

## **$\gamma$ -Hydroxybutenolide Containing Marine Natural Products and Their Synthesis: A Review**

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### **Abstract**

$\gamma$ -Hydroxybutenolides ( $\gamma$ -HB) is an important structural core found in many bioactive marine natural products (MNPS). The  $\gamma$ -HB core containing NPS served as inspiration to medicinal chemists to undertake designing of the new synthetic strategies to construct  $\gamma$ -HB core. Subsequently, it further results in development of novel physiological and therapeutic agents. The most notable example includes manoalides, cacospongionolides, petrosaspongioide M and dysidiolide from marine sponges possessing anti-inflammatory properties.  $\gamma$ -HB containing MNPS were known to possess various pharmacological properties such antimicrobial (acantholide B), cytotoxic (acantholide A-E, spongianolide A), inhibitors of secretory phospholipase A<sub>2</sub> (cladocorans A and B), BACE inhibitors (ianthellidone G) *etc.* Moreover, the  $\gamma$ -HB moiety was explored as antifouling agents as well. Owing to their numerous biological activities and attractive molecular structures, there are lots of advances in synthetic methodology of these compounds. This review gives the account on isolation and biological studies of MNPS with  $\gamma$ -HB skeleton as core unit. Furthermore, the synthesis of selective  $\gamma$ -HB containing bioactive MNPS like manoalide, sacomanoalide, cacospongionolides, luffarielloide and dysidiolide were highlighted in the article.

**Key Words:** Anti-inflammatory, Biological activities,  $\gamma$ -hydroxybutenolide, Marine natural products, Synthesis

## 1. Introduction:

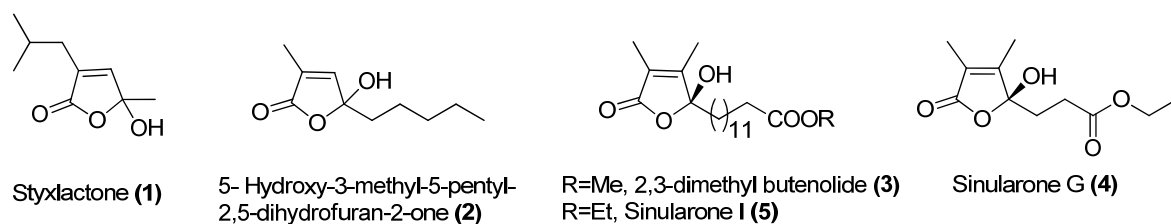
The soft-bodied and/or sessile organisms are the richest source of natural products found in marine environment. Although, these soft organisms lack physical defences against their predators, they generate strong chemical defence mechanisms by producing toxic secondary metabolites. Marine organisms have provided many bioactive marine natural products (MNPS) and several proportions of them are bearing interesting pharmacophoric group i.e.  $\gamma$ -hydroxybutenolide ( $\gamma$ -HB). There are numerous  $\gamma$ -HB containing terpenoids with different structural diversities that have been isolated from marine sources ranging from monoterpenes to sesterterpenes. Interestingly, many of them (manoalide & sacomanoalide [1], dysidiolide & cacospongionolide A [2] *etc*) are potent inhibitors of enzyme phospholipase A<sub>2</sub> (PLA<sub>2</sub>) which are intimately involved in the initial step of inflammatory response. This class of  $\gamma$ -HB were also known to have a strong potential as anticancer drugs. Cacospongionolide A and sesterstatin 6 [3] are found to significantly inhibit cancer cell growth whereas several other  $\gamma$ -HB containing metabolites have shown antimicrobial and anti-fouling activities. In this review, we have classified  $\gamma$ -HB under three different categories i.e. monoterpenoids, sesquiterpenoids, diterpenoids and sesterterpenoids for the benefit of readers. Subsequently, the total synthesis of few selective MNPS containing  $\gamma$ -HB as main skeleton is discussed in the last section of this review. In the last decades, MNPS, and particularly sesterterpenoids, have played an important role in the discovery and development of new drugs for their wide variety of chemical structures and biological activities [4]. There are several reports available in literature for their total synthesis; however, we have highlighted the total synthesis of selective bioactive sesterterpenoid molecules, manoalide, secomanoalide, cacospongionolides B & E, luffariellolide & dysidiolide with  $\gamma$ -HB core structure.

## 2. Isolation of MNPS containing $\gamma$ -HB

### 2.1. Monoterpenoids

A small molecule, styxlactone (**1**) with  $\gamma$ -HB skeleton was isolated from a marine sponge, *Myrmekioderma styx* from coast of Rio Beuno, Jamaica [5]. The absolute stereochemistry was not determined due to its low yield. Sponge *Callyspongia vaginalis* (St. Michael, Barbados) yielded 5-hydroxy-3-methyl-5-pentyl-2,5-dihydrofuran-2-one (**2**) [6]. 2,3-dimethyl butenolide (**3**) was isolated from the brittle star *Ophiomastix mixta* (Jeju Is, Korea) and the absolute configuration was determined by comparison of circular dichroism (CD) spectra with the model compounds [7]. Sinularones G (**4**) and I (**5**) along with metabolites (**2**) and (**3**) (Fig. 1) were isolated from soft coral *Sinularia sp.* with antifouling property [8]. The absolute configuration was determined to be 4*S* for all the compounds (**3-5**) on the basis of the similar specific rotation and the cotton effect. All the

compounds showed weak cytotoxicity with  $IC_{50} > 10 \mu\text{g/mL}$  against a panel of tumor cell lines including human ovarian carcinoma (A2780), human lung adenocarcinoma (A549), human gastric carcinoma (BGC823), human hepatoma (Bel7402), and human colonic carcinoma (HCT-8). Compounds **(2)**, **(4)** and **(5)** also showed antifouling activity against the larvae of the barnacle *Balanus amphitrite*. Among these, butenolide **(2)** was found to be most potent with  $EC_{50}$  value  $3.84 \mu\text{g/mL}$ .

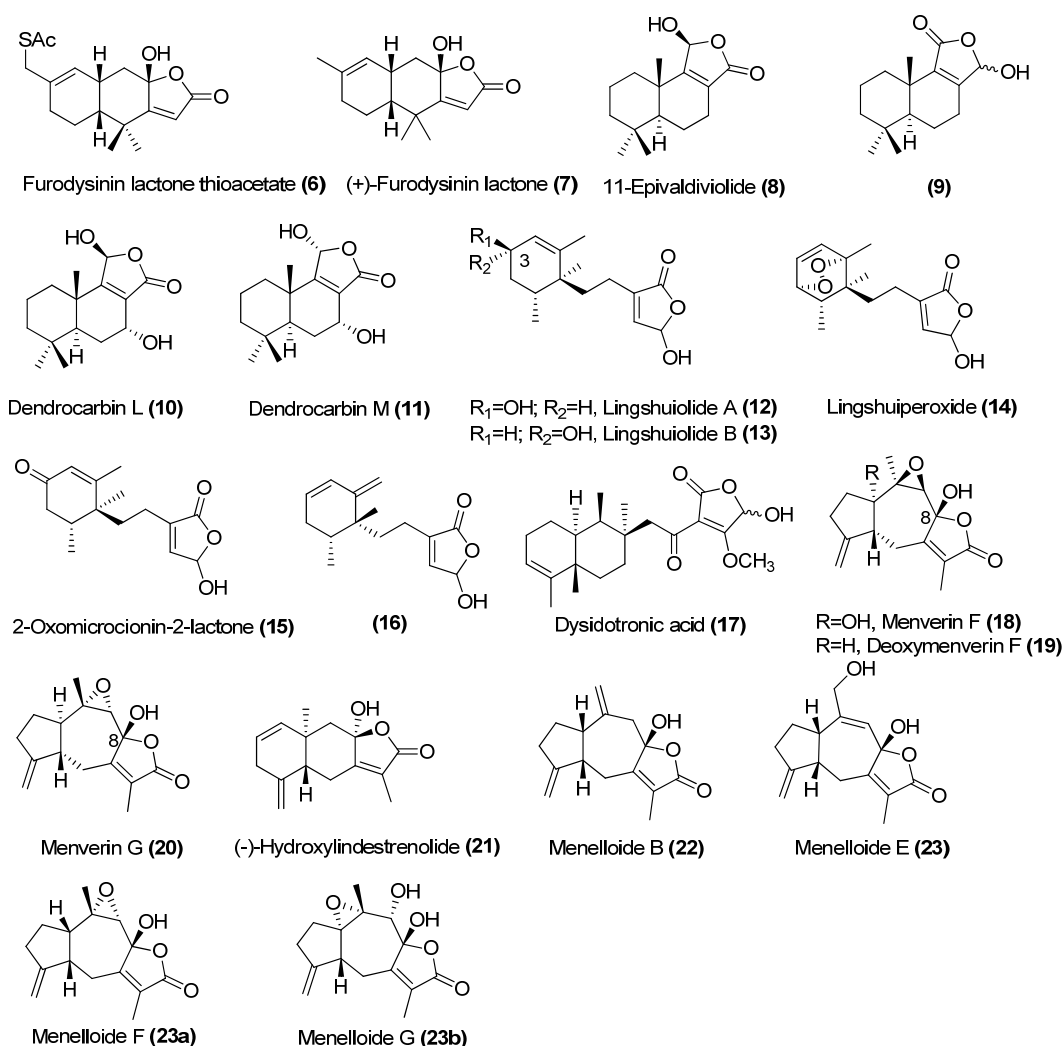


**Fig. 1: Structures of monoterpenoids (1-5) containing  $\gamma$ -HB**

## 2.2.Sesquiterpenoids

Cartè *et al.* (1989) isolated sesquiterpene thioacetate, furodysin lactone thioacetate **(6)** along with furodysin lactone **(7)** and *o*-methylfurodysin lactone from the sponge *Dysidea sp.* collected in Palau (Fig 2) [9]. Compound **(6)** showed high binding-affinity for the human leukotriene B<sub>4</sub> (LTB<sub>4</sub>) receptor. Compound **(7)** was again obtained as an antifouling agent from Palauan marine sponge *D. herbacea* [10]. This compound showed repellent activity against the blue mussel, *Mytilus edulis galloprovincialis*. Marine sponge, *D. fragilis* from southern India was found to contain (+)-furodysin lactone **(7)**, (+)-*o*-methylfurodysin lactone and spirofragilide [11]. X-ray crystal structure of compound **(7)** consisting of two six-membered rings, which adopt chair and half-chair conformations, and a furan ring were confirmed by X-ray crystal structure. The molecule is shown to be arranged in a helical pattern through O-H...O hydrogen bonds [12]. Drimane sesquiterpenes, 11-epivaldiviolide **(8)** and its isomer **(9)** (mixture of epimer) were isolated from the sponge *D. fusca* collected in New Caledonia [13]. From the list of fourteen isolated molecules, drimane sesquiterpenoids with a sharp peppery taste were isolated from nudibranch, *Dendrodoris carbunculosa* contained two compounds with  $\gamma$ -HB, dendrocarbins L-M **(10-11)** [14]. *D. septosa* (Lingshui Bay, Hainan Is., China) yielded lingshuiolides A **(12)** and B **(13)**, lingshuiperoxide **(14)** [15], 2-oxomicrocionin-2-lactone **(15)** [16] and related analogue **(16)**. The structures were determined by 1D and 2D NMR experiments. Compound **(16)** exhibited moderate inhibitory activity against human protein tyrosine phosphatase 1B (hPTP1B), an enzyme involved in the regulation of insulin signalling with  $IC_{50}$  value  $8.8 \mu\text{g/mL}$ . A *Dysidea sp.* from Vanuatu contained the oxidized and rearranged merosesquiterpene, dysidotronic acid **(17)**, which selectively inhibited phospholipase

A<sub>2</sub> (PLA<sub>2</sub>) [17]. It significantly inhibited human synovial PLA<sub>2</sub> at 10 μM, with an IC<sub>50</sub> value of 2.6 μM and a higher selectivity and potency towards this enzyme than the reference inhibitor manoolide. It inhibited the production of tumor necrosis factor alpha (TNF-α) and interleukin-1β (IL-1β) as well as the production of nitric oxide (NO), prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and leukotriene B<sub>4</sub> (LTB<sub>4</sub>). It was reported that decreased NO generation was the consequence of inhibition of the expression of NO synthase, whereas PGE<sub>2</sub> and LTB<sub>4</sub> reduction was due to inhibition of arachidonic acid bioavailability through a direct inhibitory effect of dysidotronic acid on secretory PLA<sub>2</sub> [18]. A gorgonian coral *Menella sp.* (Hainan Province, China) was found to contain highly oxygenated guaiane lactones, menverin F (**18**), 1-deoxymenverin F (**19**) and menverin G (**20**) [19]. The absolute configuration at C-8 of (**18-20**) was assigned as (*S*) by interpretation of electronic circular dichroism (ECD) data and all other configurations remained as relative only. (-)-Hydroxylindestrenolide (**21**), an enantiomer of the known sesquiterpenoid, (+)-hydroxylindestrenolide was isolated from *Menella sp* [20]. Sesquiterpenoid (**21**) exhibited marginal cytotoxicity toward HL-60 and K562 leukemia tumor cells, and displayed a weak inhibitory effect on superoxide anion generation at a concentration of 10 μg/mL by human neutrophils. Sesquiterpenoid derivatives, menelloide B (**22**) along with (**21**) have been isolated from the gorgonian *Menella sp.* collected off the waters of Taiwan [21]. Chiral centers for (**22**) (C-1, C-5, and C-8) were assigned as *S*-configuration, respectively. The same research group isolated another germacrane-type sesquiterpenoid, menelloide E (**23**) from the organic extract of octocorals *Menella sp.* (Taiwan) [22]. Its organic extract had displayed inhibitory effects on the generation of superoxide anion (inhibition rate 84.7%) and the release of elastase (inhibition rate 96.2%) at a concentration of 10 μg/mL. The relative configuration of (**23**) was elucidated mainly from a NOESY spectrum as being compatible with that of (**22**) offered by computer modelling in which the close contacts of atoms in space calculated were consistent with the NOESY correlations. (-)-Hydroxylindestrenolide (**21**), menelloides B (**22**) and E (**23**) displayed a weak inhibitory effect on generation of superoxide anions (inhibition rate 13.4%, 2.9% and 19.9 % respectively) at a concentration of 10 μg/mL [23]. Further, menelloides B (**22**) and E (**23**) inhibited the release of elastase (inhibition rate 0.7 % and 27.0%, respectively) at a concentration of 10 μg/mL [24]. Another gorgonian, *Menella woodin* from Taiwan resulted in the isolation of two guaiane derivatives, menelloides F and G (**23a-b**). Their structures were elucidated by NMR (1D & 2D) and HRESIMS data. Relative configurations of asymmetric centers were determined on the basis of NOESY and 1D NOE correlations. The absolute stereochemistries of these compounds were determined by comparison of calculated and experimental ECD [25].



**Fig 2: Structures of sesquiterpenoids (6-23).**

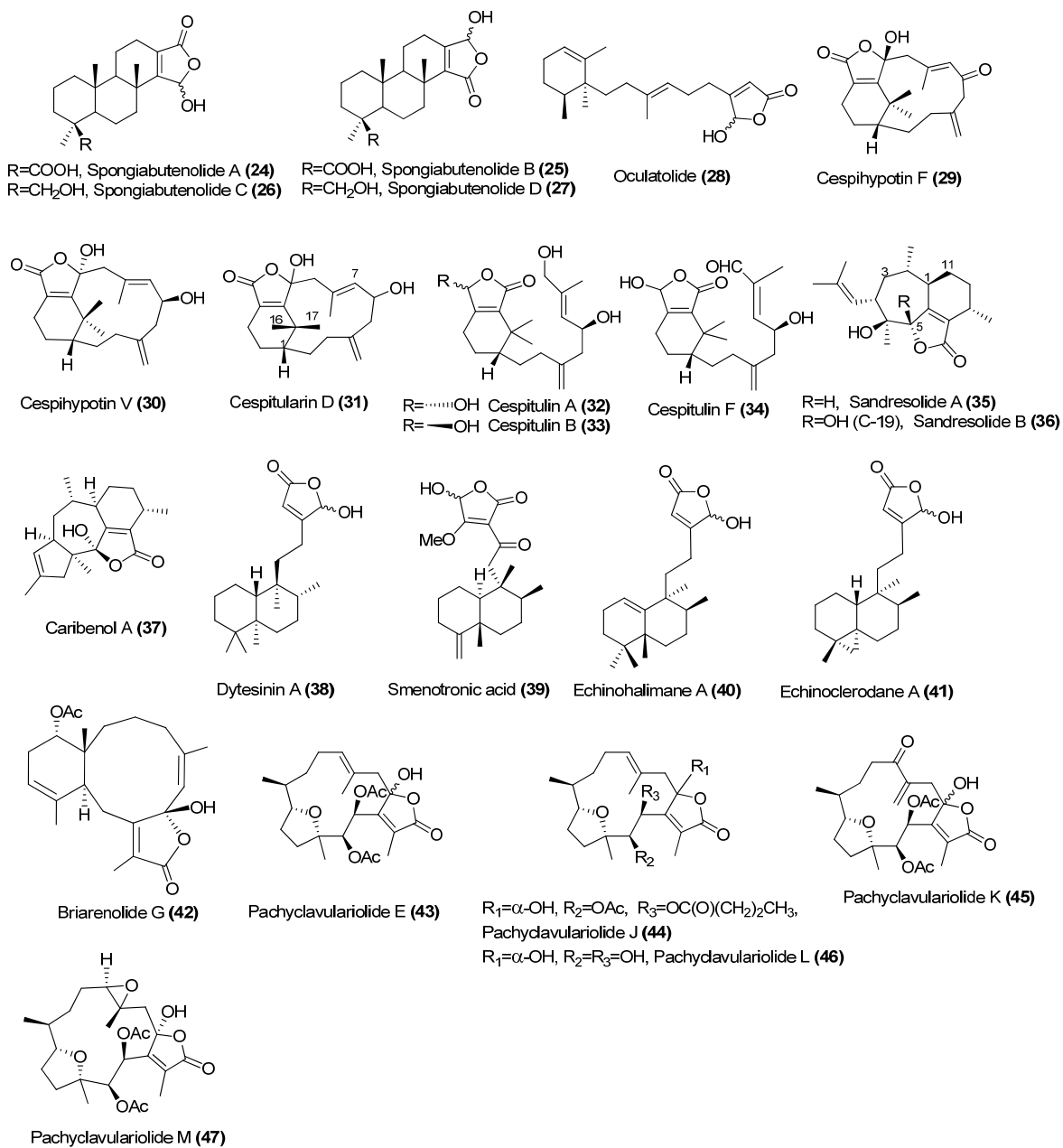
### 2.3.Diterpenenoids

A marine sponge belonging to genus *Spongia* from the Philippines contained diterpenenoids, spongiabutenolides A-D (**24-27**) (Fig 3) [26]. All the compounds (**24-27**) were tested for anti-cancer activity in a 25 cell-line panel but none showed significant cytotoxicity. Another sponge *Coscinoderma mathewsi* from Pohnpei showed presence of 15 $\xi$ -hydroxy-16-oxospongi-13-en-19-oic acid (spongiabutenolide A, **24**) [27]. Oculatolide (**28**) was isolated from sponge *Haliclona oculata* (Hainan, China) [28]. Marine soft coral, *Cespitularia hypotentaculata* (Green Is. Taiwan) produced several cespiphytins, amongst which only cespiphytin F (**29**) possesses  $\gamma$ -HB moiety [29]. It exhibited weak activity against herpes simplex virus-1 (HSV-1), peripheral blood mononuclear cell (PBMC) and proliferation induced by phytohemagglutinin (PHA). The same research group isolated another butenolide, cespiphytin V (**30**) from non-polar extract of the same specimen *C. hypotentaculata* [30]. The structure was determined through detailed spectroscopic analyses, in

particular HR-ESIMS and 2D NMR techniques. The relative configuration was deduced by interpretation of NOESY spectrum. Compound **(30)** was screened for cytotoxic activity against human Daoy and WiDr tumor cell lines which showed mild activity. Bioassay-directed fractionation of a Taiwanese collection of *C. hypotentaculata* yielded diterpene, cespitularin D **(31)** [31]. The relative stereochemistry was deduced from a 2D NOESY experiment, which indicated that Me-16, Me-17, H-7, and H-1 are on one side of the molecule, while Me-19 is on the opposite side of the molecule. The relative stereochemistry of the secondary hydroxyl at C-6 was not determined due to the flexibility of the 13-membered ring. It showed moderate cytotoxicity against P-388 cells. A collection of *C. taeniata* from the same location yielded cespitulins A **(32)** and B **(33)** as a mixture in addition to their corresponding ethyl acetals, cespitulins C and D [32]. The structures of these compounds were elucidated through detailed spectroscopic analyses, mainly 2D NMR experiments. The configuration at the chiral centers and the geometry of the double bonds were deduced from NOESY spectra and by application of molecular modeling. Again, the same research group found secoverticillane, cespitulin F **(34)** from *C. taeniata* (Green Is., Taiwan) [33]. The structure of the compound was elucidated by spectroscopic analysis, especially HR-MS and 2D-NMR techniques. Sandresolides A **(35)** and B **(36)**, norditerpenes were isolated from the gorgonian, *Pseudopterogorgia elisabethae* from Columbia [34]. The structures were determined by spectroscopic and X-ray diffraction studies. The relative configurations for the stereocenters in the bicyclic nuclei of the sandresolides (i.e., C-1, C-3, C-4, C-5, and C-11) were assigned primarily on the basis of NOESY NMR data acquired with sandresolide A. Caribenol A **(37)**, norditerpene was isolated as weakly anti-mycobacterial constituent of *P. elisabethae* (Providencia Is., Colombia) [35]. The structure and relative configuration of caribenol A were established by X-ray analysis. Dytesinin A **(38)** was reported from an Okinawan marine tunicate, *Cystodytes* sp. [36]. The structure was elucidated using 2D NMR experiments such as CH-selected editing HSQC-NOESY and *J*-resolved HMBC. The relative stereochemistry tricyclic core was elucidated mainly on the basis of NOESY correlations. A Red Sea sponge, *Smenospongia* sp. contained smenotronic acid **(39)**, which is an interesting tetric acid thought to be derived from ilimaquinone [37]. A halimane-type diterpenoid, echinohalimane A **(40)**, was isolated from a gorgonian, *Echinomuricea* sp. (Formosan). [38]. The echinohalimane A exhibited cytotoxicity toward MOLT-4 (human acute lymphoblastic leukemia), HL-60 (human acute promyelocytic leukemia), DLD-1 (human colorectal adenocarcinoma) and LoVo cells (human colorectal adenocarcinoma) with IC<sub>50</sub> value 2.111, 2.117, 0.967 and 0.563 µg/mL, respectively. *In-vitro* anti-inflammatory effects of echinohalimane A displayed a significant inhibitory effect on the release of elastase by human neutrophils. In the separate account, the same research group reported echinoclerodane A **(41)** along with dytesinin A **(38)** from the same specimen

[39]. It exhibited moderate cytotoxicity against MOLT-4, HL-60, DLD-1 and LoVo cells. *In-vitro* anti-inflammatory study of echinoclerodane A displayed a significant inhibition effect on the generation of superoxide anion (inhibition rate 68.6%) and this compound showed a moderate inhibition effect (inhibition rate 35.4%) on the release of elastase by human neutrophils at a concentration of 10  $\mu\text{g}/\text{mL}$ . The same research group collected octocoral identified as *Briareum sp.* from southern Taiwan [40]. A fraction of its organic extract displayed inhibitory effects on the generation of superoxide anion (inhibition rate 36.8%) and the release of elastase (inhibition rate 90.3%) at a concentration of 10 $\mu\text{g}/\text{mL}$ . Further isolation led to briarane-type diterpenoid briarenolide G (**42**) with  $\gamma$ -HB.

Cembranolides, pachyclavariolides E (**43**) [41] and J-M (**44-47**) [42,43] were isolated from softcoral, *Pachyclavularia violacea* from Papua New Guinea and Taiwanese collections, respectively. Pachyclavariolide M showed P388 cell line growth inhibition. The relative configuration of (**43**) was confirmed using single-crystal X-ray analysis by Sheu *et al.* [43]. The structures, including the relative configurations, of cembranolides (**44-47**) were established by spectroscopic and chemical methods. Cytotoxic assays revealed that pachyclavariolide K (**45**) had  $\text{ED}_{50}$  values of 2.8, 3.3, 6.7 and 7.6  $\mu\text{g}/\text{mL}$  against P388 (mouse lymphoma), HT-29 (human colorectal adenocarcinoma), A549 (human epithelial carcinoma), and KB cells (human nasopharynx carcinoma), respectively. While, pachyclavariolides E (**43**), J (**44**) and M (**47**) had  $\text{ED}_{50}$  values of 4.0, 2.5 and 3.2  $\mu\text{g}/\text{mL}$ , respectively against P388 cells.

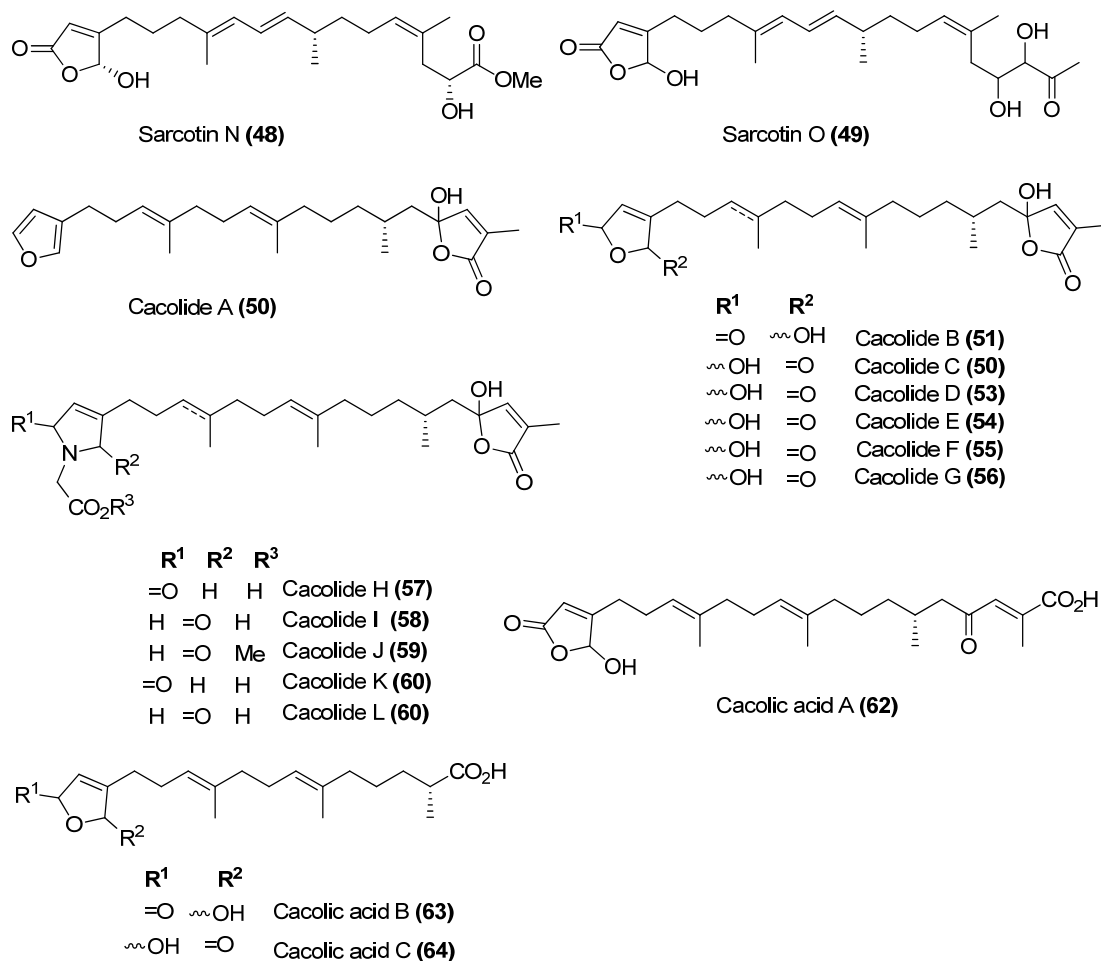


**Fig 3: Structures of diterpenoids (24-47).**



## 2.4. Sesterterpenoids

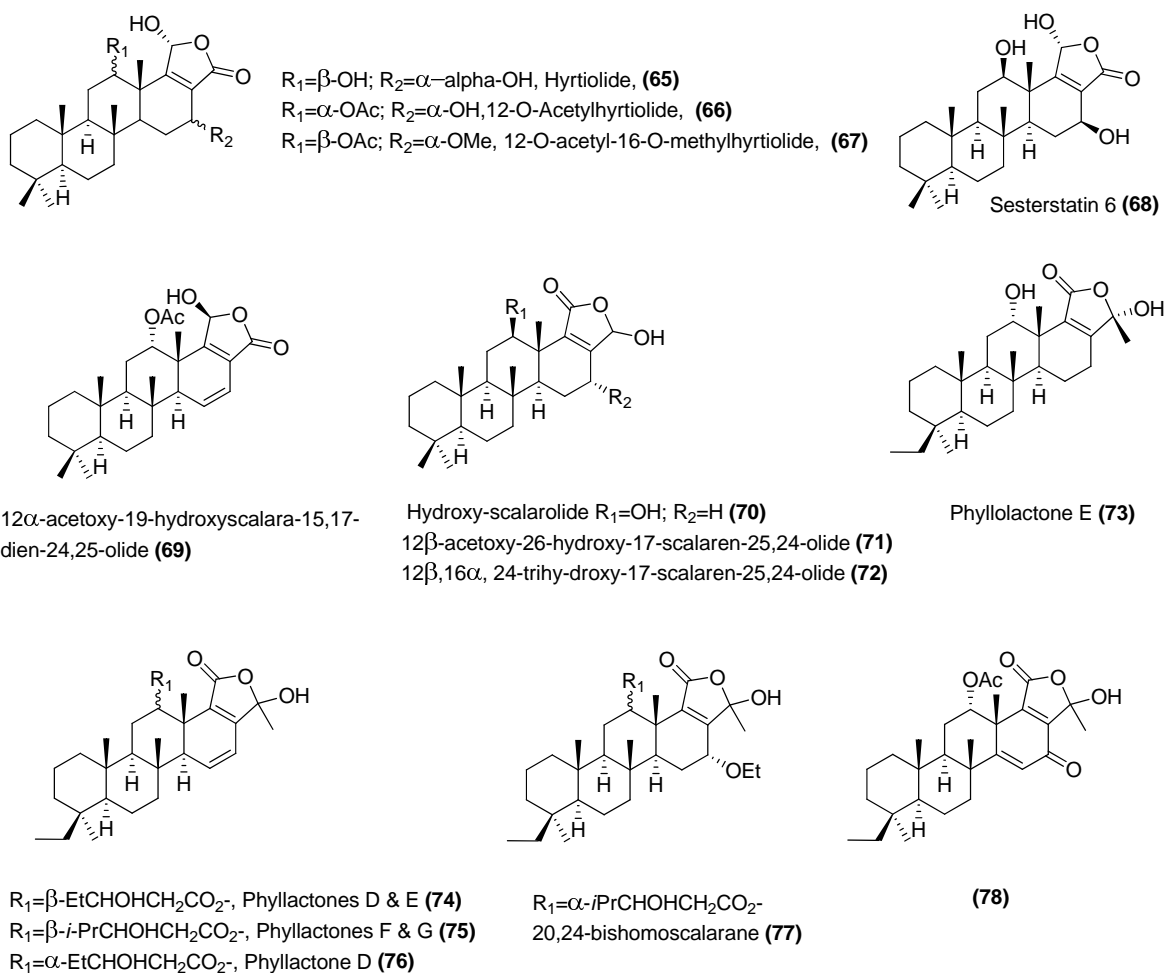
Two moderately cytotoxic norsesesterterpenoids, sarcotins N (**48**) and O (**49**) (Fig 4) were isolated from two Korean *Sarcotragus sp.* [44]. The compounds showed marginal to moderate cytotoxicity against A549 (human lung cancer), SK-OV-3 (human ovarian cancer), SK-MEL-2 (human skin cancer), XF498 (human CNS cancer), HCT 15 (human colon cancer). Marine sponge, *Cacospongia sp.* from southern coast of Australia yielded sesterterpene  $\alpha$ -methyl- $\gamma$ -hydroxybutenolides, cacolides A-L (**50-61**), together with biosynthetically related norsesesterterpene carboxylic acids, cacolic acids A-C (**62-64**). Structures were assigned on the basis of detailed spectroscopic analysis with comparisons to known natural products and biosynthetic considerations [45].



**Fig 4: Structures of sesterterpenoids (48-64).**

Scalaranes, hyrtiolide (**65**) and 12-*o*-acetylhyrtiolide (**66**) (Fig 5) was obtained from an Okinawan and Chinese specimens of *Hyrtios erectus*, respectively [46,47]. The related 12-*o*-acetyl-

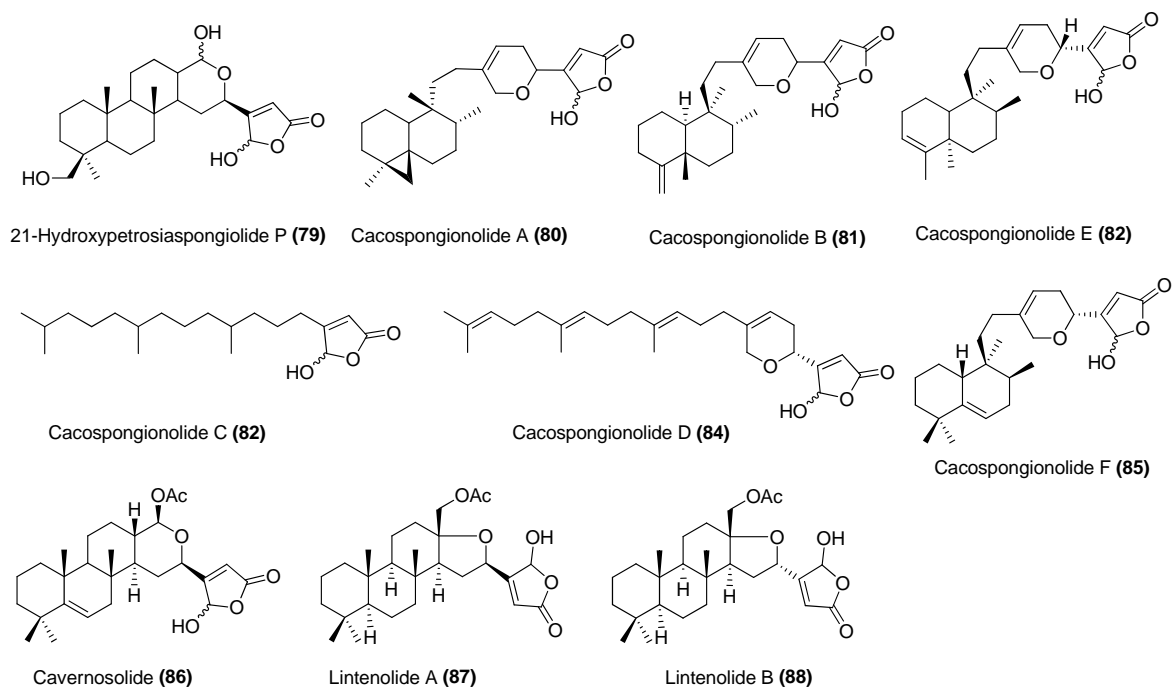
16-*o*-methylhyrtiolide (**67**) isolated from a sponge of the genus *Spongia* collected at the Japan Sea exhibited cytotoxicity against four tumour cell lines, murine leukemia (L1210), human cervix epithelioid carcinoma (HeLa), human lung carcinoma (A549), and human oral epidermoid carcinoma (KB) with IC<sub>50</sub> 2.2, 5.3, 5.3 and 15.6 µg/mL, respectively [48]. *H. erecta* (Maldives) yielded the cytotoxic scalarane-type pentacyclic sesterterpene, sesterstatin 6 (**68**) [3]. It showed significant cancer cell growth inhibition against murine P388 lymphocytic leukemia (ED<sub>50</sub> 0.17 µg/mL) and series of human tumor cell lines (human pancreas carcinoma BXPC-3, GI<sub>50</sub> 0.44 µg/mL; thyroid KAT-4, GI<sub>50</sub> 0.4 µg/mL; thyroid SW1736, GI<sub>50</sub> 0.87 µg/mL; lung-NSC NCI-H460, GI<sub>50</sub> 0.18 µg/mL; pharynx-sq FADU, GI<sub>50</sub> 0.89 µg/mL; prostate DU-145, GI<sub>50</sub> 0.37 µg/mL). 12 $\alpha$ -Acetoxy-19-hydroxyscalara-15,17-dien-24,25-olide (**69**) characterized by an additional double bond, probably formed by elimination of an oxygenated-precursor at C-16 was found in the sponge *Spongia matamata* collected at Risong marine lake, Republic of Palau [49]. Great Barrier Reef sponge *Collospongia auris* yielded 24-hydroxyscalarolide (**70**) that showed antimicrobial activity against *Staphylococcus aureus* (25 µg/disk), *Bacillus subtilis* (25 µg/disk), and *Candida albicans* (50 µg/disk) [50]. The related  $\gamma$ -HB's, 12 $\beta$ -acetoxy-26-hydroxy-17-scalaren-25,24-olide (**71**) and 12 $\beta$ ,16 $\alpha$ ,24-trihydroxy-17-scalaren-25,24-olide (**72**) were obtained as mixtures of epimers from the Thai sponge *H. Gumminae* [51]. Compound (**72**) showed weak cytotoxic activity against several cancer cell lines human cholangiocarcinoma HuCCA-1 (IC<sub>50</sub> 65 µM), human oral epidermoid carcinoma KB (IC<sub>50</sub>14.0 µM), human cervical carcinoma HeLa, (IC<sub>50</sub> 26.0 µM), hormone-independent breast cancer MDA-MB-231 (IC<sub>50</sub> 29.0 µM) and hormone-dependent breast cancer T47D (IC<sub>50</sub> 48.0 µM). Bishomoscalarane-type of sesterterpenes with  $\gamma$ -HB's (**73-78**) were isolated from different sponges belonging to genus *Phyllospongia* (Fig 5). Phyllolactone E (**73**) was isolated from the *P. lamellosa* collected at the Indo-West Pacific [52]. Phyllactones D (**74**, Me-24 $\alpha$ ) and E (**74**, Me-24 $\beta$ ) were isolated as a 1:1 mixture of epimers at C-24 from the sponge *P. foliascens* [53,54], and *P. papyracea* [55] collected both at the South China Sea. Phyllactones F (**75**, Me-24 $\alpha$ ) and G (**75**, Me-24 $\beta$ ) were also isolated as a 1:1 mixture of epimers at C-24 from the sponge *P. foliascens* collected at the South China Sea [56,57]. The corresponding C12 epimers of phyllactones D (**76**, Me-24 $\alpha$ ) and E (**76**, Me-24 $\beta$ ) were present as a 1:4 mixture in the sponge *Carteriospongia* (syn. *Phyllospongia*) *foliascens* collected at Indonesia [58]. It also contained the related epimeric 20,24-bishomoscalarane (**77**) as a 1:1 mixture at C-24. The last metabolite having a  $\gamma$ -HB group is compound (**78**), which was isolated as a 1:1 mixture of epimers at C-24 from the sponge *P. papyracea* collected at Papua New Guinea [59].



**Fig 5: Structures of sesterterpenoids (65-78).**

21-hydroxypetrosaspongiolide P **(79)** (Fig 6) was isolated as an anti-inflammatory agent from a *Spongia sp.* (Vanuatu) [60]. It significantly inhibited PLA<sub>2</sub> with IC<sub>50</sub> value of 5.8  $\mu\text{M}$ , with a higher selectivity toward this enzyme than the reference inhibitor manoalide. Marine sponges *Cacospongia mollior* (northern Adriatic) and *Fasciospongia cavernosa* (Adriatic), yielded cacospongionolides A **(80)** and B **(81)** [61], respectively. Both compounds have a bicyclic sesterterpenoidal skeleton, resembling luffarins and thorectandrols, with the addition of a  $\gamma$ -HB moiety. Compound **(80)** showed high cytotoxicity (LD<sub>50</sub> 0.1  $\mu\text{g/mL}$ ) in the brine shrimp assay. While, compound **(81)** showed potent activity (LC<sub>50</sub> 0.25 ppm) in the *Artemia salina* bioassay, a moderate toxicity (LC<sub>50</sub> 1.05 ppm) in a fish lethality assay, and a high antibacterial activity against the Gram-positive bacteria, *Bacillus subtilis* (MIC 0.78  $\mu\text{g/mL}$ ) and *Micrococcus luteus* (MIC 0.78  $\mu\text{g/mL}$ ). *In-vitro* studies of **(81)** inhibited the human synovial PLA<sub>2</sub> (IC<sub>50</sub> 4.3  $\mu\text{M}$ ), and pancreatic PLA<sub>2</sub> (IC<sub>50</sub> 4.0  $\mu\text{M}$ ), and its potency on the human synovial enzyme was comparable to that of the reference inhibitor, manoalide (IC<sub>50</sub> 3.9  $\mu\text{M}$ ) [62]. This activity was confirmed *in-vivo* on a model of

chronic inflammation, the established adjuvant-induced arthritis. It showed topical anti-inflammatory activity on the mouse ear oedema induced by 12-*o*-tetradecanoylphorbol acetate (TPA) and decreased carrageenin paw oedema in mice after oral administration of 5, 10 or 20 mg kg<sup>-1</sup>. Further, it inhibited nuclear factor- $\kappa$ B (NF- $\kappa$ B)-DNA binding activity and nuclear translocation of this transcription factor. In mouse peritoneal macrophages, cacospongionolide B (**81**) was able to down regulate the expression of inducible nitric oxide synthase (*i*NOS) and cyclooxygenase-2 (COX-2), resulting in decreased production of the two important mediators of inflammation process detected in high levels in rheumatoid synovial tissues, NO and PGE<sub>2</sub> [63]. This compound also reduced TNF- $\alpha$  - mRNA expression and TNF- $\alpha$  levels. The use of cacospongionolide B as inhibitor of the PLA<sub>2</sub> is covered by patent [64]. The other cacospongionolides C (**82**) [65] and D (**83**) are linear. Despite the structural relation with luffarins and thorectandrols, cacospongionolides together with compound (**83**) exhibited significant cytotoxicity [66]. This notion suggested a possible relation between the presence of the  $\gamma$ -HB moiety and the cytotoxicity. It showed a potent activity (LC<sub>50</sub> 0.1  $\mu$ g/mL) in the *A. salina* bioassay, and a moderate ichthyotoxicity to *G. affinis* (LC<sub>50</sub> 2.54  $\mu$ g/mL) in the fish lethality assay. Cacospongionolides E (**84**) and F (**85**) [67-69], were isolated from *F. cavernosa* from the Northern Adriatic Sea and their absolute stereochemistry was determined using the modified Mosher's method. Cacospongionolide E (**84**) was found to be most potent inhibitor towards human synovial PLA<sub>2</sub> showing higher potency than the reference compound, manoalide. Cavernosolide (**86**) [70] was isolated from the Tyrrhenian sponge *F. cavernosa*. The structure was proposed on the basis of spectroscopic data and by chemical transformations. It showed potent activity in the *A. salina* bioassay and a moderate toxicity in a fish lethality assay with LC<sub>50</sub> 0.37 and 0.75  $\mu$ g/mL, respectively. Caribbean sponge *Cacospongia* cf. *Linteiformis* yielded pentacyclic sesterterpenes, lintenolides A (**87**) and B (**88**) [71]. Ichthyotoxicity tests on the mosquito fish *Gambusia affinis* showed that (**87**) and (**88**) were toxic at a concentration of 10 ppm.



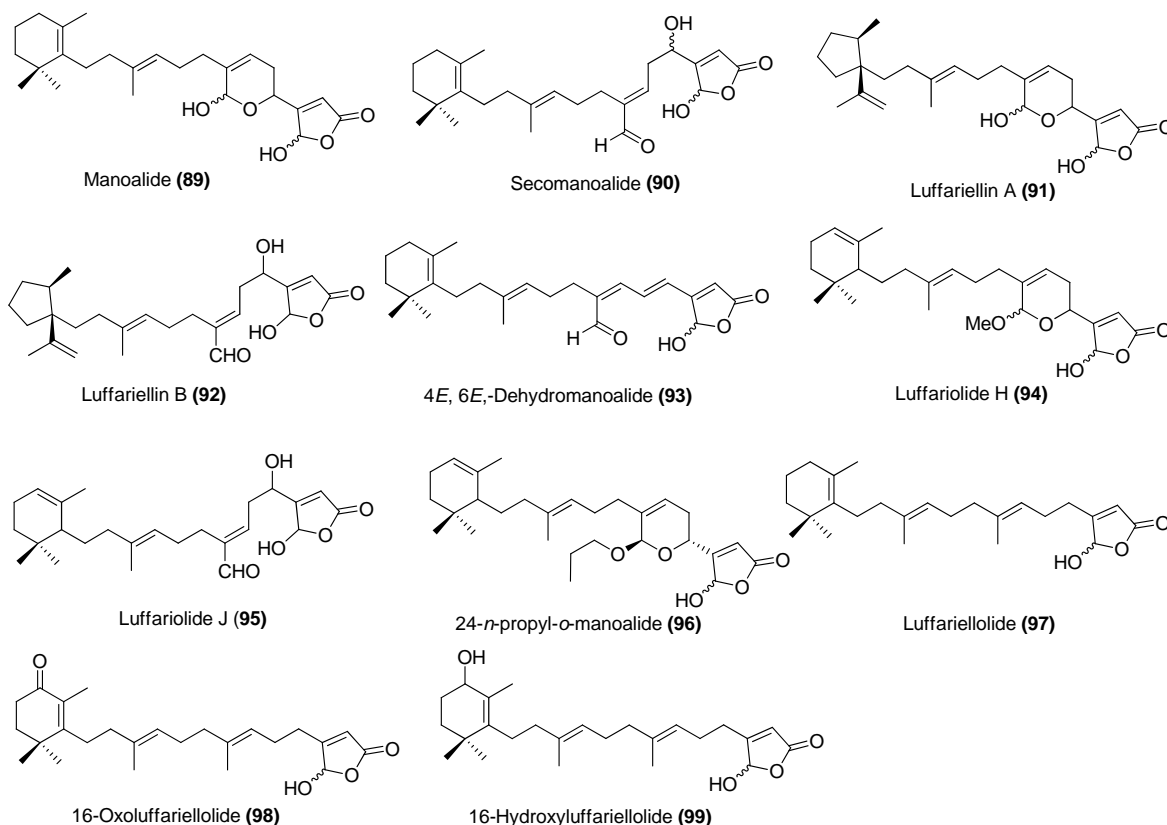
**Fig 6: Structures of sesterterpenoids (79-88).**

Manoalide (**89**) is the parent compound of a series of marine sponge metabolites belonging to the sesterterpene class with 4-hydroxy butenolide (Fig 7). Manoalide was first reported in 1980 by Scheuer from the marine sponge *Luffariella variabilis* collected in Palau with activity as an antibiotic against *Streptomyces pyogenes* and *S. aureus* [72]. And in 1981, Scheuer reported secomanolide (**90**) and other related metabolites from the same Palauan sponge. All compounds, as well as manoalide, displayed antibacterial activity against Gram positive bacteria (*S. aureus* and *B. subtilis*) [73]. Later, Kobayashi and co-workers [74] reported isolation of manoalide (**89**) from the Okinawan sponge *Luffariella sp.* It showed cytotoxic activity against LI210 cells (IC<sub>50</sub> 0.032, µg/mL) and KB cells (IC<sub>50</sub> 0.3 µg/mL) [75]. Subsequently, (**89**) showed molluscicidal activity towards *Biomphalaria glabrata* at 1.5 ppm [76], analgesic activity at 50 mg/kg in the phenylquinone test, and anti-inflammatory activity in the induced inflammation of the mouse ear, with a potency greater than that of indomethacine and less than that of hydrocortisone [77]. Very interestingly, the most important finding has been that manoalide significantly reduces chemically induced inflammation *in-vivo* and irreversibly inhibits the *in-vitro* hydrolysis of phosphotidyl choline by purified bee venom PLA<sub>2</sub> [1, 78-80]. It was suggested that the binding of manoalide to PLA<sub>2</sub> is irreversible and involves initial formation of a Schiff base (imine) between a lysine residue on PLA<sub>2</sub> and the aldehyde group of  $\gamma$ -HB, than a second lysine reacts with the aldehyde group of  $\alpha$ -hydroxy-dihydropyran ring to produce an adduct in which the manoalide is irreversibly bound to PLA<sub>2</sub>. The other geometrical isomer of manoalide, secomanolide (**90**), has similar potency and efficacy in the inhibition of bee venom PLA<sub>2</sub>, suggesting that the

inhibition reaction is not dependent on a rigid geometrical relationship between the aldehyde group and the second lysine residue [81]. Over 183 citations concerning manoalide recorded in MEDLINE show the high interest pointed to this compound. Manoalide (**89**) was licensed to Allergan Pharmaceuticals and reached phase II clinical trials as a topical antipsoriatic. Its development was, however, discontinued due to formulation problems. The compound is now commercially available as a biochemical standard tool to block the action of PLA<sub>2</sub> [81].

Luffariellins A (**91**) and B (**92**) (Fig 7) were isolated from the marine sponge *Luffariella variabilis* collected off different locations in Palau and in Australia [82]. Compound (**91**) was obtained as an oil and was isomeric with manoalide, while, (**92**) is related to secmanoalide. These compounds have 1-isoproprenyl-2-methylcyclopentane ring system replacing the trimethylcyclohexenyl moiety as in other manoalides. All other functional group are retained and thus shown to have similar anti-inflammatory properties. Both luffariellins were potent antagonists of topical induced inflammation in the mouse ear, and inhibitors of bee venom PLA<sub>2</sub>, with an IC<sub>50</sub> value of 5.6 x 10<sup>-8</sup> M and 6.2 x 10<sup>-8</sup> M, for (**91**) and (**92**), respectively. 4*E*,6*E*-dehydromanoalide (**93**) was reported from the Western Pacific sponge *L. variabilis* [83]. It showed a marked decrease in inhibition of bee venom PLA<sub>2</sub> (IC<sub>50</sub> 0.28 μM) [79]. In our group, Majik *et al.* isolated secmanoalide and dehydromanoalide from sponge *F. Cavernosa* (Tamil nadu, India) showing activity against marine fouling bacteria [84]. An okinawan *Luffariella* species yielded two luffariolides H (**94**) and J (**95**) which was found to be cytotoxic and antimicrobial [85]. Compounds (**94**) and (**95**) showed antimicrobial activity against *S. aureus*, with MIC of 16.7 and 33.3 μg/mL, respectively, *B. subtilis* (MIC, both 8.4 μg/mL) and *M. luteus* (MIC, both 8.4 μg/mL). The cytotoxic 24-*n*-propyl-*o*-manoalide (**96**) was isolated from *Luffariella sp.* (Pohnpei, Micronesia). The authors suggested that, it may be an artefact of isolation, but no use of *n*-propanol was given in the extraction procedure [86]. Faulkner and co-workers reported the isolation of luffariellolide (**97**) from a Palauan sponge *Luffariella sp.* that has anti-inflammatory properties [87]. It is a potent antagonist of topical phorbol myristate acetate (PMA) induced inflammation in the mouse ear. It inhibited *in-vitro* hydrolysis of phosphatidyl choline by purified bee venom PLA<sub>2</sub> (IC<sub>50</sub> 2.3 x 10<sup>-7</sup> M). It possesses anti-inflammatory activity through reversible inhibition of PLA<sub>2</sub>. In contrast with the irreversible action of manoalide on PLA<sub>2</sub>, luffariellolide is a slightly less potent but partially reversible PLA<sub>2</sub> inhibitor. Because, luffariellolide lacks one of the two masked aldehyde groups that appears to be responsible for the irreversible reaction of manoalide with lysine residue of PLA<sub>2</sub> [88]. Partially cyclised sesterterpenoids, 16-oxoluffariellolide (**98**), 16-hydroxyluffariellolide (**99**) and luffariellolide (**97**)

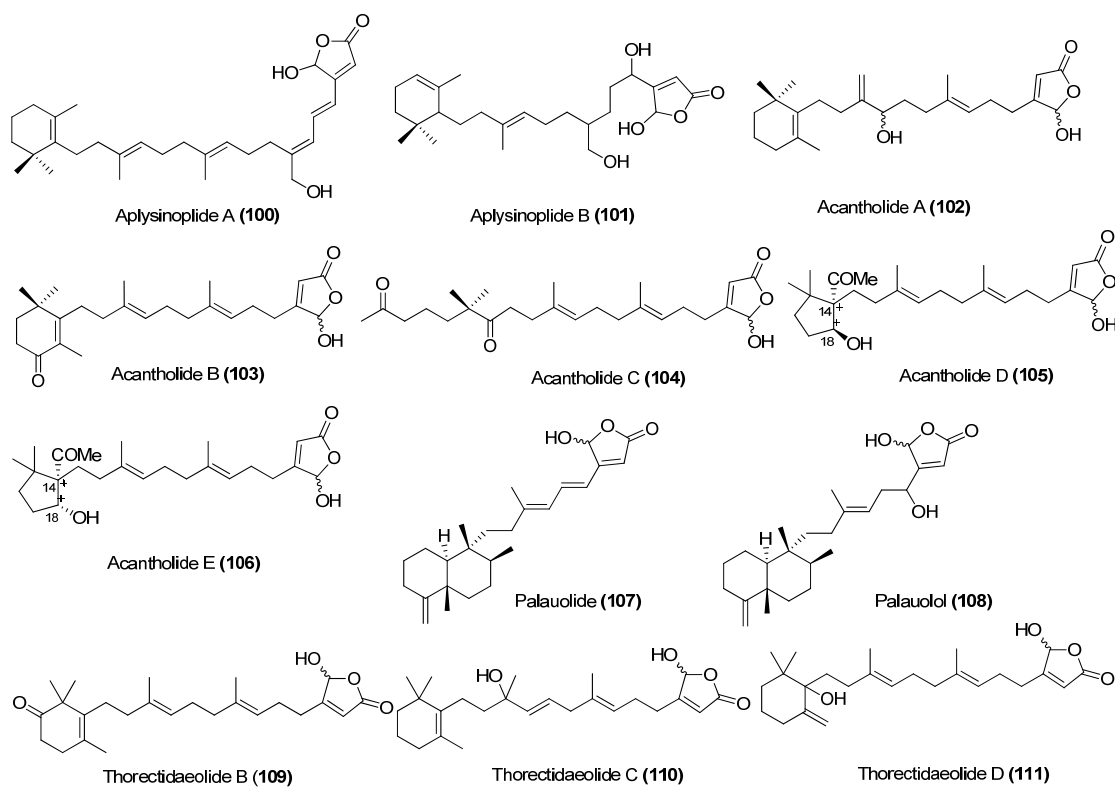
were isolated from a *Thorectandra species* (Papua New Guinea) [89]. The structures of the compounds were established on the basis of extensive 1D and 2D NMR spectroscopic data.



**Fig 7: Structures of sesterterpenoids (89-99).**

Marine sponge, *Aplysinopsis digitata* (Oshima-Shinsono, Kagoshima Pref., Japan) yielded cytotoxic sesterterpenes, aplysinoplides A (**100**) and B (**101**) (Fig 8) [90]. Compounds (**100**) and (**101**) exhibited cytotoxic activity against P388 mouse leukemia cells with IC<sub>50</sub> values of 0.45 and 0.45  $\mu\text{g/mL}$ , respectively. Both compounds did not inhibit bovine pancreas PLA<sub>2</sub> at a concentration of 100  $\mu\text{M}$ , where as manoalide exhibited a potent activity in a parallel experiment. These results confirmed the important role of the C-24 aldehyde for inhibition of PLA<sub>2</sub> [79]. An Indonesian sponge, *Acanthodendrilla sp.* provided five luffarielloide related sesterterpenes acantholides A-E (**102-106**) [91] in addition to luffarielloide (**97**) and its 25-*o*-methyl and 25-*o*-ethyl derivatives. Acantholide B (**103**) and luffarielloide (**97**) were active against bacteria *S. aureus*, *B. substilis*, *E. coli*, the yeast *Candida albicans* and plant pathogen *Cladosporium herbarum*. Acantholide E (**106**) was cytotoxic against the mouse lymphoma L5187Y cell line. Palauolide (**107**) was obtained as an antimicrobial sesterterpene from a three sponge association collected in Palau [92]. While, palauolol (**108**) was identified as an anti-inflammatory sesterterpene from the Palauan sponge *Fascaplysinopsis sp.* and chemically, it was recognized as being a secondary alcohol that upon

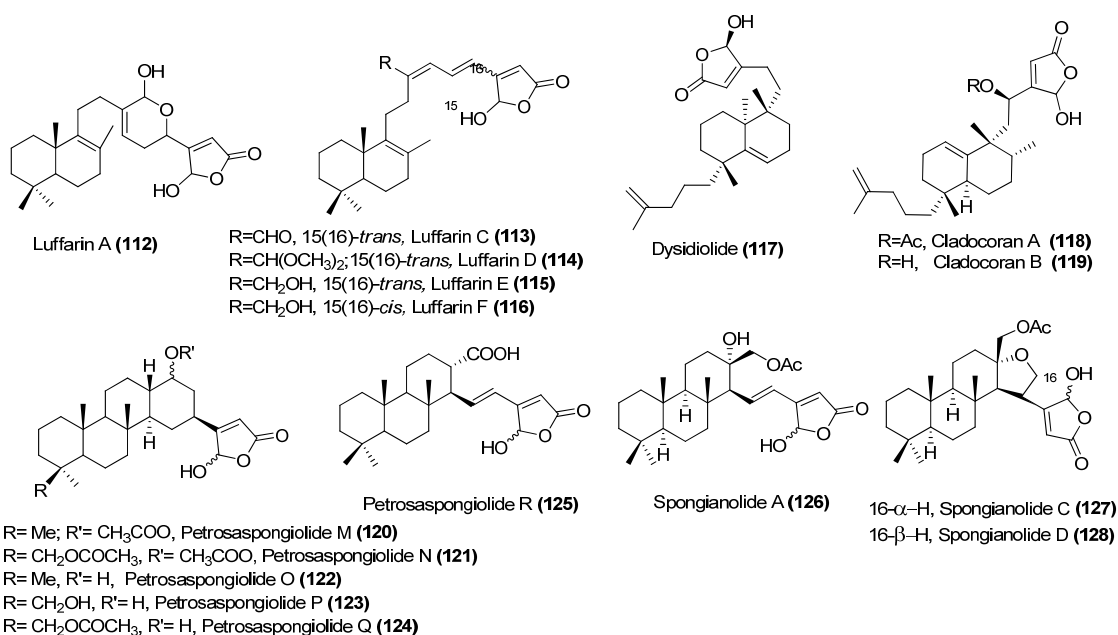
dehydration yielded (**107**) [93]. Palauolol (**108**) was active against all 12 human tumor cell lines tested except A549 (non small lung cancer), with  $IC_{50}$  values in the range 1.2-1.7  $\mu$ M, while (**89**) showed a diminished activity [94]. Both compounds (**107**) and (**108**), containing a functional group  $\gamma$ -HB ring inactivate bee venom PLA<sub>2</sub> with 85% and 82% inhibition, respectively at 0.8  $\mu$ g/mL, and showed anti-microbial activity against *B. subtilis* and *S. aureus* at 10  $\mu$ g/disc [95-96]. Bioassay-guided isolation of marine sponge *Hyrtios communis* (Northern Reef region, Palau) led to the identification of sesterterpenes, thorectidaelides B-D (**109-111**) along with known sesterterpenes, luffariellolide (**97**), 16-oxoluffariellolide (**98**), 16-hydroxyluffariellolide (**99**), acantholide A (**102**) and acantholide C (**104**) [97]. Concentration-response studies were performed to determine the effects of compounds on transcription factor hypoxia-inducible factor-1 (HIF-1) activation in a T47D cell-based reporter assay. Thorectidaelide B (**109**) that possess a simple  $\alpha,\beta$ -unsaturated- $\gamma$ -butenolide moiety inhibited hypoxia (1% O<sub>2</sub>, 16 h)-induced HIF-1 activation with  $IC_{50}$  value of 6.2  $\mu$ M (Confidence interval 5.8-6.7  $\mu$ M). Acantholide A (**102**) [ $IC_{50}$  7.1  $\mu$ M (CI 6.5-7.8  $\mu$ M)] and luffariellolide [ $IC_{50}$  3.6  $\mu$ M (CI 3.4-3.9  $\mu$ M)] significantly (i.e.,  $IC_{50}$  < 10  $\mu$ M) inhibited HIF-1 activation. Luffariellolide (**97**) exhibited a significant level of cytotoxicity that mirrored its HIF-1 inhibitory activity.



**Fig 8: Structures of sesterterpenoids (100-111).**

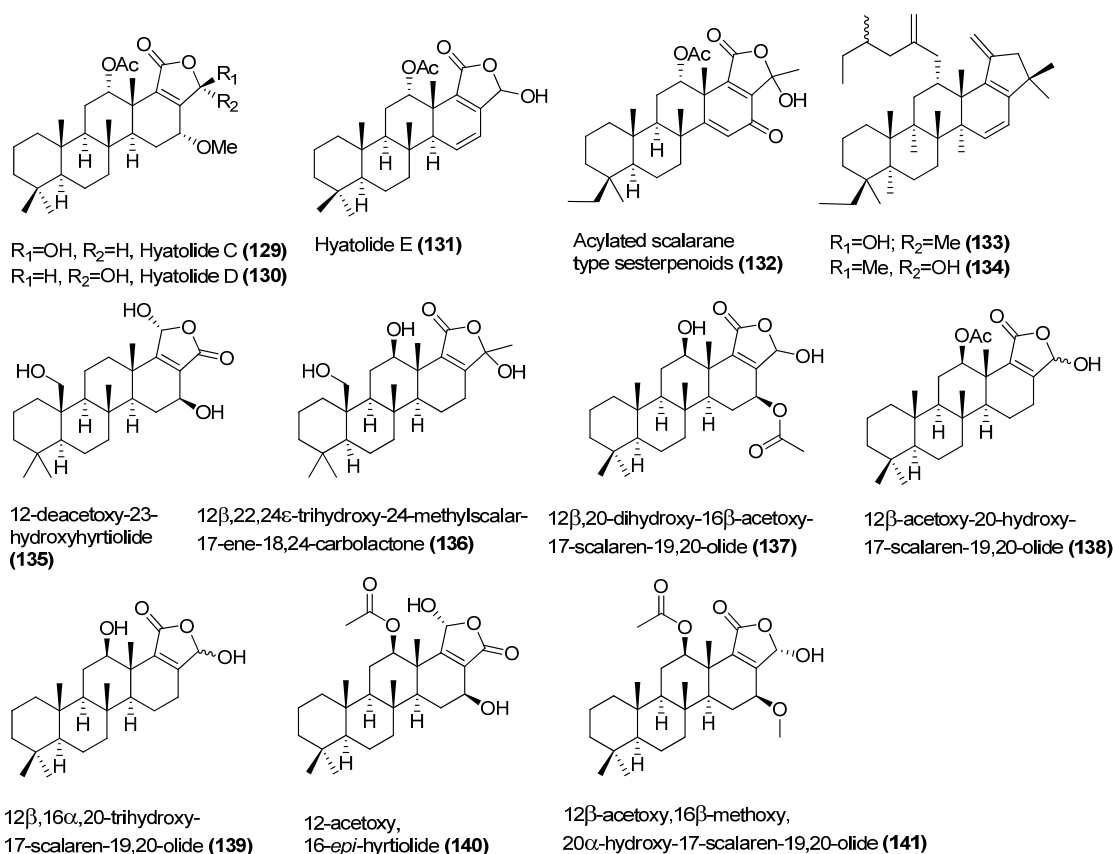


Luffarins A (**112**), C-F (**113-116**), have been reported from the Australian marine sponge, *Luffariella geometrica* (Fig 9) [98]. All luffarins showed mild antimicrobial activity against *S. aureus*, *Micrococcus sp.*, and *Saccharomyces cerevisiae*. Dysidiolide (**117**) was isolated from Caribbean sponge, *Dysidea etheria de laubenfels* [2]. The relative configuration of was determined by single-crystal X-ray diffraction and its conformation included two large side chains that occupy axial and pseudo axial positions on the same side of the decalin ring. It is the first compound to be a natural inhibitor of protein phosphatase cdc25A (IC<sub>50</sub> 9.4 μM), which is essential for cell proliferation. It inhibits the growth of A-549 human lung carcinoma (IC<sub>50</sub> 4.7 μM) and P388 murine leukemia cells (IC<sub>50</sub> 1.5 μM). Subsequently, Takahashi *et al.* (2000) confirmed that dysidiolide not only inhibits cdc25A (IC<sub>50</sub> 35 μM), but also cdc25B (IC<sub>50</sub> 87μM) [99]. Danishefsky has reported that racemic synthetic dysidiolide inhibited PC3, TSU-Pr1, DU145 prostate cancer cells and an MCF7 breast cancer cell line with IC<sub>50</sub> 2-50 μM [100]. In the MCF 7 breast cancer cell line, dysidiolide caused the loss of G2/M peak and the accumulation of cells in G1 consistent with the inhibition of cdc25A. Consequently, dysidiolide has emerged as a promising new anti-mitotic lead compound. Sesterterpenes, cladocorans A (**118**) and B (**119**) were isolated from Mediterranean Coral *Cladocora cespitosa* [101]. The absolute stereochemistry of the secondary alcohol at C-18 was assigned by the advanced Mosher's method applied to an oxidized derivative of (**118**). From New Caledonian collection of the sponge *Petrospongia nigra*, petrosaspongiolides M-R (**120-125**) were isolated [102] revealing the presence of a γ-HB moiety and a hemiacetal function. Due to these structural similarities to manoalide, compounds (**120-125**) have received special attention from the scientific community to study their inhibitory activity against PLA<sub>2</sub> from different resources to point out their specificity. Two main groups of PLA<sub>2</sub> enzymes have been reported [103], the secretory PLA<sub>2</sub> (sPLA<sub>2</sub> groups I, II, III, V, IX, and X with relatively small molecular weights) and the cytosolic PLA<sub>2</sub> (cPLA<sub>2</sub> groups IV, VI, VII, and VIII with higher molecular weights). Inhibition of specific PLA<sub>2</sub> constitutes a potentially useful approach for treating a wide variety of inflammatory disorders such as septic shock, adult respiratory distress syndrome, arthritis, and acute pancreatitis [104]. (-)-Spongianolide A (**126**), which was isolated from a marine sponge, *Spongia sp.* along with spongianolides C (**127**) and D (**128**) are tricyclic sesterterpenoids possessing a γ-HB moiety. And, it was reported to inhibit proliferation of the mammary tumor cell line MCF-7.4 [105]. The absolute configuration of (**126**) was determined by total synthesis [106].



**Fig 9: Structures of sesterterpenoids (112-128).**

A Gulf of California (Mexico) collection of *Hyatella intestinalis* was found to contain hyatolides C-E (**129-131**) (Fig 10) and hyatolides C and D were obtained as a mixture [107]. *Phyllospongia papyracea* (Papua New Guinea) yielded acylated scalarane type sesterpenoids (**132-134**) [108]. The scalarane sesterterpenoid, 12-deacetoxy-23-hydroxyhyrtiolide (**135**) was isolated from Korean marine sponge, *Psammocinia sp.* The compound showed moderate activity against human renal cancer cell lines (A498, ACHN), pancreatic cancer cell lines (MIA-paca, PANC-1) and noncancerous monkey cell line (CV-1) using MTT assays [109]. Chemical investigation of a Madagascan sponge similar to sponge *Carteriospongia sp.* afforded homoscalarane sesterterpene, 12 $\beta$ ,22,24 $\epsilon$ -trihydroxy-24-methylscalar17-ene-18,24-carbolactone (**136**). The structure was elucidated by spectroscopic methods, including UV, IR and 1D and 2D NMR. It showed moderate anti-proliferative activity (IC<sub>50</sub> value 8.7  $\mu$ M) against A2780 ovarian cell line [110].



**Fig 10: Structures of sesterterpenoids (129-141).**

Chemical investigation of the Thai sponge *Hyrtios gumminae* collected from Similan Island in the Andaman Sea, Thailand, yielded sesterterpenoids, 12 $\beta$ ,20-dihydroxy-16 $\beta$ -acetoxy-17-scalaren-19,20-olide (**137**), 12 $\beta$ -acetoxy-20-hydroxy-17-scalaren-19,20-olide (**138**), and 12 $\beta$ ,16 $\alpha$ ,20-trihydroxy-17-scalaren-19,20-olide (**139**) [111]. The structures of these compounds were elucidated on the basis of their spectroscopic data and chemical transformations. Two sesterterpene analogs, 12-acetoxy,16-*epi*-hyrtiolide (**140**) and 12 $\beta$ -acetoxy and 16 $\beta$ -methoxy, 20 $\alpha$ -hydroxy-17-scalaren-19,20-olide (**141**) along with compounds (**137-139**) containing a scalarane-based framework were isolated from marine sponge *Hyrtios erectus* (Red Sea, Egypt) [112]. The biological activity of all the bioactive  $\gamma$ -HB containing MNPS has been provided in **Table 1**. Among different class of compounds, majority of the  $\gamma$ -HB containing MNPS isolated were sesterterpenoids showing significant biological activities. Hence, different routes for the synthesis of six potent sesterterpenoids, manolide, secomanolide, cacospongionolides B & E, luffarielloide and dysidiolide have been highlighted in the following section.

**Table 1: Reported biological activities of all  $\gamma$ -HB containing MNPS.**

<b>Class</b>	<b>Compounds</b>	<b>Biological activities</b>	
Monoterpenoids	5-Hydroxy-3-methyl-5-pentyl-2,5-dihydrofuran-2-one ( <b>2</b> )	Antifouling activity	
Sesquiterpenoids	Furodysin lactone thioacetate ( <b>6</b> )	High binding affinity for human leukotriene 84 (LTB <sub>4</sub> ) receptor	
	Furodysin lactone ( <b>7</b> )	Repellent activity	
	2-oxomicrocionin-2-lactone analogue ( <b>16</b> )	hPTP1B Inhibitor	
	Dysidotronic acid ( <b>17</b> )	Human synovial PLA <sub>2</sub> inhibitor; TNF- $\alpha$ , IL-1 $\beta$ , NO, PGE <sub>2</sub> , LTB <sub>4</sub> inhibitor	
Diterpenoids	Cespihypotin F ( <b>29</b> )	HSV-1 virus	
	Cespihypotin V ( <b>30</b> )	Human Daoy & WiDr tumor cell lines activity	
	Cespitularin D ( <b>31</b> )	Cytotoxicity (P-388 cells)	
	Caribenol A ( <b>37</b> )	Antimycobacterial	
	Echinohalimane A ( <b>40</b> )	Cytotoxicity (MOLT-4, HL-60, DLD-1, LoVo cells); <i>In-vitro</i> anti-inflammatory activity	
	Echinoclerodane A ( <b>41</b> )	Cytotoxicity(MOLT-4, HL-60, DLD-1, LoVo cells); <i>In-vitro</i> anti-inflammatory activity	
	Pachyclavularioline E ( <b>43</b> )	Cytotoxicity (P388, HT-29, A549)	
	Pachyclavularioline J ( <b>44</b> )	Cytotoxicity (P388, HT-29, A549)	
	Pachyclavularioline K ( <b>45</b> )	Cytotoxicity (P388, HT-29, A549, KB)	
	Pachyclavularioline M ( <b>47</b> )	Cytotoxicity (P388, HT-29, A549)	
	Sesterterpenoids	Sarcotins N-O( <b>48-49</b> )	Cytotoxicity (A549, SK-OV-3, SK-MEL-2, XF498, HCT 15)
		12- <i>o</i> -acetyl-16- <i>o</i> -methylhyrtiolide ( <b>67</b> )	Cytotoxicity (L1210, HeLa , A549, KB)
		Sesterstatin 6 ( <b>68</b> )	Significant cytotoxicity (P288, BXPC-3, KAT-4, SW176, NSC NCI-H460, FADU, DU-145)
24-hydroxy-scalarolide ( <b>70</b> )		Antimicrobial activity ( <i>S. aureus</i> , <i>B. subtilis</i> , <i>C. albicans</i> )	
12- $\beta$ ,16 $\alpha$ ,24-trihydroxy-17-scalaren-25-24-olide ( <b>72</b> )		Cytotoxicity (HuCCA-1, KB, HeLa, MDA-MB-231, T47D)	
21-hydroxypetro-saspongionolide P ( <b>79</b> )		Anti-inflammatory activity (PLA <sub>2</sub> Inhibitor)	
Cacospongionolide A ( <b>80</b> )		High cytotoxicity (brine shrimp assay)	
Cacospongionolide B ( <b>81</b> )		Potent activity ( <i>Artemia salina</i> ) Toxicity (Fish lethality assay) Antibacterial activity ( <i>B. subtilis</i> , <i>M. luteus</i> ) Anti-inflammatory activity (Human synovial PLA <sub>2</sub> , pancreatic PLA <sub>2</sub> NF- $\kappa$ B-DNA, <i>i</i> NOS, COX-2, NO, PGE <sub>2</sub> , TNF- $\alpha$ inhibitor)	
Cacospongionolide D ( <b>83</b> )	Cytotoxicity ( <i>A. salina</i> bioassay)		

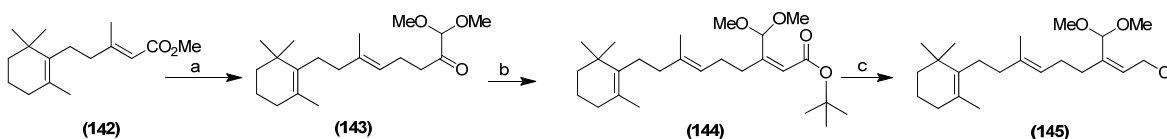
		Ichthyotoxicity ( <i>Gambusia affinis</i> in the fish lethality assay)
	Cacospongionolide E (84)	Anti-inflammatory activity (Potent human synovial PLA <sub>2</sub> inhibitor)
	Cavernosolide (86)	Cytotoxicity (potent activity in <i>Artemia salina</i> bioassay); Toxicity (Fish lethality assay)
	Lintenolides A-B (87-88)	Ichthyotoxicity ( <i>Gambusia affinis</i> in the fish lethality assay)
	Manoalide (89)	Antibacterial ( <i>S. pyogenes</i> , <i>S. aureus</i> <i>B. subtilis</i> ); Cytotoxicity (LI210 cells, KB cells); Molluscicidal activity ( <i>Biomphalaria glabrata</i> ) Analgesic activity; Potent anti-inflammatory activity (PLA <sub>2</sub> inhibitor), Topical antipsoriatic activity
	Secomanoalide (90)	Antibacterial activity ( <i>S. aureus</i> , <i>B. subtilis</i> ); Potent anti-inflammatory activity (bee venom PLA <sub>2</sub> inhibitor);Antifouling activity (Marine fouling bacteria)
	Luffariellins A-B (91-92)	Anti-inflammatory activity (Potent antagonists of topically induced inflammation in mouse ear, bee venom PLA <sub>2</sub> inhibitor )
	4 <i>E</i> ,6 <i>E</i> -dehydromanoalide (93)	Anti-inflammatory activity (bee venom PLA <sub>2</sub> inhibitor)
	Luffariolides H-I (94-95)	Cytotoxicity; Antimicrobial activity ( <i>S. aureus</i> , <i>B. subtilis</i> , <i>M. luteus</i> )
	24- <i>n</i> -propyl- <i>o</i> -manoalide (96)	Cytotoxicity
	Luffariellolide (97)	Anti-inflammatory activity (Potent antagonist of topical phorbol myristate acetate (PMA) induced inflammation in mouse ear,bee venom PLA <sub>2</sub> inhibitor; Antibacterial activity ( <i>S. aureus</i> , <i>B. subtilis</i> , <i>E. coli</i> , the yeast <i>C. albicans</i> and plant pathogen <i>C. herbarum</i> )
	Aplysinoplides A-B (100-101)	Cytotoxicity ( P388)
	Acantholide B (103)	Antibacterial activity ( <i>S. aureus</i> , <i>B. subtilis</i> , <i>E. coli</i> , the yeast <i>C. albicans</i> and plant pathogen <i>Cladosporium herbarum</i> )
	Acantholide E (106)	Cytotoxicity(L5187Y)
	Palauolide (107)	Antimicrobial activity ( <i>B. subtilis</i> , <i>S. aureus</i> ); Anti-inflammatory activity (bee venom PLA <sub>2</sub> inhibitor)
	Palauolol (108)	Cytotoxicity (12 human tumor cell lines); Anti-inflammatory activity (bee venom PLA <sub>2</sub> inhibitor)

	Luffarin A ( <b>112</b> ), Luffarins C-F ( <b>113-116</b> )	Antimicrobial activity
	Dysidiolide ( <b>117</b> )	Anti-inflammatory activity (phosphatase <i>cdc25A</i> inhibitor); Cytotoxicity (A-549, P388)
	Petrosaspongiolides M-R ( <b>120-125</b> )	Anti-inflammatory activity (PLA <sub>2</sub> inhibitor)
	(-)-Spongianolide A ( <b>126</b> )	Cytotoxicity (MCF-7.4)

### 3. Synthesis of bioactive MNPS containing $\gamma$ -HB

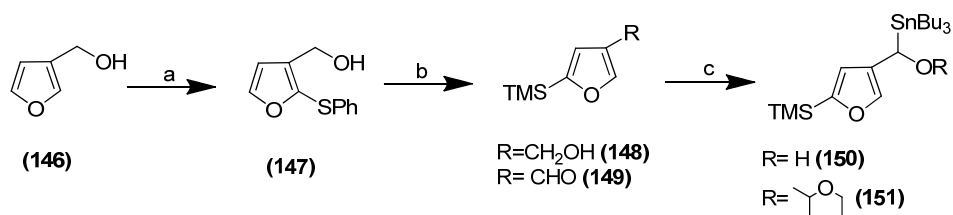
#### 3.1. Manoalide and secmanoalide

Synthesis of manoalide and sacmanoalide by Shigeo Katsumura *et al.* [113] began with the preparation of allyl chloride (**145**) using methyl *trans*-7,8-dihydro- $\beta$ -ionyliden acetate (**142**) as starting material. Reduction of (**142**) using LAH followed by bromination afforded the corresponding bromide (**Scheme 1**). This was further reacted with the lithium anion prepared from *N,N*-dimethylhydrazone of pyruvaldehyde dimethyl acetal to yield  $\alpha$ -ketodimethylacetal (**115**) after acid treatment. Compound (**143**) on treatment with the anion of *t*-butyl-2-trimethylsilyl acetate gave corresponding *t*-butyl ester (**144**) with *trans* stereochemistry. On reduction with DIBAL-H in CH<sub>2</sub>Cl<sub>2</sub> gave alcohol which was further converted into allyl chloride (**145**).



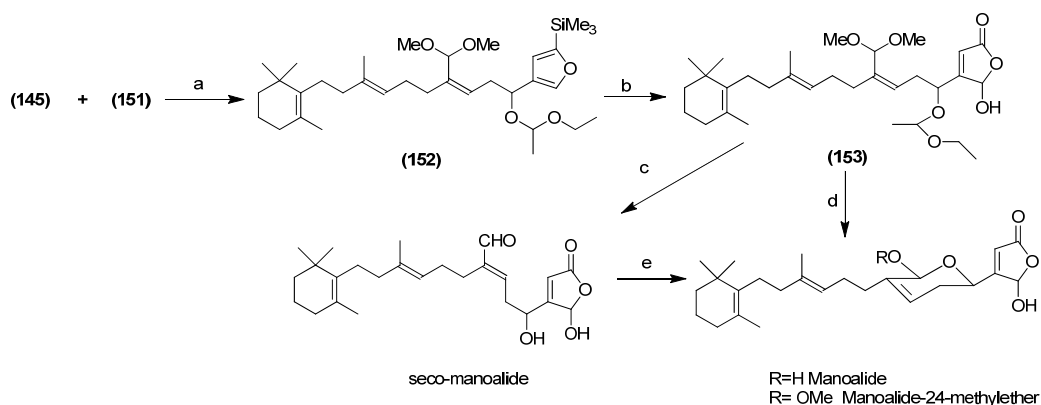
**Scheme 1:** Synthesis of allyl chloride (**145**). Reagents and conditions: a) LAH, PBr<sub>3</sub>/pyridine, 86%, *N,N*-dimethylhydrazone of pyruvaldehyde dimethylacetal, 2N HCl/0°C/3 min, 72%; b) anion of *t*-butyl-2-trimethylsilyl acetate, 95%; c) DIBAL-H in DCM, then MsCl, LiCl, DMAP, Et<sub>3</sub>N/CH<sub>2</sub>Cl<sub>2</sub>/0°C/30 min, DMF/0°C/3h, 90%.

The second part was synthesis of  $\alpha$ -alkoxy stannane (**151**). It was prepared regioselectively from 3-hydroxymethylfuran (**146**) by sulfenylation to give sulfide (**147**) (**Scheme 2**). This was followed by dilithiation, silylation, acid treatment and then desulfurization to give 5-trimethylsilyl-3-hydroxy-methylfuran (**148**). Further oxidization with Ba(MnO<sub>4</sub>)<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> gave aldehyde (**149**). Aldehyde (**149**) was converted to into  $\alpha$ -alkoxy stannane (**151**) via  $\alpha$ -hydroxy stannane (**150**) by reaction with tributylstannyl lithium and  $\alpha$ -chloroethyl ethyl ether.



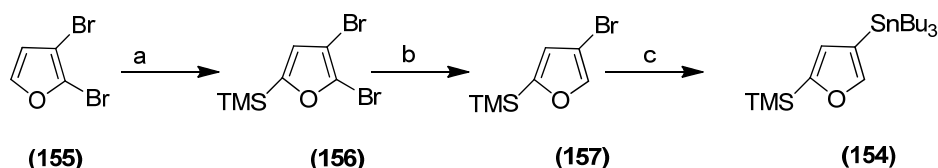
**Scheme 2:** Synthesis of  $\alpha$ -alkoxy stannane (**151**). Reagents and conditions: a) Sulfenylation of the dilithio-derivative of (**146**), 91% yield; *n*-BuLi/THF/-78 °C/1h/0°C/2h, TMSCl/0 °C/18h; 1% HCl/THF/0°C/5min; Raney-Ni/EtOH/16h; b) Ba(MnO<sub>4</sub>)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 16h, 41%; c) Bu<sub>3</sub>SnLi (THF/ -78 °C/1h), then C<sub>4</sub>H<sub>9</sub>ClO (DIPEA/ CH<sub>2</sub>Cl<sub>2</sub>/0°C/1h), 95%.

The reaction of lithium anion derived from  $\alpha$ -alkoxy stannane (**151**) and allyl chloride (**145**) in presence of *n*-BuLi/THF gave  $\alpha$ -silylfuran (**152**) (**Scheme 3**). Further, photosensitized oxygenation without any oxidation of the tri- and tetra-substitute olefins existing in the side chain was achieved in presence of Rose Bengal to give (**153**). Finally, (**153**) was hydrolysed to manoalide by treatment with aqueous acetic acid in THF while, in MeOH, manoalide-24-methylether was obtained. On the other hand treatment of (**153**) with 2N HCl in THF gave secomanalide.



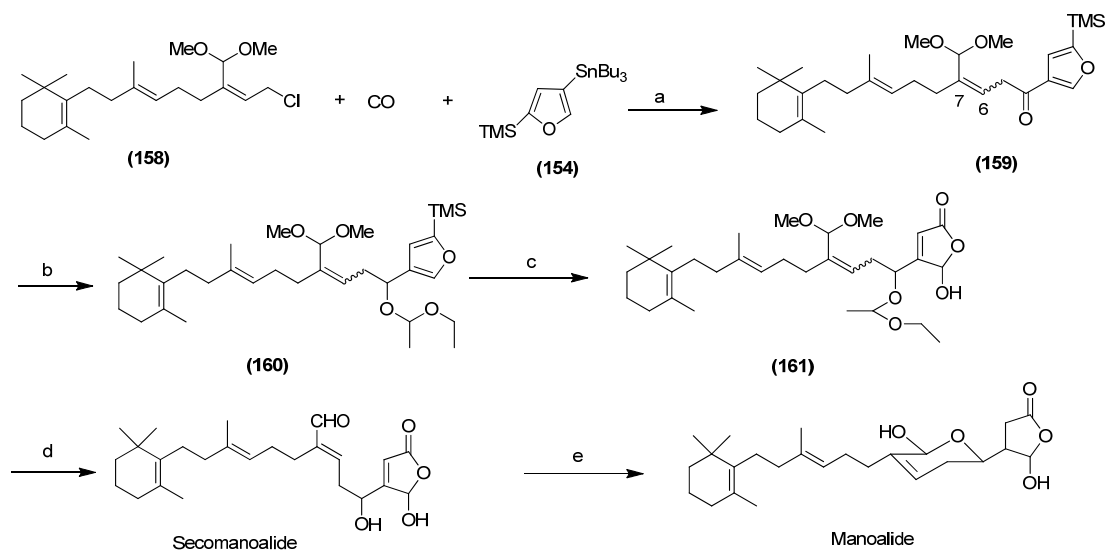
**Scheme 3:** Completion of total synthesis of manoalide and secomanalide. Reagents and conditions: a) *n*-BuLi/THF/-78°C/15 min, THF/-78°C/1h; b) O<sub>2</sub>, hv, -78°C, CH<sub>2</sub>Cl<sub>2</sub>-MeOH, Rose Bengal c) 2N HCl in THF, room temp, 2h; d) 70% aq. CH<sub>3</sub>COOH in THF, room temp./7h/ 55%; e) hv.

Another efficient and convenient route for the synthesis of manoalide and secomanalide [114] was achieved by Shigeo Katsumura *et al.*, (1988) from an allyl chloride derivative in 6 steps in 56.4% overall yield by Pd(0)catalyzed coupling with CO and 2-trimethylsilyl-4-tributylstannylfuran (**154**) followed by chemoselective oxidation of 2-trimethylsilylfuran with <sup>1</sup>O<sub>2</sub> (singlet oxygen).




**Scheme 4:** Synthesis of 2-trimethylsilyl-4-tributylstannylfuran (**154**). Reagents and conditions: a) LDA/TMSCl/THF, -78°C, room temp, 86%; b) *n*-BuLi/ether, -78°C, 3 min./H<sub>2</sub>O, 84%; c) *sec*-BuLi/ether, -78°C, 30 min./Bu<sub>3</sub>SnCl, 1h, room temp, 80%.

2-trimethylsilyl-4-tributylstannylfuran (**154**) was prepared from commercially available 2,3-dibromofuran (**155**) (Scheme 4). The regioselective lithiation of (**155**) with lithium diisopropylamide and trimethylsilyl chloride gave 2,3-dibromo-5-trimethylsilylfuran (**156**). Further, treatment with *n*-BuLi followed by addition of water yielded 2-trimethylsilyl-4-bromofuran (**157**). Successive reaction with *sec*-BuLi followed by trapping the generated anion with tributylstannyl chloride afforded (**154**). The next segment allylchloride required for the synthesis is prepared using their previous established procedure [113]. The allyl chloride (**158**), CO and 2-silyl-4-stannylfuran (**154**) were coupled using Pd(0) catalyst developed by J. K. Stille (Scheme 5) [115]. The reaction was stirred under 3 atm. pressure of CO in the presence of palladium dibenzylideneacetone (10 M%) and triphenylphosphine (20 M%) at 50 °C for 36hr. The product (**159**) was obtained as a mixture of *E* and *Z*-isomers of C<sub>6,7</sub> double bond. Further acid treatment and reduction with LAH yielded alcohol which was protected with ethoxyethyl group to afford (**160**). Photosynthesis oxygenation of (**160**) yielded (**161**). Further, acid treatment yielded secomanoalide. Manoalide was obtained by photoirradiation of secomanoalide.

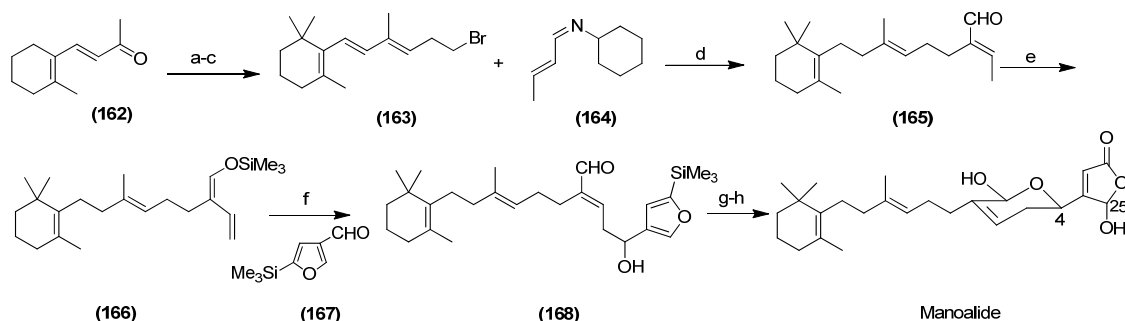


**Scheme 5:** Completion of total synthesis of manoalide and secomanoalide. Reagents and conditions:



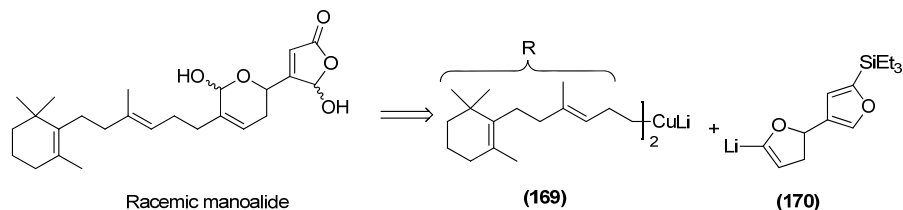
a) Stirring under 3 Atm pressure of CO, Pd(dba)<sub>2</sub>, 10M%/Ph<sub>3</sub>P(20M%), 50°C, 36h; b) LAH, ; c) <sup>1</sup>O<sub>2</sub>; d) 2N HCl/THF, -H<sub>2</sub>O, 60%; e) hv.

Synthesis of manoalide by Michael E. Garst *et al.* was initiated using commercially available  $\beta$ -ionone (**162**) and converting it to bromide (**163**) using Schlessinger alkylation in 3 steps (**Scheme 6**) [116]. Firstly,  $\beta$ -ionone by reduction with triphenyltin hydride yielded dihydro- $\beta$ -ionone. This was followed by Wittig condensation with 3-hydroxypropyltriphenyl phosphonium bromide to afford 1:1 mixture of *E*- and *Z*-alcohols [117,118]. Further, chromatographic separation afforded the *E*-alcohol in 29% yield. Finally, bromide (**163**) was prepared by treatment of the alcohol with TsCl/Py followed by LiBr/acetone. The alkylation of cyclohexylimine (**164**) was effected by anion formation with LDA/DMPU complex, followed by the addition of bromide (**163**) at -60 °C. After, aqueous NH<sub>4</sub>Cl hydrolysis for 20 hrs afforded aldehyde (**165**) and was further converted into its silyl enol ether (**166**). Reaction of (**166**) and furan aldehyde (**167**) with boron trifluoride etherate catalyst at -55 °C provided hydroxyaldehyde (**168**). Furan aldehyde (**168**) was prepared from 3-furfural [119].



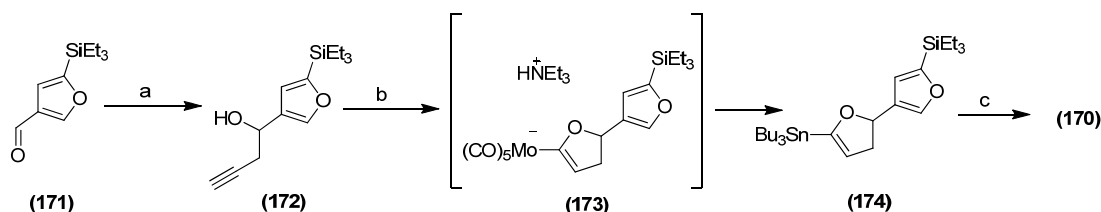
**Scheme 6:** Total synthesis of manoalide. Reagents and conditions: a) Ph<sub>3</sub>SnH b) Ph<sub>3</sub>P(CH<sub>2</sub>)<sub>3</sub>OH Br/*n*-BuLi/THF; separate c) TsCl/Py; LiBr, (CH<sub>3</sub>)<sub>3</sub>CO d) LDA/DMPU/THF-78°C; e) TMSCl/Et<sub>3</sub>N/PnH; f) BF<sub>3</sub>.OEt<sub>2</sub>/CH<sub>2</sub>Cl<sub>2</sub>/-55°C; g) 300nm/PhH; h) <sup>1</sup>O<sub>2</sub>/MeOH.

Pommier and Kociński (1997) reported synthesis of racemic manoalide from the homocuprate (**169**) and lithiated dihydrofuran (**170**) using 1,2-metallate rearrangement of a higher order cuprate and a Pd<sup>0</sup>-catalysed carbonylation of an iodo alkene generating the central dihydropyranone ring (**Scheme 7**) [120].



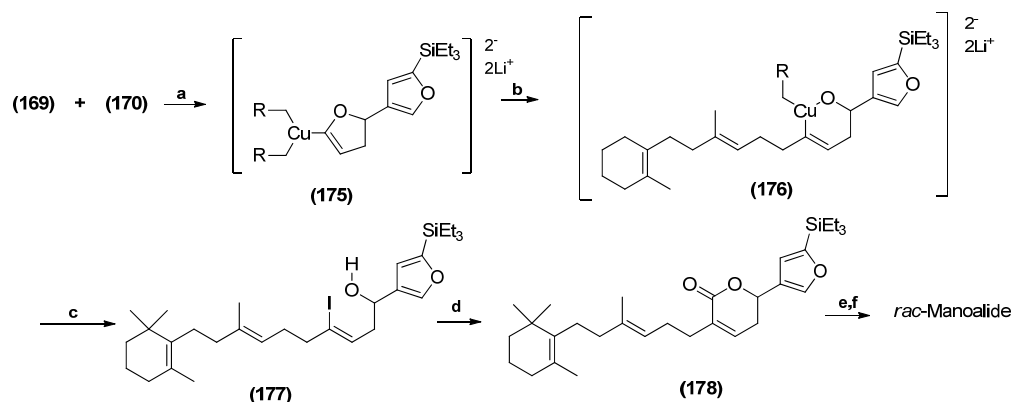
**Scheme 7:** Retrosynthesis of racemic manoalide

The lithiated dihydrofuran (**170**) was prepared by addition of prop-2-ynyl magnesium bromide to 5-triethylsilyl-3-furaldehyde (**171**) [119] to give homoprop-2-ynylic alcohol (**172**). The Fischer carbene complex (**173**) generated by electrophilic cyclisation of (**172**) with  $(\text{CO})_5\text{Mo}\cdot\text{NEt}_3$  was further converted *in situ* to the alkenylstannane (**174**) in the presence of  $\text{Bu}_3\text{SnOTf}$  as reported by McDonald *et al.* This was followed by transmetalation of (**174**) to the desired alkenyl lithium (**170**) with *s*-BuLi in a diethyl ether-pentane mixture at  $260\text{ }^\circ\text{C}$  for 20 min and the lithium reagent (**170**) was used immediately in the next step (**Scheme 8**).



**Scheme 8:** *Synthesis of lithiated dihydrofuran (170).* Reagents and conditions: a) prop-2-ynylmagnesium bromide,  $\text{Et}_2\text{O}$ ,  $40\text{ }^\circ\text{C}$  to room temp.; b)  $(\text{CO})_5\text{Mo}\cdot\text{NEt}_3$ ,  $\text{Bu}_3\text{SnOTf}$ ,  $\text{Et}_2\text{O}\text{-Et}_3\text{N}$ , room temp., 48 h; c) *s*-BuLi,  $\text{Et}_2\text{O}\text{-pentane}$ ,  $-60\text{ }^\circ\text{C}$ , 20 min.

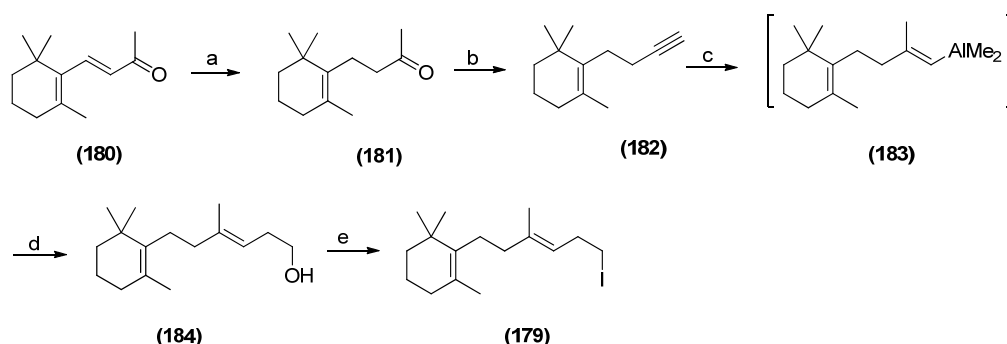
Further, synthesis involved 1,2-metallate rearrangement of the higher order cuprate (**175**) derived from addition of alkenyl lithium (**170**) to homocuprate (**169**) which yielded alkenylcuprate (**176**). This was further quenched with iodine at  $30\text{ }^\circ\text{C}$  to give iodo alkene (**177**) followed by introduction of the remaining carbon by  $\text{Pd}^0$ -catalysed carbonylation using a modification of conditions previously described by Heck [122]. Finally, the reduction of the lactone (**178**) to the lactol with DIBAL-H and photooxidation of the silylfuran gave *rac*-manoalide (**Scheme 9**).



**Scheme 9:** *Completion of total synthesis of rac-Manoalide.* Reagents and conditions: a) Add a solution of (**170**) in  $\text{Et}_2\text{O}\text{-pentane}$  to a solution of (**169**) in  $\text{Et}_2\text{O}\text{-Me}_2\text{S}$  (1:1) at  $40\text{ }^\circ\text{C}$ ; b) 1,2-metallate

rearrangement; c) I<sub>2</sub> (4 equiv.), 30 °C; d) Pd(PPh<sub>3</sub>)<sub>4</sub>, Pri<sub>2</sub>NEt, THF-MeOH, CO (2 atm), 60 °C, 24 h; e) DIBALH, CH<sub>2</sub>Cl<sub>2</sub>, 80 °C; f) O<sub>2</sub>, hv, Rose Bengal, MeOH, 80 °C.

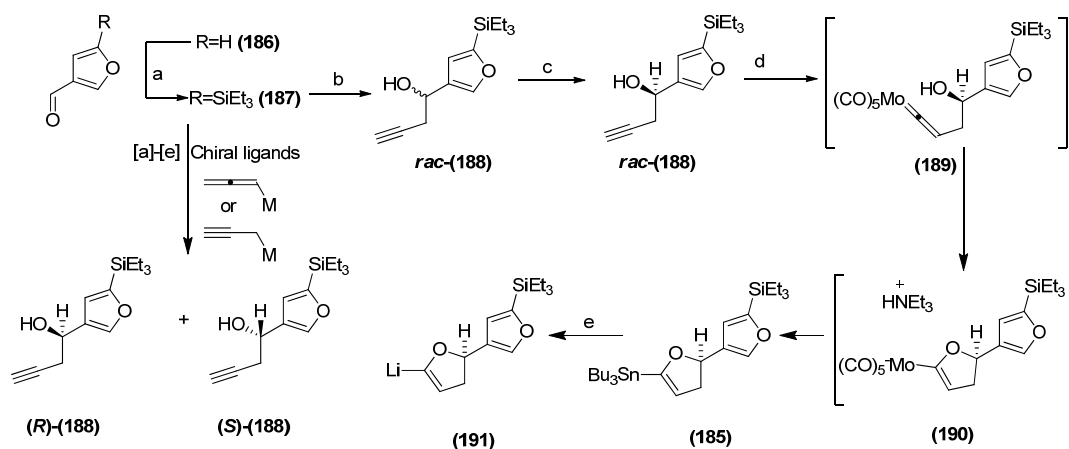
Once again, Pommier *et al.* (2003) reported the synthesis of (4*R*)-manoalide derived from 6 simple commercial fragments: 3-furaldehyde, trimethylalane, oxirane, CO,  $\beta$ -ionone, and propargyl bromide [123]. The first key intermediate, iodoalkane (**179**) was prepared by beginning conjugate reduction of  $\beta$ -ionone (**180**) reported by Laube and co-workers [124]. It involved Rh catalyzed conjugate hydrosilylation of  $\beta$ -ionone with triethylsilane followed by hydrolysis of the enol silane intermediate to give the dihydro- $\beta$ -ionone (**181**) in 90% yield (**Scheme 10**). The reaction was performed on large scale under solvent-free conditions and only 1 mol % of the commercial Rh[Ph<sub>3</sub>P]<sub>3</sub>Cl catalyst. Regioselective dehydration of dihydro- $\beta$ -ionone *via* the enol phosphate derivative gave the terminal alkyne (**182**) in 73% yield for the 3-step sequence [125]. Further alkyne (**182**) was converted to alkenyl dimethylalane intermediate (**183**) by Negishi carboalumination reaction in the presence of 1 equiv of water as recommended by Wipf and co-workers [126] and a reduction using zirconocene dichloride. This was followed by direct reaction of the alkenyl dimethylalane (**183**) with oxirane to give the homoallylic alcohol (**184**). Finally, alcohol (**184**) is converted to iodoalkane (**179**) with standard procedures using triphenylphosphine-I<sub>2</sub>-Imidazole.



**Scheme 10:** Synthesis of iodoalkane (**179**). Reagents and conditions: a) Et<sub>3</sub>SiH (1.5 equiv), Rh[PPh<sub>3</sub>]<sub>3</sub>Cl (1 mol%), 80 °C, then HF, MeCN-H<sub>2</sub>O, rt, 90%; b) LDA, (EtO)<sub>2</sub>POCl, LDA, 73%; c) Cp<sub>2</sub>ZrCl<sub>2</sub> (10 mol%), Me<sub>3</sub>Al (3 equiv), H<sub>2</sub>O (1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -23 °C; d) oxirane (3 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -23 °C to rt, 12h, 62% ; e) I<sub>2</sub>, PPh<sub>3</sub>, imidazole, CH<sub>2</sub>Cl<sub>2</sub>, rt, 1h, 92%.

The second key intermediate 2,3-Dihydro-[2,3']-bifuranyl (**185**) was prepared using 3-furaldehyde (**186**) by nucleophilic addition of lithium morpholide to give an adduct that was further lithiated at the 5-position with *s*-BuLi (**Scheme 11**). Addition of triethylsilyl chloride followed by aqueous workup yielded 5-triethylsilyl-3-furaldehyde (**187**) in 73% yield [127]. The kinetic resolution of *rac*-160 under Sharpless asymmetric epoxidation conditions [128] was used to get (*R*)-alcohol in 41% yield after column chromatography. Asymmetric addition of 5 different allenyl metallic reagents to

aldehyde (**187**) were evaluated (**Table 2**) to get enantioselectivities. Among these, addition of an allenyl stannane to aldehyde (**187**) under the aegis of an (*R*)-BINOL-modified Lewis acid (entry 4) [129-130] gave excellent enantiomeric ratio (96:4) (**188**) and high yield (87%) vitiated by the long reaction times (ca 10 days) at the low temperature. Further, transmetalation of stannane (**185**) with *s*-BuLi at -60 °C in a mixture of Et<sub>2</sub>O and pentane as a solvent resulted in the corresponding lithium reagent (**191**).

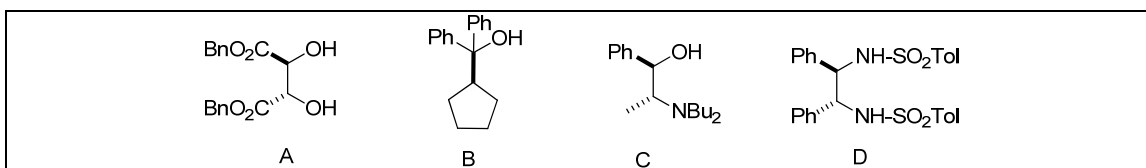


**Scheme 11:** Synthesis of lithium reagent (**191**). Reagents and conditions: a) 3 steps, Lee *et al.*, 1992 [127], 73%; (b) HC=CH-CH<sub>2</sub>MgBr, Et<sub>2</sub>O, -40 °C to rt, 90%; (c) *t*-BuOOH, (+)DIPT, Ti(*i*PrO)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -20°C, 24 h, 41%; (d) Et<sub>3</sub>N.Mo(CO)<sub>5</sub>, Bu<sub>3</sub>SnOTf, Et<sub>2</sub>O, NEt<sub>3</sub>, rt, 2d, 65%; (e) *s*-BuLi, Et<sub>2</sub>O-pentane, -60°C, 20 min.

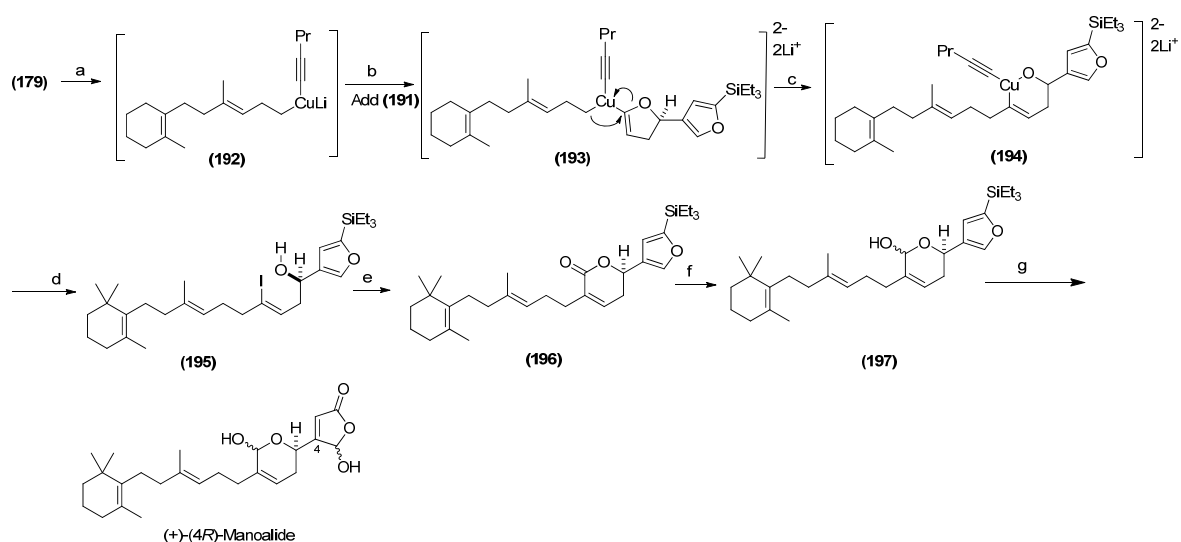
**Table 2:** Evaluation of asymmetric addition of allenylmetallic reagents to aldehyde

entry	Reagents and conditions	Yield (%)	er <sup>b</sup> (R:S)
1	[a]: H <sub>2</sub> C=C=CH-B(OH) <sub>2</sub> (2.5 equiv), A (1.9 equiv), 5 Å MS, CH <sub>2</sub> Cl <sub>2</sub> , -78 °C, 3 d	71	80:20
2	[b]: H <sub>2</sub> C=C=CH-I/HC≡C-CH <sub>2</sub> I (2:1, 2.2 equiv), ZnEt <sub>2</sub> (2.2 equiv), B (20 mol %), PhMe, 0 °C, 4 h	80	30:70
3	[c]: H <sub>2</sub> C=C=CH-I/HC≡C-CH <sub>2</sub> I (2:1, 2.2 equiv), ZnEt <sub>2</sub> (2.2 equiv), C (20 mol %), PhMe, 0 °C, 4 h	84	55:45
4	[d]: H <sub>2</sub> C=C=CHSnBu <sub>3</sub> (2.0 equiv), ( <i>R</i> )-BINOL (25 mol %), Ti( <i>i</i> -PrO) <sub>4</sub> (25 mol %), 4 Å MS, PrS-BE <sub>2</sub> (2.0 equiv), CH <sub>2</sub> Cl <sub>2</sub> , -20 °C, 10 d	87 <sup>a</sup>	96:4
5	[e]: D (1.1 equiv), BBr <sub>3</sub> (1.1 equiv), CH <sub>2</sub> Cl <sub>2</sub> , rt, 40 min; add HC≡C-CH <sub>2</sub> SnPh <sub>3</sub> , 0 °C, 40 min; add aldehyde, -78 °C, 4 h	49	91:9

<sup>a</sup>yield based on 40% recovered starting material. <sup>b</sup>the ratio and configuration was determined by <sup>1</sup>HNMR of the (*S*)-*o*-acetyl mandelate esters.



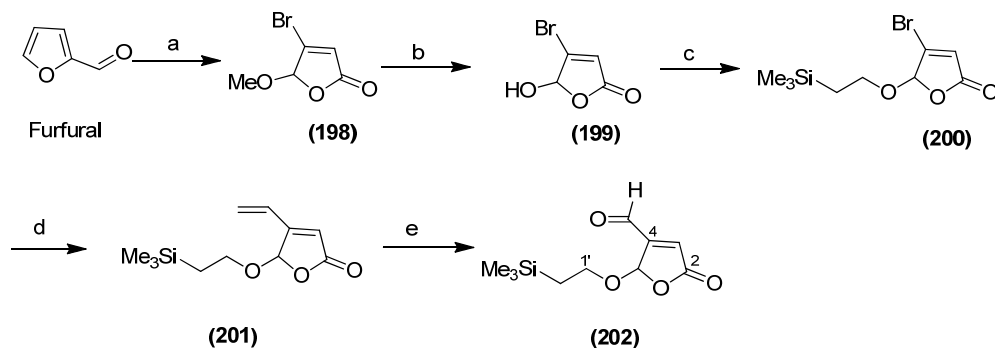
A Cu(I)-mediated 1,2-metalate rearrangement of iodoalkane (**179**) was done by halogen-metal exchange using *t*-BuLi followed by reaction with 1-pentynylcopper to afford mixed cuprate (**192**) (**Scheme 12**). This cuprate was added to a solution of the lithiated dihydrofuran (**191**) at  $-78\text{ }^{\circ}\text{C}$  to give higher order cuprate (**193**) which undergoes 1,2-metalate rearrangements on gradual warming to room temperature to form oxycuprate (**194**). After quenching (**194**) with iodine gave trisubstituted iodoalkene (**195**). This was subjected to a Pd(0)-catalysed carbonylation which yielded lactone (**196**) followed by reduction with DIBAL-H. Photooxidation of the silylfuran (**197**) generated the hydroxyfuranone of manoalide in 60% yield.



**Scheme 12:** Completion of total synthesis of (+)-(4*R*)-manoalide. Reagents and conditions: a) *t*-BuLi, Et<sub>2</sub>O-pentane,  $-78\text{ }^{\circ}\text{C}$ , 30 min;  $0\text{ }^{\circ}\text{C}$ , 1h; PrC≡CCu- $78\text{ }^{\circ}\text{C}$  to rt; b)  $-78\text{ }^{\circ}\text{C}$ ; c)  $-78\text{ }^{\circ}\text{C}$  to rt over 12h, 1,2-metallate rearrangement; d) I<sub>2</sub>,  $-78\text{ }^{\circ}\text{C}$ , 5 min; e) CO, [PPh<sub>3</sub>]<sub>4</sub>Pd (3 mol%), DIPEA-MeOH-THF,  $65\text{ }^{\circ}\text{C}$ , 24h, 91%; f) DIBAL-H, CH<sub>2</sub>Cl<sub>2</sub>-PhMe,  $-78\text{ }^{\circ}\text{C}$ , 5 min, 89%; g) O<sub>2</sub>, hv, Rose Bengal, MeOH,  $-78\text{ }^{\circ}\text{C}$ , 15 min, 60%.

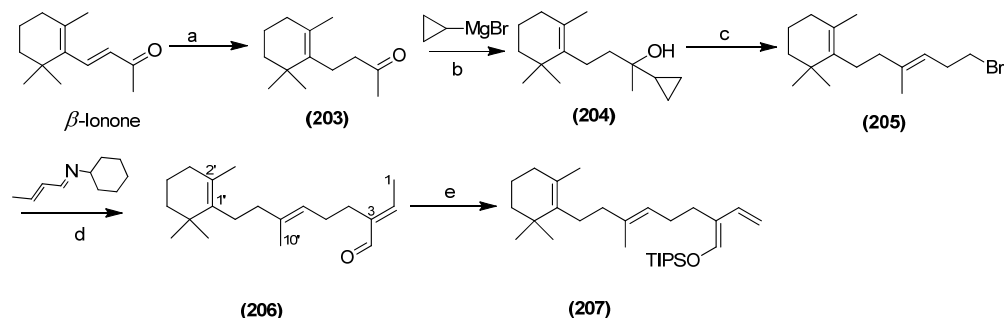
New approach was reported by Coombs *et al.* [131] using a 3-formylated butenolide which was submitted to Lewis acid mediated hetero Diels-Alder (HAD) reaction. The synthesis started with furfural to furnish 4-bromo-5-methoxyfuran-2(5*H*)-one (**198**) in 2 steps (**Scheme 13**) [132]. Further, transacetalization of (**198**) *via* hemiacetal (**199**) was subjected to azeotropic distillation with 2-

trimethylsilylethanol which gave protected  $\gamma$ -hydroxybutenolide (**200**). This was followed by cross coupling with vinyl stannane to yield vinylated butenolide (**201**). On careful ozonolysis and anhydrous workup resulted in 4-formyl-5[2-(trimethylsilyl)eth-1-oxy]furan-2(5H)-one (**202**), a key intermediate.



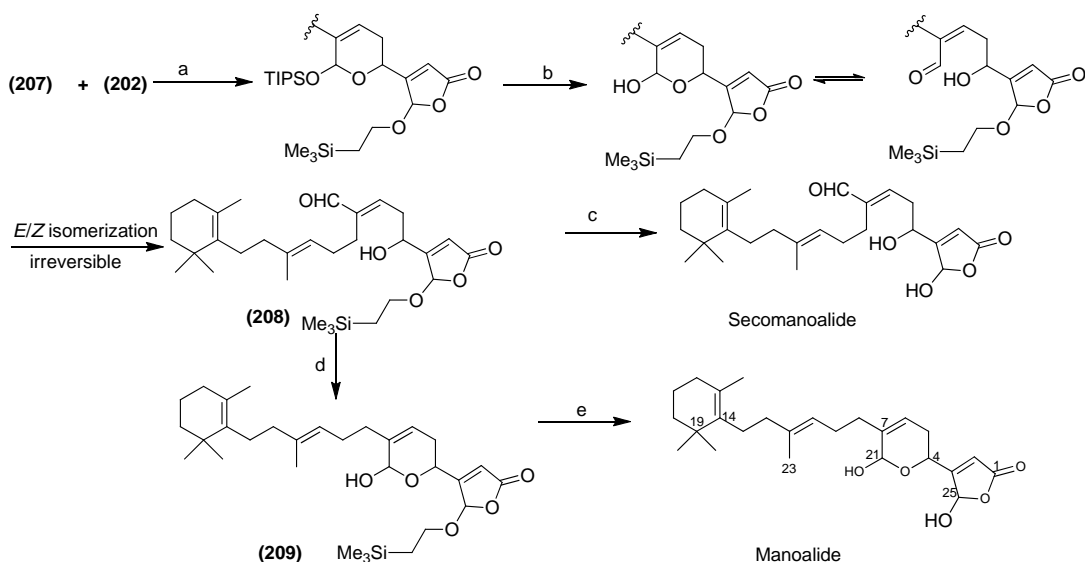
**Scheme 13:** Synthesis of intermediate 4-formyl-5[2-(trimethylsilyl)eth-1-oxy]furan-2(5H)-one (**202**). Reagents and conditions: a) 2 steps, Ref. [132], 67%; b) H<sub>2</sub>SO<sub>4</sub> (30%), dioxane,  $\Delta$ , 1.5h, 93% ; c) (3 eq), Me<sub>3</sub>Si-CH<sub>2</sub>-CH<sub>2</sub>-OH, *p*-TsOH (cat), benzene, azeotropic distillation, 4d, 60%, 90% borsm; d) H<sub>2</sub>C=CH-SnBu<sub>3</sub>, (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub>, MeCN/THF, 50 °C, 3d, 81%; e) 1. O<sub>3</sub>, -78 °C, DCM/MeOH(10:1), 2. thiourea, 0 °C, 78%.

The second intermediate silyloxydiene was prepared using  $\beta$ -ionone in 5 steps. Site-specific hydrogenation under phase-transfer condition yielded ketone (**203**) which was converted to cyclopropylcarbinyl alcohol (**204**) [134]. Further, it was subjected to Julia-Johnson reaction using LiBr, ZnBr salt at low temperature. Under optimized conditions, the homoallylic bromide proceeded (*E*) selectively, and in 2 steps yielded (**205**). Further, treatment of (**206**) with cyclohexyl amine in presence of LDA and DMPU resulted in aldehyde (**206**). This was followed by reaction with TIPSOTf and Et<sub>3</sub>N resulting in diene (**207**).



**Scheme 14:** Synthesis of Silyloxydiene (**207**). Reagents and conditions: a) Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>, NaHCO<sub>3</sub>, Bu<sub>4</sub>NHSO<sub>4</sub>, CH<sub>3</sub>(CH<sub>2</sub>)<sub>15</sub>N(CH<sub>3</sub>)<sub>3</sub>Cl, toluene/H<sub>2</sub>O (1:2),  $\Delta$ , 3h, 61%, [133]; b) THF, 0 °C to reflux, 95%; c) LiBr (1.2 eq), ZnBr<sub>2</sub> (1.2 eq), PBr<sub>3</sub> (1.0 eq), THF, -60 °C, 6h, 83%; d) 1. LDA, DMPU, THF, -78 °C, 2. Hydrolysis, 53%, [116]; e) TIPSOTf, NEt<sub>3</sub>, benzene, 0 °C, 30 min, 100%.

Silyloxydiene (**207**) and aldehyde (**202**) were combined to afford  $\text{AlCl}_3/\text{Me}_3\text{Al}$  mediated hetero-Diels-Alder (HAD) cycloadduct which was desilylated *in situ* (silica gel,  $\text{H}_2\text{O}$ ) at carbon C-24 giving monoprotected secomanoalide (**208**). Further, deprotection with TFA yielded seco-manoalide. Alternatively, cyclization of (**208**) gave monoprotected manoalide (**209**) and further deprotection yielded manoalide.



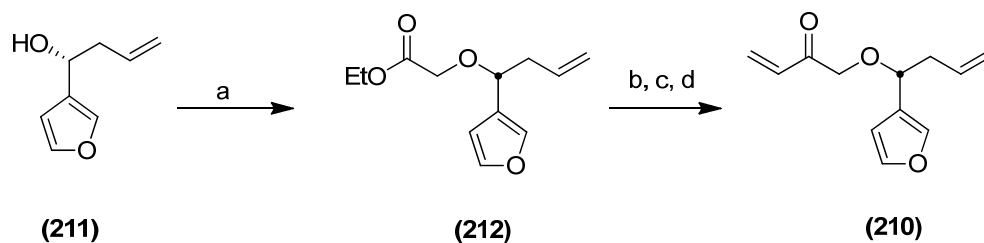
**Scheme 15:** Completion of total synthesis of manoalide. Reagents and conditions: a)  $\text{AlCl}_3/\text{Me}_3\text{Al}$  (2M in THF), benzene, r.t., 2h; b) deprotection *in situ*; c) TFA (90%), DCM, 0 °C, 1h; d) hv, benzene, 0 °C, 2h; e) TFA (90%), DCM, 0 °C, 1h.

So overall, in the synthesis of manoalide and secomanolide, the construction of  $\gamma$ -HB moiety was carried out using furan compounds. Shigeo Katsumura *et al.* used 3-hydroxymethylfuran converted into  $\alpha$ -hydroxystannane and then coupling with allyl chloride using lithium anion to get manoalide. Later, Shigeo Katsumura *et al.* used 2-silyl-4-stannylfuran from commercially available 2,3-dibromofuran and coupled with allyl chloride using Pd(0) catalyst with CO. Michael *et al.* used  $\beta$ -ionone and 2-silyl-4-stannylfuran. While, Pommier *et al.* used lithiated dihydrofuran prepared from 5-triethylsilyl-3-furaldehyde and coupled with homocuprate. Later, they used 3-furaldehyde and  $\beta$ -ionone as starting materials. Also, Coombs *et al.* carried out synthesis using furfural and  $\beta$ -ionone to get manoalide compound.

### 3.2. Cacospongionolides B & E

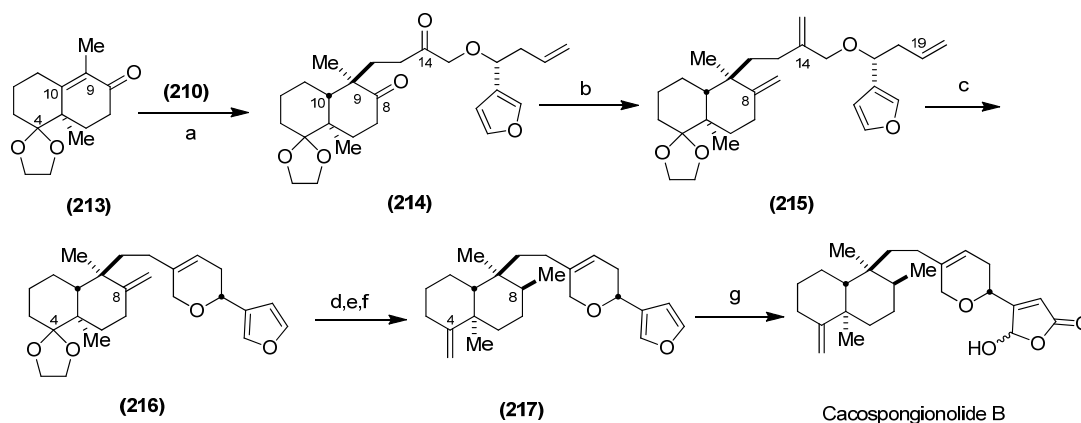
The total synthesis of cacospongionolides B and E by Cheung & Snapper (2002) involved ring closing metathesis for construction of a dihydropyran moiety. The synthesis [134] initiated with the preparation of ketone (**210**) in 4 steps from the homoallylic alcohol (**211**) (Scheme 16). Brown's asymmetric allyl boration yielded alcohol (**211**) in 73% and 94% ee [135]. Further, etherification

with ethyl bromoacetate provided ester **(212)**. This was followed by saponification and conversion to the Weinreb amide in 2 steps [136]. Treatment of Weinreb amide with vinyl Grignard resulted in vinyl ketone **(210)** in an enantiomerically enriched fashion.



**Scheme 16:** Preparation of ketone **(210)**. Reagents and conditions: a) NaH, THF, 0 °C to rt; BrCH<sub>2</sub>CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, 0 °C (84% at 76% conv.); b) LiOH, MeOH/H<sub>2</sub>O (3:1), rt; c) MeO(Me)NH.HCl, DIC, DMAP, TEA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C-rt (86%. 2 steps); d) H<sub>2</sub>C=CHMgBr, THF, -78 to 0 °C, (83%).

Li/NH<sub>3</sub> reduction of the enone **(213)** followed by trapping of the resultant enolate with vinyl ketone **(210)** in Et<sub>2</sub>O provided compound **(214)** with the desired relative decalin stereochemistry (**Scheme 17**). Further, treatment with Ph<sub>3</sub>P=CH<sub>2</sub> yielded triene **(215)** followed by Grubbs metathesis catalyst [137] generated dihydropyran **(216)** selectively in 91% yield. Selective reduction of the decalin C8 *exo*-olefin was obtained with a chiral rhodium catalyst to get desired isomer. Further, conversion of the protected C4 ketone into an *exo*-olefin is carried out by removal of acetal under acid condition followed by a Wittig olefination yielded furan **(217)**. Finally, photooxidation of the furan moiety under basic condition resulted in cacospongionolide B.

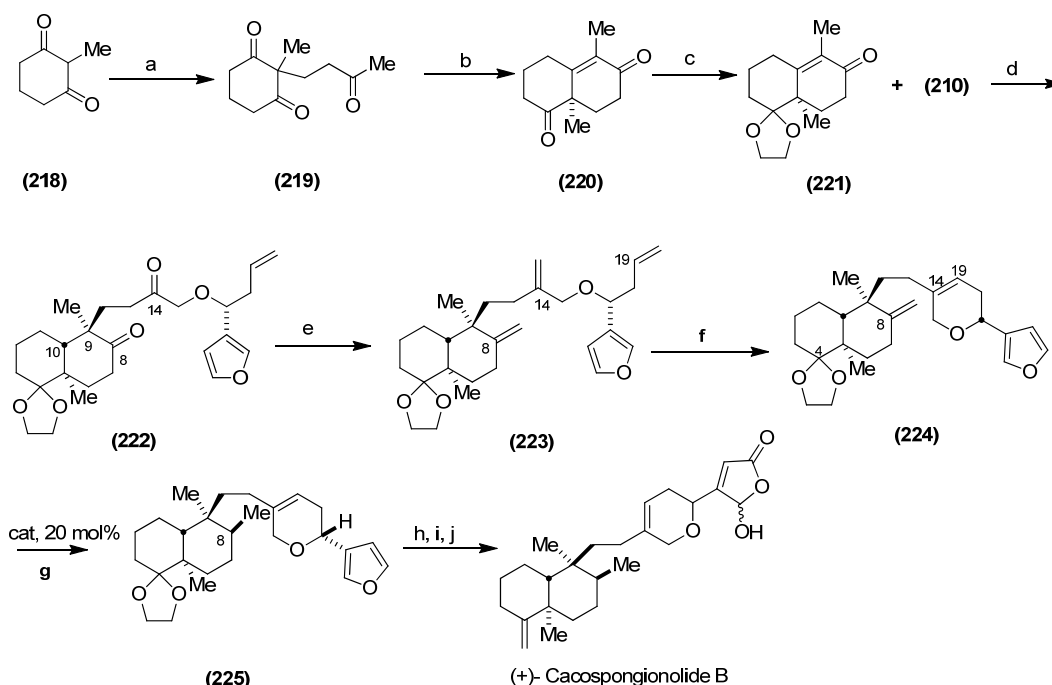


**Scheme 17:** Completion of total synthesis of cacospongionolide B. Reagents and conditions: a) Li/NH<sub>3</sub>, *t*-BuOH, Et<sub>2</sub>O, -33 °C, Et<sub>2</sub>O, -78 °C; b) Ph<sub>3</sub>P=CH<sub>2</sub>, DMSO, 75 °C; c) Cy<sub>3</sub>P(*i*Mes)(Cl)<sub>2</sub>Ru=CHPh, CH<sub>2</sub>Cl<sub>2</sub>, rt; d) [(COD)RhCl]<sub>2</sub>, (*R*)-BINAP, H<sub>2</sub> (3 atm), CH<sub>2</sub>Cl<sub>2</sub>, 30



°C, 3.3:1 dr; e) 1N HCl/THF (1:2), rt (90%); f)  $\text{Ph}_3\text{P}=\text{CH}_2$ , DMSO, 75 °C (84%); g)  $\text{O}_2$ , Rose Bengal, *i*- $\text{Pr}_2\text{NEt}$ , 150 W tungsten filament lamp,  $\text{CH}_2\text{Cl}_2$ , -78 °C.

Atwood *et al.* [138] reported the total synthesis of (+)-cacospongionolide B with preparation of vinyl ketone (**210**) as described in Cheung & Snapper, 2002 [134]. The second Decalin portion was prepared by using commercially available, 2-methyl-1,3-cyclohexadienone (**218**) which was treated with ethyl vinyl ketone (**210**) in the presence of KOH in methanol at 65 °C to provide compound (**219**) (**Scheme 18**). Addition of D-Phenylalanine and camphor sulfonic acid (CSA) in DMF generated enone (**220**) in 79% yield and 93% ee. Further, enone (**221**) was generated in ethylene glycol as solvent, *p*TsOH and 4° A molecular sieves at room temperature. Lithium ammonia reduction of enone (**221**) in the presence of *t*-BuOH generates the *trans*-decalin lithium enolate that was trapped by vinyl ketone (**210**) which provided the alkylation product (**222**) as a single diastereomer. The high stereoselectivity of this reaction arises through the kinetic facial selectivity of the Michael addition. To get the core structure of the natural product, the bis-olefination of diketone (**222**) was carried out in the presence of the  $\text{Ph}_3\text{P}=\text{CH}_2$  in DMSO to afford triene (**223**). Further, exposure of triene (**223**) to 8 mol% of Grubb's Ru metathesis catalyst in  $\text{CH}_2\text{Cl}_2$  provided the dihydropyran (**224**). The selective reduction of the exocyclic olefin on the Decalin (C8) was obtained with the chiral rhodium catalyst developed by Takaya *et al.* [139]. As depicted in **Table 3**, the *R*-BINAP/Rh(I) catalyst (20 mol%) in  $\text{CH}_2\text{Cl}_2$  at 30 °C under  $\text{H}_2$  (3 atm) provided the desired isomer (**225**) in 91% yield. Finally, removal of acetal under acidic conditions and subsequent Wittig olefination followed by photooxidation of furan moiety completed synthesis of (+)-cacospongionolide B (**Scheme 19**).

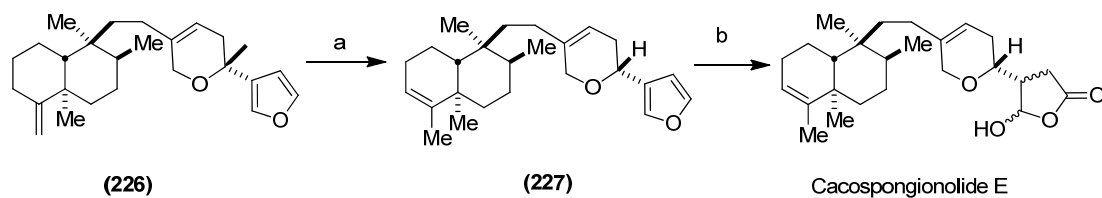


**Scheme 18:** Total synthesis of (+)-cacospongionolide B. Reagents and conditions: a) Ethyl vinyl ketone (**210**), MeOH, KOH, 65 °C; b) D-Phenylalanine, (+)-(CSA), DMF, 30-70 °C; c) Ethylene glycol, *p*-TsOH, 4 Å, MS, rt; d) Li/NH<sub>3</sub>, *t*-BuOH, -33 °C, Et<sub>2</sub>O, then Et<sub>2</sub>O, -78 °C; e) Ph<sub>3</sub>P=CH<sub>2</sub>, DMSO, 75 °C; f) Cy<sub>3</sub>P(*i*Mes)(Cl)<sub>2</sub>Ru=CHPh, CH<sub>2</sub>Cl<sub>2</sub>, rt; g) cat, 20 mol%, H<sub>2</sub> (3 atm), CH<sub>2</sub>Cl<sub>2</sub>, 30 °C; h) 1N HCl/THF (1:2), rt (90%); i) Ph<sub>3</sub>P=CH<sub>2</sub>, DMSO, 75 °C (84%); j) O<sub>2</sub>, Rose Bengal, *i*-Pr<sub>2</sub>NEt, 150 W tungsten lamp, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C (69%).

**Table 3: Percentage yield of isomer (225) using different rhodium catalyst**

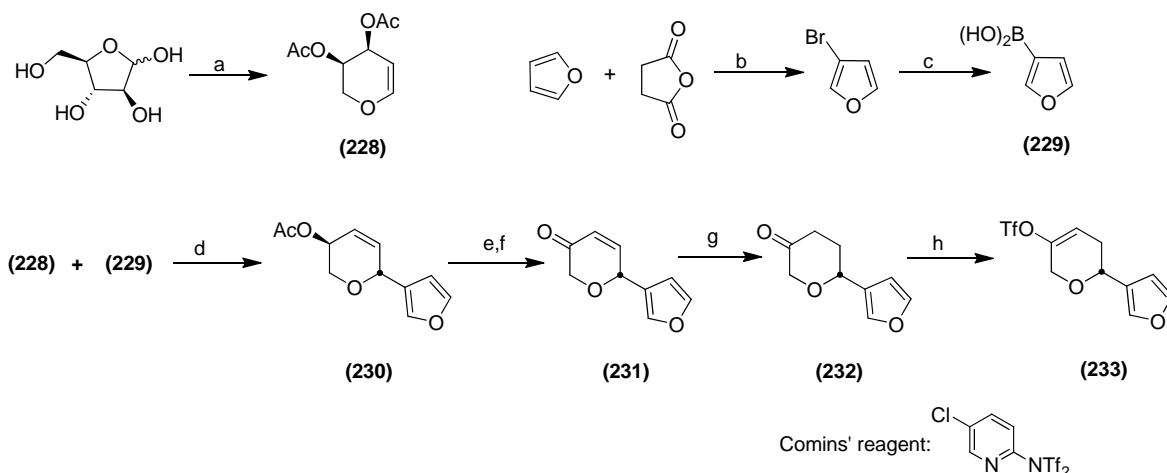
Cat	Yield	dr
Rh(I)/(R)-BINAP	91%	3.3:1
Rh(I)/(S)-BINAP	95% <sup>1</sup>	3.0:1
(Ph <sub>3</sub> P) <sub>3</sub> RhCl <sup>2</sup>	90%	1.7:1
<sup>1</sup> Yield based on 60% conversion		
<sup>2</sup> Conditions: rt, 1 atm H <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub>		

Subsequently, the *exo*-cyclic olefin of furanyl intermediate (**226**) was isomerised to the more stable internal position utilizing RhCl<sub>3</sub>•H<sub>2</sub>O in a mixture of EtOH/CHCl<sub>3</sub>(1:1). The reaction was heated at 70 °C for 6 days provided the desired olefin isomerisation product (**227**) which on photooxidation yielded cacospongionolide E.



**Scheme 19:** Synthesis of cacospongionolide E from intermediate (226). Reagents and conditions: (a)  $\text{RhCl}_3 \cdot \text{H}_2\text{O}$ ,  $\text{EtOH}/\text{CHCl}_3$ ,  $70^\circ\text{C}$  (70%). (b)  $^1\text{O}_2$ , Rose Bengal,  $i\text{-Pr}_2\text{NEt}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$  (54%).

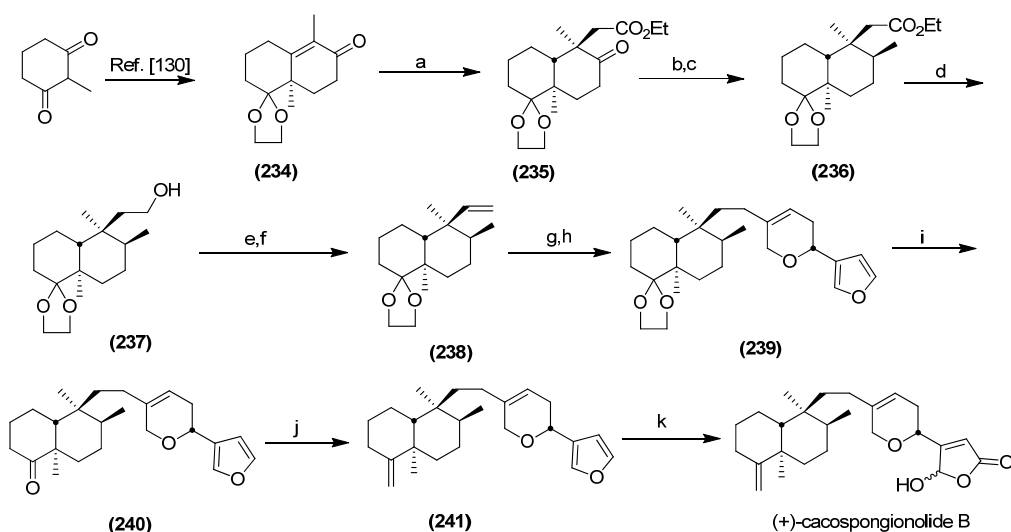
Oshida *et al.* synthesis involved highly stereoselective C-glycosidation of a glycal derived from D-arabinose with furyl boronic acid in the presence of a palladium catalyst and B-alkyl Suzuki-Miyaura coupling of *in situ* generated alkylborane prepared by the reaction of vinyl *trans*-decalin with alkenyl triflate [140]. First, acetal glycal (228) was prepared from D-arabinose using procedure reported by Smiatacz *et al.* [141] Subsequently, 3-furyl boronic acid (229) was synthesized from 3-bromofuran using procedure reported in the literature [142] through bromine-lithium exchange and further addition of triisopropyl borate and acid hydrolysis (Scheme 20). Further, aryl C-glycosidation of (228) with (229) was carried out in acetonitrile in the presence of 10 mol% of  $\text{Pd}(\text{OAc})_2$  at rt under an oxygen atmosphere to afford furyl C-glycoside (230) as a single diastereomer in 2%. Yield was improved by using DMF solvent afforded (230) in 21%. Still, by treating 0.2 M of (228) in NMP provided (230) in 29% yield. Further, hydrolysis and oxidation gave enone (231) in 90% yield. This was followed by hydrogenation under conventional conditions with a slight excess of KHMDS in THF at  $-78^\circ\text{C}$  and treatment with the same amount of Comins' reagent to give furan derivative (233) in 71% yield as a single regioisomer.



**Scheme 20:** Synthesis of 3-substituted furan (233). Reagents and conditions: a) Ref. [141]; b) Ref. [142]; c)  $n\text{-BuLi}$ ;  $(i\text{-PrO})_3\text{B}$ ; aq.  $\text{HCl}$ , 67%; d)  $\text{O}_2$  (1 atm), additive,  $\text{Pd}(\text{OAc})_2$  (10 mol %), solvents,

rt; e) NaOMe, MeOH, rt; (f) IBX, DMSO, rt, 90% (2 steps); (g) H<sub>2</sub> (1 atm), Pd/C, EtOH, rt, 92%; (h) KHMDS, Comins' reagent, THF, -78 °C, 71%.

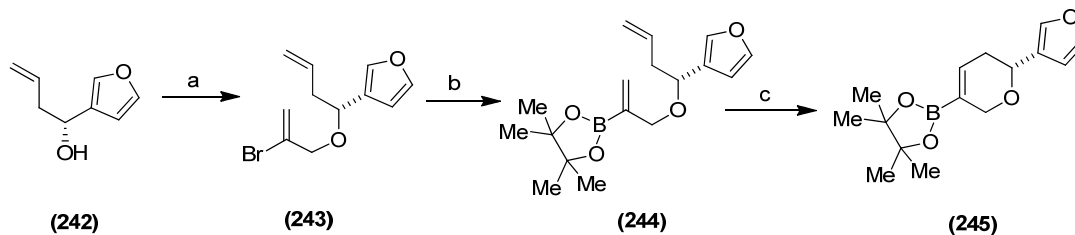
Next, intermediate vinyl *trans*-decalin (**238**) was synthesized from 5-methyl Wieland-Miescher ketone derivative (**234**). For this, enone (**234**) was prepared from 2-methyl cyclohexan-1,3-dione by method used by Hagiwara & Uda, 1988 [143]. Treatment of (**234**) with ethyl bromoacetate, lithium in liquid ammonia and H<sub>2</sub>O afforded *trans*-decalin (**235**) with high stereoselectivity (**Scheme 21**). Using Wittig reaction, carbonyl group of (**235**) was transformed to *exo*-methylene group followed by hydrogenation at 10 atm with Wilkinson's catalyst gave desired (**236**) along with *epi*-(**236**) in 73% and 17% yield respectively. Further LAH reduction gave primary alcohol (**237**) which was converted to vinyl decalin (**238**). Reaction of *trans*-decalin (**238**) and alkenyl triflate (**233**) was carried out using Suzuki-Myaura coupling [144] to afford (**239**) in 83% yield. This was followed by Snapper's protocol to complete the total synthesis. Deprotection and one-carbon homologation of the resulting ketone (**240**) yielded (**241**). Finally, photo-oxidation of the furan moiety resulted in (+)-cacospongionolide B.



**Scheme 21:** Completion of total synthesis of (+)-cacospongionolide B. Reagents and conditions: Ref. [143]; a) Li, NH<sub>3</sub>, H<sub>2</sub>O, ethyl bromoacetate, THF, -78 °C to -30 °C; b) Ph<sub>3</sub>PCH<sub>3</sub>Br, *t*-BuOK, THF, rt, 65%; c) H<sub>2</sub> (10 atm), (Ph<sub>3</sub>P)<sub>3</sub>RhCl, toluene, rt, 13: 73%, *epi*-13: 17%; d) LAH, THF, 0 °C; e) *o*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>SeCN, *n*-Bu<sub>3</sub>P, THF, rt; f) 31% aq. H<sub>2</sub>O<sub>2</sub>, pyridine, THF, rt; g) 9-BBN dimer, THF, rt; h) (**233**), PdCl<sub>2</sub>(dppf).CH<sub>2</sub>Cl<sub>2</sub>, aq. Cs<sub>2</sub>CO<sub>3</sub>, THF-1,4-dioxane, rt; i) 1N HCl, THF, rt; j) Ph<sub>3</sub>PCH<sub>3</sub>Br, NaH, DMSO, 75 °C; k) <sup>1</sup>O<sub>2</sub>, hv, Rose Bengal, *i*-Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C.

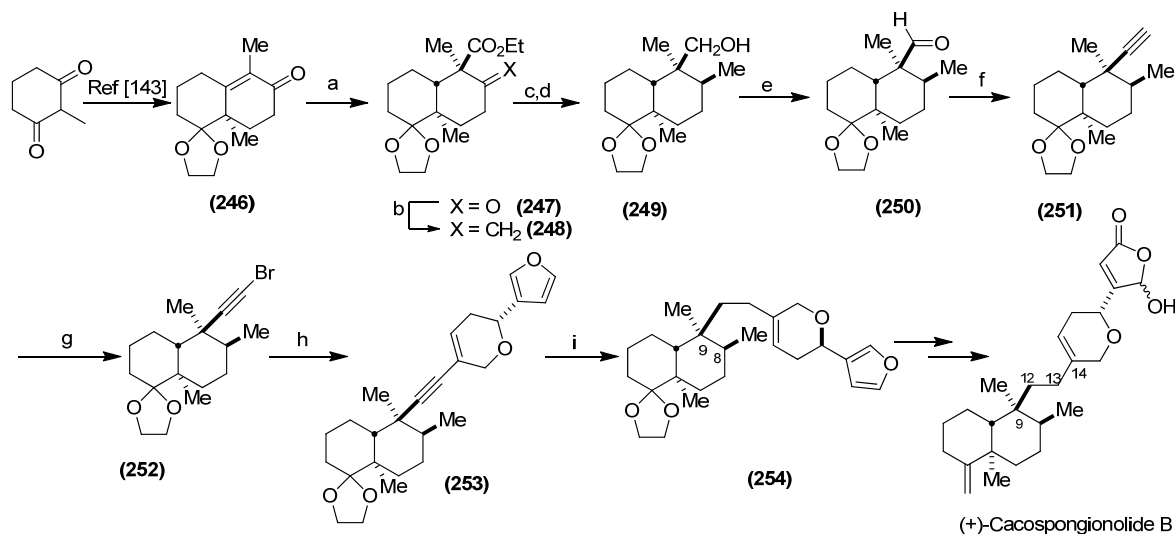
The synthesis reported by Murelli *et al.* (2007) [145] initiated with preparation of homoallylic alcohol (**242**) from commercially available 3-furfuradehyde through Brown's

asymmetric allylboration. Further, O-alkylation of **(242)** with 2,3-dibromopropene afforded allylic ether **(244)**. Lithium-halogen exchange followed by isopropoxy borolane trap provided the pinacolborolane **(245)** through a ring closing metathesis (RCM) by Grubb's second generation catalyst [146].



**Scheme 22:** Synthesis of pinacolborolane **(245)**. Reagents and conditions: (a) NaH, 15-C-5, benzene, 0 °C to rt; 2,3- dibromopropene, 0 °C (75%); (b) *t*-BuLi, Et<sub>2</sub>O, -78 °C; 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, -78 °C to rt; (c) IMes(Cy<sub>3</sub>P) (Cl<sub>2</sub>)RuCHPh, 10 mol %), benzene (45%, 2 steps).

The second part of the started with preparation of enone **(246)** as reported by Hagiwara & Uda, 1988 [143] using commercially available 2-methyl cyclohexan-1,3-dione. Further, enone **(246)** was subjected to a reductive alkylation with Mander's reagent [147] which yielded β-keto ethyl ester **(247)** in 85% yield (14:1 dr) (**Scheme 23**). The Wittig olefination of **(247)** provided the exocyclic C8 alkene **(248)** [148,149]. A stereoselective reduction of **(248)** with platinum oxide followed by LAH reduction afforded diastereomer **(249)** which on further oxidation yielded aldehyde **(250)**. Conversion of aldehyde **(250)** to acetylene **(251)** was carried out using modified Seyferth-Gilbert protocol [150]. And, using an excess of the Ohira-Bestmann reagent [151] and extended reaction times gave acetylene **(251)**. Bromination of acetylene **(251)** using *N*-bromosuccinimide in the presence of catalytic silver nitrate gave **(252)**. Further, Suzuki coupling of **(252)** with borane **(245)** afforded enyne **(253)**. Extended hydrogenation times and increased catalyst loading during the Lindlar reduction of alkyne led to the over-reduced product **(254)**. Finally, this intermediate completed synthesis of (+)-cacosponginiolide B by using end steps reported in their earlier synthesis in Atwood *et al.* 2004 [138].

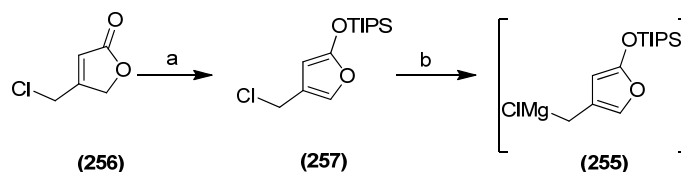


**Scheme 23:** Completion of total synthesis of (+)-cacospongionolide B. Reagents and conditions: Ref. [143]; a)  $\text{Li}^+/\text{NH}_3$ , *t*-BuOH,  $\text{Et}_2\text{O}$ ,  $-33\text{ }^\circ\text{C}$ ; ethyl cyanoformate,  $\text{Et}_2\text{O}$ ,  $-78\text{ }^\circ\text{C}$ , 14:1 dr, 85%; b)  $\text{Ph}_3\text{PCH}_3\text{Br}$ , *t*-BuOK, THF, rt, 83%; c)  $\text{PtO}_2$ , 1 atm of  $\text{H}_2$ ,  $\text{CH}_2\text{Cl}_2$ , rt; d) LAH, THF, rt, 7.7:1 dr, 84%; e) TPAP, NMO,  $\text{CH}_2\text{Cl}_2$ , 4 Å MS, >98%; f)  $\text{CH}_3\text{COCN}_2\text{PO}(\text{OMe})_2$  (Ohira-Bestmann reagent),  $\text{K}_2\text{CO}_3$ , MeOH, rt, (86%, 93% conversion); g) 30 mol%  $\text{AgNO}_3$ , NBS, acetone, rt (>98%); h) Dihydropyranyl borane (**245**), 5 mol % of  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{KOH}(\text{aq})$ , THF, rt (85%); i) Lindlar cat,  $\text{H}_2$ , quinoline, EtOAc, 1 atm of  $\text{H}_2$  (>98%).

In the synthesis of cacospongionolides B by Cheung & Snapper and Atwood *et al.* constructed  $\gamma$ -HB moiety using homoallylic alcohol (furan-3-(3-butene-1-ol)) for the preparation of vinyl ketone. This was treated with decalin portion prepared using commercially available 2-methyl-1,3-cyclohexadienone. While, Oshida *et al.* prepared  $\gamma$ -HB unit using D-arabinose and furan. This was then coupled with decalin unit by Suzuki-Myaura coupling. Murelli *et al.* used commercially available 3-furfuradehyde to prepare pinacolborolane and then coupled with decalin unit to prepare cacospongionolide.

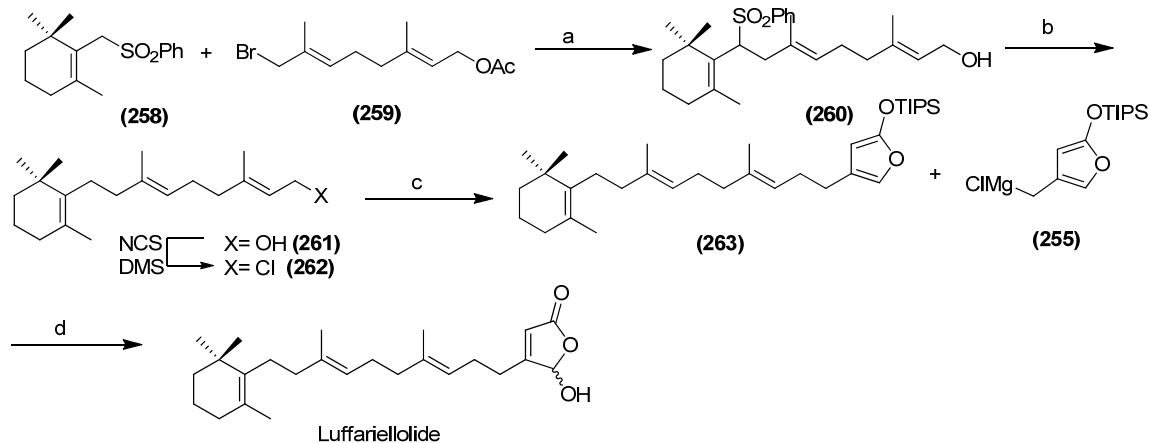
### 3.3. Luffariellolide & Dysidiolide

Boukouvalas *et al.* [152] achieved first synthesis of luffariellolide in highly convergent fashion by the combined use of  $\text{sp}^3$ - $\text{sp}^3$  cross-coupling and silyloxyfuran oxyfunctionalisation. The synthesis initiated by preparation of Grignard reagent (**255**). From the readily available butenolide (**256**), 4-(chloromethyl)-2-(triisopropylsilyloxy)-furan (**257**) was prepared as previously described by Boukouvalas, 1998 [153]. Further, treatment of (**257**) with properly activated magnesium turnings in tetrahydrofuran at  $0^\circ\text{C}$  generated (**255**) by conventional means (**Scheme 24**).



**Scheme 24:** Preparation of Grignard reagent (**255**). Reagents and conditions: a) TIPSOTf, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 87 %; b) Mg<sup>+</sup>, THF, 0 °C

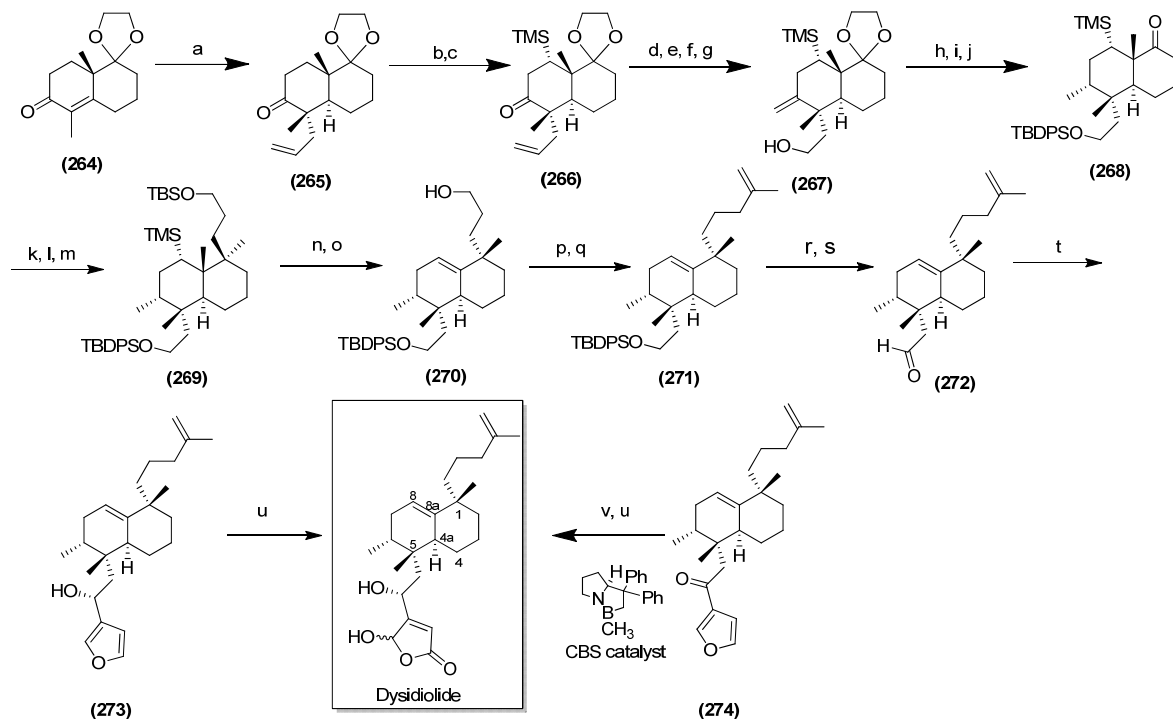
The coupling of sulfone (**258**) [154] with bromide (**259**) [155] followed by treatment of the resulting mixture of alcohol and its acetate with sodium methoxide in methanol yielded (**260**). Further, removal of the phenylsulfonyl group using procedure of Sato [156] gave alcohol (**261**) followed by treatment with NCS and DMS afforded chloride (**262**). Coupling of (**262**) with (**255**) and ensuing oxyfunctionalisation of silyloxyfuran (**263**) delivered luffariellolide (**Scheme 25**).



**Scheme 25:** Completion of total synthesis of luffariellolide. Reagents and conditions: a) *n*-BuLi, HMPA, THF, -78 °C, then MeONa, MeOH, r.t., 81%; b) Li, EtNH<sub>2</sub>, Et<sub>2</sub>O, -78 °C, 76%; c) Li<sub>2</sub>CuCl<sub>4</sub>, THF, 0 °C, d) DMDO, -78 °C, then H<sub>3</sub>O<sup>+</sup>.

Dysidiolide is a rearranged sesterterpene class whose [4.4.0] bicyclic nucleus and appendant side chains define a type of structure not previously encountered in a natural product. The synthesis by Corey & Roberts [157] is a controlled, biomimetic carbocation rearrangement which created the unusual quaternary center at C-1 and the endocyclic double bond within the highly substituted bicyclic core. It also determined the absolute stereochemistry. The synthesis started with reduction of enantiomerically pure bicyclic ketal eneone (**264**) [143] with Li and H<sub>2</sub>O in liquid NH<sub>3</sub>-THF, followed by reaction of the excess Li with isoprene and enolate alkylation with excess allyl bromide. This provided allyl ketone (**265**) with 82% yield as a single diastereomer (**Scheme 26**). Further, (**265**) was converted to the corresponding  $\alpha$ ,  $\beta$ -enone (69%) in three steps; (i) deprotonation with

LDA in hexamethylphosphoramide (HMPA)-THF, followed by phenylsulfenation with diphenyl disulfide; (ii) oxidation with excess *m*-CPBA in dichloromethane; and (iii) elimination of the resulting  $\alpha$ -phenylsulfinyl ketone by heating at reflux in benzene in the presence of trimethyl phosphite to form the  $\alpha,\beta$ -unsaturated analogue of (265). Slow addition of (265) to excess TMSLi in HMPA-Et<sub>2</sub>O at -78 °C formed exclusively the axial  $\beta$ -TMS ketone (266).



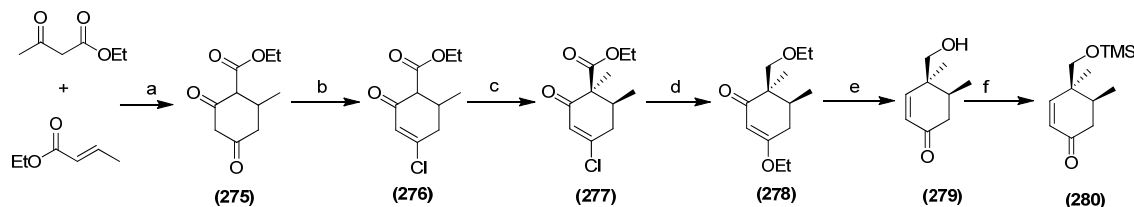
**Scheme 26:** Completion of total synthesis of dysidiolide. Reagents and conditions: (a) Li-NH<sub>3</sub>, THF, -40 °C, 10 min, then isoprene, -78 °C, 15 min; allyl bromide, -78 to -35 °C, then -35 °C for 30 min (82% yield). (b) LDA, PhSSPh, HMPA-THF, 23 °C, 20 min; *m*-CPBA, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 2 h; (MeO)<sub>3</sub>P, C<sub>6</sub>H<sub>6</sub>, 80 °C, 13 h (69% yield and 21% (c) TMSLi, HMPA-Et<sub>2</sub>O, -78 °C, 3 h (64% yield). (d) KH, DMSO, Ph<sub>3</sub>PCH<sub>3</sub>Br, 23 °C, 2 h (97% yield). (e) (DHQD)<sub>2</sub>PYDZ, K<sub>2</sub>OsO<sub>4</sub>·2H<sub>2</sub>O, K<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>Fe(CN)<sub>6</sub>, MeSO<sub>2</sub>NH<sub>2</sub>, 1:1 *t*-BuOH-H<sub>2</sub>O, 0 °C, 4 h (97% yield). (f) NaIO<sub>4</sub>, 4:1 THF-H<sub>2</sub>O, 23 °C, 30 min. (g) NaBH<sub>4</sub>, 6:1 THF-EtOH, 0 °C, 20 min (94% yield for two steps). (h) PPTS, 4:1 acetone-H<sub>2</sub>O, 65 °C; 2 h (100% yield). (i) TBDPSCl, DMAP, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 1.5 h (96% yield). (j) (Ph<sub>3</sub>P)<sub>3</sub>RhCl, H<sub>2</sub> (1000 psi), C<sub>6</sub>H<sub>6</sub>, 65 °C, 23 h (76% yield). (k) allyl MgBr, Et<sub>2</sub>O, -78 to 23 °C, 10 min (99% yield). (l) BH<sub>3</sub>-DMS, Et<sub>2</sub>O, 23 °C, 2.5 h; EtOH, NaOH, H<sub>2</sub>O<sub>2</sub>, 23 °C, 3.5 h (95% yield). (m) TBSCl, DMAP, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 12 h (97% yield). (n) BF<sub>3</sub> (g), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 3 h. (o) PPTS, EtOH, 55 °C, 2.5 h (70% yield for two steps). (p) I<sub>2</sub>, Ph<sub>3</sub>P, imidazole, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 10 min (97% yield). (q) 2-bromopropene, *t*-BuLi, CuI, Et<sub>2</sub>O, -30 to 0 °C, 30 min (97% yield). (r) TBAF, THF, 23 °C, 8.5 h (96% yield). (s) Dess-Martin periodinane, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 1 h (94%



yield); (t) 3-bromofuran, *n*-BuLi, THF, -78 °C, 30 min (98% yield, 1:1 234-*epi*-234). (u) O<sub>2</sub>, hv, Rose Bengal, *i*-Pr<sub>2</sub>EtN, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 2 h (98% yield). (v) CBS catalyst, BH<sub>3</sub>-DMS, toluene, -30 °C, 15 h (91% yield).

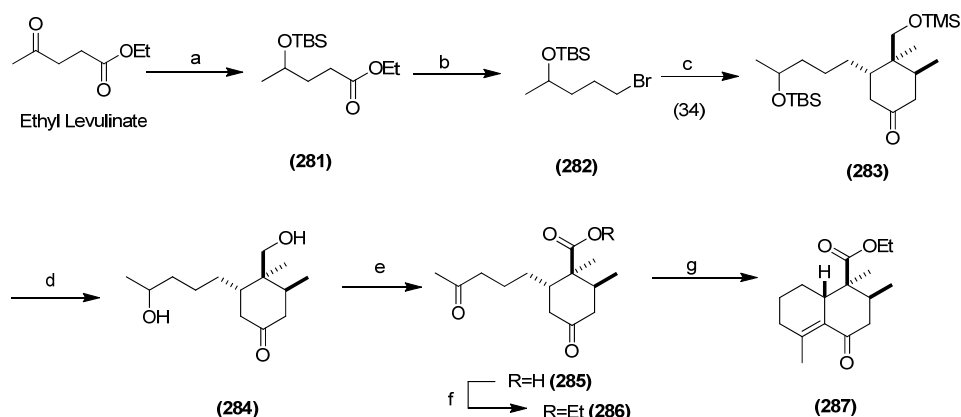
Further, Wittig methylation with methylenetriphenylphosphorane in DMSO was followed by allyl conversion of the appendage to a 2-hydroxyethyl group to produce **(267)** by the following three-steps; (i) position-selective dihydroxylation of the vinyl group by the Sharpless reagent system to form the corresponding 1,2-diol; (ii) glycol cleavage with NaIO<sub>4</sub> in 4:1 THF-H<sub>2</sub>O; and (iii) reduction of the aldehyde with NaBH<sub>4</sub> in 6:1 THF-EtOH to provide alcohol **(267)**. Deketalization of **(267)** using PPTS in 4:1 acetone-H<sub>2</sub>O, protection of the hydroxyl functionality as the *t*-butyldiphenylsilyl (TBDPS) ether, and hydrogenation using Wilkinson's catalyst, followed by silica gel radial chromatography, gave diastereomerically pure **(268)**. Addition of allylmagnesium bromide in Et<sub>2</sub>O afforded stereospecifically the axial tertiary alcohol. Hydroboration of the vinyl group with excess BH<sub>3</sub>, DMS in Et<sub>2</sub>O and subsequent treatment with excess EtOH, NaOH, and H<sub>2</sub>O<sub>2</sub> gave a primary-tertiary diol, which was then selectively protected at the primary hydroxyl by reaction with *t*-butyldimethylsilyl (TBS) chloride to provide **(269)**. Treatment of **(269)** with BF<sub>3</sub>(g) and subsequent selective cleavage of the TBS ether furnished alcohol **(270)** (70% yield over two steps), which contains the fully substituted bicyclic core of dysidiolide. The relative stereochemistry of **(270)** was confirmed by single-crystal X-ray diffraction analysis of its *bis*(3,5-dinitrobenzoate) derivative. In the rearrangement of **(269)** to form **(270)**, the TMS group facilitates the migration of methyl to the cationic carbon generated by C-O heterolysis of **(269)** (by β-hyperconjugation of TMS in TMSC-C<sup>+</sup>). In addition, the very facile elimination of that TMS group guarantees the location of the double bond. The next stage of the synthesis involved the elaboration of the two ring appendages of **(270)** to generate the complete dysidiolide. The C-1 side chain was emplaced via a two-step sequence: (1) iodination of alcohol **(270)** (I<sub>2</sub>, Ph<sub>3</sub>P, imidazole, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 10 min) and (2) iodide displacement with the vinyl cuprate derived from 2-lithiopropene (10 equiv of 2-bromopropene, 21 equiv of *t*-BuLi, 5 equiv of CuI, Et<sub>2</sub>O, -30 to 0 °C, then 0 °C for 30 min) to afford **(271)**. Cleavage of the TBDPS ether in **(271)** with excess tetrabutylammonium fluoride and subsequent oxidation provided aldehyde **(272)**. Treatment of **(272)** with excess 3-lithiofuran afforded a 1:1 mixture of the diastereomeric carbinols **(273)** and *epi*-**(273)**, which were readily separated by silica gel chromatography. Undesired *epi*-**(273)** was efficiently converted to **(273)** by a two-step sequence: (1) oxidation of *epi*-**(273)** to ketone **(274)** and (2) oxazaborolidine-catalyzed (CBS) reduction using CBS catalyst to give **(273)** in 91% yield. The recycling of *epi*-**(273)** allows for an overall 95% yield for the transformation of **(272)** to **(273)**. Photochemical oxidation of **(273)** furnished dysidiolide in 98% yield.

Demeke and Forsyth constructed dysidiolide bicyclic nucleus from an initial cyclohexanone template for the B-ring (C6-C11) that bears the vicinal *trans*-dimethyl substituent at C6 and C7 [158]. This was initiated with condensation of ethyl acetoacetate with ethyl crotonate resulting in compound **(275)** which was dehydrated with  $\text{PCl}_3$  to give **(276)**. Reaction of **(276)** with NaH and  $\text{CH}_3\text{I}$  resulted in **(277)** which upon treatment with sodium ethoxide in ethanol yielded enol ether **(278)**. This was followed by reduction with LAH at ambient temperature and hydrolysis with 2M HCl gave expected enone **(279)** which was silylated to give intermediate **(280)** (Scheme 27).



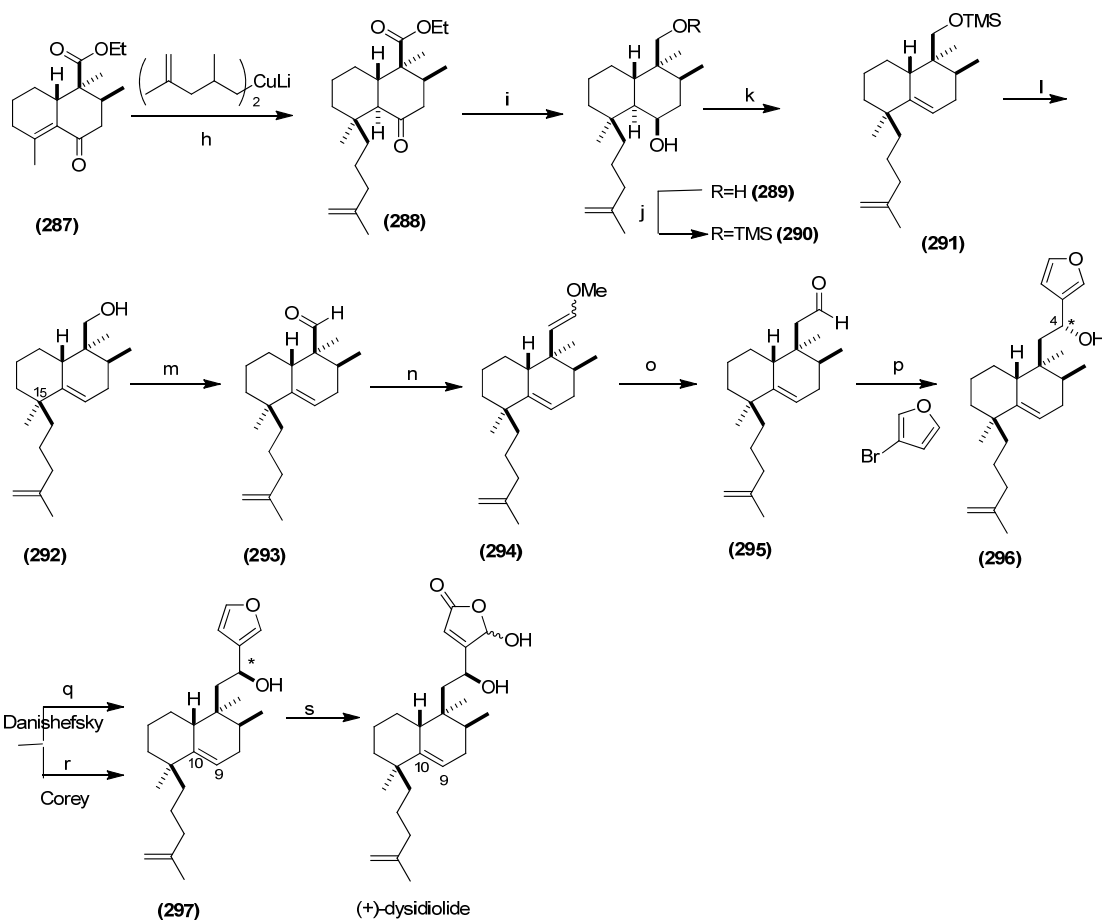
**Scheme 27: Preparation of intermediate (280).** Reagents and conditions: a) NaOEt, EtOH, 70%; b)  $\text{PCl}_3$ ,  $\text{CHCl}_3$ , 82%; c) NaH,  $\text{CH}_3\text{I}$ , THF, HMPA, 85-96%; d) NaOEt, EtOH, quant.; e) 1) LAH,  $\text{Et}_2\text{O}$ , rt, 2) 3M HCl, 82-90%; f) TMSCl, DMAP,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 93%.

The synthesis of the bicyclic enone was carried out with reduction of ethyl levulinate using  $\text{NaBH}_4$  and the resulting alcohol is protected to yield *t*-butyldimethylsilyl ether **(281)** (Scheme 28). Further, reduction of **(281)** using LAH gave primary alcohol which on treatment with LiBr in the presence of  $\text{NaHCO}_3$  yielded bromide **(282)**. Conjugate additions of enone **(280)**, both higher order cyanocuprate and the lower order Gilman reagent and **(282)** were successful to yield silyl ethers of **(283)**. This was cleaved under acidic conditions to get diol **(284)** which was further oxidized to keto-acid using Jones's reagent. Treatment of the keto-acid with ethyl iodide and potassium bicarbonate yielded **(286)**. Cyclization of 1,7-diketone **(286)** under optimized condition for annulations using 2-3 equiv. of potassium *t*-BuOK gave 70-80% conversion to bicyclic enone **(287)**.



**Scheme 28:** Preparation of bicyclic enone (**287**). Reagents and conditions: a. 1) NaBH<sub>4</sub>, THF/H<sub>2</sub>O, 95%; 2) TBSCl, Im. DMF, 83%; b. 1) LAH, Et<sub>2</sub>O, 87%; 2) TsCl, DMAP, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 97%; 3) LiBr, NaHCO<sub>3</sub>, Acetone, 89%; c. 1) *t*-BuLi, CuCN, 2) (**280**), 82%; d. TsOH (Cat.), MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 94%; e. Jones reagent, Acetone, 67%; f. EtI, K<sub>2</sub>CO<sub>3</sub>; g. *t*-BuOK, EtOH, 72%

The cuprate mixture was prepared by lithiation of 5-bromo-2-methyl-1-pentene with *t*-BuLi in diethyl ether followed by the addition of CuI and tri-*n*-butylphosphine in THF which was treated with (**287**) and BF<sub>3</sub>.OEt<sub>2</sub> to yield adduct (**288**). The reduction of (**288**) using LAH yielded diol (**289**) which was further mono-silylated at the primary alcohol to provide (**290**). Dehydration of (**262**) followed by cleavage of the trimethylsilyl ether provided primary alcohol (**292**) bearing core structure of dysidiolide. Further, a Wittig homologation *via* oxidation of the hydroxyl group afforded aldehyde (**293**). Exposure of (**293**) to methoxymethyltriphenylphosphorane yielded isomeric (*E,Z*)-vinyl methyl ethers (**294**). Further, hydrolysis with 2N HCl in dioxane yielded C4 aldehyde (**295**). Addition of furan was accomplished by lithiation of 3-bromofuran and treating further with aldehyde (**295**) at -78 °C provided epimeric alcohols (**297**) and (**296**) (1:1). Compound (**296**) could be epimerized *via* either Mitsunobu inversion [159] or an oxidative diastereoselective reduction [160] process. A final regioselective photooxidation fragmentation of an incorporated furan moiety completed the total synthesis of (±)-dysidiolide.



**Scheme 29:** Completion of total synthesis of (+) dysidiolide. Reagents and conditions: h)  $\text{Bu}_3\text{P}$ ,  $\text{BF}_3 \cdot \text{OEt}_2$ , 86%, THF i. LAH,  $\text{Et}_2\text{O}$ , 91%; j. TMSCl, DMAP,  $\text{Et}_3\text{N}$ , 86%; k.  $\text{POCl}_3$ , Py, 73% or  $\text{SOCl}_2$ , Py, 89%; l. TBAF, THF, 88%; m. PCC,  $\text{CH}_2\text{Cl}_2$ , 91%; n.  $\text{MeOCH}_2\text{PPh}_3\text{Br}$ , KHMDS, THF 71%; o. 2N HCl, dioxane, 91%; p. BuLi, THF, 82 % 26:67 ~1:1; q. Mitsunobu; r. 1) [O], 2) CBS; s.  $\text{O}_2$ , Rose Bengal, *i*-Pr<sub>2</sub> NEt,  $\text{CH}_2\text{Cl}_2$ , 28 W fluorescent lamp, -78 C to rt, 78 %

### Conclusion:

A report on isolation chemistry along with relevant biological activities of  $\gamma$ -hydroxy butenolide containing bioactive marine natural products has been presented in this review. It has been observed that the  $\gamma$ -hydroxy butenolide served as privileged scaffold of many metabolites found preferentially in marine sponges and softcorals. The  $\gamma$ -hydroxy butenolide core embedded in various terpenoids reported in this article has been widely tested dominantly for anticancer activity using different cell lines. The natural source usually produces the chemicals in trace amount which hampered research to achieve complete biological studies. Considering this drawback, we had also endeavored our effort to summaries various synthetic strategies directed towards most potent molecules i.e. manoalide, saco-manoalide, cacospongiolides B & E, luffariolide and dysidiolide. We

believe that, the libraries of  $\gamma$ -hydroxy butenolide reported in this article along with detailed synthetic explanations, will definitely provide a reader with prosperity of additional knowledge and might be of great interest to those working in branches of pharmaceutical, chemical and medical biosciences to develop new therapeutics.

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### List of abbreviations

Acetic acid	=CH <sub>3</sub> COOH
Acetonitrile	=MeCN
Aluminium chloride	= AlCl <sub>3</sub>
Ammonia	=NH <sub>3</sub>
Ammonium chloride	=NH <sub>4</sub> Cl
Barium permanganate	= Ba(MnO <sub>4</sub> ) <sub>2</sub>
Benzene	=C <sub>6</sub> H <sub>6</sub>
( <i>R</i> )-(+)-1,1'-Bi(2-naphthol)	= (R)BINOL
Boron tribromide	= BBr <sub>3</sub>
Boron trifluoride	= BF <sub>3</sub>
Boranedimethylsulfide	=BH <sub>3</sub> – DMS
9-Borabicyclo(3.3.1)nonane	=9 BBN
Boron trifluoride diethyl etherate	=BF <sub>3</sub> .OEt <sub>2</sub>
<i>N</i> -Bromosuccinimide	=NBS
<i>n</i> -Butyllithium	= <i>n</i> BuLi
<i>tert</i> -Butyl hypochlorite	=C <sub>4</sub> H <sub>9</sub> ClO
<i>tert</i> -Butyllithium	= <i>t</i> BuLi
<i>tert</i> - Butyl alcohol	= <i>t</i> BuOH
<i>tert</i> - Butyl hydroperoxide	= <i>t</i> BuOOH
<i>tert</i> -Butyldiphenylsilyl ether	=TBDPS
<i>tert</i> -Butyl(chloro)diphenylsilane	=TBDPSCI
Carbon monoxide	= CO
Camphorsulfonic acid	=CSA
Caesium carbonate	=Cs <sub>2</sub> CO <sub>3</sub>
Chlorotrimethylsilane	=TMSCl
Chlorotris(triphenylphosphine)rhodium(I)	= [PPh <sub>3</sub> ] <sub>3</sub> RhCl
<i>m</i> -Chloroperbenzoic acid	= <i>m</i> -CPBA
<i>N</i> -Chlorosuccinimide	=NCS
Copper	=Cu
Copper iodide	=CuI
Copper dilithium tetrachloride	=Li <sub>2</sub> CuCl <sub>4</sub>
Cyclooctadiene rhodium chloride dimer	= [(COD)RhCl]
Dichloromethane	=CH <sub>2</sub> Cl <sub>2</sub> (DCM)
Diethyl ether	=Et <sub>2</sub> O
Diethylchlorophosphate	= (EtO) <sub>2</sub> POCl
Diethylzinc	=ZnEt <sub>2</sub>
Dibutyl boron trifluoromethanesulfonate	=Bu <sub>2</sub> BOTf

Diisobutylaluminium hydride	=DIBAL-H
Diisopropyl tryptamine	= DIPT
<i>N,N'</i> -Diisopropylcarbodiimide	=DIC
<i>N,N'</i> -Diisopropylethylamine	=DIPEA
4-Dimethylaminopyridine	=DMAP
Dimethyldioxirane	=DMDO
Dimethyl formamide	=DMF
Dimethylsulfide	=DMS
Dimethyl sulfoxide	=DMSO
<i>N,N'</i> -Dimethylpropyleneurea/ 1,3-Dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone	=DMPU
Ethyl amine	=EtNH <sub>2</sub>
Ethyl acetate	=EtOAc
Ethyl iodide	=EtI
Ethanol	=EtOH
Grubb's catalyst	IMes(Cy <sub>3</sub> P)(Cl <sub>2</sub> )RuCHPh
Hydrogen	=H <sub>2</sub>
Hydrochloric acid	=HCl
Hydrofluoric acid	=HF
Hexamethylphosphoramide	=HMPA
Hydrogen peroxide	=H <sub>2</sub> O <sub>2</sub>
(3-Hydroxypropyl)triphenylphosphonium	=Ph <sub>3</sub> P(CH <sub>2</sub> ) <sub>3</sub> OH
Iodine	=I <sub>2</sub>
2-Iodobenzoic acid	=IBX
Lithium diisopropylamide	=LDA
Lithium	=Li
Lithium aluminium hydride	=LAH
Lithium bromide	=LiBr
Lithium chloride	=LiCl
Lithium hydroxide	=LiOH
Methanol	=MeOH
Methanesulfonamide	=MeSO <sub>2</sub> NH <sub>2</sub> Mo(CO) <sub>5</sub>
Molybdenum pentacarbonyl	=MsCl
Mesyl chloride	=NMP
<i>N</i> -Methyl-2-pyrrolidone	=Ph <sub>3</sub> PCH <sub>3</sub> Br
Methyltriphenylphosphonium bromide	
Nickel	=Ni
Oxygen	=O <sub>2</sub>
Ozone	=O <sub>3</sub>
Potassium <i>tert</i> -butoxide	= <i>t</i> BuOK
Potassium carbonate	=K <sub>2</sub> CO <sub>3</sub>
Potassium hydride	=KH
Potassium hexamethyldisilazide	=KHMDS
Potassium hydroxide	=KOH
Potassium osmate	=K <sub>2</sub> OsO <sub>4</sub>
Phosphorus tribromide	=PBr <sub>3</sub>
Phosphorus trichloride	=PCl <sub>3</sub>
Palladium	=Pd <sup>0</sup>
Palladium on Carbon	=Pd/C

Palladium(II) chloride	=PdCl <sub>2</sub>
Palladium(II) acetate	=Pd(OAc) <sub>2</sub>
Platinum dioxide	=PtO <sub>2</sub>
Pyridine	=Py
Pyridinium- <i>p</i> -toluenesulfonate	=PPTS
Silver nitrate	=AgNO <sub>3</sub>
Sodium borohydride	=NaBH <sub>4</sub>
Sodium hydride	=NaH
Sodium bicarbonate	=NaHCO <sub>3</sub>
Sodium methanolate methanol	=MeONa
Sodium periodate	=NaIO <sub>4</sub>
Sodium hydrosulfite	=Na <sub>2</sub> S <sub>2</sub> O <sub>4</sub>
Sulphuric acid	=H <sub>2</sub> SO <sub>4</sub>
Tetrabutylammoniumhydrogensulfate	=Bu <sub>4</sub> NHSO <sub>4</sub>
Tetra- <i>n</i> -butylammonium fluoride	=TBAF
Tetramethylsilane	=TMS
Tetrapropylammonium perruthenate- <i>N</i> -methyl morpholine	=TPAP-NMO
Tetrakis(triphenylphosphine)palladium(0)	=[PPh <sub>3</sub> ] <sub>4</sub> Pd
Tributylstannyl lithium	=Bu <sub>3</sub> SnLi
Tributyltin chloride	= <i>n</i> -Bu <sub>3</sub> SnCl
Tributyltin-trifluoroacetic acid	=Bu <sub>3</sub> SnTf
Tri- <i>n</i> -butylphosphine	= <i>n</i> -Bu <sub>3</sub> P
Triethylamine	=Et <sub>3</sub> N
Triethylsilane	=Et <sub>3</sub> SiH
Trimethylphosphite	=(MeO) <sub>3</sub> P
Trimethylsulfonium	=Me <sub>3</sub> S <sup>+</sup>
Triphenyltin hydride	=Ph <sub>3</sub> SnH
Triphenylphosphine	=PPh <sub>3</sub>
Triethylamine	=TEA
Trifluoroacetic acid	=TFA
Tetrahydrofuran	=THF
Titanium isopropoxide	=Ti(O- <i>i</i> Pr) <sub>4</sub>
Triethyl amine-Molybdenum pentacarbonyl	(CO) <sub>5</sub> Mo.Net <sub>3</sub>
Triisopropyl borate	=( <i>i</i> -PrO) <sub>3</sub> B
Triisopropylsilyl trifluoromethanesulfonate	=TIPSOTf
Trimethylsilyllithium	=TMSLi
Trimethylaluminium	=Me <sub>3</sub> Al
Toluene	=PhMe
<i>p</i> -Toluenesulfonic acid	=TsOH
Tosyl chloride	=TsCl
Tris Buffered Saline	=TBS
Rhodium	=Rh
Rhodium trichloride	=RhCl <sub>3</sub>
Ruthenium olefin metathesis catalyst	=Cy <sub>3</sub> P(IMes)(Cl <sub>2</sub> )Ru (=CHPh)
Water	=H <sub>2</sub> O
Zirconocene dichloride	=Cp <sub>2</sub> ZrCl <sub>2</sub>
Zinc bromide	=ZnBr

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