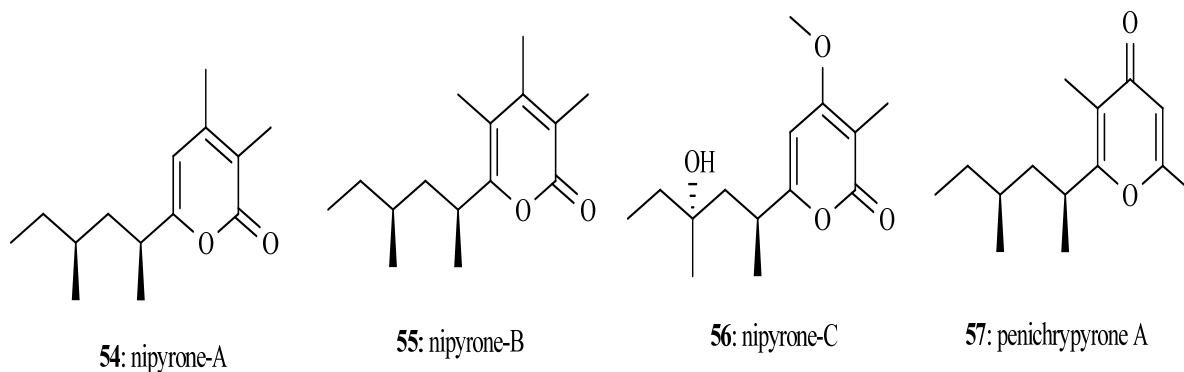


Figure 11. Chemical structures of nipyrones A-C (**54-56**) and penichrypyrone A (**57**).

In 2011, nigerapyrones A-H (**58-65**) and asniapyrones A&B (**66&67**), featuring α -pyrone ring was obtained from the *Aspergillus niger* MA-132 (Figure 12)[39]. Nigerapyrone-E (**62**) was cytotoxic against MDA-MB-231, SW1990 and A549 cell lines with IC_{50} values of 38, 48, 43 μM , respectively. On the other hand nigerapyrone-B (**59**) showed selective activity against HepG2 cell line (IC_{50} value of 62 μM) while asniapyrone A (**66**) against the A549 cell line (IC_{50} value of 62 μM). A moderate to weak activity against HepG2, MCF-7, and A549 cell lines were observed for nigerapyrone-D (**61**) ($IC_{50} = 81 \approx 121 \mu M$). However, antimicrobial assay of all these pyrone-derivatives against the two bacteria, *E. coli*, and *S. aureus* as well as four plant pathogenic fungi *alternaria brassicis*, *fusarium oxysporium*, *physalospora piricola* and *coniella diplodiella* did not show any activity.

In 2003, chemical investigation of fungus *Aspergillus niger* EN-13 by Zhang *et al.* afforded three naphtha- γ -pyrone derivatives nigerasperones A-C (**68-70**) (Figure 13)[40]. A few years later, they reported, isopyrophen (**71**) and aspergillusol (**72**) from the same endophytic fungus (Figure 14)[41]. Subsequently, chemical investigation of other endophytic fungus *Penicillium* sp. SK5GW1 isolated from mangrove resulted in the isolation of α -pyrone meroterpenoids, namely, arisugacin B (**73**), arisugacin D (**74**), territrem C (**75**), terreulactone C (**76**) and 3-epiarisugacin-E (**77**) (Figure 14) [42]. The *in vitro* anti-acetylcholinesterase (AChE) inhibitory activities of the compounds (**73-77**) showed a weak activity for 3-epiarisugacin-E (**77**) whereas, arisugacin B (**73**), territrem C (**75**) and terreulactone C (**76**) displayed significant activity with IC_{50} values of 3.03, 0.23 and 0.028 μM , respectively.

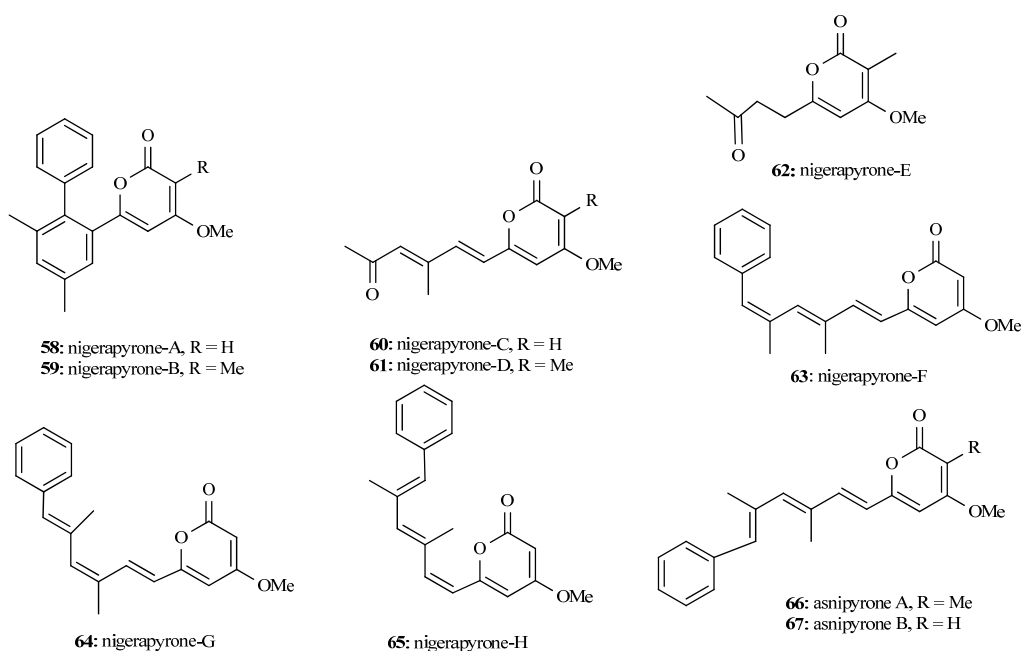


Figure 12. Chemical structures of nigerapyrones A-H (**58-65**) and asniapyrones A&B (**66 & 67**).

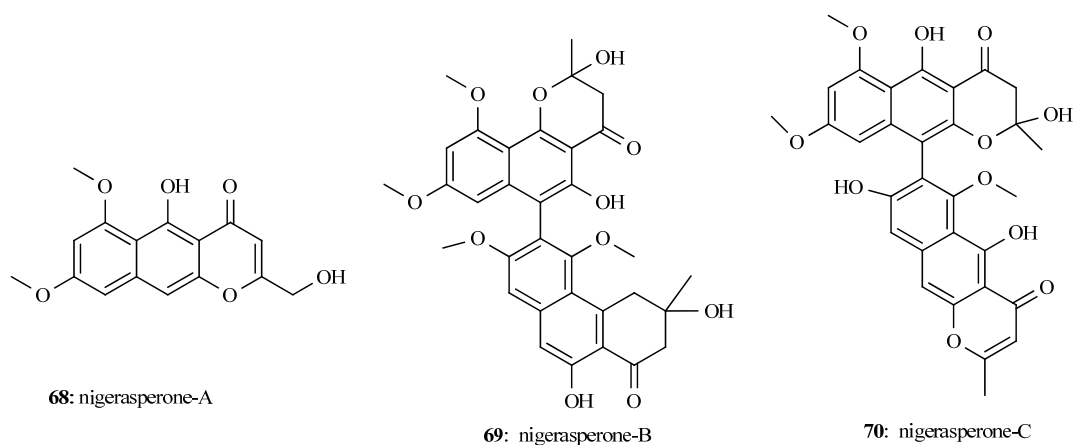


Figure 13. Structures of naphtha- γ -pyrone derivatives nigerasperones A-C (68-70).

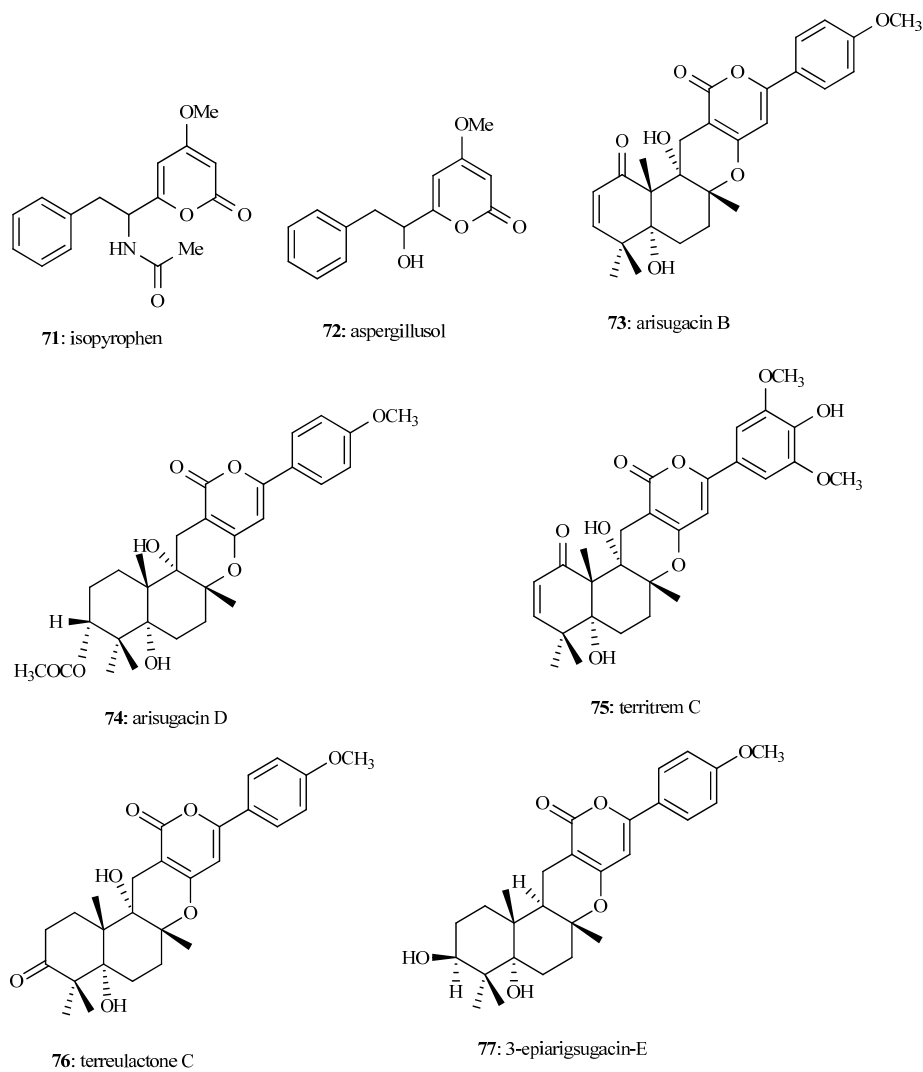


Figure 14. Structures of isopyrophen (71), aspergillusol (72), arisugacin B (73), arisugacin D (74), territrem C (75), terreulactone C (76) and 3-epiarisugacin-E (77).

Six another α -pyrone-derived metabolites (**78-83**) possessing cytotoxicity were obtained from another marine-derived fungus, *Neosartorya pseudofischeri*(Figure 15) [43]. The cytotoxicity assay of the compounds (**78-83**) against the insect cultured cell line Sf9 isolated from *Spodoptera frugiperda* showed significant activity at concentration 50 mg/L. However, compounds did not show an inhibitory effect on the cytotoxicity assay against A549 and SMMC-7721 tumor cell lines. Further, compound (**83**) showed a moderate activity on DPPH radical scavenging assay and weak antifungal activity against *Candida albicans*. Recently, two bioactive α -pyrone derivatives, dothideopyrones E (**84**) and F (**85**), were reported from the endolichenic fungus *Dothideomycetes sp.* EL003334 by Ahn and Jang's research group (Figure 15)[44]. Dothideopyrone-F (**85**) exhibited inhibition on nitric oxide (NO) production (IC_{50} $15.0 \pm 2.8 \mu M$) in lipopolysaccharide (LPS)-induced BV2 cells and also effective to decrease the mRNA expression levels of pro-inflammatory cytokines, namely, tumour necrosis factor- α (TNF- α), interleukin (IL)-1 β , and IL-6.

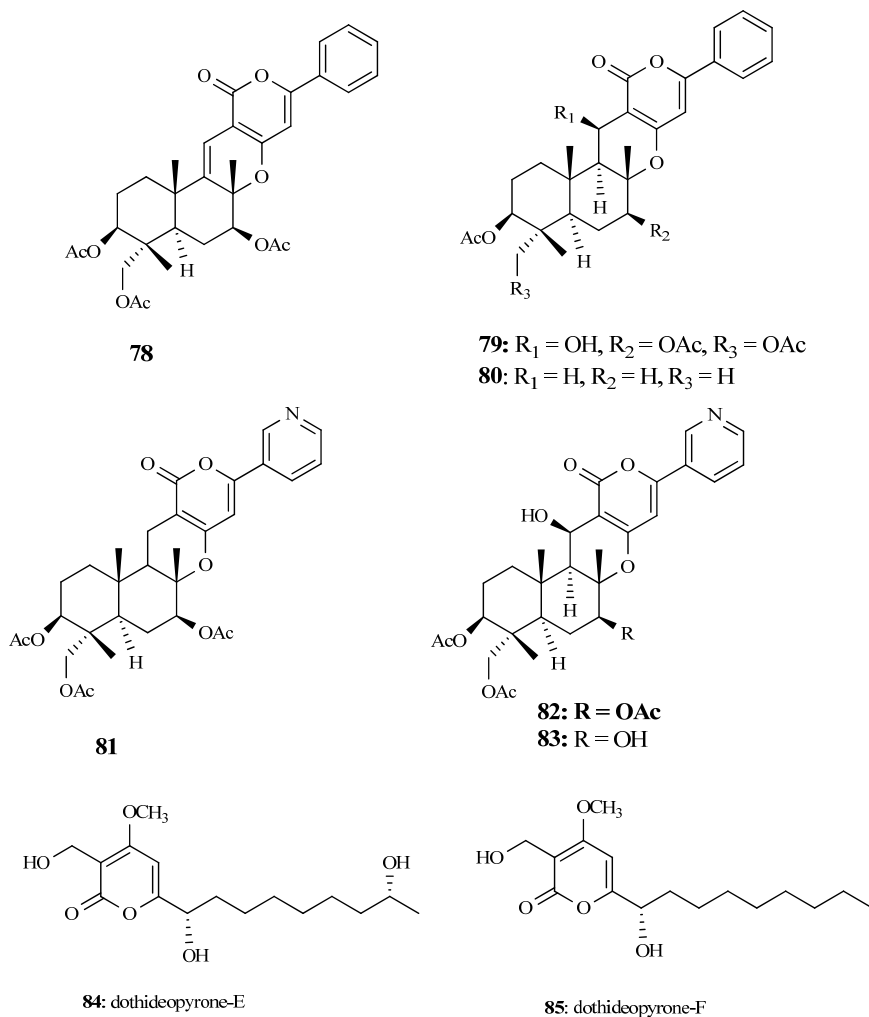


Figure 15. Chemical structures of α -pyrone-derived metabolites (**78-85**).

2.2. Derived from Bacteria and Microbial Strain

Marine bacteria particularly, sponge-associated actinomycetes produced several metabolites including pyrone derivative [45]. In 1995, four new α -pyrones, elijopyrones A-D (**86-89**) were isolated from the cultured of marine actinomycetes (Figure 16) [46]. Subsequently, several new α -pyrone containing metabolites namely, wailupemycins A-C (**90-92**) (Figure 16), and 3-epi-(S)-deoxyenterocin (**93**) along with the known compounds, entemcin (**94**) and (S)-deoxyenterocin (**95**) were isolated from marine-derived actinomycetes (Figure 17) [47]. The designated actinomycetes was isolated from sediment collected at Wailupe, on the south-east shore of Oahu, Hawaii.

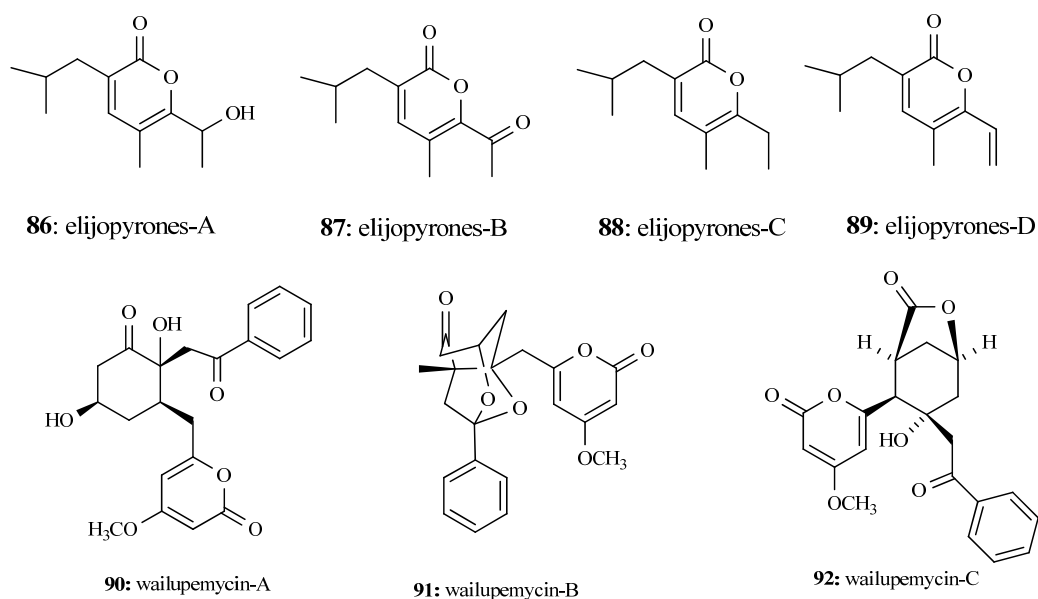


Figure 16. Chemical structures of elijopyrones A-D (**86-89**) and wailupemycins A-C (**90-92**).

Four new γ -pyrone derivatives, nocapyrones A-D (**96-99**) were obtained from *Nocardioopsis* strain HB383 of marine sponge *Halichondria panacea* (Figure 17) [48]. Nocapyrones A & B (**85 & 86**) did not show activity against gram-positive and gram-negative bacteria as well as the yeast *Candida glabrata*. Further, all these compounds showed insignificant cytotoxic activity against the mouse fibroblast cell line NIH-3T3, the human hepatocellular carcinoma cell line HepG2 and the human colon adenocarcinoma cell line HT-29.

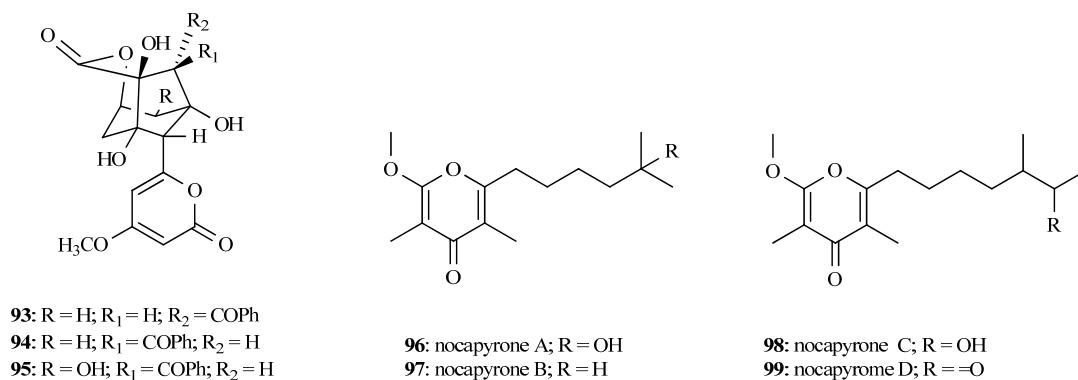


Figure 17. Structures of α -pyrone derivatives (**93-95**) and γ -pyrone compounds, nocapyrones A-D (**96-99**).

In the subsequent year, Fu *et al.* isolated three new nocapyrones E-G (**100-102**) from the marine-derived actinomycete *Nocardiopsis dassonvillei* HR10-5 (Figure 18) [49]. The compounds (**100-102**) did not show cytotoxicity effects against HL-60 cell line and A549 cell line. Further, antimicrobial screening of the compounds (**100-102**) against *Aerobacter aerogenes*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans* and *staphylococcus aureus* showed insignificant activity.

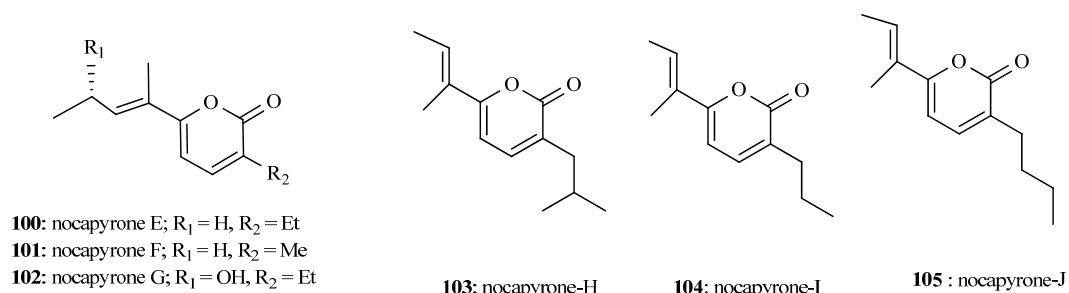


Figure 18. Chemical structures of nocapyrones E-J.

In 2013, another three new nocapyrones H-J (**103-105**) were isolated by Kwon and co-workers from the marine actinomycete *Nocardiopsis* sp. KMF-001 (Figure 18) [50]. Nocapyrone-H (**103**) showed significant inhibition of NO production in lipopolysaccharide (LPS)-stimulated BV-2 microglial cells while nocapyrones I & J (**104&105**) displayed a weak effect on NO production. Interestingly, nocapyrone-H (**103**) displayed a 5.82% stronger inhibitory effect on NO production than chrysin at the concentration of 10 μ M. Further, nocapyrone-H (**103**) showed the ability to decrease the production of prostaglandin-E₂ (PGE₂) and it also suppressed IL-1 β secretion in BV-2 cells and increased TNF- α secretion in dose-dependent manner. In the same year Fu *et al.* isolated other members of nocapyrone family namely, nocapyrones H & I (**103&104**) along with several

nocapyrones K-N (**106-109**) from the marine-derived actinomycete *Nocardiopsis dassonvillei* subsp. *dassonvillei* XG-8-1 (Figure 19) [51].

The compounds (**103-109**) were cytotoxic to the HL-60 and A549 cell lines ($IC_{50} \geq 100 \mu M$) and did not show antibiotic activity against *B. subtilis*, *E. coli*, *E. aerogenes*, *P. aeruginosa*, *S. aureus* or *C. albicans* ($MIC \geq 100 \mu g mL^{-1}$). However, nocapyrones H & I (**103&104**) and nocapyrone M (**108**) exhibited inhibition on quorum sensing (QS) at the concentration, $100 \mu g mL^{-1}$. A few years later, Zhang *et al.* isolated five new nocapyrones O-S (**110-114**) (Figure 19) along with the known nocapyrone-F (**101**) from the strain of *Nocardiopsis sp.* YIM M13066 [52]. Screening of cytotoxic activity of the compounds against HeLa, H1299, MCF-7, HL7702, PC3 and U251 cell lines did not show any significant activity at $50 \mu M$.

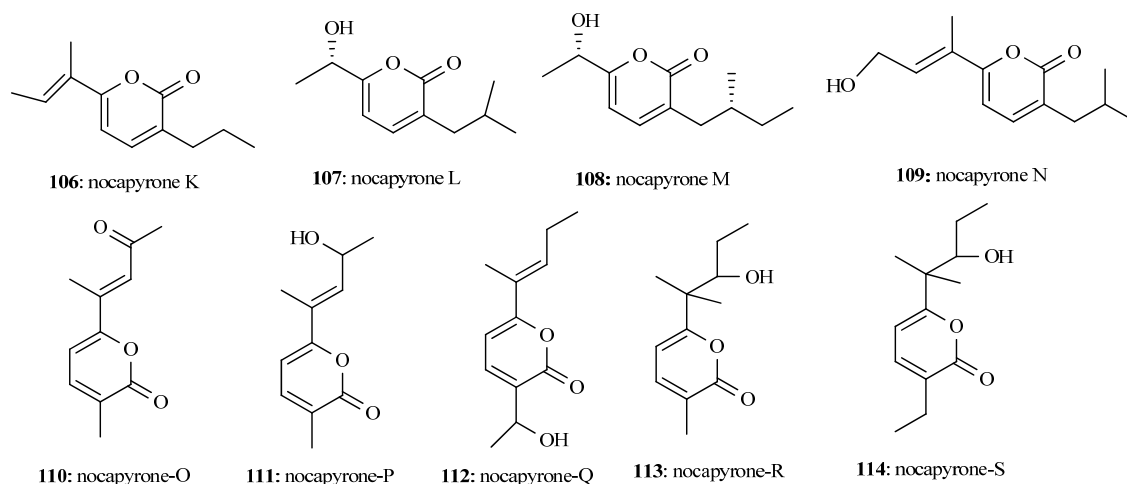


Figure 19. Chemical structures of nocapyrones K-S (**106-114**).

Zhang *et al.* isolated eight new α -pyrone metabolites (**115-122**) along with three known α -pyrones (**123-125**) from the marine-derived *Nocardiopsis* strains (Figure 20) [53]. Evaluation of *in vitro* antibacterial activity of the compounds against *Escherichia coli* ATCC 25922, *Bacillus thuringiensis* SCSIO BT01, *Staphylococcus aureus* ATCC 29213, *Bacillus subtilis* SCSIO BS01, *Micrococcus luteus* SCSIO ML01, and *Enterococcus faecalis* ATCC 29212 showed compound (**123**) exhibited activity only against *Micrococcus luteus* ($MIC = 16 \mu g/mL$), whereas, the compounds **116**, **120** and **124** showed moderate activity with the MIC value of $32 \mu g/mL$. In the subsequent year, new nocapyrones **126** & **128** along with the known nocapyrones **127** and **97** were isolated from the marine-derived *Nocardiopsis sp.* (Figures 21 & 17) [54]. The compounds **97**, **127** & **128** induced adiponutrin production in murine ST-13 preadipocyte cells whereas, **126** did not show activity. Earlier, Lin *et al.* isolated several other metabolites containing a γ -pyrone ring (**129-138**) from the symbiotic bacteria

*Nocardiopsisalba*CR 167 present in mollusc (Figure 21) [55]. These compounds were active in neurological assays only at low micromolar levels.

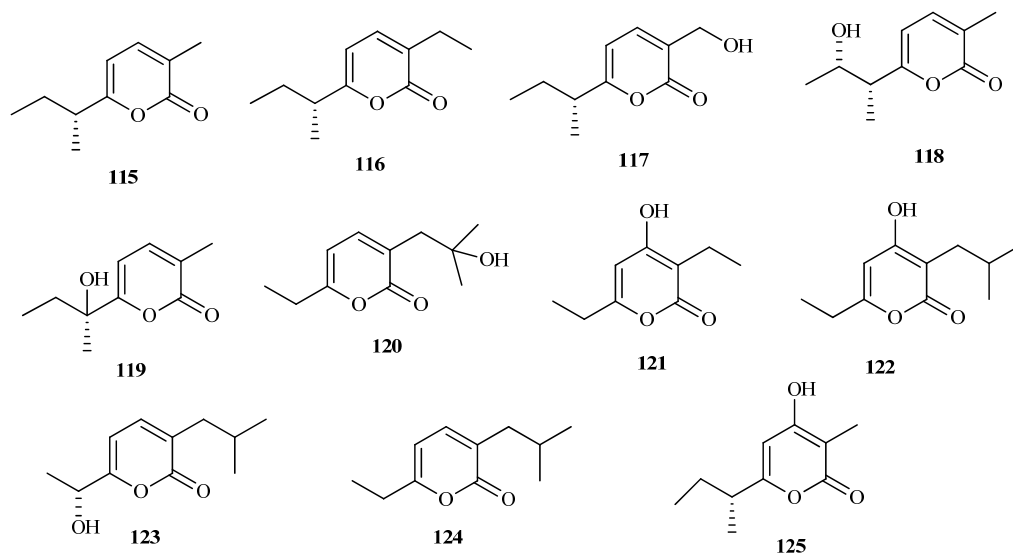


Figure 20. Chemical structures of α -pyrone metabolites (115-125) from the marine-derived *Nocardiopsis* strains.

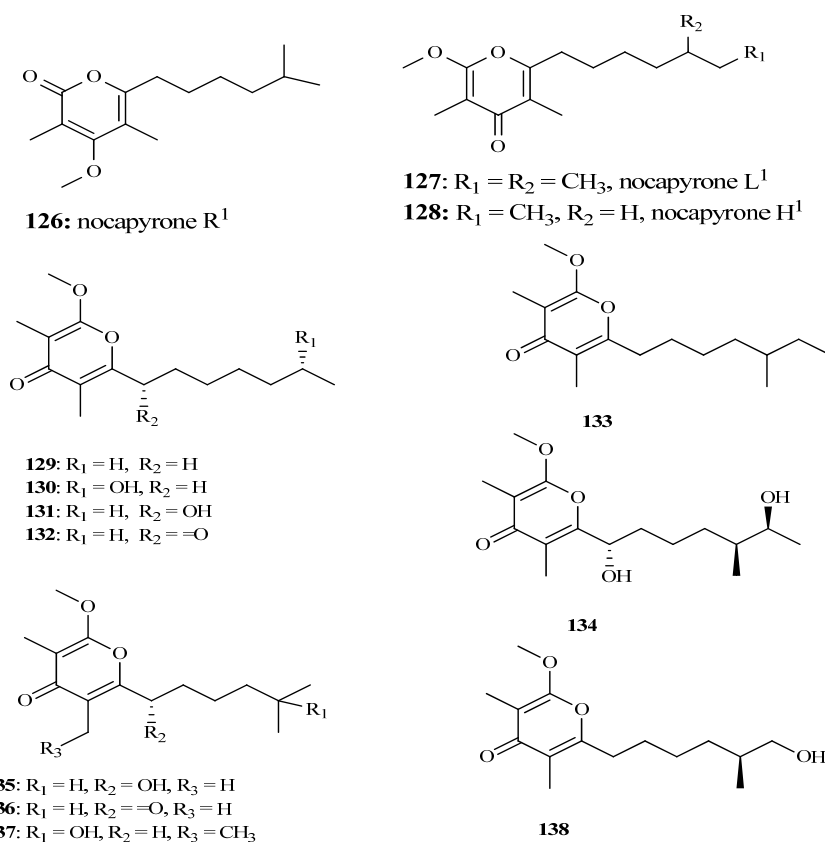


Figure 21. Chemical structures of pyrone metabolites (126-138) from the marine-derived *Nocardiopsis* strains.

In 2016, Lee *et al.* isolated marinopyrones A-D (**139-142**) which contain an α -pyrone ring from a marine-derived actinomycetes, *Nocardiopepsaceae*(Figure 22) [56]. The compounds **139-142**were obtained by HPLC-UV guided fractionations of two actinomycetes strains CNQ-675 and CNQ-082, respectively isolated from marine sediment. Screening of the compounds **128-131**for inhibitory effects on NO production in LPS-stimulated RAW 264.7 macrophage cells showed only the marinopyrone D (**142**) exhibited inhibition in NO production with the IC₅₀ value of 13 μ M, while the rest of the compounds did not show significant activity. Earlier, Fenical and co-workers isolated related α -pyrone metabolites, salinipyrones A & B (**143&144**) from the marine actinomycete, *Salinispora pacifica* (Figure 22)[57].Both the salinipyrones A & B (**143&144**) did not exhibit significant activity in the cytotoxicity assay against HCT-116 human colon cancer. Further, the compounds **143&144** did not exhibit significant antibiotic activity against the methicillin-resistant *staphylococcus aureus* and *candida albicans*. However, salinopyrone A (**143**) displayed a moderate inhibition of interleukin-5 production at 10 μ g/mL without measurable cytotoxicity to a human cell.

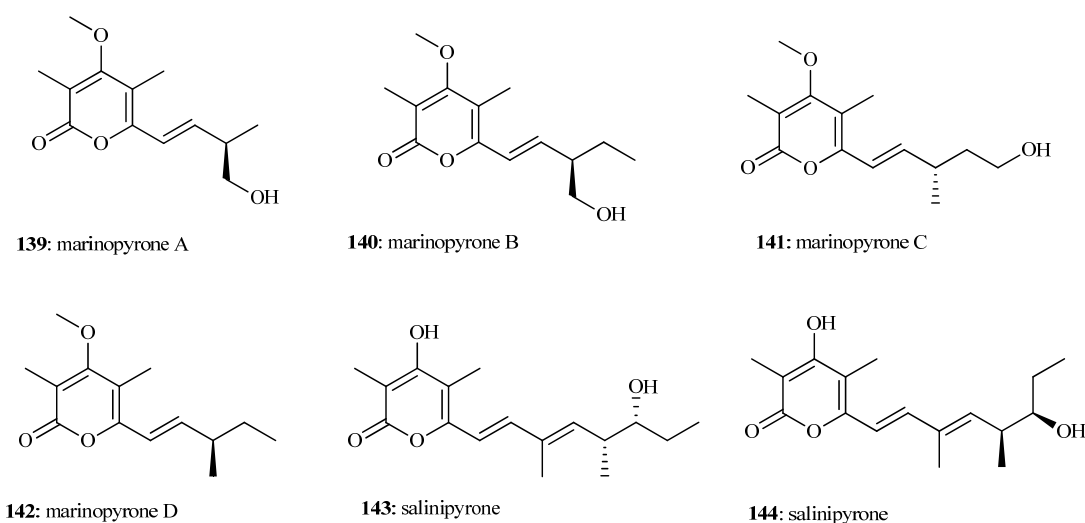


Figure 22. Chemical structures of α -pyrone metabolites (**139-144**) from the marine-derived actinomycetes, *Nocardiopepsaceae*.

Recently, Rab *et al.* isolated four new α -pyrone polyketides (**145-148**) along with the known polyketides, wailupemycins D & E (**149&150**), germicidin A (**151**),germicidin B (**152**), 5-deoxy-enterocin (**94**) and vulgamycin (**95**) from the *Streptomyces ambofaciens*BI0048 (Figures 23 & 17)[58].Earlier wailupemycin D & E (**149&150**) were reported as polyketide synthases(PKS)-derived products [59] whereas; germicidin A & B (**151 &152**) were isolated from the supernatant of germinated spores [60].The antibacterial activity of the isolated α -pyrone polyketides **94, 95** and

145-152 against the methicillin-resistance strain EMRSA-15 and multidrug resistance strain SA1199B of *S. aureus*, as well as the *E. coli* strain NCTC-10418 did not show activity. However, germicidin metabolites A & B (**151 & 152**) showed inhibition of porcine Na⁺/K⁺-activated ATPase and retarded the germination of the cress *Lepidium sativum*.

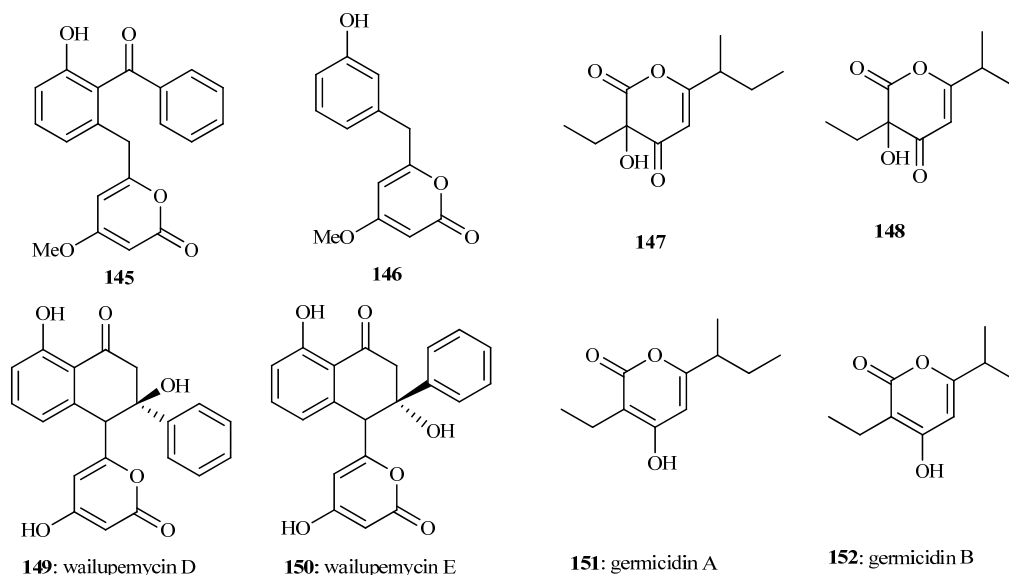


Figure 23. Chemical structures of α -pyrone metabolites (**145-152**).

In 2013, Djinni *et al.* reported the presence of several pyrone polyketides (**153-165**) in the marine-alga derived endophytic *Streptomyces sundarbansensis* (Figure 24) [61]. They isolated other member of wailupemycin family namely, wailupemycins F & G (**157 & 159**). The pure compounds **159**, **161**, **163** and **165** were isolated by HPLC analysis from the actinomycetes crude extract and were tested against pathogenic bacteria. All the compounds showed a weak inhibition against the tested bacteria but significant bacteriostatic activity was observed against MRSA by **165**. Further, the compound **165** showed selective antibacterial activity against MRSA with a MIC value of 6.0 μ M but no inhibition against *S. aureus* ATCC25923.

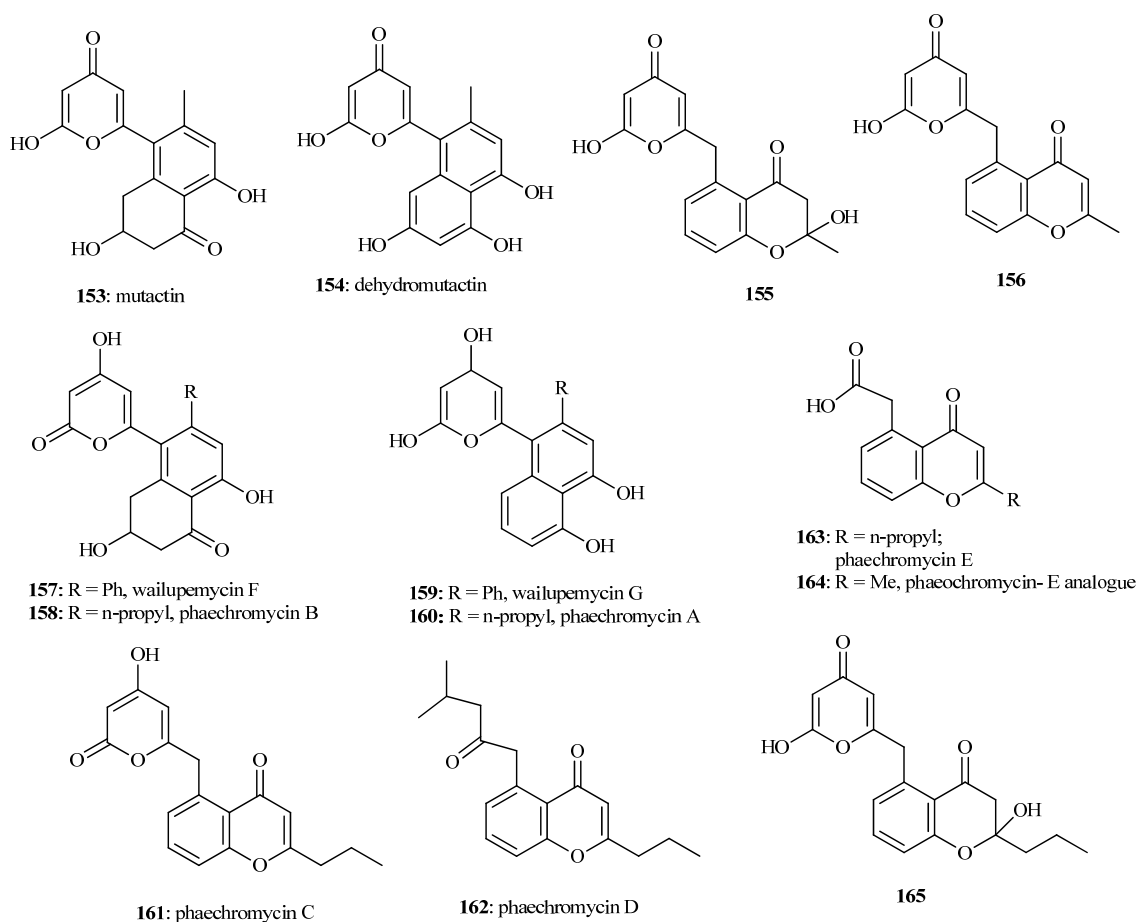


Figure 24. Chemical structures of pyrone metabolites (**153-165**) isolated from endophytic *Streptomyces sundarbansensis*.

In subsequent year Chen *et al.* reported two other α -pyrone polyketides, wailupemycins-H & I (**166** & **167**) from another marine algae-derived *Streptomyces* sp. (OUCMDZ-3434) (Figure 24) [62]. Compounds **166** & **167** were α -glucosidase inhibitors with the K_i/IC_{50} values of 16.8/19.7 and 6.0/8.3 μM , respectively. Natural product featuring γ -pyrone kalkipyronone A (**168**) was originally isolated by Gerwick's research group from a mixed assemblage of marine cyanobacteria *Tolypothrix* sp. and *Lyngbya majuscula* (Figure 24)[63]. Kalkipyronone (**168**) exhibited toxicity to brine shrimps with LD_{50} value of 1 $\mu\text{g}/\text{mL}$ and ichthyotoxicity to goldfish with LD_{50} values of 2 $\mu\text{g}/\text{mL}$. Further, kalkipyronone A (**168**) displayed modest inhibitory effect to several renal and melanoma cell lines in the *in vitro* assay against NCI's 60 human-tumor cell line. Later his group also isolated other related γ -pyrone namely kalkipyronone B (**169**) and yoshinone A (**170**) along with the known kalkipyronone A (**168**) from the marine cyanobacteria *cf. Schizothrix* sp. collected from Panama (Figure 25)[64]. Kalkipyronone A exhibited a significant cytotoxicity to H-460 human lung cancer cells ($EC_{50} = 0.9$

μM) while kalkipyronone B (**169**) and yoshinone A (**170**) displayed less activity with EC_{50} were $9.0 \mu\text{M}$ and $>10 \mu\text{M}$, respectively. Further, kalkipyrones A & B (**168**&**169**) exhibited moderate toxicity to *Saccharomyces cerevisiae* ABC16- with the IC_{50} values of 14.6 and $13.4 \mu\text{M}$, respectively, whereas very low cytotoxicity was observed for yoshinone A (**170**) with $\text{IC}_{50} = 63.8 \mu\text{M}$. Recently, Koyama et al. studied anti-obesity property of yoshinone A and related γ -pyrone compounds [65]. They found that yoshinone A (**170**) displayed inhibitory activity against the adipogenic differentiation cells with an IC_{50} value of 420 nM . Further, they studied anti-obesity effect of kalkipyronone A (**168**) by an *in vivo* experiment and it was observed that an oral ingestion of kalkipyronone A (**168**) is effective for suppressing adipose tissue weight gain in mice. The study suggested that the suppression of adipose tissue gain when treated with kalkipyronone A (**168**) is due to consumption and/or excretion of absorbed triglyceride (TG) in the body.

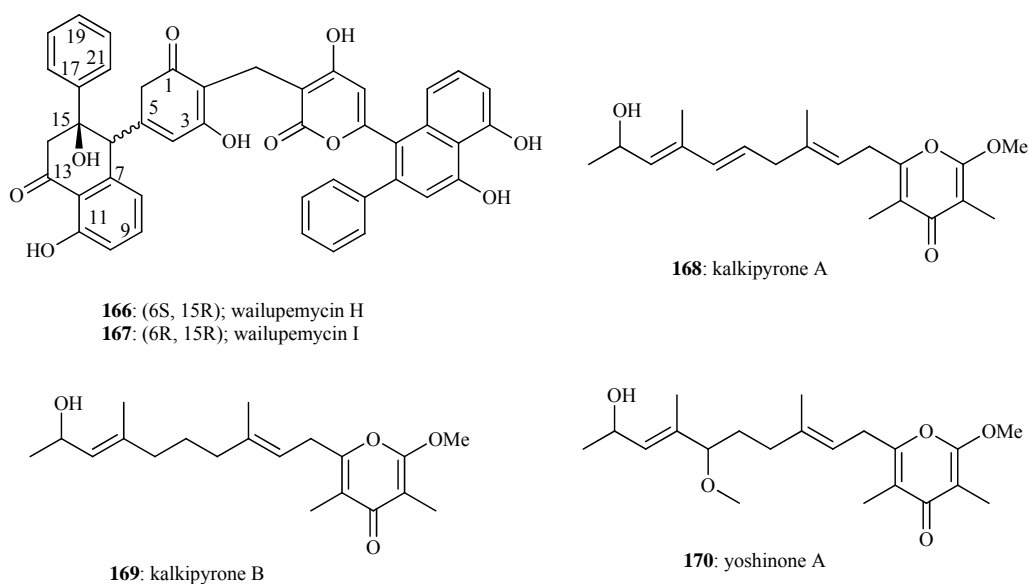


Figure 25. Structures of wailupemycins-H & I (**166** & **167**) and kalkipyronone A (**168**) kalkipyronone B (**169**) and yoshinone A (**170**).

Recently, Leutou *et al.* reported violapyrones B, C & J (**171-173**) featuring an α -pyrone from the marine actinomycetes, *Streptomyces sp.* SC0718 (Figure 26) [66]. Violapyrones B & C (**171**&**172**) was earlier reported from *Streptomyces violascens* isolated from Hylobates hoolock faces. The compounds were exhibited antibacterial activities against *Staphylococcus aureus* and *Bacillus subtilis* (MIC $4\text{--}16 \mu\text{g/mL}$) [67]. A few years later, saccharomonopyrones A-C (**174-176**), featuring α -pyrone were isolated from the marine bacterium *Saccharomonospora sp.* (Figure 26) [68]. Saccharomonopyrones A-C (**174-176**) did not show significant activity on various assay including monoamine oxidase (MAO) inhibitory, acetylcholinesterase (AChE) inhibitory,

cytotoxicity, antibacterial, and anti-tyrosinase, etc. However, saccharomonopyrone-A (**174**) displayed a weak antioxidant activity with the IC₅₀ value of 140 μM.

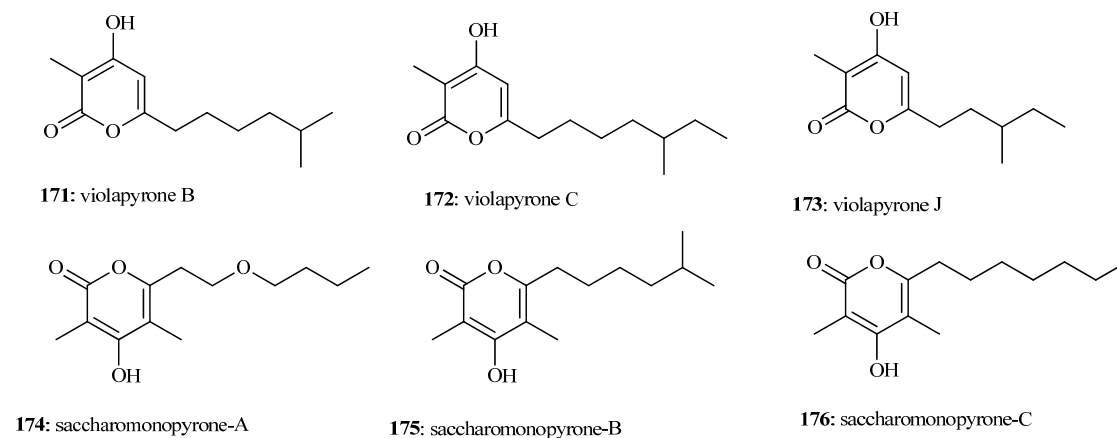


Figure 26. Chemical structures of violapyrones B, C, J (**171-173**) and saccharomonopyrones A-C (**174-176**).

3. Derived from Molluscs

Molluscs are a rich source of various marine natural products featuring pyrone ring specifically polypropionates. In 1987, Cimeno *et al.* isolated two new polypropionates, alganins-2&3 (**177 & 178**) during the chemical investigation of opisthobranch mollusc *Bulla striata* (Figure 27)[69]. They have determined the absolute stereochemistry at C-3 and C-6 of alganine-3 (**178**) by NMR experiments. A few years later, they isolated cyercenes A & B (**179&180**) consisting of two 2-methoxy-γ-pyrone from the Mediterranean mollusc *Cyerce crzstallzna* [70] followed by the isolation of α- and γ-pyrone containing polypropionates (**181-185**) along with the known metabolite **180** from the opisthobranch molluscs of the order Ascoglosan (Figure 27)[71]. Ichthyotoxic test of the compounds (**180-185**) on *Gambusia affinis* showed toxicity only for cyercene-B (**180**) and 7-methyl-12-norcedene B (**183**) at the concentrations 16 and 20 ppm, respectively.

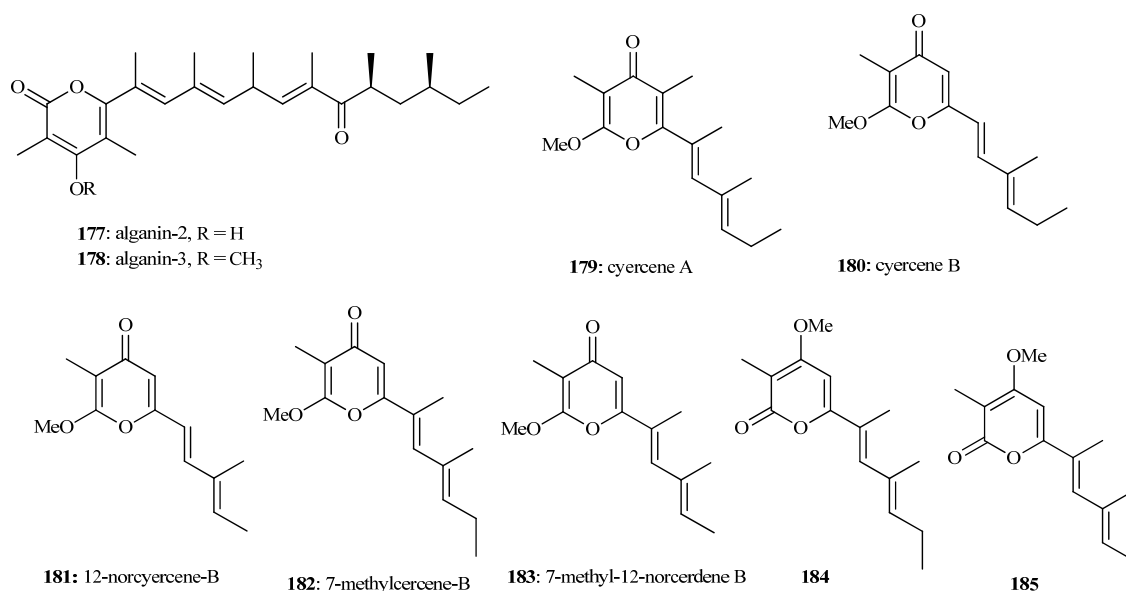


Figure 27. Structures of polypropionates, alganins-2 & 3 (**177 & 178**) and γ -pyrone polypropionates (**181-185**).

Subsequently, Cimino's research group isolated several other related γ -pyrone polypropionates, placidenes (**186-189**) from the Mediterranean ascoglossan *Placida dendritica* (Figure 28) [72]. They isolated four other new placidenes C-F (**190-193**) featuring α -pyrone propionates, and hydroperoxypolypropionate (**194**) from the same Mediterranean Sacoglossan, *Placida dendritica* [73] followed by the isolation of four new α -pyrone propionates, aplysiopsenes (**195-198**) from the mollusc hermaeidean sacoglossan *Aplysiopsis formosa* Pruvot-Fol collected from the coast of coasts of São Jorge Island in the Azores (Figure 28) [74]. Evaluation of bioassay revealed that placidines did not show toxic to either *Gambusia affinis* or tumor cells.

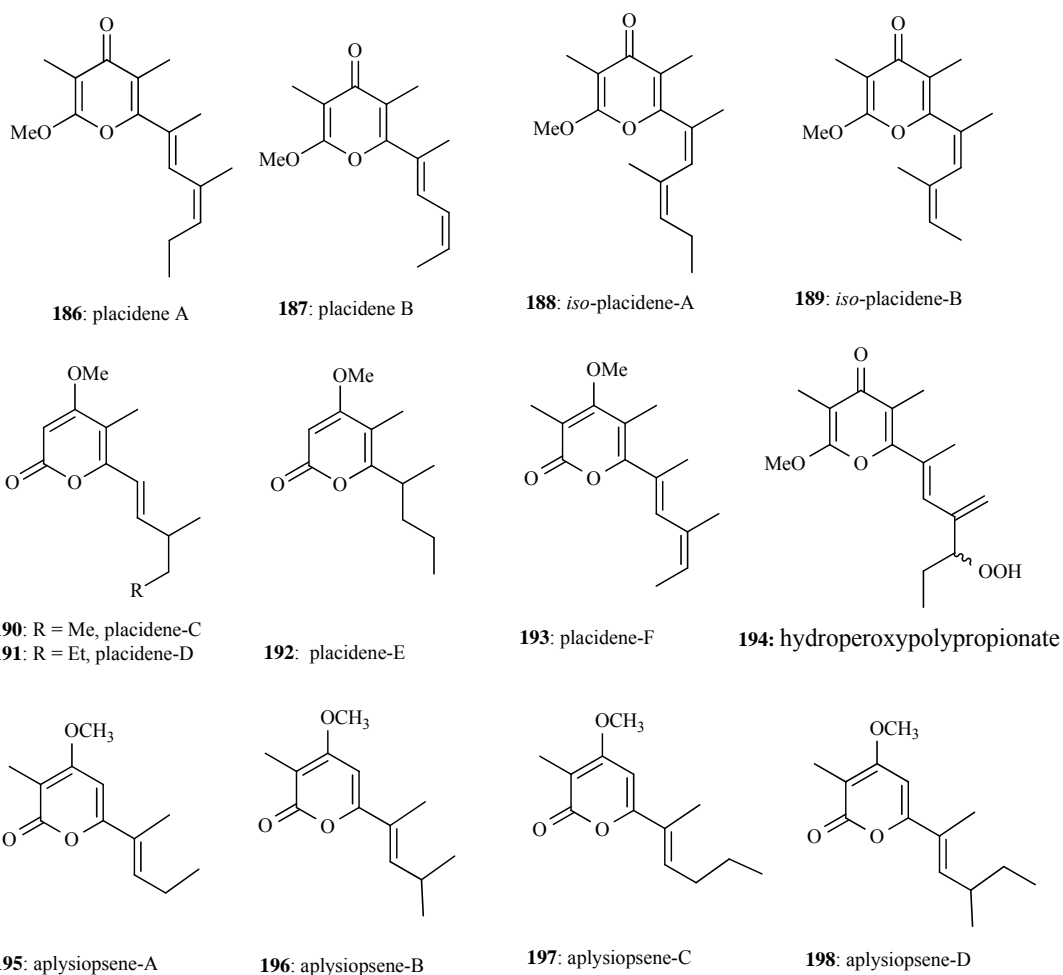


Figure 28. Chemical structures of placidenes (**186-193**), hydroperoxypolypropionate (**194**) and alysiopsenes (**195-198**).

During a chemical investigation of two marine molluscs *Tridachiella diomedea* and *Tridachia crispata* by Faulkner and Ireland lead to the isolation of γ -pyrone metabolites, tridachione (**199**) and 9,10-deoxytridachine (**200**) from the first species while crispatone (**201**) and crispatene (**202**) from the later mollusc (Figure 29)[75]. The solid state structures of 9,10-deoxytridachine (**200**) and crispatene (**202**) were determined by X-ray analysis.

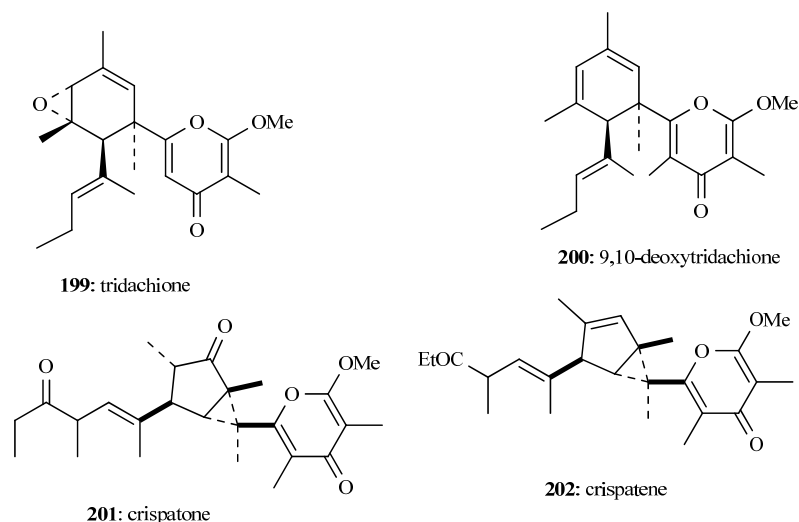


Figure 29. Structures of tridachione (**199**), 9,10-deoxytridachione (**200**), crispatone (**201**) and crispatene (**202**).

In 1994, Gavagnin *et al.* isolated four γ -pyrone polypropionate (**203-205**) along with the known metabolite (**200**) from the Mediterranean mollusc *Elysia timida* collected by Scuba diving near Sorrento Italy (Figure 30) [76]. Ichthyotoxicity assay of the compounds **203-205** showed toxicity against mosquito fish *G. affinis* at concentrations 10, 5 and 1 ppm, respectively. A few years later six new γ -pyrones (**206-211**) along with the known 9,10-deoxytridachione (**200**) were isolated by Schmitz and co-workers from the Philippine Sacoglossan Mollusc *Placobranchus ocellatus* (Figure 30) [77]. This was followed by the isolation of two new γ -pyrone propionates **212 & 213** (Figure 30) along with the several known γ -pyrone propionates (**203, 200, 205-207**) by Manzo *et al.* during the chemical investigation of the Indian Ocean sacoglossan *Placobranchus ocellatus* [78]. The compound **207** is a peroxy derivative of **206** and contained an unprecedented bicyclo [4.2.0] octane carbon skeleton. Notably, compound 9, 10-deoxytridachione (**200**) can undergo photorearrangement to give **203** [79].

In 1992, Rodriguez *et al.* isolated new polypropionates, onchitriol-I (**214**) and onchitriol-II (**215**) from the saponified extract of pulmonate mollusc *Onchidium sp.* (Figure 31) [80]. In the same year, they also isolated eight other new polypropionate-derived esters featuring γ -pyrone namely onchitriol-I A-D (**216-219**) and onchitriol-II A-D (**220-223**) from a pulmonate mollusc of the genus *Onchidium* (Figure 31) [81]. The pulmonates of this family found mainly in intertidal zones of many tropical shorelines and considered to be a rich source of cytotoxic and antineoplastic substances. The compounds exhibited *in vitro* cytotoxic activity against KB human epidermoid carcinoma cells.

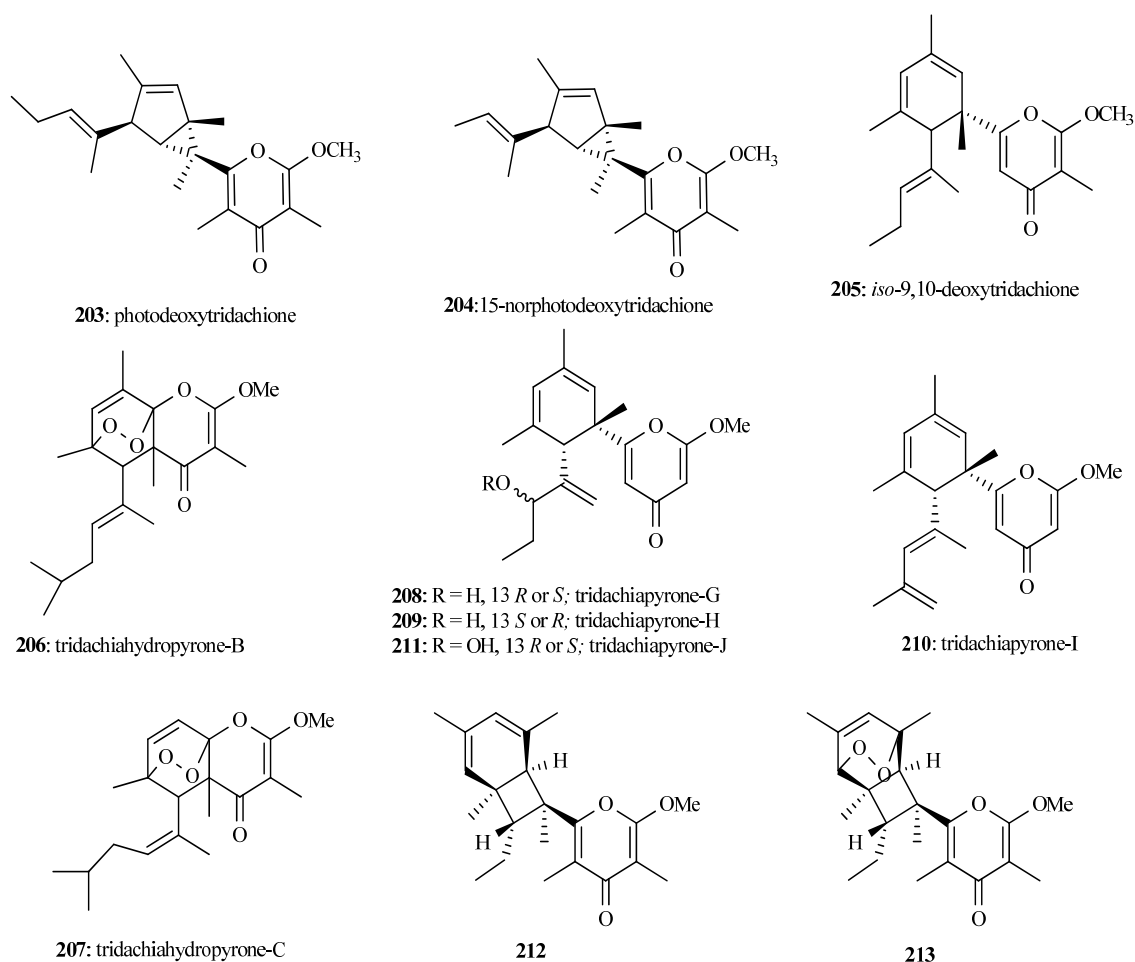


Figure 30. Chemical structures of γ -pyrone propionates (203-213).

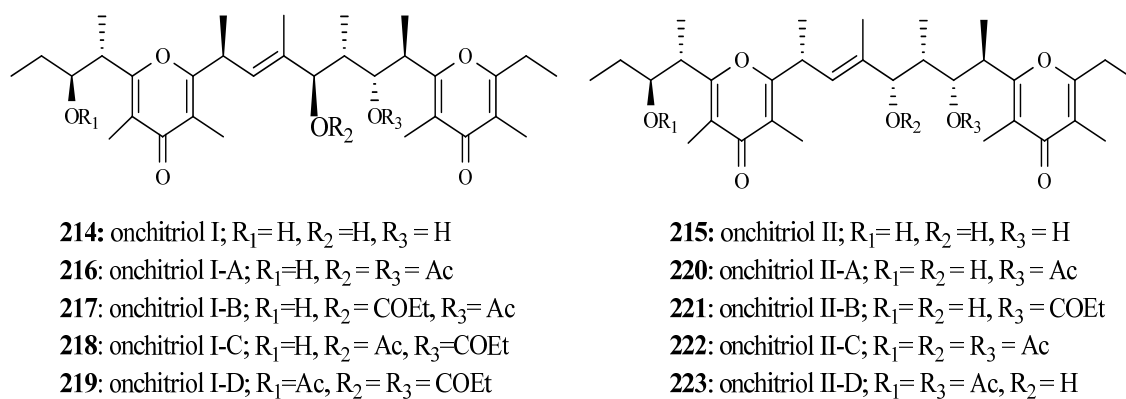


Figure 31. Chemical structures of onchitriol-I (214), onchitriol-II (215) and their derivatives (216-223).

Cimino and co-workers reported the isolation of a novel polypropionate, onchidione (**224**) from *Onchidium sp.*(Figure 32)[82]. The relative configuration of onchidione (**224**) was established by X-ray crystallography. In later years, Wang *et al.* isolated the related γ -pyrone polypropionates, onchidiol (**225**) and 4-epionchidiol (**226**) which was first described as the methanolysis product of onchidiol(Figure 32) [83]. They have also established the absolute configuration of onchidione (**224**) by X-ray analysis. It is noteworthy that onchidione (**224**) belongs to a group of pyrone-propionates family comprising of onchitriol-II(**215**)[80],ilikonapyrone (**227**) isolated from *Onchidium verruculatum* [84],and peronatriol I (**228**)&peronatriol-II (**229**) isolated from *Peronia peronei* [85].

New bis- γ -pyrone polypropionates (**230-238**) were obtained from two *Onchidium sp.*, collected from Lingshui, Hainan province, China (Figure 32) [86]. The evaluation of the compounds (**230-237**&**213-221**) to the *in vitro* growth-inhibitory activity against six-panel of human cell lines *viz.* A549 NSCLC, MCF-7 breast, PC-3 prostate, Hs683 oligodendroglia, U373 and, SKMEL-28 showed the compound **237** was the most active against all the tested cell lines ($IC_{50} < 10 \mu M$). Whereas, the compounds **234**, **235** and **236** exhibited *in vitro* growth inhibition only against the PC-3 cell line. Interestingly, the activity of **237** against MCF7, A549, Hs683, and SKMEL28 cells was comparable to that of the reference compound, etoposide.

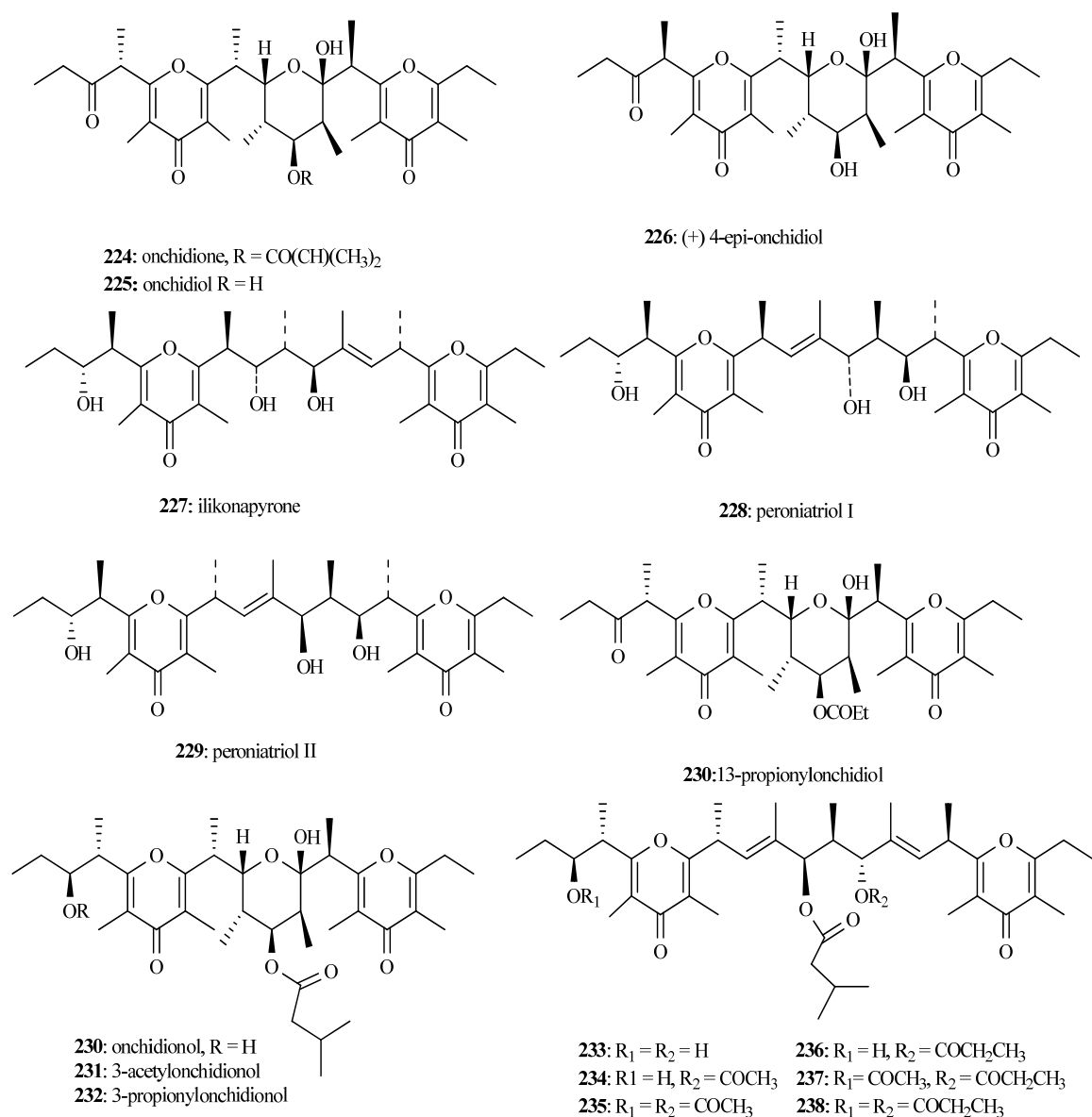


Figure 32. Chemical structures of γ -pyrone polypropionates (**224-238**) isolated from *Onchidium sp.*

In 1996 Yamada and co-workers isolated two polypropionates, auripyrones A (**239**) and B (**240**) from *Dolabella auricularia* (Figure 33) [87]. Auripyrones A (**239**) and B (**240**) contained a γ -pyrone ring and exhibited cytotoxicity against HeLa S₃ cells with IC₅₀ values of 0.26 and 0.48 $\mu\text{g/mL}$, respectively. On the other hand, two new α -pyrone polypropionates, fusipyrene-A & fusipyrene-B (**241** & **242**) were reported from the Mediterranean mollusc *Haminoea fusari* [88] and a related polypropionate, exiguapyrone (**243**) from cephalaspidean mollusc *Haminoea exigua* (Figure 33) [89]. Very recently, Chen *et al.* isolated a new γ -pyrone propionate, onchidione-II **244** (Figure 33) along with the known compounds, onchidione (**224**), (-) onchidiol (**225**) and (+)-4-*epi*-onchidiol

(**226**) from the marine pulmonatemollusc *Onchidium struma*[90].This is followed by isolation of other bis-pyrone propionate of onchidiol family, 4, 16-di-*epi*-onchidiol (**245**) by Li *et al.* from a marine pulmonate mollusk *Onchidium sp.*(Figure 33)[91]. Cytotoxicity evaluation of onchidione-II (**244**) and onchidione (**224**) against the tumor cell lines A549, MCF-2 and HepG-2 showed moderate activity. Whereas, cytotoxicity screening of the compound (**245**)against the four cell lines *viz.* HT-29, A549, Capan-1, and SNU-398 exhibited a weak activity.

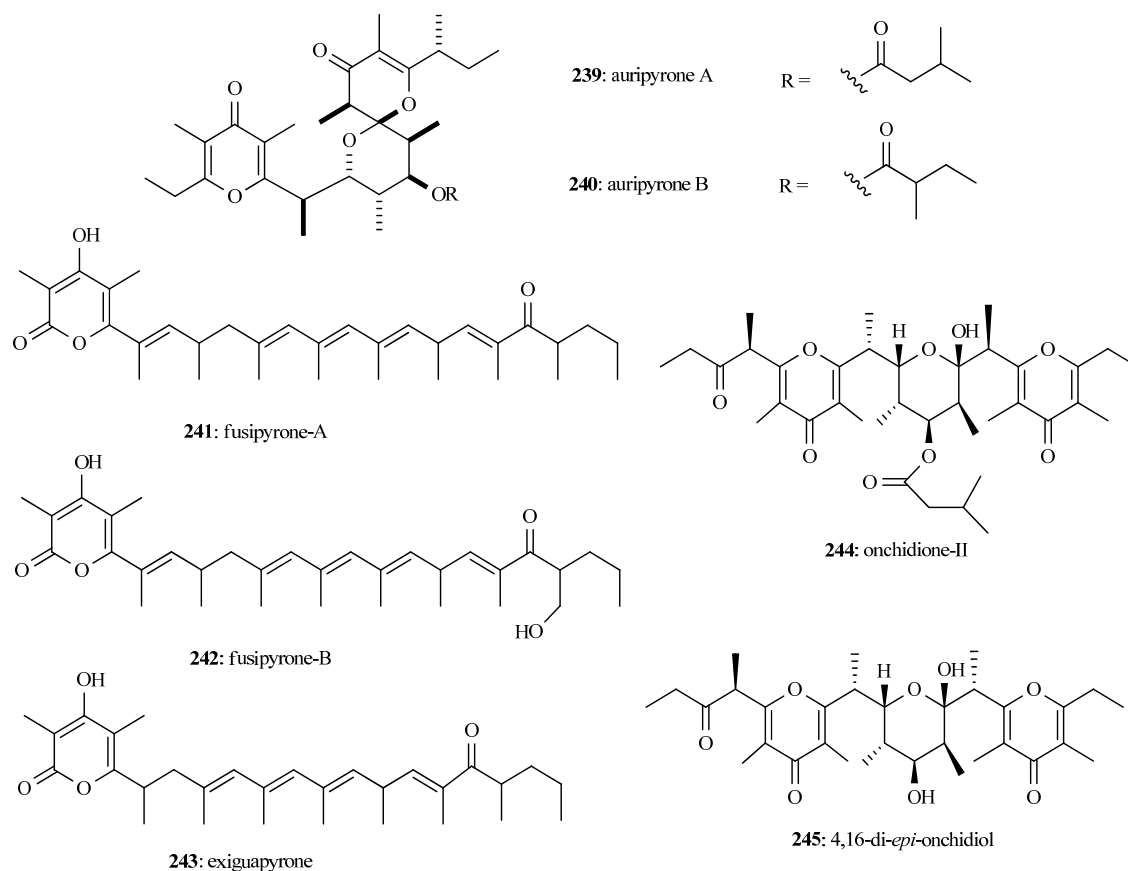


Figure 33. Chemical structures of auripyrones A & B (**239&240**), fusipyrone-A & B (**241&242**), exiguapyrone (**243**) and bis-pyrone propionates (**244 &245**).

4. Derived from Sponges and Algae

Secondary metabolites containing pyrone ring are not very common in sponges and algae. Su *et al.* isolated a triterpenoid, stelletin-A (**246**) was isolated from the marine sponge *Stelletta tenuis* [92]. Earlier, in 1982, Clardy and co-workers isolated stelletin B (**247**) from the marine sponge *Stelletta sp.* collected from Mogadishu Somalia (Figure 34)[93]. Stelletin-A (**246**) displayed toxicity against leukemia cells with an ED value of 0.001 μ g/mL. More triterpenoid of this family featuring α -pyrone namely stelletin-C (**248**) and stelletin-D (**249**) have been isolated from this sponge

species (Figure 34) [94]. Since stellettin-C (**248**) and stellettin-D (**249**) were unstable, a rapid equilibration occurred between them therefore, authors have tested *in vitro* assay for the mixture of **248&249** against NCI's 60 human cell lines but respond was observed with GI₅₀ concentration in low-to-mid nanomolar range for the more sensitive cell lines such as leukemia, CNS and renal cell lines.

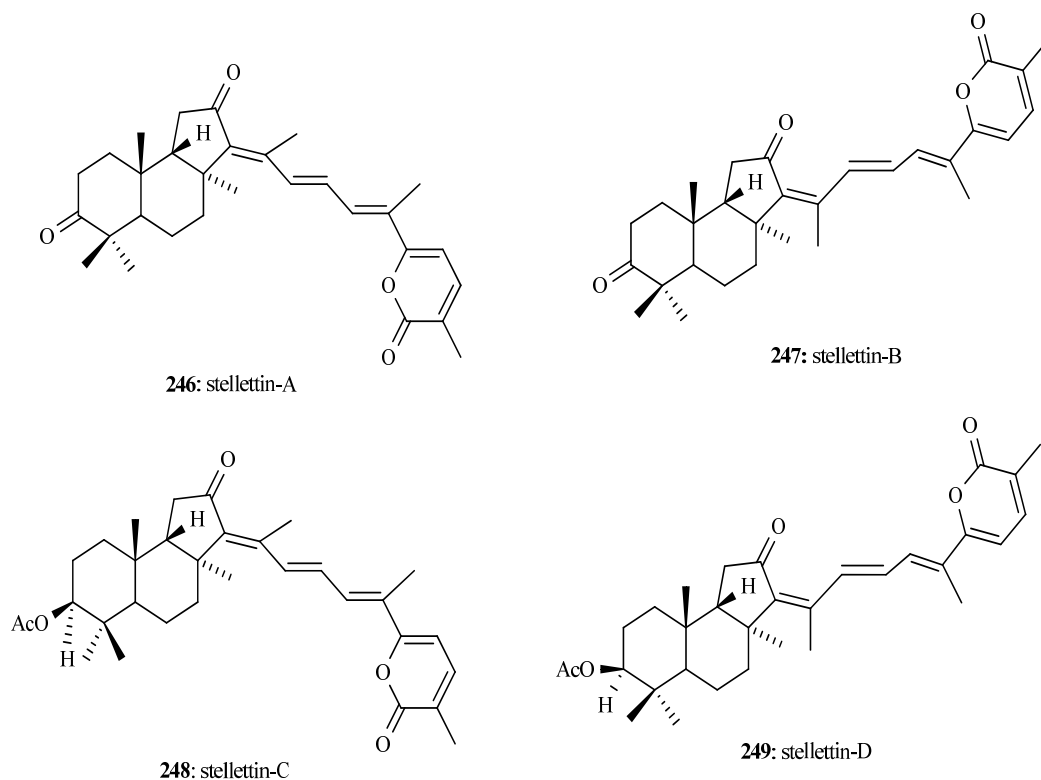


Figure 34. Structures of stellettins A-D (**246-249**) from the marine sponge *Stelletta tenuis*.

Recently, Esposito *et al.* isolated a bis- γ -pyrone propionate, smenopyrone (**250**) from the Caribbean sponge *Smenospongia aurea*(Figure 35)[95]. Smenopyrone represents the first polypropionate metabolite, isolated from a marine sponge. They claimed that the presence of smenopyrone (**250**) is not occasional in *S. aurea*as the compound has been found consistently in all the studied specimens of Caribbean *S. aurea*and even it is also found to be present in *S. conulosa*, a closely related species of *S. aurea*. Earlier, pyrone metabolite, lehualides A-D (**251-254**) were isolated by Sata *et al.* from an unidentified marine sponge of genus *Plakortis* collected from Hawaii(Figure 35)[96]. Lehualides are unique marine pyrone metabolites that contain fully substituted pyrone ring. They constitute the first set of marine polyketides possessing α -and γ -pyrones isolated from the sponge *Plakortis sp.* Lehualide A (**251**)displayed toxicity against the brine shrimp with LD₅₀ 50 μ g/mL while lehualides B-D (**252-254**) with LD₅₀ 15 μ g/mL. Lehualides-B

(252) & D (254) exhibited moderate cytotoxicity to the *in vitro* assay against the ovarian cancer cell line (IGROV-ET) with the GI_{50} values of 0.83 and 0.73 μ M, respectively. Lehualide D (254) also displayed moderate cytotoxicity against leukemia (K562) with the GI_{50} value of 0.23 μ M, however, lehualides A (251) and C (253) did not show significant cytotoxicity against any of the tested cancer cell lines [96].

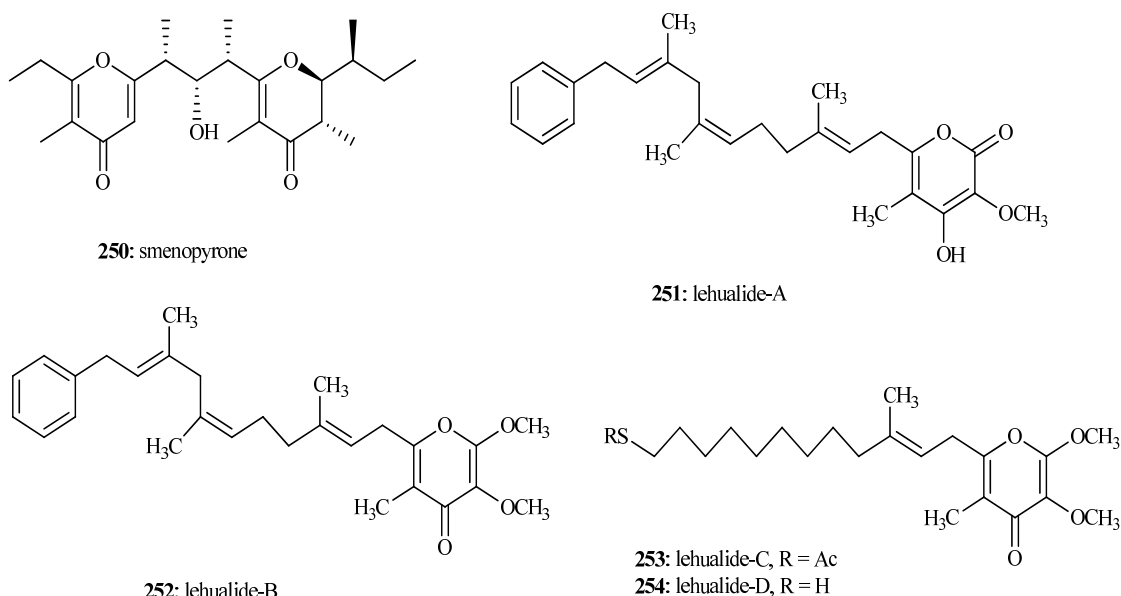


Figure 35. Chemical structures of smenopyrone (250) and lehualides A-D (251-254).

Subsequently, more metabolites belonging to this family namely lehualides E-K (255-261) were isolated from this sponge of genus *Plakortis* (Figure 36) [97]. Lehualides E-J (255-260) contained an α -pyrone ring while lehualide K (261) has a bis- α -pyrone ring. Lehualides F, G & I (256, 257 & 259) showed inhibition on the growth of DS strain but lehualide-H (258) did not show inhibition of yeast growth at any concentration. Further, lehualides F and G (238 & 239) showed a significant growth inhibition against promyelocytic leukemia (HL-60) cell line with IC_{50} values of 6.2 and 5.4 μ M, respectively, however, a weak inhibition was observed for the thioacetate and sulfide compounds namely, lehualides H & I (258 & 259) which showed IC_{50} values of 14.6 and 10.8 μ M, respectively.

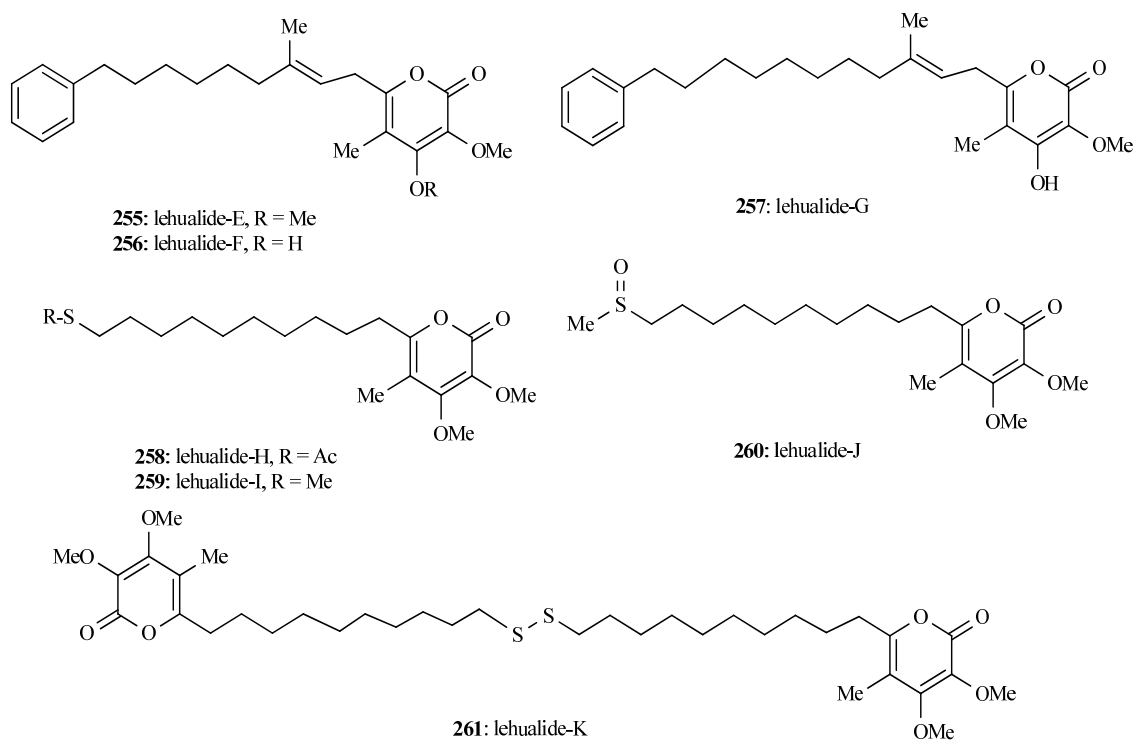


Figure 36. Chemical structures of smenopyrone (**250**) and lehualides E-J (**255-261**).

Most of the pyrone-derived compounds of algal origin are found in the macro-cyclic structure. In 1982, Kazalauška *et al.* isolated macrocyclic enol ether containing pyrone ring (**262-265**) from the red alga *Phacelocarpus labillardieri* (Figure 37) [98]. All the isolated compounds except **265** contained an acetylene group and the metabolites **262**, **263**, **264** and **265** were present in the extract in the ratio 20:13:9.4:1. A few years later, Shin *et al.* isolated other macrocyclic ethers (**266-269**) along with the previously described metabolite **262** from the new collection of the same alga species (Figure 37) [99]. The metabolites (**266&269**) contained an α -pyrone ring while metabolites **266&269** featured a γ -pyrone ring. This initial discovery of macrocyclic metabolite was followed by Braekman *et al.* isolation of another brominated α -pyrone macrocyclic ether (**270**) from the fresh collection of *P. labillardieri* and the isolation of a new macrocyclic- γ -pyrone (**271**) along with **263** and **267** by Murray *et al.* in 1995 from a Victorian algae *Phacelocarpus peperocarpus* (Figure 37) [100]. They have also established a *Z* geometry about the double bond carbon adjacent to the oxygen atom in **263**.

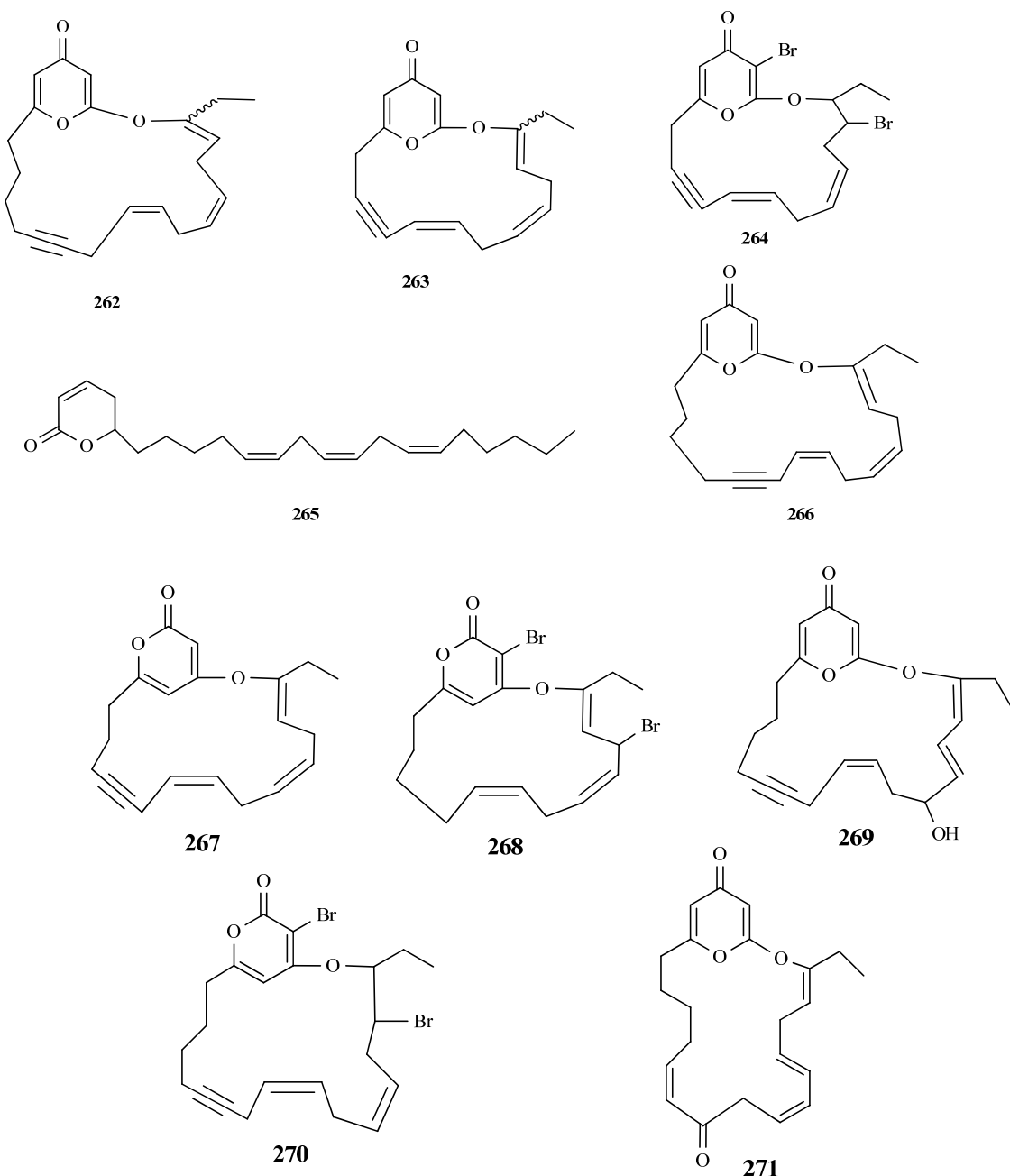


Figure 37. Chemical structures of macrocyclic enol ether isolated from the red alga *Phacelocarpus sp.*

5. Synthesis of Marine Natural Products containing pyrone ring

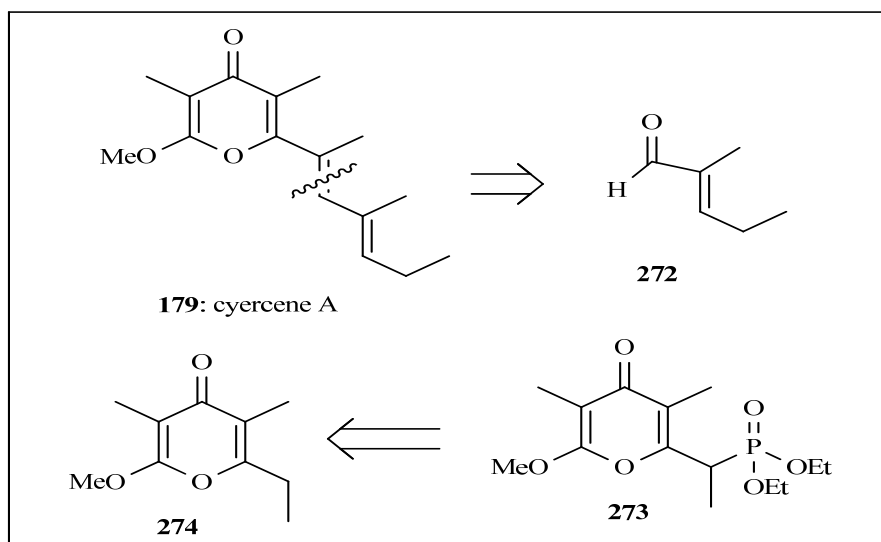
During the past decades, total synthesis of marine natural products containing pyrone ring has been paid considerable attention due to their promising bioactivities. However, to the best of our knowledge, a review dedicated on this topic is scarce except a few reports appeared on pyrone-derived polypropionate natural products [101, 102]. Keeping this in mind, this review described in brief, the

total synthesis of marine pyrone metabolites reported until 2018. In the subsequent section, the total synthesis of fourteen pyrone derived metabolites of marine origin namely, cyercene-A (**178**), placidenes (**186-189**), onchitriol-I (**214**), onchitriol-II (**215**), crispatene(**202**), photodeoxytrichidione (**203**), (-)-membrenone-C (**334**), lihualide-B (**262**), macrocyclic enol ether (**264**), auripyrones-A & B (**239&240**) have been presented.

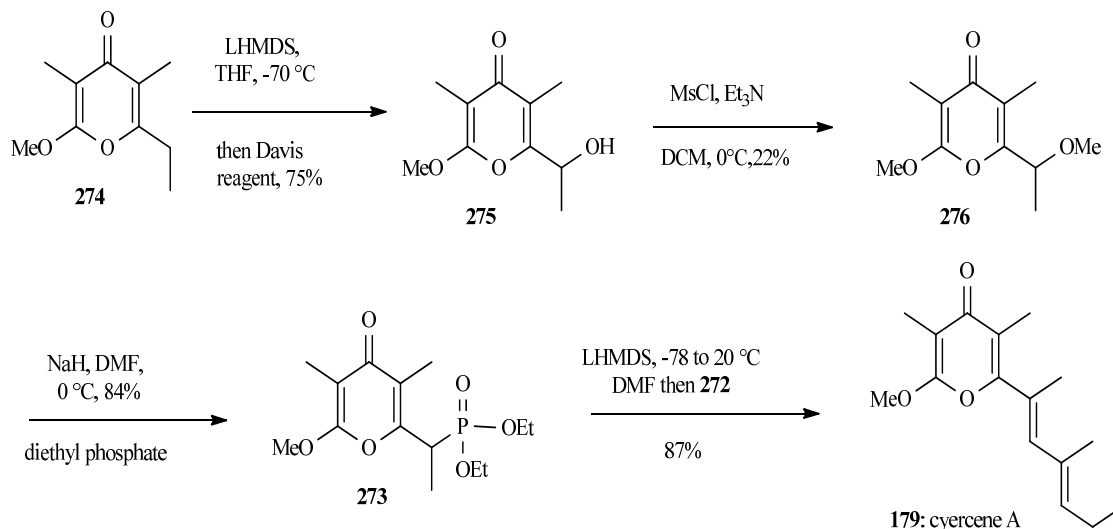
5.1.Synthesis of Cyercene A and Placidenes

Cyercene A (**179**) belongs to the group of γ -propiوناتemetabolites which was isolated by Verda *et al.* during a chemical investigation of Mediterranean mollusc *Cyerce crzstallzna*[70]. The related propionates, placidenes (**186-189**) were isolated from the Mediterranean ascoglossan *Placida dentritica*[73]. Synthesis of cyercene A (**179**) was described by Moses *et al.* in 2004 [103] and subsequently, Lianget *al.* reported a stereoselective synthesis of cyercene A (**179**) and placidenes (**186-189**) employing a palladium catalyst, Pd(PPh₃)₄[104].

Synthesis of cyercene A (**179**) by Moses *et al.* [103] involved coupling of commercially available aldehyde **272**, and the phosphono- γ - α -pyrone unit **273**. They have proposed a retrosynthetic analysis of cyercene A(**179**) as depicted in Scheme 1. From the retrosynthetic analysis, they revealed that the disconnection of double bond would give the required coupling compounds **272&273** which could undergo coupling in a diastereoselective manner to furnish the target compound **179**. In this synthesis, they have utilized the Wadsworth–Emmons approach to generate *E*-trisubstituted olefins diastereoselectively [105]. The synthesis involved deprotonation of **274** by lithium hexamethyldisilazane (LHMDS) which was followed by quenching of the product with Davis reagent [106], to give hydroxypyronone **275** that was smoothly converted into mesylate (**276**) by treatment with MsCl in the presence of Et₃N. The desired Wadsworth–Emmons reagent **273** was readily obtained by the reaction of **275** with the sodium salt of diethyl phosphite. Finally, the reaction of the lithium salt of **273** with LHMDS at -78 to 20 °C in DMF followed by treatment with the aldehyde **272** gave the desired product cyercene A (**179**) as the major diastereoisomer (Scheme 2).



Scheme 1. Depicted retrosynthetic towards cyercene A



Scheme 2. Reaction pathway for the synthesis of cyercene A (**179**).

Synthesis of cyercene A and placidenes by Liang *et al.* [104]: Liang *et al.* synthesis of cyercene A (**179**) and placidenes (**186-189**) involved a Stille cross-coupling of the key iodovinyl pyrone building blocks, **277** or **278** (Figure 38) with an appropriate vinyl stannane. The synthesis involved an initial preparation of two key building blocks **277** and **278**. The synthesis of *E*-iodovinyl pyrone **277** was achieved from the known *E*-3-iodo-2-methyl propenal (**279**) [107] which was added to ketoester **280** and then subsequently oxidized with Dess-Martin periodinane to give diketoester **281** (Scheme 3). After which cyclization of **281** with DBU in benzene afforded a γ -hydroxy- α -pyrone **282** in good yield. Finally, methylation of **282** in a regioselective manner using excess methylfluorosulfonate provided the α -methoxy- γ -pyrone **277** (Scheme 3).

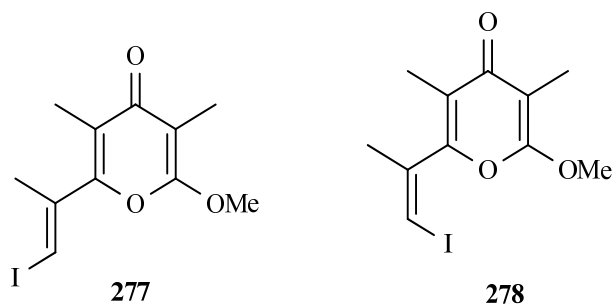
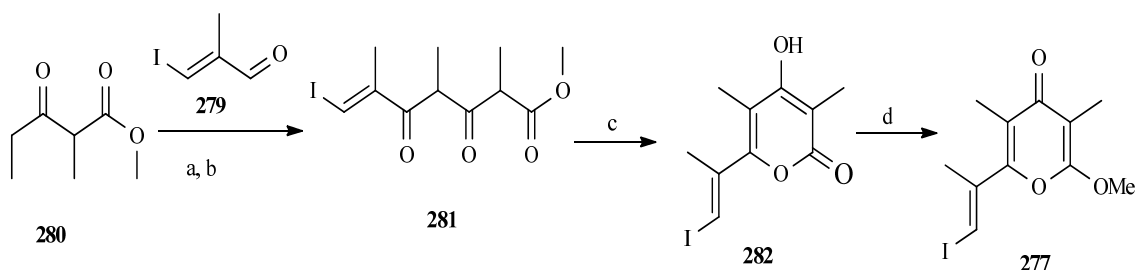
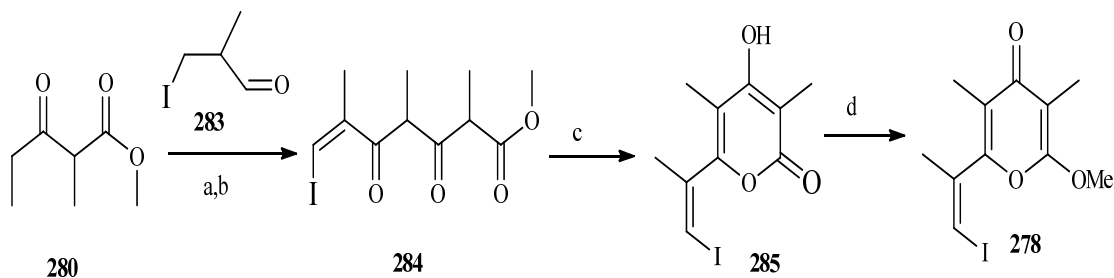


Figure 38. Chemical structure of the key iodovinyl pyrone building blocks **277** & **278**.

Analogously, (*Z*)-iodovinyl pyrone **278** was synthesized from the (*Z*)-3-iodo-2-methyl proenal **283** [108]. The reaction involved addition of dianion **280** to the proenal **283** followed by oxidation provided the compound **284**. Subsequently, the product was cyclized to give γ -hydroxy- α -pyrone **285** which was then subjected to regioselective methylation to give **278** (Scheme 4).

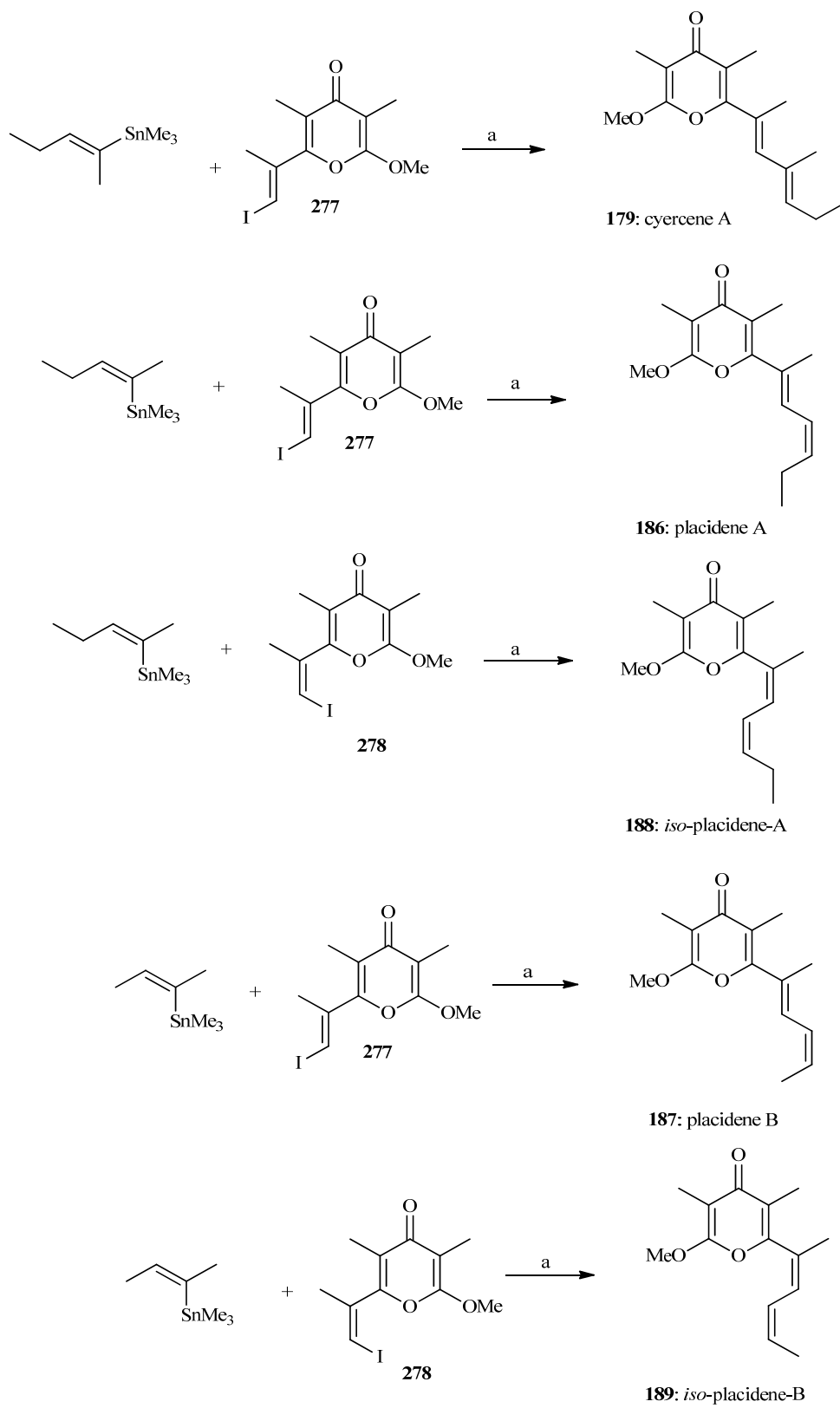


Scheme 3. Synthesis of (*E*)-iodovinyl pyrone **277**. Reagents and conditions: (a) NaH, THF, 0°C then *n*-BuLi, 0°C then **279**, 0°C to room temperature. (b) Dess-Martin periodinane, CH₂Cl₂, rt. (c) DBU, Ph-H, reflux, (three steps). (d) MeOSO₂F, CH₂Cl₂, rt, 12h, 95%.



Scheme 4. Synthesis of (*Z*)-iodovinyl pyrone **278**. Reagents and conditions: (a) NaH, THF, 0°C then *n*-BuLi, 0°C then **283**, 0°C to room temperature. (b) Dess-Martin periodinane, CH₂Cl₂, rt. (c) DBU, Ph-H, reflux, (three steps). (d) MeOSO₂F, CH₂Cl₂, rt, 12h, 81%.

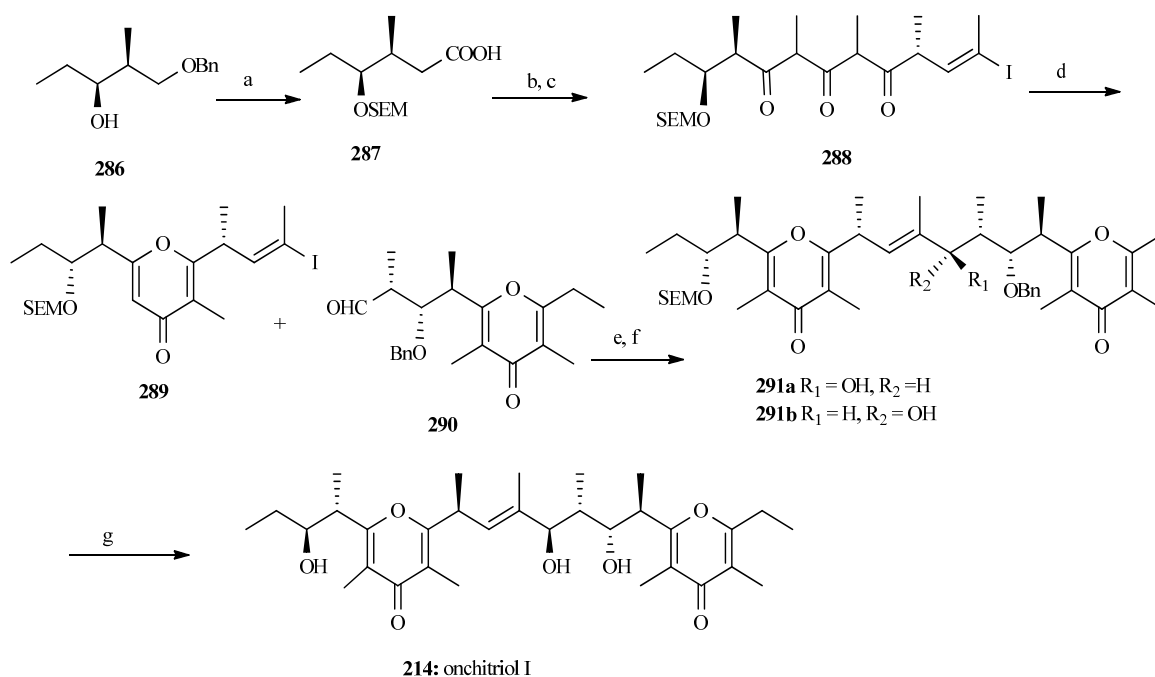
Finally, the targeted compounds, cyercene A **279** and placedenes *viz*, placidene A **186**, *iso*-placidene A **188**, placidene B **187**, *iso*-placidene B **189** were obtained employing Stille cross-coupling of either **277** or **278** with an appropriate vinyl stannane in the presence of palladium catalyst as depicted in Scheme 5.



Scheme 5. Synthesis of cyercene (**179**), placidene A (**186**), *iso*-placidene-A (**188**), placidene B (**187**) & *iso*-placidene-B (**189**). (a) Reagents and conditions: Pd(PPh₃)₄ (5 mol%), CuI (10 mol%), CsF (2 equiv.), DMF, 45 °C.

Synthesis of onchitriol-I and onchitriol-II

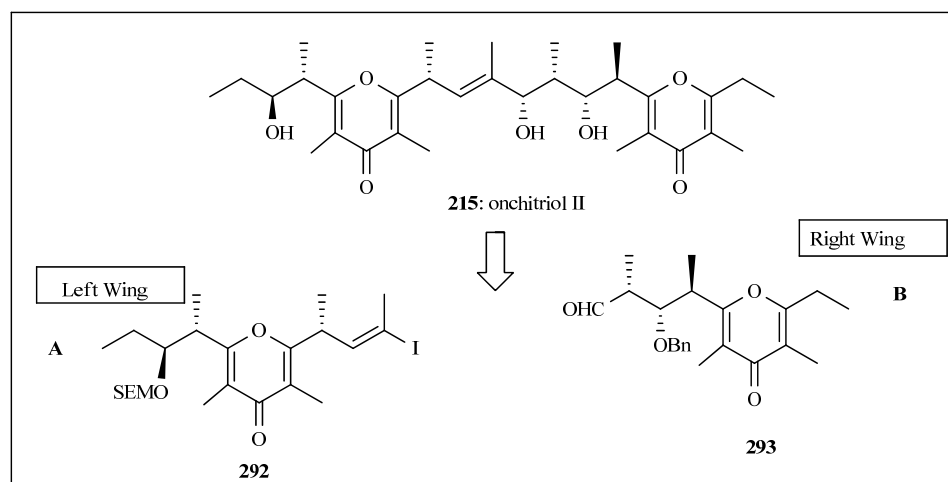
Onchitriol-I (**214**) and onchitriol-II (**215**) belong to polypropionate metabolites of pulmonate mollusc *Onchidium sp.*[80]. The total synthesis of onchitriol-I [109] and onchitriol-II [110] was reported by Yamamura and co-workers. The synthesis of onchitriol-I (**214**) began with the preparation of carboxylic acid (**287**) from the known alcohol (**286**)[111] in four steps (Scheme 6). The acid **287** was subjected to condensation with 3-pentanone followed by acylation with imidazolide resulted in β -triketoester **288** which was then subjected to $\text{PPh}_3\text{-CCl}_4$ -cyclization [112] afforded **289**. Then coupling of vinyl iodide **289** with aldehyde **290**[110] by $\text{NiCl}_2\text{-CrCl}_2$ provided a mixture of diastereomers **291a** & **291b** which were separated from the mixture after acylation. Finally, deprotection of the major isomer **291a** in two steps afforded the targeted compound, onchitriol-I **214** in 30%.



Scheme 6. *Synthesis of onchitriol-I. Reagents and conditions:* a. i) SEMCl , Pr_2NEt ; ii) $\text{Pd-C} / \text{H}_2$, MeOH ; iii) Swern oxid. then Jones oxid. (92%), b. i) Imd_2CO ; ii) 3-pentanone, LDA-DMPU/THF , -70°C (55%). c. i) LDA (2 eq.), DMPU / THF , $-70\text{--}10^\circ\text{C}$; ii) Imd_2CO , -73°C d. PPh_3 (3 eq.)- CCl_4 (10 eq.) / THF (37%). e. 0.5% $\text{NiCl}_2\text{-CrCl}_2$, DMSO , rt, 1 day. f. Ac_2O , pyr (**291a** 22%, **291b** 11% in 2 steps). g. i) $\text{TFA} / \text{CH}_2\text{Cl}_2$, -10°C ; ii) $\text{DDQ} / \text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$; $\text{K}_2\text{CO}_3 / \text{MeOH}$ (30% in 3 steps).

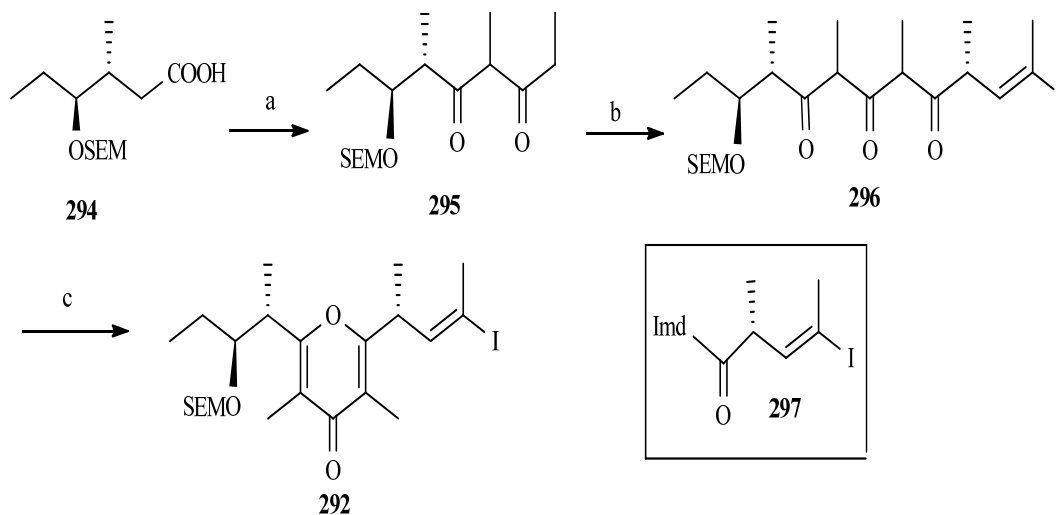
To begin the synthesis of onchitriol II **215**, Yamamura and co-workers analysed the retrosynthetic pathways of **215** (Scheme 7) which revealed that the vinyl iodide **292** (left-wing A) and aldehyde **293** (Right-Wing B) could be connected to form **215**. Further, both the wings could be converted to the simple corresponding carboxylic acids and ketones *via* β -triketone using the $\text{PPh}_3\text{-CCl}_4$ cyclization method (Scheme 8 & 9) [112]. The synthesis involved three distinct steps namely,

construction of the left-wing A **292** & right-wing B **293** followed by coupling of left wing A (**292**) and right wing B (**293**) using the Chromium-Nickel coupling process [113] to give onchitriol-II.



Scheme 7. Retrosynthetic analysis of onchitriol II

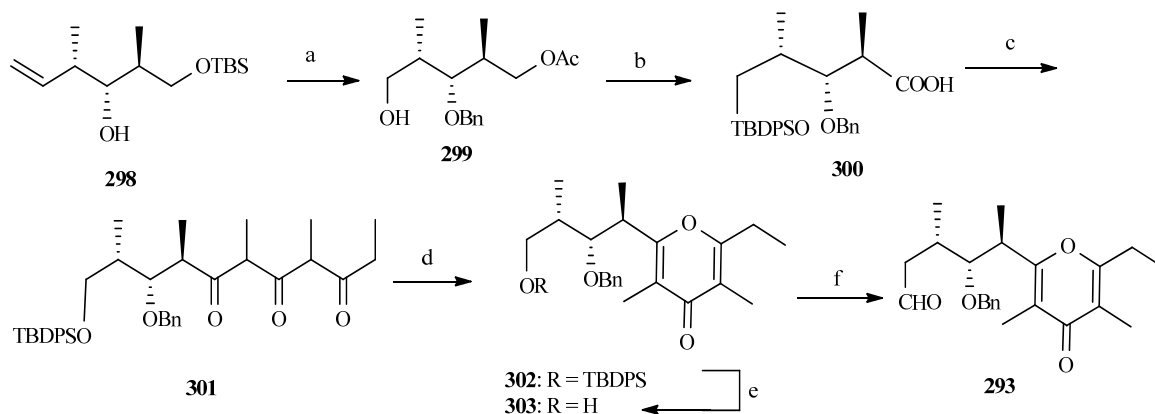
Step-1. Construction of the left wing A **292**: They have initiated the synthesis of onchitriol-II (**215**) starting from an enantiomerically pure carboxylic acid **294** [114] by condensation with 3-pentanone to give **295** followed by acylation with imidazolide **297** affording β -triketone **296**. The product was then subjected to $\text{PPh}_3\text{-CCl}_4$ cyclization afforded the desired left-wing A **292** (Scheme 8).



Scheme 8. Synthesis of left wing A. Reagents and reactions and conditions. a. i) Imd_2CO ; ii) 3-pentanone, LDA-DMPU, -70°C . b. i) LDA (2 eq.)-DMPU / THF, -70 – 10°C ; ii) **297**, -73°C (47%). c. PPh_3 (3 eq.) CCl_4 (10 eq.) / THF (40%).

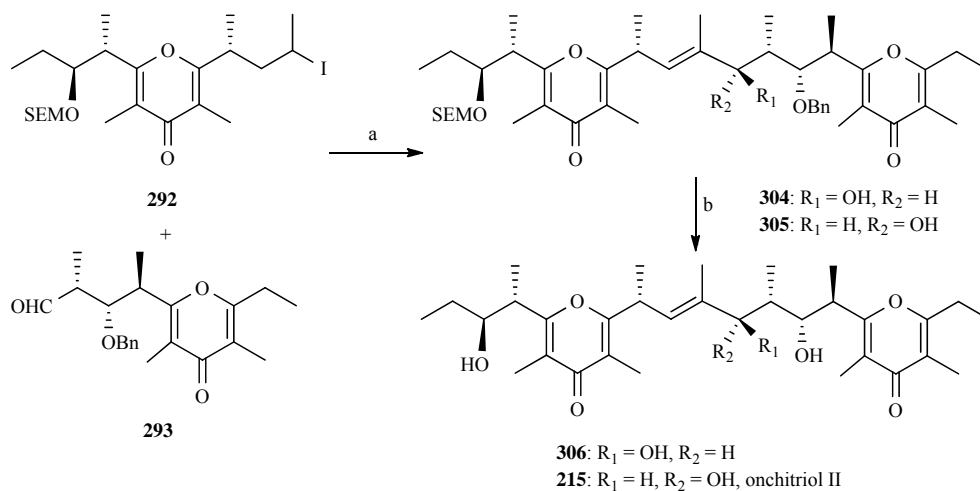
Step-2. Construction of right wing B **293**: Assembly of right-wing was achieved in five steps. The allyl alcohol **298** was converted into the carboxylic acid **300** which was then reacted with β -diketone

dienolate to give **301**. The resulting product on cyclization to pyrone **302** followed by manipulation afforded the right-wing aldehyde **293** (Scheme 9).



Scheme 9. Synthesis of right wing B. Reagents and reaction conditions. a. i) TBAF, ii) PhCH(OMe)₂, P-TsOH/ CH₂Cl₂; iii) DIBAL-H / CH₂Cl₂, 0 °C; iv) Ac₂O, Pyr. (100%); v) O₃ / CH₂Cl₂-MeOH, then Me₂S; vi) NaBH₄ (83% in 2 steps). b. i) TBDPSCl, imidazole; ii) K₂CO₃, MeOH (99%); iii) Swern Oxid. then KMnO₄ (87%). c. i) (COCl)₂; ii) 4-methyl-heptane-3,5-dione, LDA-DMPU, -70 °C (56%). d. PPh₃-CCl₄ (86%). e. TBAF. f. Swern Oxid. (99 %).

Step-3. Coupling of left wing and right wing by CrCl₂-NiCl₂ to give onchitriol II: Coupling of left-wing **292** and right-wing **293** in DMSO by CrCl₂-NiCl₂ coupling method [113] provided a mixture of **304** and **305**. Then deprotection of the coupling products by four steps manipulation from **304** gave **306** in 64% and similarly from **305** afforded onchitriol-II **215** in 97% yields (Scheme 10).

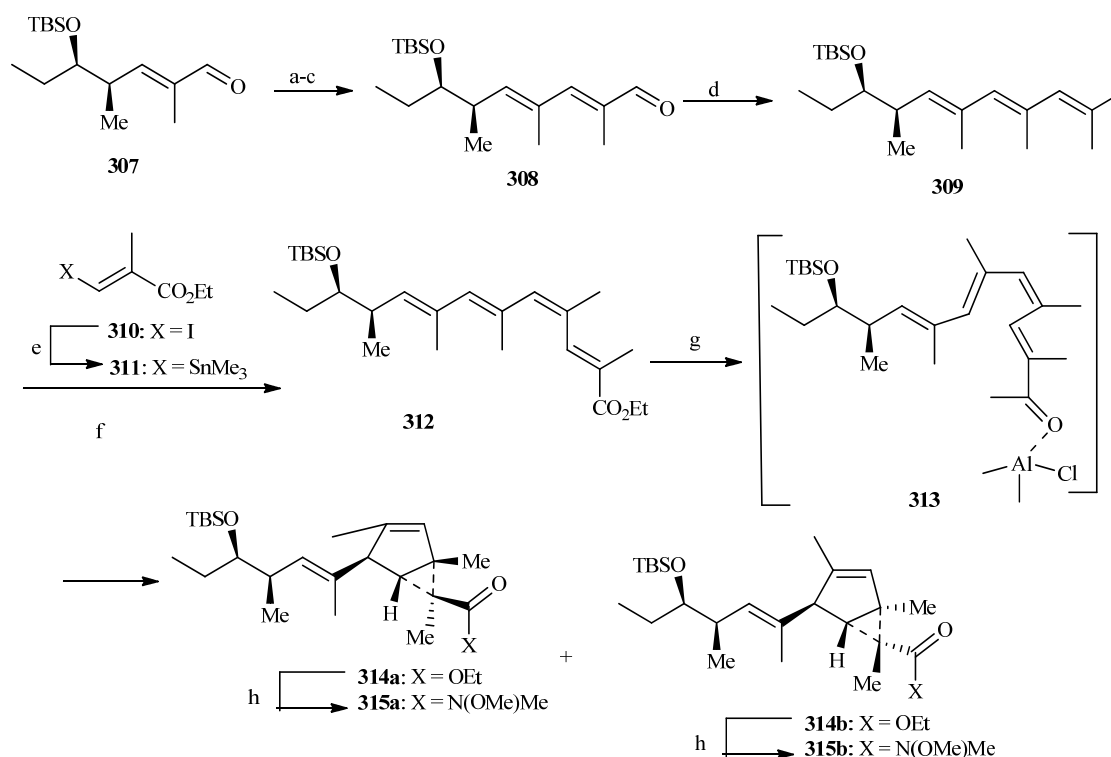


Scheme 10. Synthesis of onchitriol II by coupling of **292** and **293**. Reagents and reaction conditions. a. NiCl₂-CrCl₂ (0.5 %), DMSO rt, 1 day. b. i) Ac₂O, Pyr.; ii) TFA / CH₂Cl₂, -10 °C; iii) DDQ / CH₂Cl₂-H₂O, iv) K₂CO₃ / MeOH (**306**: 64% in 4 steps from **304**, **215** 97% in 4 steps from **305**).

5.2. Total synthesis of crispatene (202)

In 2004 Miller *et al.*[115] reported the total synthesis of crispatene (**202**), a marine polypropionate isolated from Mediterranean mollusc [75]. The synthesis of crispatene (**202**) commenced from the

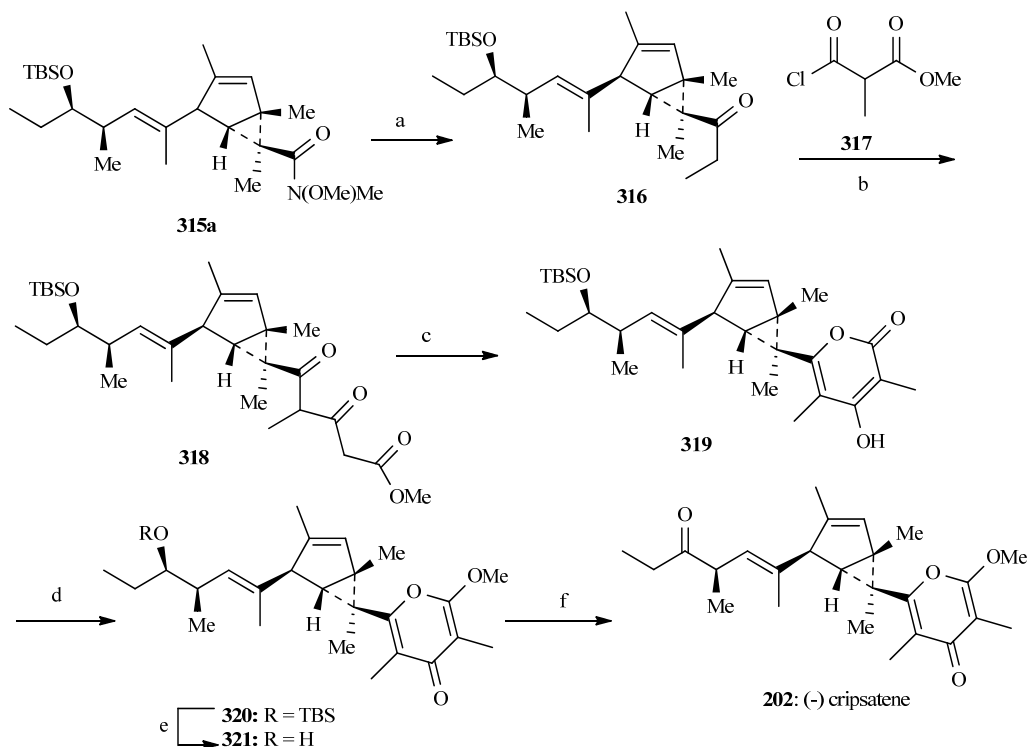
known aldehyde **307** which can be readily obtained from the corresponding Evans *syn*-aldol adduct by a standard method to give doubly unsaturated aldehyde **308**. After which stereoselective Stork–Zhao olefination [116] of **308** produced (*Z*)-vinyl iodide **309**. Then the tetraene system **312** was obtained by Stille-coupling [117] of **309** with the stannane **311**, which was obtained from the known iodide **310** [118]. Then the tetraene **312** undergoes a cleaned cycloisomerization in the presence of 20 mol% of dimethylaluminum chloride *via* the Lewis acid adduct **313** afforded an inseparable mixture of diastereomers **314a** and **314b** (1:1.5) in good yields which were readily separated after conversion to the corresponding Weinreb amides **315a** and **315b** (Scheme 11).



Scheme 11: Preparation of the bicyclo[3.2.0] hexane core. Reagents and conditions. a) $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{COOEt}$, THF, reflux, 94%; b) diisobutylaluminum hydride, CH_2Cl_2 , -78°C , 98%; c) Dess-Martin periodinane, CH_2Cl_2 , 88%; d) $\text{Ph}_3\text{P}=\text{CHCH}_3$, I_2 , sodium hexamethyldisilazide, -78°C , 86%; e) $\text{Pd}(\text{Ph}_3\text{P})_4$, $\text{Me}_3\text{SnSnMe}_3$, *i*- Pr_2NEt , PhH, rfx, 90%; f) $\text{Pd}_2(\text{dba})_2\text{-CHCl}_3$, (2-furyl) $_3\text{P}$, CuI, 1-methyl-2-pyrrolidinone, 57%; g) Me_2AlCl (0.2 eq.), CH_2Cl_2 , 83%; and (h) MeHNOMe.HCl, *i*-PrMgCl, THF, 76%.

In the next step, **315a** was treated with ethylmagnesium bromide to give ethyl ketone **316** which was then subjected to deprotonation with excess base followed by treatment with malonyl chloride **317** gave **318**. After which cyclization of **318** in the presence of a base gave γ -hydroxy- α -pyrone **319**. Subsequently, regioselective methylation under Beak's conditions resulted in significant desilylation to afford 2:1 mixture of α -methoxy- γ -pyrones **320** and **321**. The former compound **320** could be converted to later, **321** with hydrofluoride pyridine. At the end oxidation of secondary alcohol group

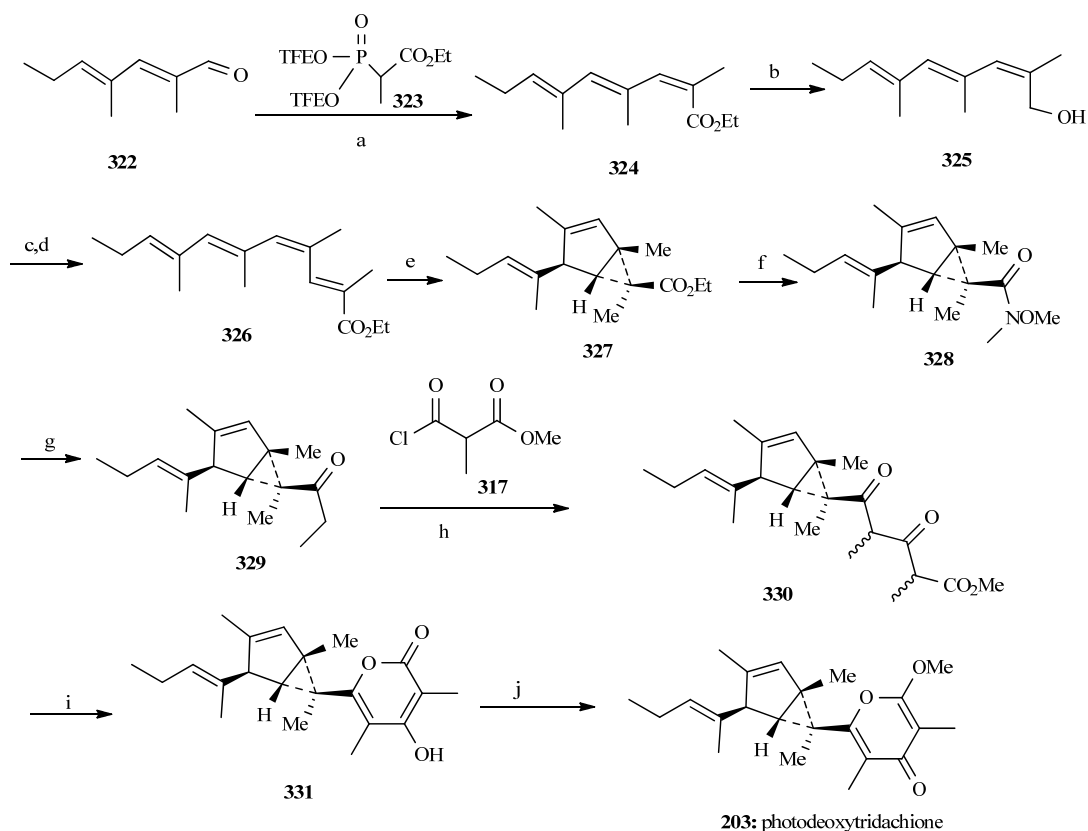
of **321** to ketone by Dess-Martin periodinane afforded the targeted natural product, crispatene **202** (Scheme 12).



Scheme 12. *Synthesis of crispatene. Reagents and conditions.* a) EtMgBr, THF, 0 °C, 87%; b) **317**, lithiumhexamethyldisilazide (3 eq.), THF, hexanes, -78 °C, 74%; c) 1,8-diazabicyclo[5.4.0]undec-7-ene, PhH, 60 °C, 87%; d) FSO₂OMe, CH₂Cl₂, -5 °C, 32% **320**, 17% **321**; e) HF-Pyridine, THF, 77% (f) Dess-Martin periodinane, CH₂Cl₂, 86%.

5.3. Total synthesis of photodeoxytridachione(203)

Miller and Trauner reported a total synthesis of photodeoxytridachione **203** starting from a known unsaturated aldehyde **322** through a Lewis acid-catalyzed cyclization [119]. In this synthesis, the unsaturated aldehyde **322** was subjected to Still-Gennari condensation with trifluoroethyl phosphonate (**323**) to give an intermediate **324** (≈20:1 dr). Then the resulted product was reduced with DIBAL affording the alcohol **325** which was then subjected to oxidation using TPAP/NMO followed by Horner-Wadsworth-Emmons condensation gave the tetraenoic ester **326**. The next step is the treatment of **326** with a catalytic amount of dimethylaluminium chloride to give bicycle [3.1.0]hexene **327**. Then they have attempted the transformation of **327** into the Weinrebamide **328** and treated with ethyl magnesium bromide to give ethyl ketone **329**. The product was then subjected to deprotonation with excess base followed by addition of malonyl chloride **317** afforded **330** in good yield. Subsequently, diketone **330** was subjected to cyclization under a basic condition to give the pyrone **331**. Finally, regioselective methylation of **331** under Baek's conditions [120] afforded photodeoxytridachione **203** (Scheme 13).



Scheme 13. *Synthesis of photodeoxytridachione 203. Reagents and conditions.* a. **323**, KHMDS, 18-crown-6, THF, $-78\text{ }^{\circ}\text{C}$, 79%; b) DIBAH, CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$, 93%; c) TPAP, NMO, CH_2Cl_2 ; d) $(\text{Et}_2\text{O})\text{P}(\text{O})\text{CHCO}_2\text{Et}$, LiCl, DBU, MeCN, 43%; e) Me_2AlCl (0.2 eq.), CH_2Cl_2 , 73%; f) MeHNOMe.HCl, *i*PrMgCl, THF, $0\text{ }^{\circ}\text{C}$, 63%; g) EtMgBr, THF, 87%; h) LiHMDS (3 eq.), **317**, THF, hexanes, $-78\text{ }^{\circ}\text{C}$, 59%; i) DBU, benzene, reflux, 78%; j) FSO_2OMe , CH_2Cl_2 , 77%. HMDS = hexamethyldisilazide; DIBAH = diisobutylaluminium hydride; TPAP = tetra-*n*-propyl ammonium peruthane; NMO = *N*-methylpyrrolidine-*N*-oxide; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TFE = trifluoroethyl.

5.5. Total synthesis of (-)-Membranone-C (**334**):

In 1993 Ciavatta *et al.* isolated three γ -dihydropyrone containing polypropionates, membranone-A (**332**), membranone-B (**333**) and membranone-C (**334**) (Figure 39) from the skin of a Mediterranean mollusc [121]. A few years later, Perkins *et al.* reported the first stereoselective synthesis of **334d**, one of the isomer of membranone-C (**334**) [122] which has four possible diastereomeric structures *viz.* **334a**-**334d**, as shown in Figure 40.

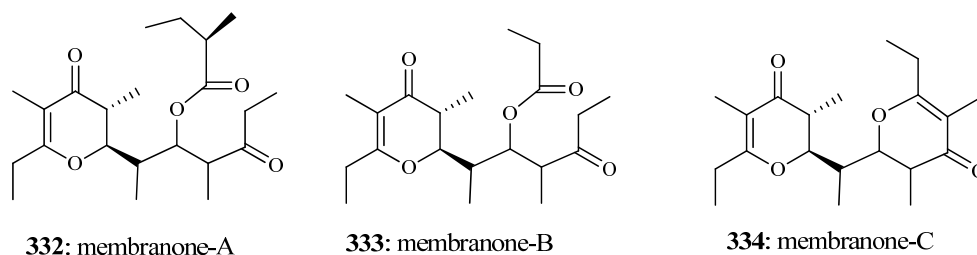


Figure 39. Chemical structures of membranones A-C (**332**-**334**).

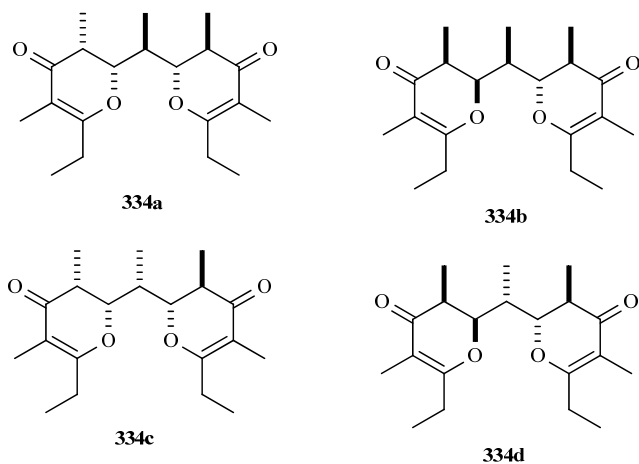
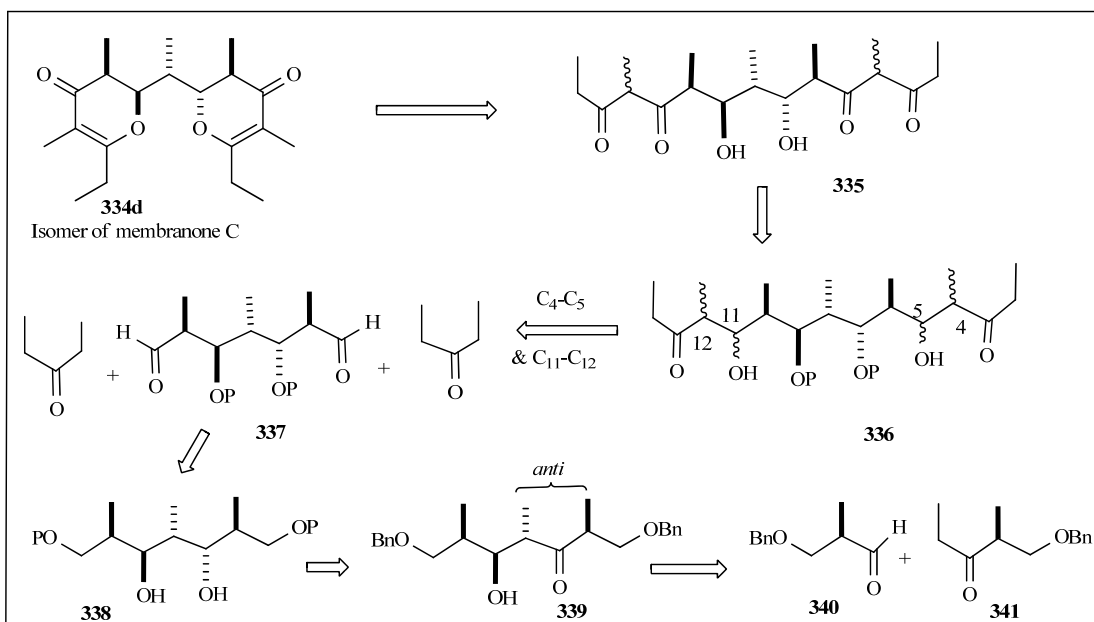
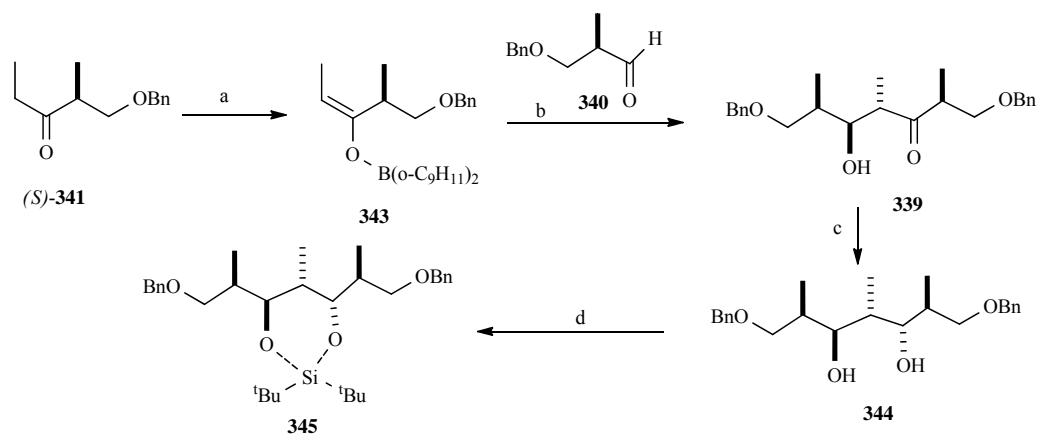


Figure 40. Four distereomeric structures of memprenone-C.

Parkin *et al.*, synthesis of memprenone-C isomer, **334d** involved a double titanium aldol coupling. The outlines strategy for the synthesis of memprenone C (**334d**) is depicted in Scheme 15. Perkin's proposed the synthesis of memprenone-C isomer (**334d**) via **335** and **336** based on double aldol disconnection of C₄-C₅ and C₁₁-C₁₂ segments. They have suggested that the product obtained by the *anti*-reduction of the *anti-anti* adduct **339** derived from ketone (*S*)-**341** and aldehyde (*R*)-**340** could be the appropriate precursor for the synthesis of this natural product (Scheme 14). With the synthesis strategy established, they started the synthesis of memprenone-C isomer (**334d**) by the addition of *E*-enol dicyclohexyl borinate **343** to a chiral aldehyde **340** to give *anti-anti* aldol isomer **339** with 95% ds. The compound **343** was obtained by enolization of (*S*)-**341** with (*c*-C₆H₁₁)₂BCl/Et₃N. The compound **339** was then reduced to *anti*-1,3-diol **344** by employing stereoselective Evans *anti*-reduction [123]. Subsequently, diol **344** was protected as the *di-tert*-butylsilylene to give the key intermediate **345**. Thus, they succeeded to obtain the required C₅-C₁₁ segment **345** in 34% yield in three steps from (*S*)-**341** and (*R*)-**340** with 93% ds (Scheme 15).



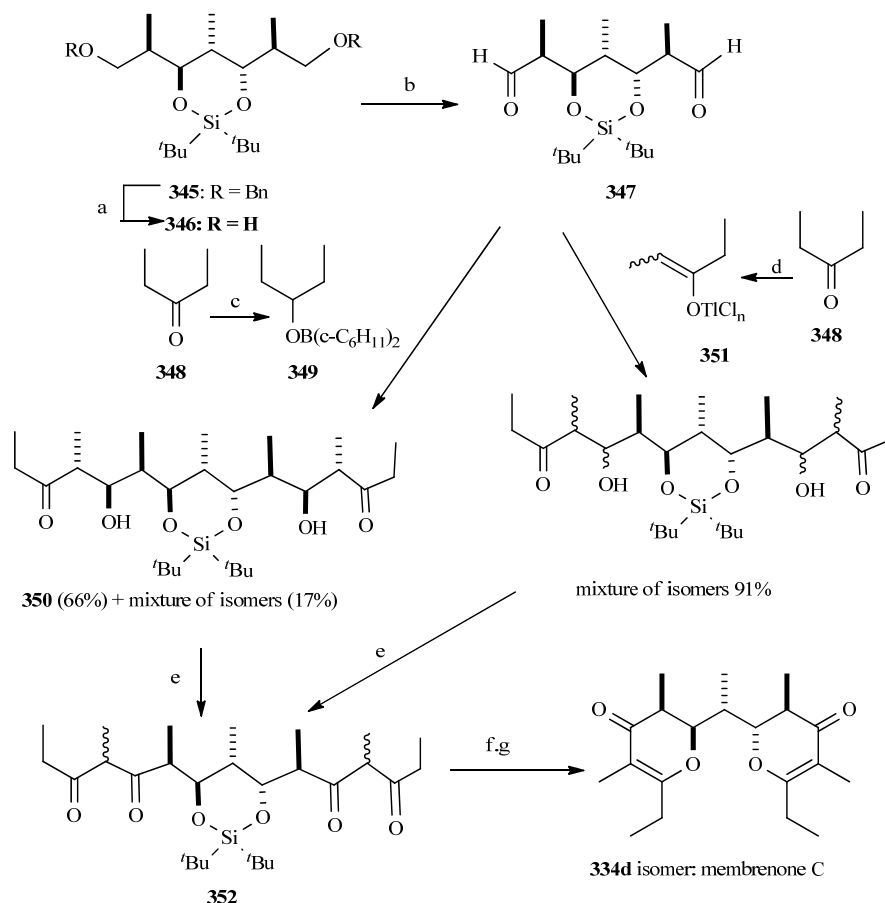
Scheme 14. Outlines for Perkin's synthesis of membranone-C isomer (**334d**).



Scheme 15. Perkin's synthesis of C_5 - C_{11} segment. Reagents and conditions. a) $(c\text{-}C_6H_{11})_2\text{BCl}$, Et_3N , Et_2O , $-22\text{ }^\circ\text{C}$, 2h; b) **340**, 2h, H_2O_2 , MeOH-pH7 buffer, $0\text{ }^\circ\text{C}$ to RT 2h; c) $\text{Me}_4\text{NBH}(\text{OAc})_3$, MeCN , AcOH , $-23\text{ }^\circ\text{C}$; d) $\text{tBu}_2\text{Si}(\text{OTf})_2$, 2,6-lutidine, CH_2Cl_2 , $20\text{ }^\circ\text{C}$, 5h.

The next step is the debenzoylation of **345** followed by oxidation to give dialdehyde **346** which was treated with 10 equivalent of enolate **348** followed by oxidative removal of boron gave 66% of double aldol chain **350** along with a mixture of minor isomers (19%). They have also attempted the synthesis of a double aldol chain in higher yields using $\text{Ti}(\text{IV})$ enolate **351** of diketone which produced an inseparable mixture of four isomers in 91% yield. Tetrone **352** was obtained in quantitative yield as a mixture of C_4 and C_{12} epimers by Double Swern oxidation of either of the double aldols (Scheme 16). Finally, removal of protecting the group from **352** by treatment with $\text{HF}\cdot\text{pyr}$, buffer resulted in a mixture of diols and hemiacetals which was subjected to rapid acid-

catalyzed cyclization/dehydration by treatment with trifluoroacetic acid afforded a single isomer of membranone-C **334d** (Scheme 16).

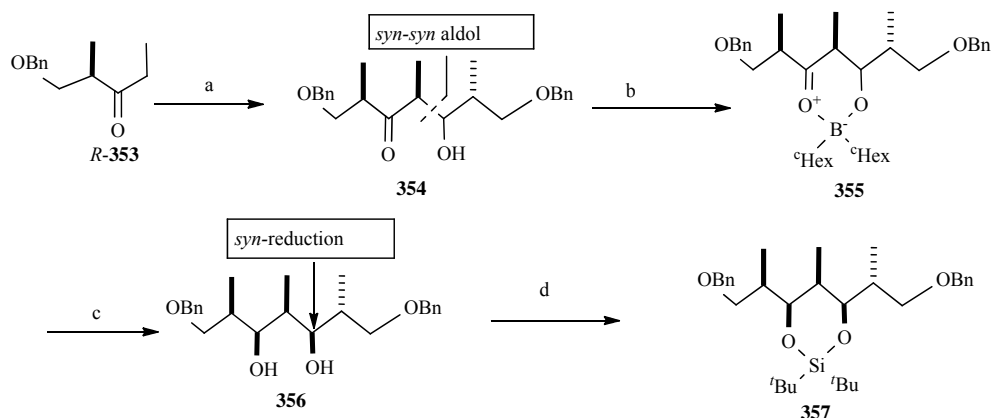


Scheme 16. Perkin's synthesis of membranone-C isomer **334d**. Reagents and conditions: a) H₂, 10% Pd/C, EtOH, 20 °C, 5h; b) PCC, CH₂Cl₂, 20 °C, 3.5 h; c) Diethylketone, 11 eq. (c-C₆H₁₁)₂BCl 10 eq., Et₃N, 10 eq. Et₂O, -22 °C, 2h; **347**, 3.5 h, H₂O₂, MeOH-pH7 buffer; d) Diethyl ketone 10 eq., TiCl₄ 9 eq. CH₂Cl₂, -78 °C, 45 min; ^tPr₂NEt 9 eq. 1h, **347**, 2h, @ -5 °C, 5 min; e) (COCl)₂ 10 eq., DMSO, CH₂Cl₂ 20 eq., -78 °C, 20 min, Et₃N, → -5 °C, 5 min; (f) HF-pyr/pyr, THF, 20 °C, 4h (g) TFA, 5 min.

In 2001 Perkin's *et al.* also reported the total synthesis of the remaining three isomers of membranone-C (**334a**, **334b** and **334c**) adopting a similar strategy and established that the relative and absolute configuration of the natural product membranone-C **334c** to be the enantiomer of **334c** (i.e. *ent*-**334c**) [124].

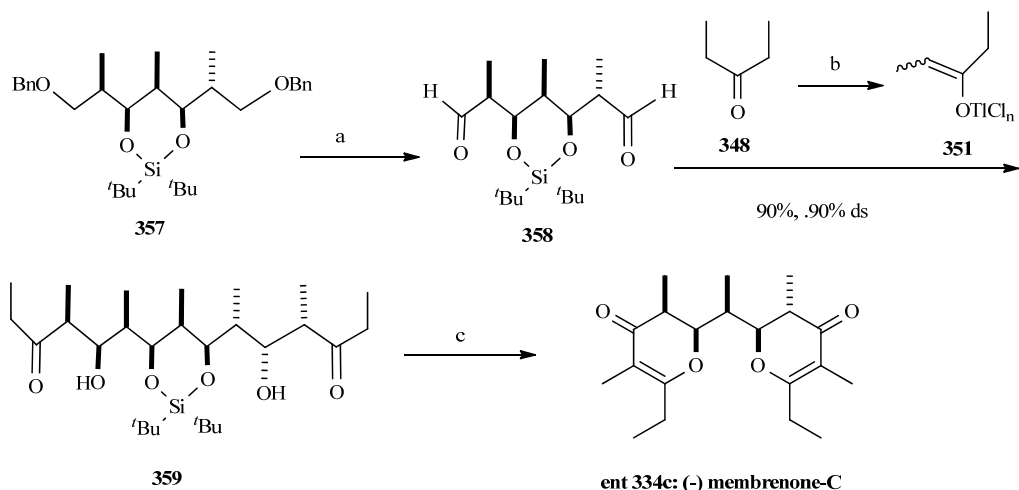
The isomer **334c** was synthesis by the addition of titanium enolate [125]to aldehyde(*R*)-**340** at -90 °C affording *syn-syn* aldol isomer **354**with >95% ds. The titanium enolate was obtained by the treatment of(*R*)-**353** with TiCl₄followed by reaction of diisopropylethylamine. Subsequently, the product was reduced to the *Syn*-1,3-diol **356**following a modified procedure[126] in which the alcohol **354**was added to (cC₆H₁₁)₂BCl/Et₃N to form a borinate complex **355**which was then reduced with LiBH₄ to give **356**in 88% yield with 95>ds (Scheme 17). The next step wasthe protection of **356**as the *di*-

tertbutylsilylene to give the key intermediate **357** in 44.3%. Thus, they accomplished the synthesis of key intermediate **355** in three steps starting from (*R*)-**340** and (*R*)-**353** with 90% ds.



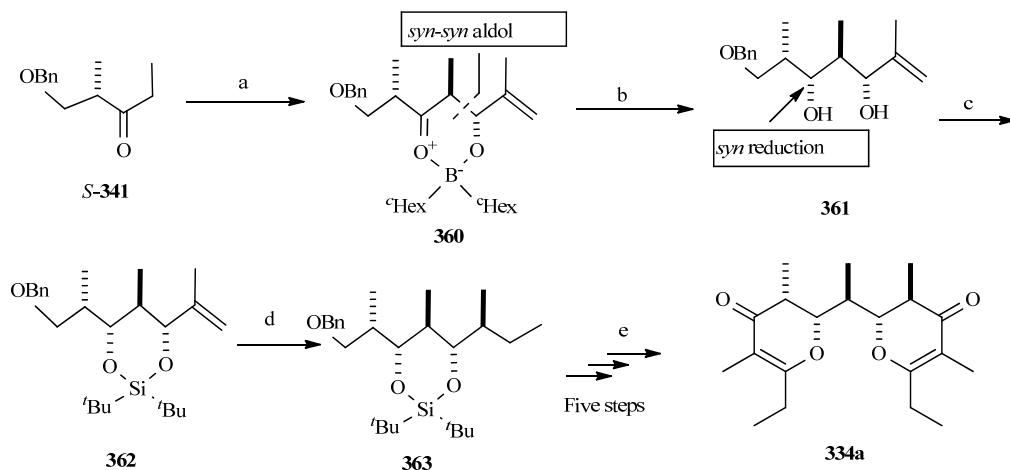
Scheme 17. *Synthesis of intermediate 357 of membranone C-isomer: Reagents and conditions.* a) (i) TiCl_4 , -78°C , 30 min, $^t\text{Pr}_2\text{NEt}$, CH_2Cl_2 , 1h, (ii) -90°C , (*R*)-**340**; b) $^c\text{Hex}_2\text{BCl}$, EtN_3 , Et_2O , -22°C ; c) (i) *in situ* LiBH_4 , H_2O_2 , pH7 buffer, MeOH (88%, > 95% ds; d) $^t\text{Bu}_2\text{Si}(\text{OTf})_2$, 2,6-lutidine, CH_2Cl_2 (72%).

In the next step, the key intermediate **357** was subjected to debenzoylation and oxidation to give di-aldehyde **358**. Treatment of **358** with TiCl_4 [125] enolate **351** of diethyl ketone gave predominantly one isomer **359** in 90% yield. Finally, double Swern oxidation of **359** afforded teraone as a mixture of C_4 and C_{12} epimers which was then subjected for removal of protection group by treatment with HF-pyridine buffer followed by acid-catalyzed cyclization/dehydration with trifluoroacetic acid gave a single product of membranone-C isomer *ent*-**334c** as a crystalline solid (Scheme 18).



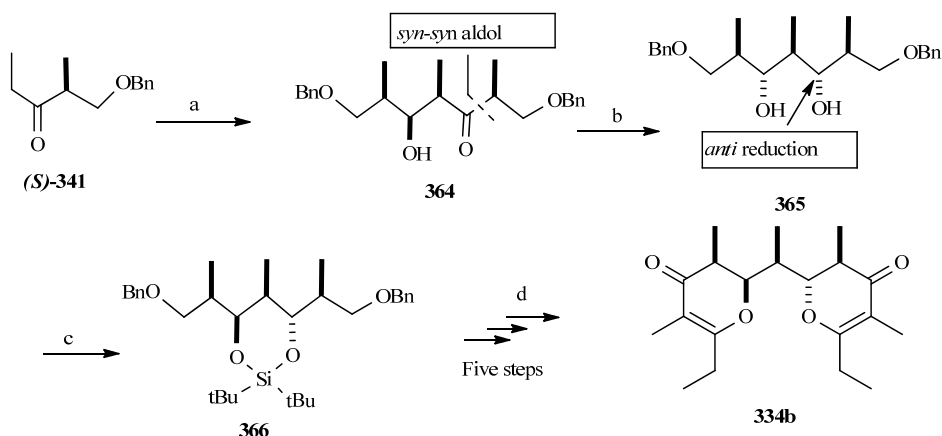
Scheme 18. *Synthesis of membranone-C, ent-334c. Reagents and conditions.* a) (i) H_2 , Pd/C , (ii) PCC , CH_2Cl_2 ; b) Diethyl ketone, TiCl_4 , CH_2Cl_2 , -78°C , 45 min, $^t\text{Pr}_2\text{NEt}$, 9 eq. 1h, **358**, 2h; c. (i) Swern Oxid, HF-pyr/pyridine (iii) TFA (52%).

Then they attempted the synthesis of the remaining two isomers of memprenone-C namely, **334a** and **334b**. The synthesis of isomer **334a** was commenced with the addition of methacrolein to E-enol dicyclohexylborinate of ketone **341** followed by *in situ* reductions of the intermediate **360** which provided diol **361** with >95% ds. This was followed by protection of **361** as the *di*-tertiary-butylsilylene **362** which was then selectively hydroborated with $\text{BH}_3 \cdot \text{SMe}_2$ to give the key intermediate **363**. Finally, memprenone-C isomer **334a** was obtained from **363** by following a similar process *i.e.* debenzylation, double aldol formation, oxidation, deprotection/cyclization/dehydration sequence that they have employed in the synthesis of memprenone-C isomer (*ent*)-**334c** (Scheme 19).



Scheme 19. Synthesis of intermediate **334a** of Memprenone C-isomer: Reagents and conditions. a) (i) $^{\text{C}}\text{Hex}_2\text{BCl}$, Et_3N , Et_2O , $-22\text{ }^\circ\text{C}$; c) (ii) methacrolein; b) *in situ* LiBH_4 , H_2O_2 , pH7 buffer, MeOH (90%, > 95% ds); c) $^{\text{t}}\text{Bu}_2\text{Si}(\text{OTf})_2$, 2,6-lutidine, CH_2Cl_2 (82%); d. (i) $\text{BH}_3 \cdot \text{SMe}_2$ (ii) $\text{H}_2\text{O}_2/\text{NaOH}$, THF ; e. Five steps: debenzylation, aldol, oxidation, deprotection/cyclization/dehydration.

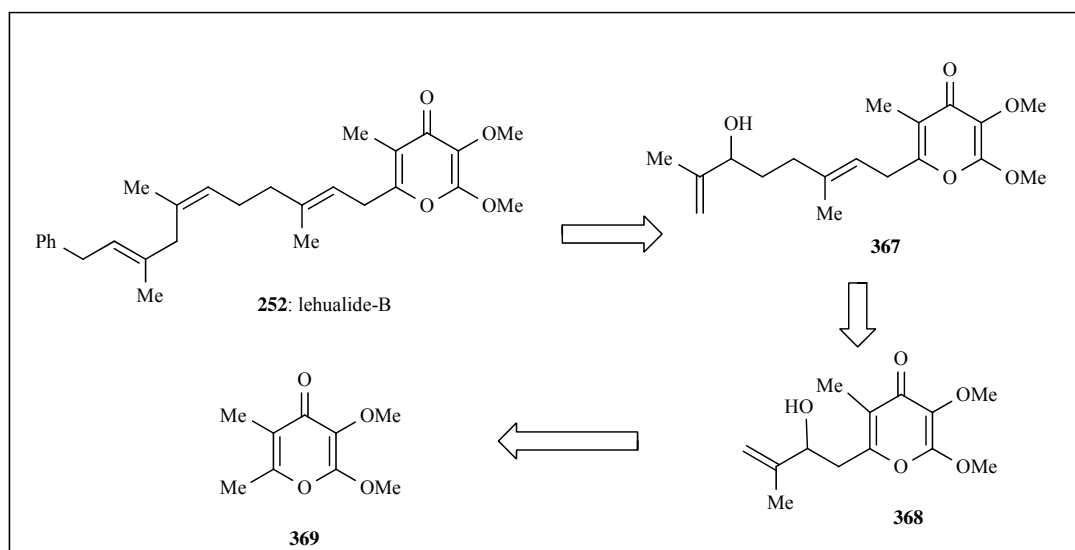
Similarly, synthesis of isomer **334b** was achieved by the treatment of the TiCl_4 enolate of (*S*)-**341** with (*R*)-**340** to give *syn-syn* aldol product **364** in 70% yield with >95% ds. This was followed by selective anti-reduction [123] to give **365** and subsequently protected the product as the *di*-tertiary-butylsilylene to give the key intermediate **366**. Then the product was subjected to the usual debenzylation, aldol formation, oxidation, and deprotection/cyclization/dehydration sequence to give the isomer **334b** of memprenone-C in 9.6% overall yield (Scheme 20).



Scheme 20. Synthesis of **334b** of Membrenone C-isomer: Reagents and conditions. a). (i) TiCl_4 , -78°C , 30 min, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , 1h, (ii) -90°C , (*R*)-**340**, 70%, > 95% ds; b). $\text{Me}_4\text{NBH}(\text{OAc})_3$, MeCN, AcOH, -23°C , 88%, >95% ds; c) $t\text{Bu}_2\text{Si}(\text{OTf})_2$, 2,6-lutidine, CH_2Cl_2 (77%); d). Five steps: debenzoylation, aldol, oxidation, deprotection/cyclization/dehydration.

5.6. Total Synthesis of lehualide-B(252)

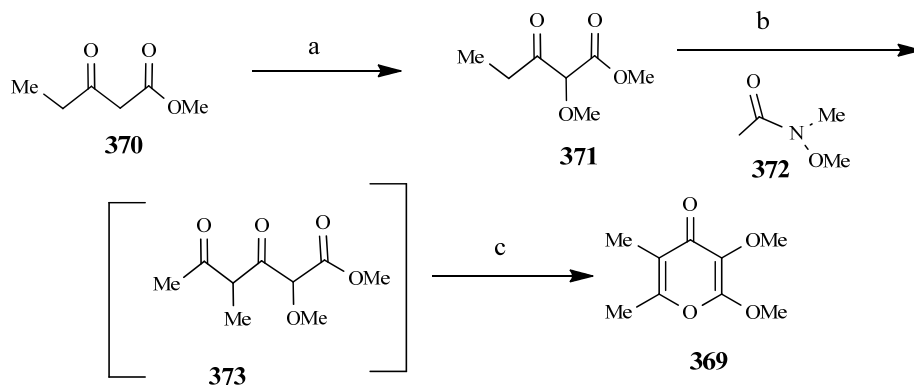
Lehualides are a group of marine metabolites containing a fully substituted pyrone ring isolated for the first time from the marine sponge *Plakortis sp.* [96]. Jeso and Mecalizio achieved the total synthesis of one of the members of this family, lehualide-B [127]. The retrosynthetic analysis of lehualide B (**252**) is depicted in Scheme 21. From the retrosynthetic analysis, they revealed that synthesis of the basic γ -pyrone unit **369** is needed to build up the targeted compound.



Scheme 21. Retrosynthetic analysis of lehualide-B

Thus, they started the synthesis of **369** from the β -ketoester **370** by iodobenzene diacetate-mediated oxidation in methanol providing the α -methoxy- β -ketoester **371**. This was followed by the addition of Weinreb amide **372** to furnish the tricarbonyl **373** as a mixture of isomers. Treatment of

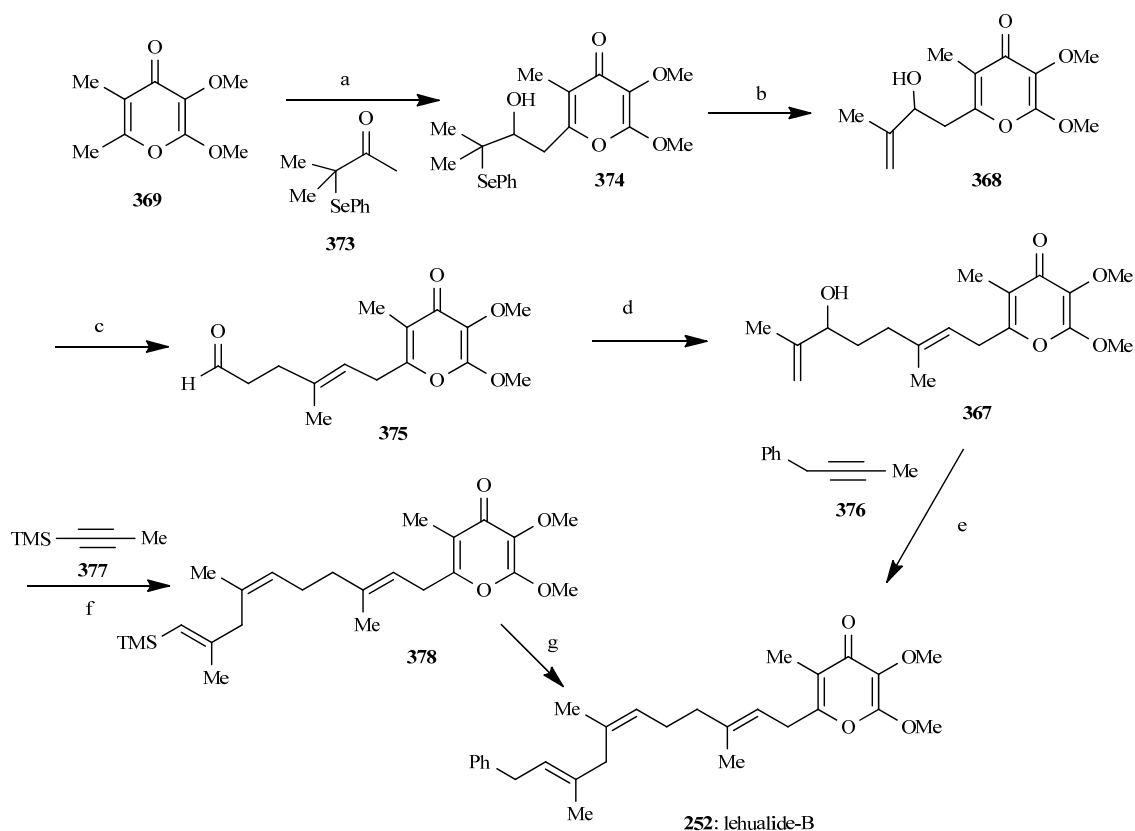
the isomers mixture directly in neat H₂SO₄ for 21 h resulted in the formation of γ -pyrone **369** (Scheme 22). The next step is methylation of γ -pyrone **369** with LiHMDS followed by addition to the α -phenylseleno aldehyde **373** to give pyrone **374** in 78%.



Scheme 22. Jeso's synthesis of γ -pyrone unit **369**. Reagents and conditions. a). PhI(OAc)₂, BF₃·OEt₂, MeOH, 70%; b). LDA (2.2 eq.), Weinreb amide **372**; c). H₂SO₄ 24%.

The product was then subjected to oxidation and *syn*-elimination to furnish allylic alcohol **368** in 94% yield. Subsequently, alcohol **368** was converted to a stereodefined, γ , δ -unsaturated aldehyde **375** in 90% yield by treating successively with ethylvinylether and Hg(OCOCF₃) followed by reflux in toluene. After which nucleophilic addition of 2-propenylmagnesium bromide provided the alcohol **367** in 59% yield.

After which the lithium dianion of **367** generated by exposure of **367** with LiHMDS in THF was treated with Ti-alkyl complex derived from **376** with ClTi(Oi-Pr)₃ and *c*-C₃H₉MgCl at -78 to -40 °C affording a coupled product in 50% yield. However, the lehuaide-B **252** produced by this C-C coupling was poor and gave a mixture of isomeric products in 1.3:1. To overcome this problem they pursued the reductive cross-coupling using TMS-propyne **377** with the allylic alcohol **367** and then the reaction proceeded *via* preformation of a Ti-alkyne complex of **377** which was obtained by treatment **377** with a combination ClTi(Oi-Pr)₃ and *c*-C₃H₉MgCl at -78 to -40 °C in THF. This was followed by a cannula transferred to a solution of the Li-dianion of **367** after which slow warming to 0 °C resulted in reductive cross-coupling and provided stereodefined vinylsilane **378** in 61% yield (*Z,E* = 7:1; *ds* ≥ 20:1). Subsequently, vinylsilane **378** was converted into the corresponding vinyl iodide in two steps successively by the treatment of NIS, ClCH₂CN, and ethyl acetate [128]. Finally, the vinyl iodide formed was subjected to a Pd-catalysed cross-coupling with benzyl zinc bromide to give lehuaide-B **252** (Scheme 23).

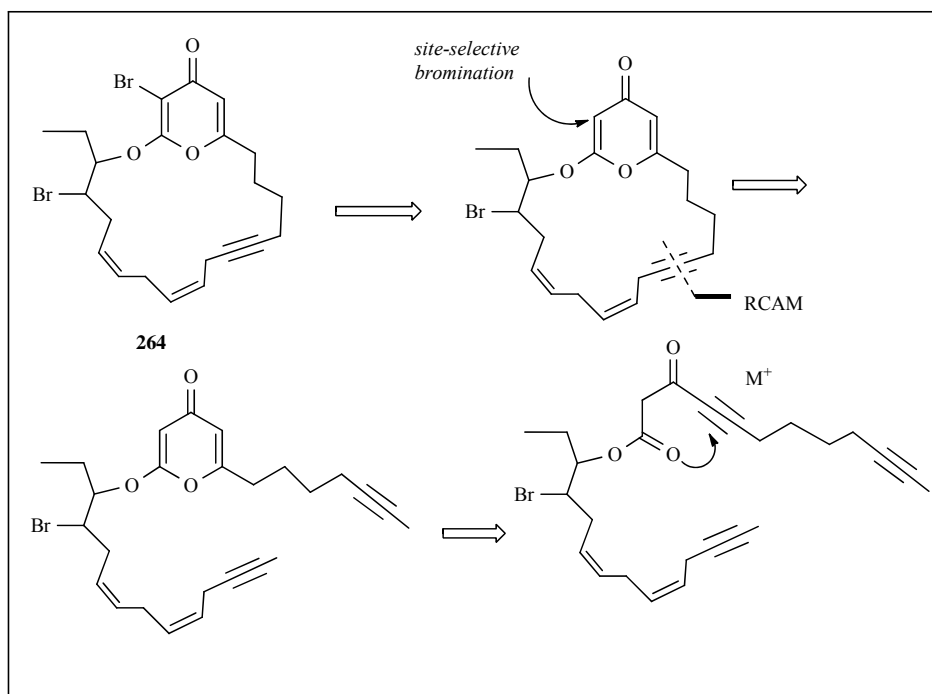


Scheme 23. Total Synthesis of lehualide-B **252**. Reagents and conditions. a). i. LiHMDS, then ii. **373**; b). *m*-CPBA, Et₃N, 94%; c) (i) ethylvinyl ether, Hg(OAc)₂, (ii) PhMe, 150 °C, 90%; d). CH₂=C(Me)MgBr, THF, -78 to -25 °C, 59%; e) **376**, dianion of **367**, C(Ti(O^{*i*}-Pr)₃), *c*-C₅H₉MgCl, PhMe, -78 to 0 °C, 50 % (rr = 1.3:1); f). **377**, C(Ti(O^{*i*}-Pr)₃), *c*-C₅H₉MgCl, PhMe, -78 to -40 °C then added dianion of **367**, 61%; g). (i) NIS, ClCH₂CN:EtOAc (2 : 1), 93%, (ii) BzZnBr, Pd(PPh₃)₄, THF, rt, 68%.

5.7. Total Synthesis of macrocyclic enol ethers (**264**):

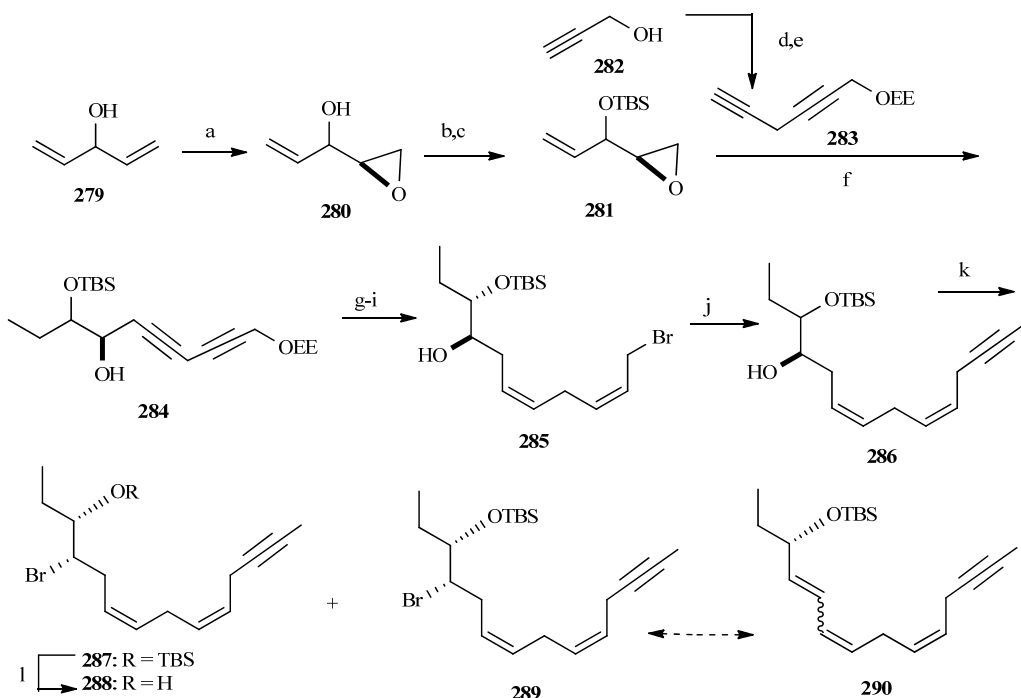
Macrocyclic enol ethers are a family of algal metabolites having exceptional pyrone macrocyclic scaffold. They were mainly isolated from the Australian red algae *Phacelocarpus labillardieri*[98]. For more than three decades total synthesis of these exceptional algal metabolites remained unattempted. This was mainly due to the lack of stereochemical assignment of the chiral centres in these compounds and limited information available on their bioactivities.

In 2015, Fürstner and co-workers reported the total synthesis of one of the algal metabolite **264** which involved formation of 2-alkoxy-4-pyrone ring through a gold-catalyzed procedure [129]. The transformation engaged only the acetylenic β -ketoester substructure of **263** leaving un-touched all the other pi-bonds. The retrosynthetic analysis of **264** is depicted in Scheme 24.



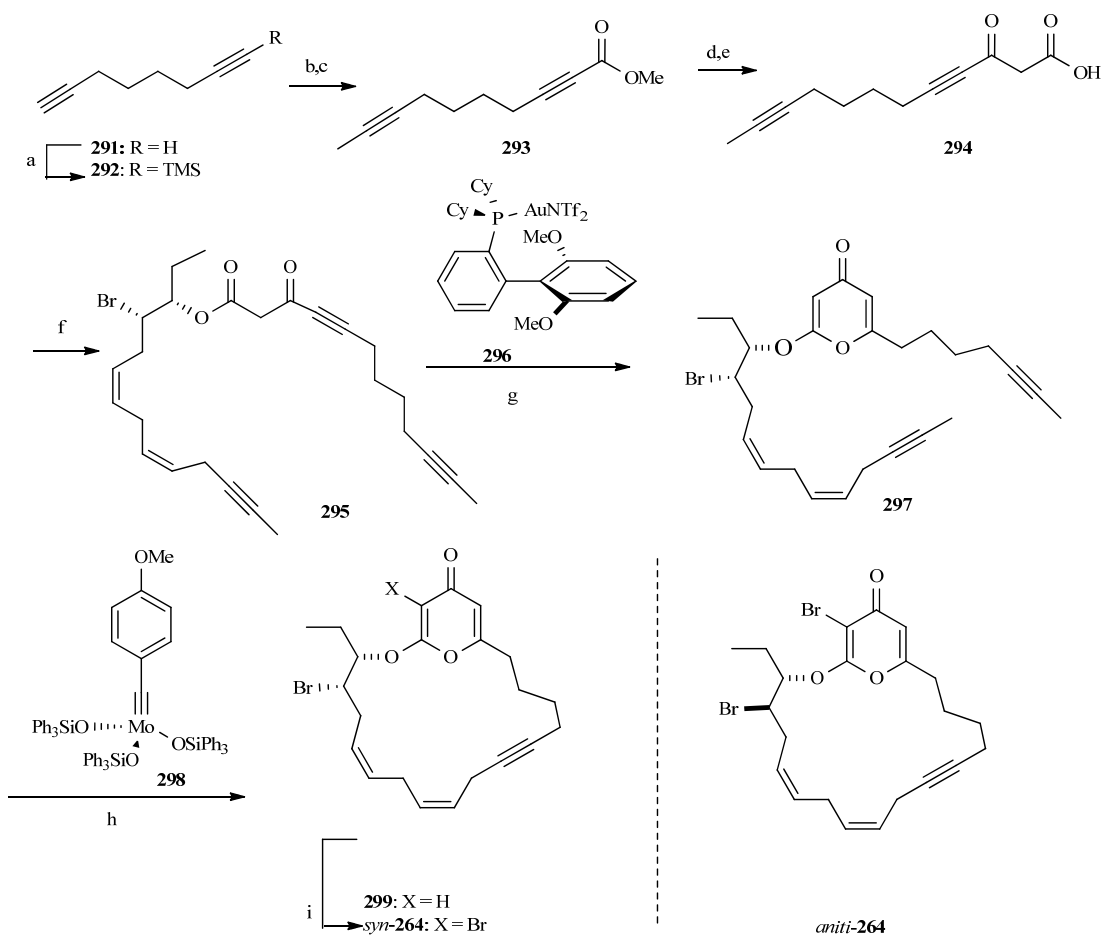
Scheme 24. Retrosynthetic analysis of **264**.

Füstner's total synthesis of **264** commenced with the desymmetrization of a readily available **279** using Sharpless epoxidation to give epoxide **280** (Scheme 25) [130]. This was followed by protection of the resulting product **280** as TBS then hydrogenation of the remaining double bond with Pd/charcoal which provided compound **281**. After the epoxide ring was opened by the lithiated skipped diene **283** in the presence of Lewis acid [131] followed by the cleavage of the acetyl protecting group afforded **284**. The product was immediately proceeded for catalytic semi-reduction of both the triple bonds over nickel boride (P2-Ni) [132] and subsequently, converted the primary hydroxyl group into the corresponding bromide **285**. The resulting bromide **285** was then treated with propynylmagnesium bromide in the presence of sub-stoichiometric amount of CuI to give skipped diene-yne **286** in fairly good yield. The product was then converted into the homoallylic bromide **287** under harsh conditions to give 60% yield. However, the reaction also produced other impurities **289** (12%) and **290** (11%) which were removed during workup (Scheme 25). The homoallylic bromide **287** was then converted into alcohol **288** by the treatment with HF-pyridine in THF. The next step was esterification of alcohol **288** with β -keto acid **294** to give ester derivative **295**. They obtained β -keto acid **294** from commercial 1, 7-octadiyne **291** over five robust steps. The ester **295** formed contained five different series of un-saturation in addition to β -keto ester unit. However, on treatment with a catalytic amount of gold complex **296** resulted in the formation of exclusively the desired 2-alkoxy-4-pyrone derivative **297** in quantitative yields.



Scheme 25. Synthesis of crucial building block homoaallylic bromide **287**. a) $\text{Ti}(\text{OiPr})_4$ (10 mol%), (+)-diisopropyl tartrate (13 mol%), cumene hydroperoxide, CH_2Cl_2 , MS 4, $-25\text{ }^\circ\text{C}$, 82%; b) TBSCl, imidazole, DMF, $0\text{ }^\circ\text{C}$ @ RT, 90%; c) H_2 (1 atm), Pd/C (10 mol% Pd), EtOAc, 95%; d) ethyl vinyl ether, $p\text{TsOH}\cdot\text{H}_2\text{O}$ (10 mol%), $0\text{ }^\circ\text{C}$, 84 %; e) (i) EtMgBr, THF, $45\text{ }^\circ\text{C}$; (ii) CuCl (5 mol%), propargyl bromide, $60\text{ }^\circ\text{C}$, 68%; f) (i) 11, $n\text{BuLi}$, THF, $-78\text{ }^\circ\text{C}$; (ii) $\text{BF}_3\cdot\text{Et}_2\text{O}$, then **281**, $-78\text{ }^\circ\text{C}$, 72%; g) PPTS, MeOH, $30\text{ }^\circ\text{C}$, 98%; h) H_2 (1 atm), P2-Ni (25 mol%), EtOH, 79%; i) CBr_4 , PPh₃, CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 91%; j) propynylmagnesium bromide, CuI (50 mol%), THF, $15\text{ }^\circ\text{C}$ to $-10\text{ }^\circ\text{C}$, 81%; k) CBr_4 , PPh₃, PhMe, $65\text{ }^\circ\text{C}$, **287** (60%); **289** (ca.12%), **290** (ca.11%) ;l) HF-pyridine, THF, $0\text{ }^\circ\text{C}$, 83%.

Subsequently, the highly sensitive diene **297** was subjected to ring-closing alkyne metathesis (RCAM) [133] by treating with molybdenum alkylidene **298** at ambient temperature in the presence of MS 5Å to provide the cycloalkyne **299** in excellent yield. The last step was the vinylsilane selective bromination of 4-pyrone ring of cycloalkyne **299** for which they have screened various $[\text{Br}^+]$ sources under different conditions. They found that using a freshly crystallized NBS at ambient temperature gave the desired product *syn*-**264** in a 40 % yield. The reaction requires constant monitoring of the conversion so that as soon as the starting material consumed the reaction needed to be stopped as stirring for a longer time aggravated the isomerization problem. The spectroscopic data of this *syn*-**264** is well matched with the reported natural product **264** and the structure was confirmed by X-ray diffraction. Further, they have prepared *anti*-**264** following an analogous route employing an inverted OH group in **288** and proceeded a similar route to achieve the *anti*-**264** (Scheme 26).



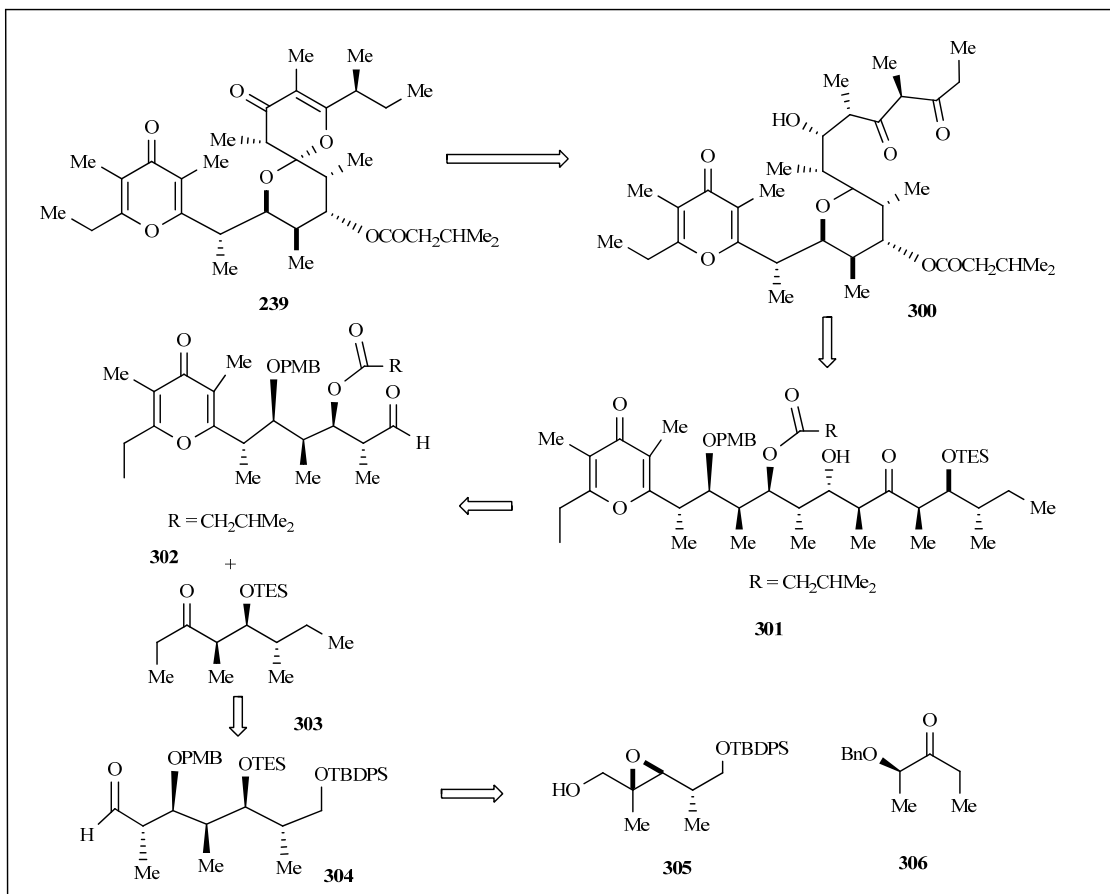
Scheme 26. Total synthesis of macrocyclic enol ether **264**. *Reagents and Conditions*. a) LiHMDS, THF, -78°C , then TMSCl, 78°C @ RT, 52%; b). nBuLi, THF, -78°C , then MeI, 78°C @ RT, 91%; c). MeLi, THF, -78°C , then ClC(O)OMe, -78°C @ 0°C , 86%; d) $t\text{BuOAc}$, LDA, -78°C , then **293**, 87%; e) TFA, CH_2Cl_2 , 99%; f) **288**, DCC, DMAP cat., CH_2Cl_2 , 0°C , 70 %; g) **296** (3 mol%), MeCN/HOAc (4:1), 97%; h) **298** (5 mol%), MS 5, PhMe, 82%; i) NBS, THF, 40%.

Total synthesis of auripyrones-A & B:

In 2006, Yamada and co-workers isolated cytotoxic metabolites, auripyrones A & B (**239**&**240**) from the sea hare *Dolabella auricularia* [89]. The total synthesis of auripyrones-A (**239**) was first reported by Perkins and Lister in 2006 [134], where the key reaction was spiroacetalization. Subsequently in 2009 Jung's *et al.* [135] reported the total synthesis of auripyrones A **239** by employing tandem non-aldol aldol/Paterson Aldol process and subsequently, the total synthesis of auripyrones-B (**240**) using similar route [136]. In the same year, Hayakawa *et al.* reported the total synthesis of auripyrones A & B (**239**&**240**) employing a diastereoselective aldol-type reaction of γ -pyrone as the key step of synthesis [137, 138]. In this review, the total synthesis of auripyrones A & B described by Jung *et al.* [135, 136] and Hayakawa *et al.* [137] have been discussed along with their retrosynthetic analysis.

5.8.1 Total synthesis of auripyrones A by Jung *et al.* 2009 [135]: The total synthesis of auripyrones-A **239** by Jung *et al.* commenced with the preparation of **304** using convergent tandem non-aldol aldol

[139]/Paterson-lactate derived aldol reaction [140]. The retrosynthetic analysis of auripyrrone-A **239** is depicted in Scheme 27.

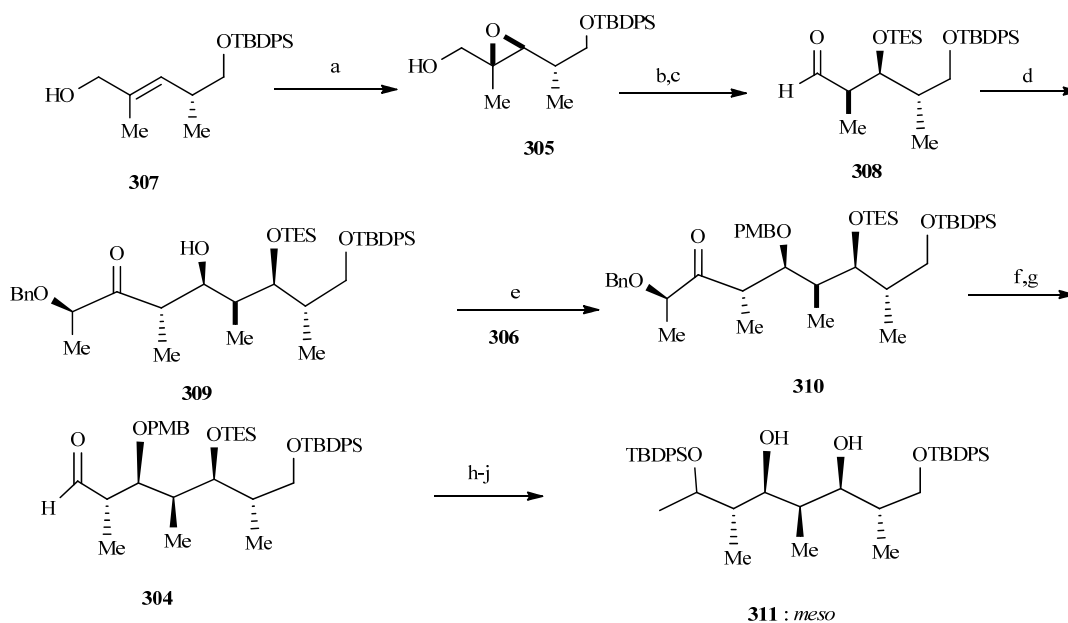


Scheme 27. Retrosynthetic analysis of auripyrrone-A **239**.

The allylic alcohol **307** was obtained over five steps from (*R*)-Roche ester [141] and it was subjected to epoxidation under either Sharpless conditions [142] or substrate controlled conditions using *m*-CPBA [143] which gave the epoxide **305** in 85% with 20:1 dr or 90% with 16:1 dr, respectively. In the next step **305** was protected as silyl ether by treatment with TESCOI then treated with TESOTf at -45 °C to give the *syn*-aldol adduct **308** by a non-aldol reaction in 86% yield with 20:1 d.r. This non-aldol aldol reaction was an efficient process and provided direct access to pure silyl-protected aldehydes without tedious chromatography purification. Subsequently, the aldehyde **308** undergoes anti-aldol reaction with the E-boron enolate of ketone **306** [144] to provide the desired anti-aldolate **309** as a single isomer in 86% yield. The alcohol **309** was then protected as PMB ether by mild Lewis's acid-catalyzed protection reaction to give the ketone **310** in 93% yield (Scheme 28).

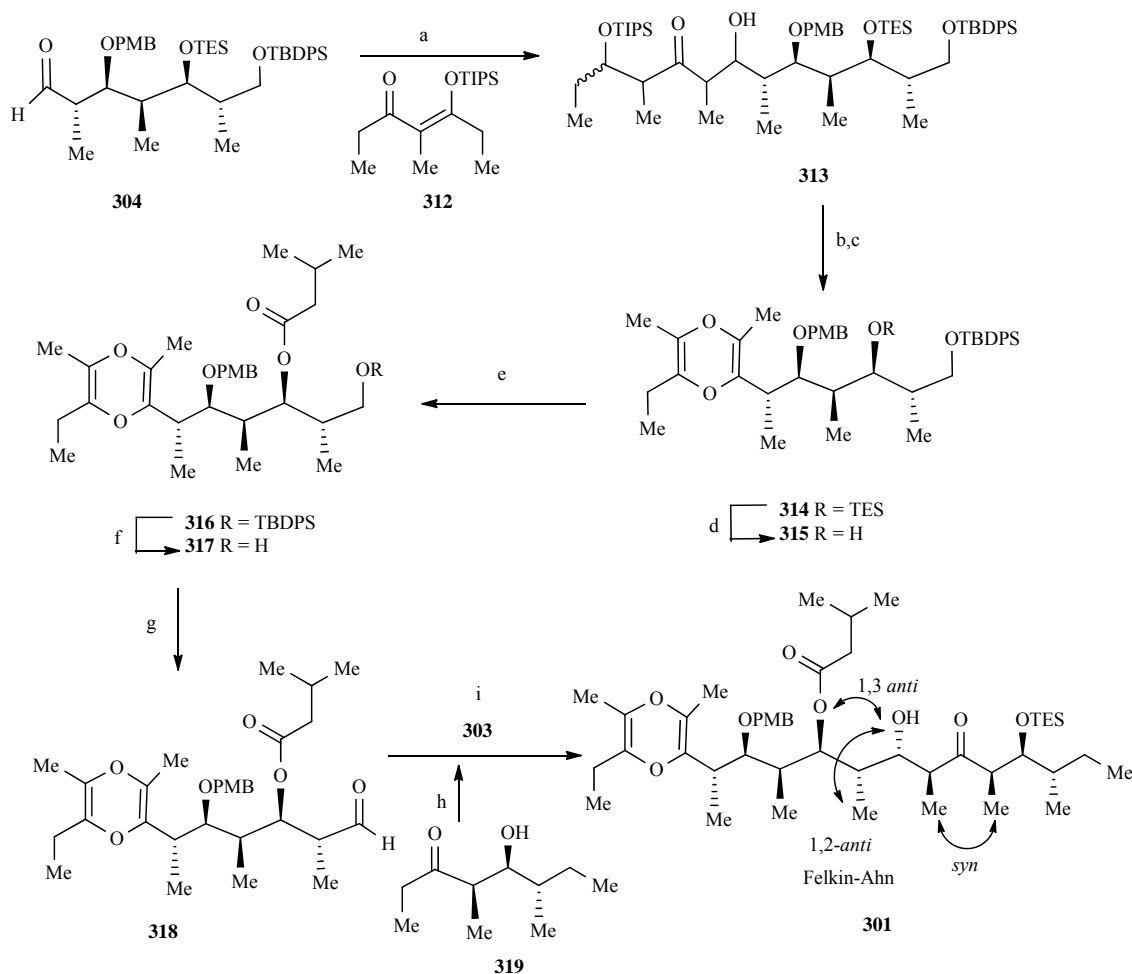
The aldehyde **304** was obtained in 83% yield over two steps successively by the reduction of **310** and removal of benzoate using LiBH₄ followed by periodate cleavage of the resulting diol

[145]. They have found that this tandem non-aldol aldol//Paterson-lactate-derived aldol protocol was a highly efficient approach for the synthesis of stereopentad **304** furnishing four aldol stereocenters in two steps. Then the aldehyde **304** was converted into *meso*-polypropionate **311** in three steps and confirmed its symmetrical structure by ^{13}C -NMR.



Scheme 28. Synthesis of *meso*-polypropionate **311** *meso*. Reagents and conditions: a) $\text{Ti}(\text{O}i\text{Pr})_4$, $t\text{BuOOH}$, (+)-DIPT, CH_2Cl_2 , -10°C , 85%, 20:1 d.r. or *m*CPBA, K_2HPO_4 , DCM, -10°C , 90%, 16:1 d.r.; b) TESCl, imidazole, CH_2Cl_2 , 98%; c) TESOTf, DIPEA, CH_2Cl_2 , -45°C , 86%, 20:1 d.r.; d) **306**, cHex_2BCl , Me_2NEt , Et_2O , $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$, 2 h; $0^\circ\text{C} \rightarrow 78^\circ\text{C}$; **308**, $-78^\circ\text{C} \rightarrow 25^\circ\text{C}$, 15 h; H_2O_2 , MeOH, pH 7 buffer, 0°C , 1 h, 86%, one isomer; e) PMBOC(=NH)- CCl_3 , $\text{Sc}(\text{OTf})_3$, toluene 93%; f) LiBH_4 , THF, 97%, 8:1 d.r.; g) NaIO_4 , MeOH/pH 7 buffer (2:1), 86%. h) NaBH_4 , EtOH, 0°C , 81%; i) TBDPSCl, imidazole, CH_2Cl_2 ; j) CAN, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (9:1), 78% over two steps.

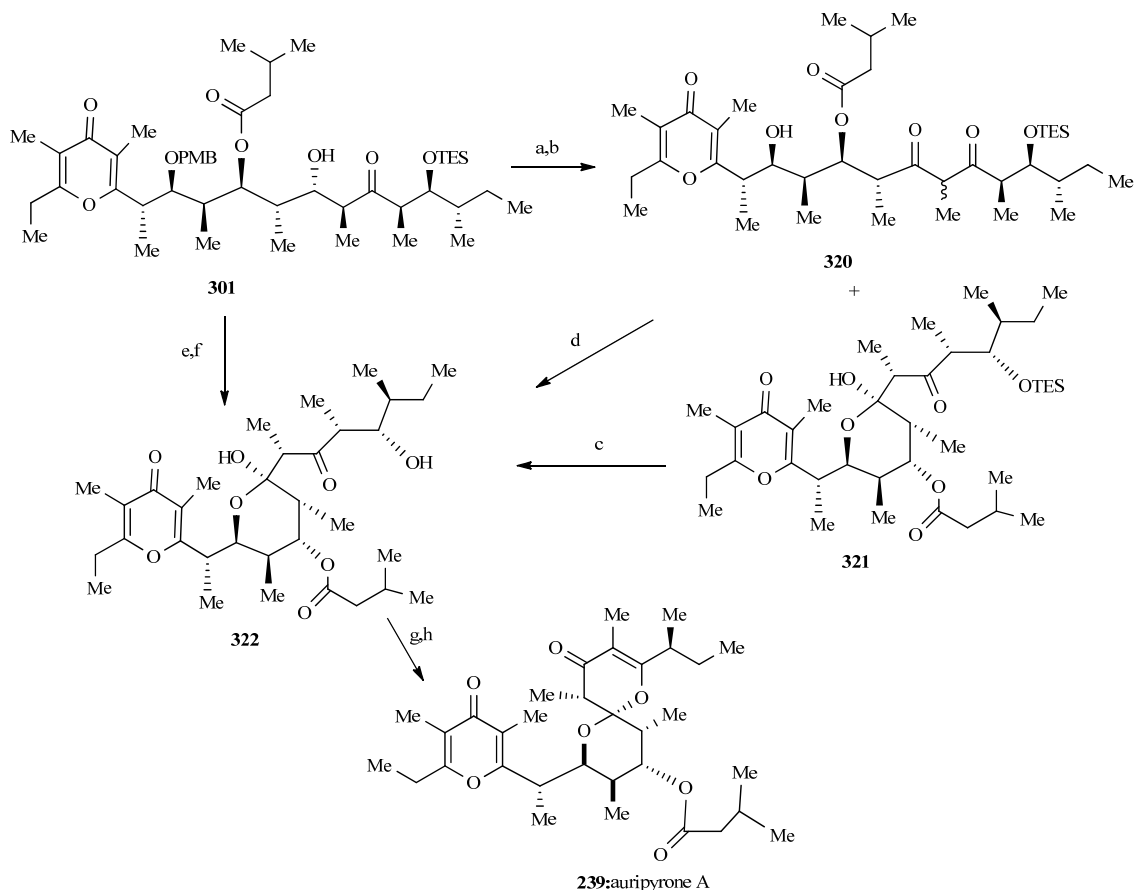
With the accomplishment of the synthesis of **311**, they attempted the synthesis of the γ -pyrone moiety **301** (Scheme 29) following the Gillingham and Hoveyda protocol [146]. They succeeded to obtain the aldolate **313** in 94% yield as a mixture of isomers [143] through the aldol reaction of the lithium enolate **312** with the aldehyde **304**. The isomeric mixture of **313** was then oxidized with DMP and subsequently, the resulting diketone was heated providing the desired γ -pyrone **314** in 68% yield. This was followed by the removal of TES ether under acidic conditions to give alcohol **315** and then subjected to esterification with isovaleric acid following Yamaguchi's conditions [147] to furnish the ester **316** in 98% yield. In the next step **316** was treated with HF.pyridine to give primary alcohol which was then oxidized by DMP to give the aldol precursor **302**. The other component α -methyl- β -hydroxy ketone **303** was also readily obtained by protecting the known ketone **319** [134] as the TES ether. Finally, the diastereoselective anti-aldol reaction of the E-boron enolate of the ketone **303** with **302** provided the desired product **301** in 94% yield with 21:1 ds (Scheme 29).



Scheme 29. Synthesis of key intermediate **301**. Reagents and conditions: a) **312**, LDA, -78 °C, **304**, 94%; b) DMP, CH₂Cl₂, NaHCO₃; c) DMF, 55 °C mw, 6 h, 68% over two steps; d) PPTS, CH₂Cl₂/MeOH (3:1), 96%; e) 2,4,6-trichlorobenzoyl chloride, DMAP, Et₃N, isovaleric acid, 98%; f) HF-pyridine/MeCN/py (7:1), 94%; g) DMP, CH₂Cl₂, NaHCO₃, 98%; h) TESCl, imidazole, CH₂Cl₂, 96%; i) **6**, cHex₂BCl, Me₂NEt, Et₂O, -78 °C → 0 °C, 2 h, 0 °C → -78 °C, **302**, -78 °C → -25 °C, 15 h, H₂O₂, MeOH, pH 7 buffer, 0 °C, 1 h, 94%, 21:1 d.r.

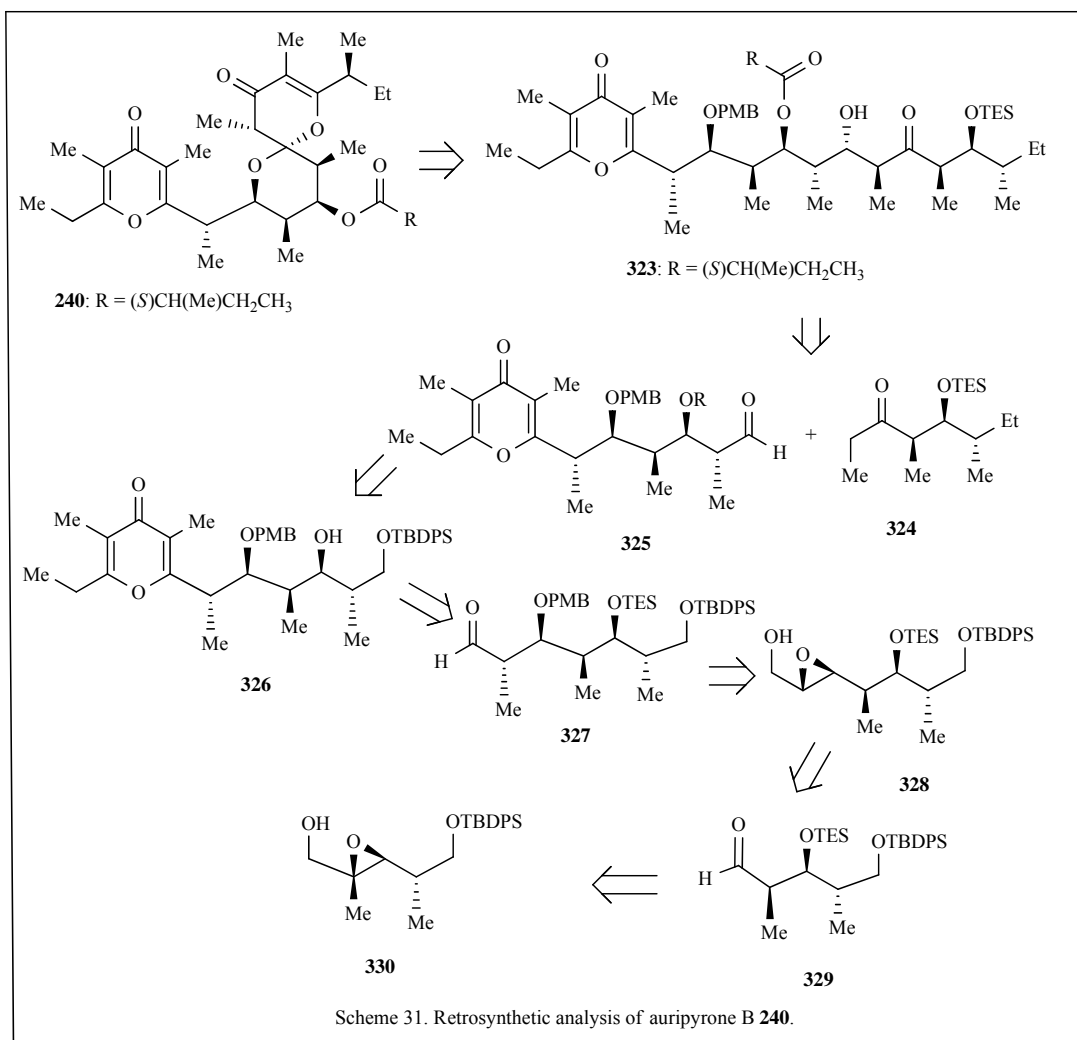
After accomplished the synthesis of the key intermediate **301**, they investigated the formation of spiroketal moiety of auripyronone A **239**. They have attempted the formation of spiroketal by the oxidation of key intermediate alcohol **301** to give the corresponding diketone as a single isomer. Then the diketone was deprotected with DDQ providing the hemiketal **321** as the major product. However, after purification, they could manage to obtain only 66% of **321** as a single isomer along with open-chain isomer **320** in 21% as a mixture of methyl epimers. The desired hemiketal **322** was obtained in 86% yield after removal of TES ether of **321** with HF.pyridine. To avoid purification step involved for the unstable hemiketal **321** and to enable recycle the acyclic diketone **320**, they developed an alternative method for the synthesis of the hemiketal **322**. After screening the reaction under various conditions they succeeded in the synthesis of hemiketal **322** without a need for purification by the

oxidation of aldolate **301** and treatment with CAN in acetonitrile/water (9:1) provided the desired hemiketal **322** in 74% yield as a single isomer (Scheme 30). Finally the alcohol of **322** was oxidized and the resulting diketone was treated with Amberlyst-15 to give the natural product auripyrone-A **239** as a single isomer in 80% yield (Scheme 30).

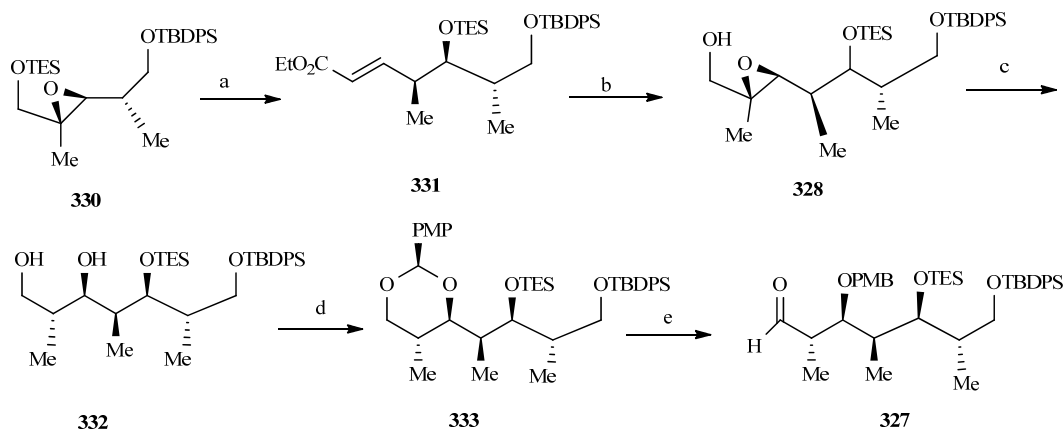


Scheme 30. *Synthesis of auripyrone A 239. Reagents and conditions:* a) DMP, CH₂Cl₂, NaHCO₃, 94%; b) DDQ, CH₂Cl₂/ pH7 buffer (9:1), 66% **321**, 21% **320**; c) HF-py, CH₃CN/py (5:1), 86%; d) HF-py, CH₃CN/py (5:1), 78%; e) DMP, CH₂Cl₂, NaHCO₃; f) CAN, MeCN:H₂O (9:1), 74% over two steps; g) DMP, CH₂Cl₂, NaHCO₃; h) mberlyst-15, CH₂Cl₂, 0 °C-25 °C, 80% over two steps.

5.8.2. Total synthesis of auripyrone-B by Jung *et al.* 2010: In 2010, Jung *et al.* [136] reported the total synthesis of auripyrone-B **240** through a *syn*-aldol aldol [148]/anti-cuprate opening [149] process. This synthesis adopted a similar route that they described previously for auripyrone-A [135] and provided a highly reliable route for the synthesis of stereopentad. The retrosynthetic analysis of auripyrone-B **240** is shown in Scheme 31 from which it has revealed that the metabolite can be derived from the key intermediate **323** through a regioselective hemiketalization of the keto diol then subjected to spiroketalization to stable hemiketal [135].



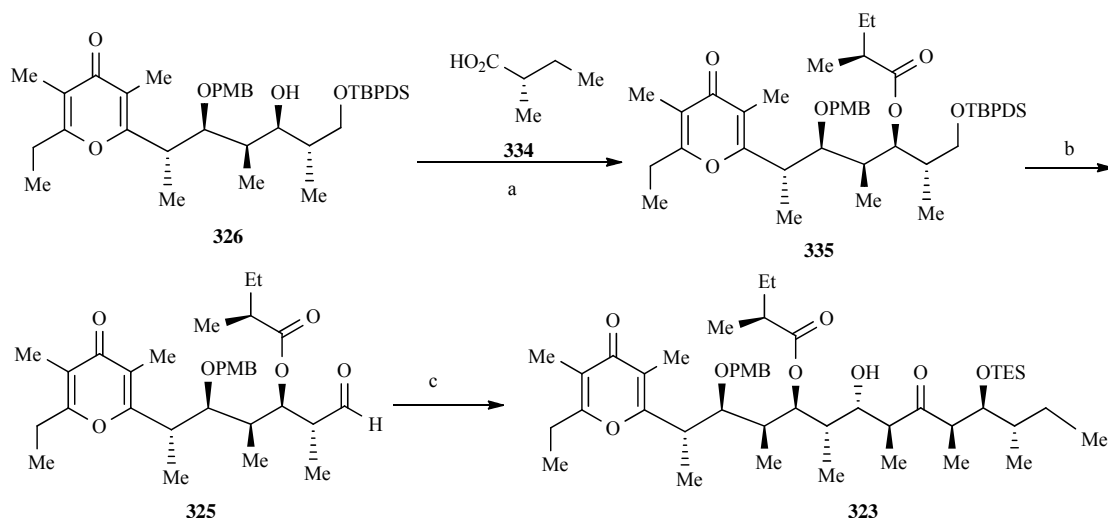
The synthesis was initiated with the construction of the stereopentad **327** (Scheme 32). The known epoxy silyl ether **330** [135] was treated with TESOTf and Hunig's base to give the desired *syn*-non-aldol aldol product which was then subjected to Wittig olefination with ethyl 2-triphenylphosphoranylidene acetate to give *E*-enoate **331** in 88% yield. The next step is the reduction of **331** with DIBAL-H followed by stereoselective epoxidation of the *E*-allylic alcohol using Sharpless conditions [142] to give the epoxide **328** as a single diastereomer. After which epoxide **328** was treated with lithium dimethylcuprate to provide the diol **332** in 88% yield which possessed the desired *anti* stereochemistry. Subsequently, diol **332** was reacted with *p*-methoxybenzaldehyde dimethyl acetal and in the presence of a catalytic amount of PPTS to afford the *p*-methoxybenzylidene acetal **333** in 89% yield with 16:1 ds. The resulting product **333** was subjected to selective reduction with DIBAL-H in dichloromethane to give exclusively the primary alcohol **328** in 86%. The product was then subjected to Dess-Martin periodimane oxidation [150] to give the desired stereopentad **327**.



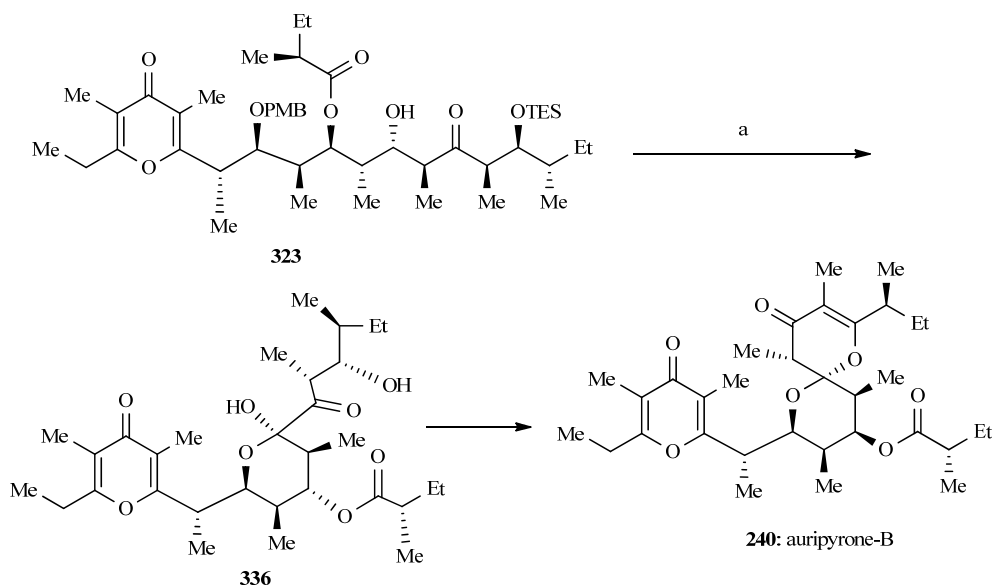
Scheme 32. *Synthesis of stereopentad 327. Reagents and conditions.* a). (i) TESOTf, DIPEA, 89% 20:1 dr, (ii) $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$, PhMe, reflux, 88%; b). (i) DIBAL, $-50\text{ }^\circ\text{C}$, 1h, 92%, (ii) $\text{Ti}(\text{iPrO})_4$, $t\text{BuOOH}$, (+)-DIPT 87%; c). Me_2CuLi , THF, $0\text{ }^\circ\text{C}$, 83%; d). $p\text{-MeOC}_6\text{H}_4\text{CH}(\text{OMe})_2$, PPTS, PhH, 89%, 16:1 dr; e). (i) DIBAL, DCM, $0\text{ }^\circ\text{C}$, 86%, (ii) DMP 98%.

Having accomplished the synthesis of stereopentad **327** as a single isomer, next they initiated the synthesis of the key intermediate **323** (Scheme 33). Thus the alcohol **326** which was obtained in 4 steps from the stereopentad **327** by following a previously reported method [135] was subjected to esterification following Yamaguchi conditions [147] with (*S*)-2-methylbutanoic acid **334** to give the polypropionate **335** in 97% yield. The silyl ether **334** was then treated with HF.pyridine to furnish the primary alcohol which was then subjected to DMP oxidation to give the aldol precursor **325** in 92% yield. Then the boron enolate of the ketone **324** undergoes double stereodifferentiating [151] anti-aldol reaction with the aldehyde **325** which furnished the aldolate **323** in 81% yield with 20:1 ds.

Finally, oxidation of alcohol **323** by Dess-Martin periodinane to the corresponding diketone followed by removal of PMB and TES ethers with CAN resulted in exclusively the stable hemiketal **336** as a single diastereomer in 66% yield. Then the hemiketal **336** was oxidized with DMP to give diketone which was treated with Amberlyst-15 to provide auripyron-B **240** as a single diastereomer in 72% yield (Scheme 34).



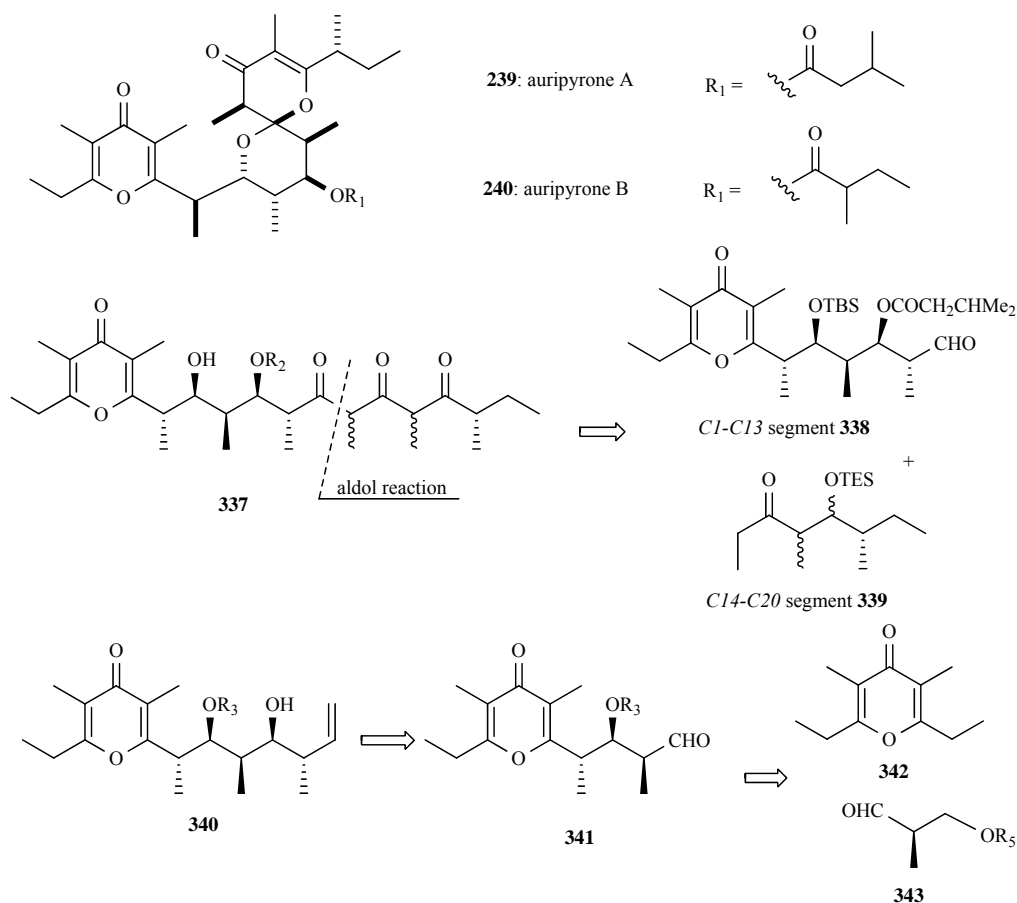
Scheme 33. Synthesis of key intermediate **323**. Reagents and Conditions. a). **334**, 2,4,6-(Cl)₃C₆H₂COCl, DMAP, Et₃N, 97%; b). (i) HF, pyr, MeCN, 94%, (ii) DMP 98%; c). **324**, cHex₂BCl, Me₂NEt, -78 °C→25 °C, H₂O₂, MeOH, 81%, 20:1 dr.



Scheme 34: Total Synthesis of auriopyrone-B **240**. Reagents and Conditions. a). (i) DMP 99%, (ii) CAN, 67%; b). (i) DMP 98%, (ii) Amberlyst-15, DCM, 0-25 °C, 79%.

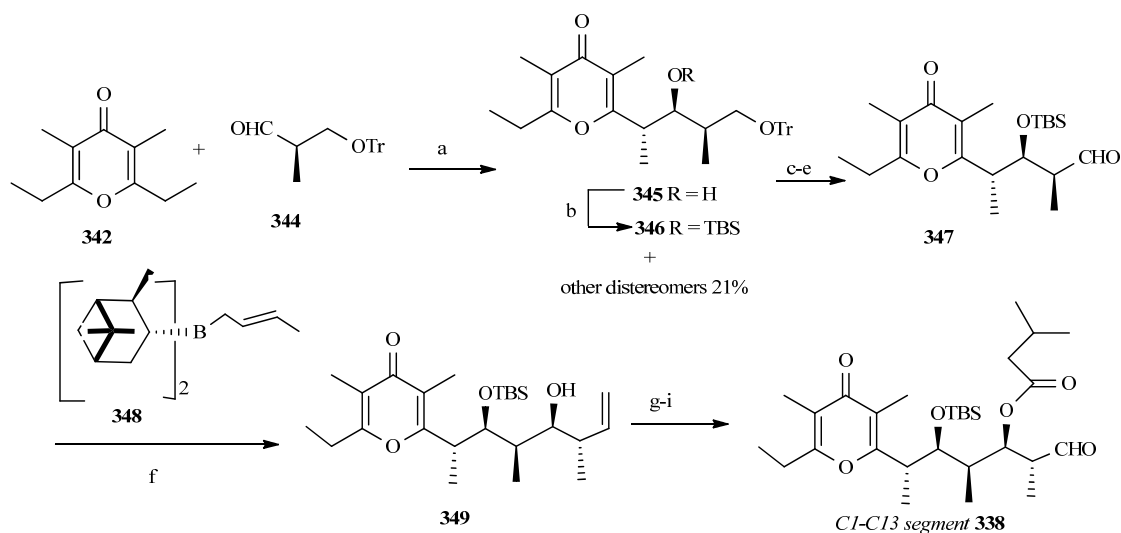
5.8. Total Synthesis auriopyrone A and auriopyrone B (Hayakawa *et al.* 2010) [137]:

The total synthesis of auriopyrones-A and B in this method proceeded *via* aldol-type reaction of γ -pyrone as the key steps. The retrosynthetic analysis of auriopyrones-A and B is shown in Scheme 35. They proposed that triketone **337** could be obtained from the aldol reaction between *C1-C13* segment **338** and *C14-C20* segment **339**. Further, the chiral centres in segment **338** could be obtained by crotylboration and diastereoselective aldol reaction between **342** and aldehyde **343**.



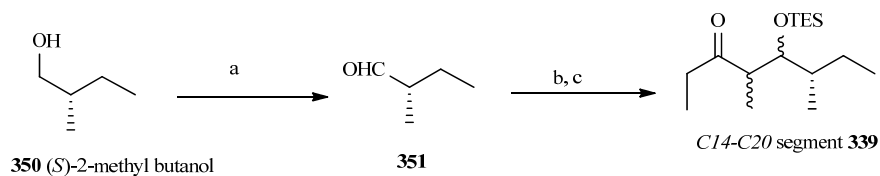
Scheme 35. Retrosynthetic analysis of auripyrones A **239** and B **240**

The synthesis commenced with the construction of *CI-C13* segment **338** (Scheme 36). The aldol reaction between 2,6-diethyl-3, 5-dimethyl-4-pyrone **342** [112] and known aldehyde **344** [152] provided **345** along with other diastereomers [153]. After which the secondary alcohol in **345** was protected as a TBS ether to give **346**. Then the removal of the trityl group from **346** followed by oxidation of the primary alcohol with Swern oxidation provided **347**. The resulting product was subjected to crotyl boration reaction with boronate **348** afforded homoallylic alcohol **349** as a single isomer. This was followed by acylation of the secondary hydroxyl group in **349** and subsequent dehydroxylation of the terminal olefin provided a diol which was then subjected to oxidative cleavage with NaIO_4 afforded aldehyde, *CI-C13* segment **338** (Scheme 36).



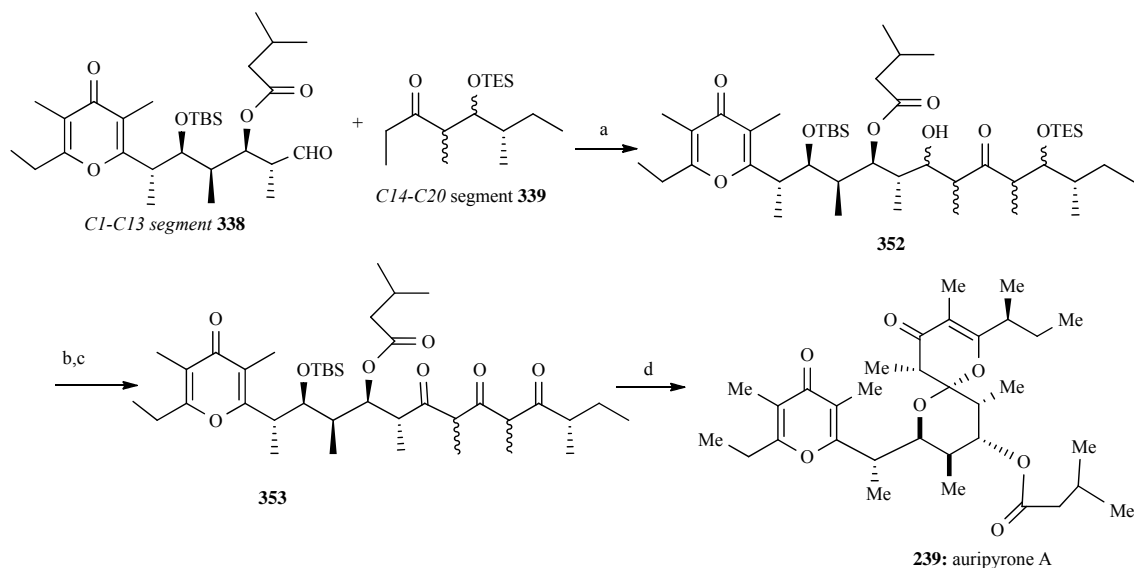
Scheme 36. Synthesis of the *C1-C13* segment (**338**). Reagents and conditions: a) NaHMDS, THF, -78 °C, 47% yield; b) TBSCl, imidazole, DMF, 99% yield; c) HCO₂H, Et₂O, RT; d) 25% NH₃ aq., MeOH, RT, 92%; e) (COCl)₂, DMSO, ^tPr₂NEt, CH₂Cl₂, -78 °C then 0 °C, 99% yield; f) **348**, BF₃·OEt₂, THF, -40 °C then NaOH, H₂O₂, 71% yield; g) isovaleryl chloride, DMAP, pyr, RT, quantitative yield; h) OsO₄, NMO, acetone/H₂O (1:1), RT, 90% yield; i) NaIO₄, acetone/H₂O (1:1), RT, 72%.

The next step of the synthesis is the assembly of *C14-C20* segment **339** starting from the commercially available (*S*)-2-methyl-1-butanol **350** over two steps to provide **351** [154]. Then aldol reaction between the aldehyde **351** and 3-pentanone followed by protection of the resulting secondary hydroxyl group afforded the *C14-C20* segment **339** (Scheme 37).



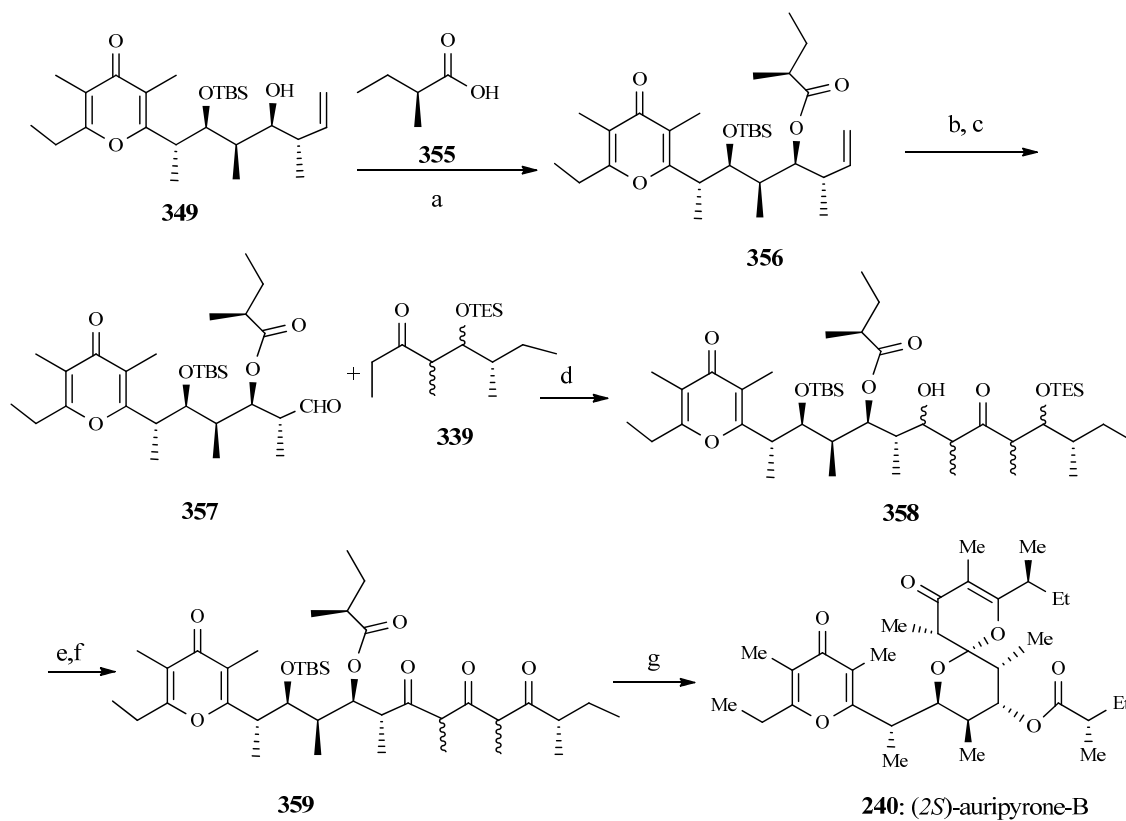
Scheme 37. Synthesis of the *C14-C20* segment (**339**). Reagents and conditions: a) (COCl)₂, DMSO, ^tPr₂NEt, CH₂Cl₂, -78 °C then 0 °C, 30% yield; b) LDA, 3-pentanone, THF, -78 °C, 89% yield; c) TESCl, imidazole, DMF, RT, 95% yield.

Having accomplished in the synthesis of both *C1-C13* segment **338** and *C14-C20* segment **339**, they attempted the coupling of **338** and **339**. The coupling could be achieved by Paterson's aldol reaction using Sn(OTf)₂ and Et₃N which furnished the coupling product **352** as a mixture of diastereomers in good yield. Subsequently, selective removal of the TES group in **352** provided a diol which was converted into triketone **353** by the Dess-Martin periodinane. Then the TBS group was removed from the triketone **353** by HF·pyridine followed by spiroacetalization reaction afforded auripyronone A **239** (Scheme 38).

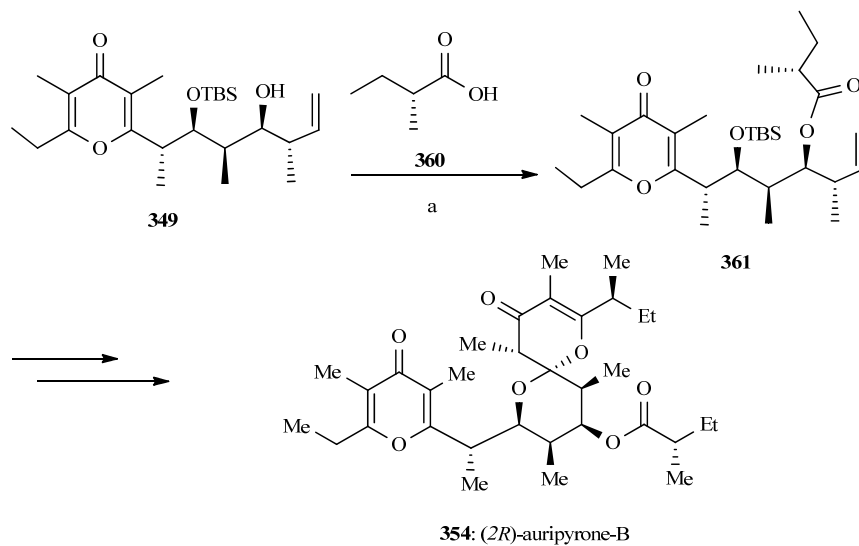


Scheme 38. Completion of the total synthesis of auripyron A (**339**). Reagents and conditions: a) Sn(OTf)₂, Et₃N, CH₂Cl₂, -78 °C, 99% yield; b) AcOH/THF/H₂O (4:1:4), RT, 73% yield; c) Dess–Martin periodinane, CH₂Cl₂, RT, 83% yield; d) HF·pyr/THF/pyr (5:7:3), 60 °C, 22%.

With the success in the synthesis of auripyron-A (**239**), next, they have turned on the synthesis of (2^S) (**240**) and (2^R) auripyron B (**354**). Initially to obtain the desired products they have attempted to remove the acyl group in auripyron A **239**. However, the reaction was failed to give a deacylated product instead, a bis(pyron) compound was produced. Then they changed the synthesis strategy and attempted the synthesis by converting the homolytic alcohol **349** into auripyron B employing the similar synthetic protocol adopted for auripyron A (**239**) (Scheme 39). The synthesis was initiated with the esterification of compound **349** with (*S*)-2-methylbutyric acid **355** [155] following Yamaguchi conditions [147] to give the compound **356**. Subsequently, dehydroxylation of the terminal olefin in **356** gave a diol, then the hydroxyl group was oxidatively cleaved to give the aldehyde **357**. The next step is the Paterson aldol reaction of aldehyde **357** and segment **339** to give the coupling product **358** as a diastereomeric mixture. The removal of the TES group in **358** followed by oxidation of dihydroxyl group afforded the triketone **359** as a mixture of keto and enol forms. Finally, removal of the TBS group in triketone **359** by HF·pyridine and a spontaneous spiroacetalization afforded (2*S*)-auripyron B **240** (Scheme 38). Analogously, they have synthesized the (2*R*)-auripyron B **354** from **349** using (*R*)-2-methylbutyric acid (**360**) [155] (Scheme 40). They have found that the NMR and optical rotation data of synthetic (2*S*)-auripyron **240** was in well agreement with the natural product auripyron **240** and thus confirmed the absolute configuration of natural product auripyron-B **240** and thus enable to determine the stereochemistry and absolute configuration at C2' of the auripyron B (**240**).



Scheme 39. Completion of the synthesis of (2'S)-auripyrrone B **240**. Reagents and conditions: a) **339**, 2,4,6-trichlorobenzoyl chloride, Et₃N, DMAP, toluene, -78 °C to 0 °C, 93% yield; b) OsO₄, NMO, acetone/H₂O (1:1), RT, 94% yield; c) NaIO₄, acetone/H₂O (1:1), RT, 82% yield; d) Sn(OTf)₂, Et₃N, CH₂Cl₂, -78 °C, 99% yield; e) AcOH/THF/H₂O (4:1:4), RT, 90% yield; f) Dess–Martin periodinane, CH₂Cl₂, RT, 95% yield; g) HF·pyr/THF/pyr (5:7:3), 60 °C, 17% yield.



Scheme 40. Completion of the synthesis of (2'R)-auripyrrone B (**354**). Reagents and conditions: a) **360**, 2,4,6-trichlorobenzoyl chloride, Et₃N, DMAP, toluene, -78 °C to 0 °C, 94% yield.

6. Application of marine pyrone derivatives:

In the previous sections, a brief account on isolation, biological activity and synthesis of pyrone compounds isolated from marine organisms have been discussed. It is noteworthy that both the alpha and gamma pyrone displayed various biological activities anticancer, Anti-HIV, Alzheimer's disease, cancer and antimicrobial, antityrosinase etc. Owing to their interesting biological activities the synthesis of these pyrone compounds has been paid considerable attention [8, 115]. Although there is no specific demarcation on the biological activities shown by alpha- and gamma pyrones, the two pyrone moieties exhibited different biological activity particularly for isomeric or compounds having similar structure. For instance, the gamma pyrone compounds (**127** & **128**) showed significant activity for enhanced the expression of adiponectin but no such effect was observed for the alpha-pyrone compound (**126**) [54]. Moreover, due to conjugated structure, gamma pyrone exhibited photosensitizing properties [156, 157] which is not shown by the lactonic structure, alpha pyrone. It is noteworthy that the pyrone compounds from marine organisms find various applications in pharmaceuticals as well as in food and cosmetic industries. The bioactivities and applications for some of these marine pyrone compounds is summarized in Table 1.

Table 1. Biological activities and applications of some α - and γ -pyrone compounds isolated from marine organisms.

Pyrone Compounds	Biological Activity	Applications	References
Kojic acid (1)	Anti-tyrosinase, activity against human pathogenic fungi <i>C. albicans</i> , <i>C. neoformans</i> , and <i>T. rubrum</i> , pathogenic bacteria <i>Escherichia coli</i> , growth inhibition of <i>L. amazonensis</i>	Cosmetic, antifungal, antibacterial, Antioxidant, anti-leishmanial	[20], [158-160]
Rubrofusarin (19) & Pyrophen (24)	Activity against <i>C. albicans</i>	Antibiotic	[26]
Peninaphones A-C (26-28)	Activity against <i>Staphylococcus aureus</i> ATCC 43300	Antibacterial	[27]
isochaetochromin-B ₂ (30) ustilaginoidin D (31)	Antitubercular activity against <i>Mycobacterium phlei</i>	Antitubercular agent	[28]
fusaresters A–E (32-36)	Weak activity against human cancer cell lines	Anticancer	[29]
nigrosporapyrones A (42)	Activity against <i>staphylococcus aureus</i> ATCC 25923 (SA) and MRSA	Antibacterial	[33]
Nipyron-C (56)	activity against <i>S. aureus</i> and <i>B. subtilis</i> and <i>M. tuberculosis</i>	Antibacterial and antitubercular	[37]
Nigerapyrone-B (59)	Cytotoxicity against HepG2 cell line	anticancer	[39]
Nigerapyrone-E (62)	Cytotoxicity against MDA-MB-231, SW1990 and A549 cell lines	anticancer	[39]
Asnipyrones A (66)	Cytotoxicity against A549 cell line	anticancer	[39]
Arisugacin B(73), territrem C (75) and terreulactone C (76)	Potent inhibitory of anti-acetylcholinesterase (AChE)	Alzheimer's disease	[42]
Dothideopyrone-F (85)	Inhibited NO production in lipopolysaccharide (LPS)-induced BV2 cells and effective to decrease TNF- α , interleukin (IL)-1 β , and IL-6	Identification of protein kinase inhibitors and anti-inflammatory	[44]
Nocapyrone H (103)	Inhibited NO production in lipopolysaccharide (LPS)-stimulated BV-2 microglial cells	Identification of protein kinase inhibitors and anti-	[50]

	and suppressed IL-1 β	inflamaotory	
Marinopyrone D (142)	Inhibition of Nitric Oxide (NO) production in lipopolysaccharide(LPS)-stimulated <i>mouse macrophage-like RAW 264.7 cells</i>	Identification of protein kinase inhibitors	[56]
Salinopyrone (143)	inhibit interleukin-5 production	Anti-inflammatory	[57]
Kalkipyrene A (168)	Inhibit against NCI's 60 human-tumor cell line and adipogenic differentiation cells	Antitumor & anti-obesity	[63, 65]
Yoshinone (170)	inhibition of adipogenic differentiation	Anti-obesity	[65]
Violapyrones B & C (171 &172)	Antibacterial	Medical	[67]
Saccharomonopyrone-A (174)	Activity for free radical scavenging	Antioxidant	[68]
Onchitriol-I (214) and Onchitriol-II (215)	Inhibit KB human epidermoid carcinoma cells Activity against Herpes simplex virus (HSV-1) and Vesicular stomatitis virus (VSV)	Anticancer Antiviral	[80, 81]
Bis- γ -pyrone polypropionate (237)	Inhibition to human cancer cell lines: A549 NSCLC, MCF-7 breast, PC-3 prostate, Hs683 oligodendroglia, U373 and, SKMEL-28	Anticancer	[86]
Auripyrene A (239) & Auripyrene B (240)	cytotoxicity against HeLa S ₃ cells	anticancer	[87]
Onchidione (224) & Onchidione-II (244)	Inhibit against tumor cell lines A549, MCF-2 and HepG-2;	anticancer	[90]
4,16-di-epi-onchidiol (245)	Inhibit against tumor cell lines cell lines <i>viz.</i> HT-29, A549, Capan-1, and SNU-398	anticancer	[91]
Stelletin A (247)	Toxicity against leukemia cells	anticancer	[93]
Lehualide B (252) & Lehualide D (254)	Cytotoxicity to the ovarian cancer cell line (IGROV-ET)	anticancer	[96]
Lehualides F and G (238 & 239)	Inhibition against promyelocytic leukemia (HL-60)	anticancer	[97]
Membrenone A (332)	Feeding deterrent to <i>Curussius aurutus</i>	Chemical defense	[121]

7. Conclusion

This manuscript gives a brief account of metabolites containing pyrone ring from various marine organisms with their biological properties. The review also covered the total synthesis of marine metabolites featuring pyrone ring namely, cyercene-A, placidenes, onchitriol-I, onchitriol-II, crispatene, photodeoxytrichidione, (-) membrenone-C, lihualide-B, macrocyclic enol ethers and auripyrones-A & B. Isolation of 271 pyrone-derived metabolites from various marine sources such as fungi, bacteria, microbial strain, mollusc, sponges and algae have been deliberated under four major headings detailing their chemical structures and reported biological properties. Marine polypropionates featuring pyrone ring that possess fascinating carbon skeleton which is considered to be characteristic of mollusc family have been presented in detailed covering report as early as 1978 until a very recent report of 2019. The later section of the manuscript presented the total synthesis of 17 marine pyrone metabolites including four isomers of membrenone-C (**334a**, **334b**, **334c**, and **334d**), algal metabolite *syn*-(**264**) and *anti*-(**264**), and isomers of auripyrene-B. Two different approaches have been described for the synthesis of cyercene-A namely Wadsworth–Emmons type and palladium-catalyzed reaction. Similarly, synthesis of auripyrenes A and B have been discussed referring to two reported methods namely Jung’s protocol which used a non-aldol aldol approach and Hayakawa’s method which employed adia stereotropic aldol type as the key step for the synthesis. Further, absolute configuration assignment of membrenone-C isomer (**334c**), algal metabolite, macrocyclic ether (**264**) and auripyrene-B (**240**) through synthesis have been highlighted. I believed that the studies on chemicals and biological properties of marine derived-pyrone metabolites highlighted herein will be helpful to identify potential marine pyrone-metabolites for the synthetic target. Further, detail synthesis on pyrone containing marine metabolites discussed in this review may provide additional knowledge and encouraged the scientific community towards the synthesis of bioactive MNPs and pharmaceutically important compounds.

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Table 2. List of Abbreviations

Ac	Acetyl	LiHMDS	Lithium hexamethyldisilazide
ATCC	American Type Culture Collection	<i>m</i> CPBA	<i>meta</i> -Chloroperbenzoic acid,
Bn	Benzyl	MIC	Minimum Inhibition Concentration
Bz	Benzoyl	MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
C AMP	Cyclic adenosine monophosphate	MS	Molecular sieves
CAN	Ceric ammonium nitrate	NaHMDS	Sodium hexamethyldisilazide
CCl ₄		NBS	N-Bromosuccinimide
DCC	Dicyclohexylcarbodiimide	NCI	National Cancer Institute
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	NMO	N-Methylmorpholine oxide
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone	NMR NO	Nuclear Magnetic Resonance Nitric Oxide
DIBAH	Diisobutylaluminium hydride	OTf	Trifluoromethanesulfonate
DIBAL-H		PCC	Pyridiniumchlorochromate
DMAP	4-Dimethylaminopyridine	PMB	<i>para</i> -Methoxybenzyl
DMF	N,N-dimethylformamide	PPTS	Pyridinium <i>para</i> -toluenesulfonate
DMP	Dess–Martin periodinane	PTP1B	protein tyrosine phosphatase 1B
DPPH	diphenylpicrylhydrazyl	pyr	Pyridine
⁶ Hex ₂ BCl	Dicyclohexylboron Chloride	SK1	Sphingosine Kinase 1
DMSO	Dimethyl sulfoxide	TBAF	
DIPEA	Diisopropylethylamine	TBDPS	Tert-butyl diphenylsilyl
DIPT	Diisopropyltartrate	TBS	Tert-butyl dimethylsilyl
GPR	G-protein-coupled receptors	TBDPSCI	Tert-butyl diphenylsilyl Chloride
^t Pr ₂ NEt	Diisopropylethylamine	^t Bu	Tert-butyl
ds	Diastereoisomer	TESCl	Triethylsilyl Chloride
EE	1-Ethoxyethyl	Tf	Trifluoromethanesulfonyl,
Et ₃ N, Et ₂ O		TFA	Trifluoroacetic acid
HIV	Human Immunodeficiency Virus	TFE	Trifluoroethyl
HK1	Human embryonic kidney	THF	Tetrahydrofuran
HeLa	Henrietta Lacks	TMS	Trimethylsilyl
HMDS	Hexamethyldisilazide	TES	Triethylsilyl
HPG2	hepatoma G2	TIPS	Triisopropylsilyl
IC	Inhibition Concentration	TNF- α	Tumor necrosis factor- α

IL	Interleukin	TPAP	Tetra- <i>n</i> -propyl ammonium perruthane
LDA	Lithium diisopropylamide	Tr	Triphenylmethyl
LPS	lipopolysaccharide	TsOH	<i>p</i> -Toluenesulfonic acid
LiBH ₄	Lithium boronhydride		
LHMDS			
HEK293	human embryonic kidney cells		

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