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# Terpenoids from marine organisms: unique structures and their pharmacological potential

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**Abstract**

Marine organisms produce a wide array of fascinating terpenoid structures distinguished by characteristic structural features. Certain structural classes, e.g. cembrane, chamigrene, amphilectane skeletons, and unusual functional groups such as isonitrile, isothiocyanate, isocyanate, dichloroimine and halogenated functionalities occur predominantly in marine metabolites. Especially striking is the frequent occurrence of sesterterpenes in marine organisms, and sponges must be considered as one of the prime sources of these $C_{25}$ terpenoid compounds. In most cases however, these structural features are not strictly unique for marine natural products. The prominent biological activity of marine terpenes is evident in their ecological role in the marine environment, and makes them interesting as potential drugs. Several terpenoid compounds, e.g. eleutherobin, sarcodictyin, contignasterol derivatives, are in preclinical or clinical development. Despite the many structures known and their ecological and pharmacological importance, only a few biosynthetic studies on marine terpenoid compounds have been performed.

## Introduction

Terpenes comprise primary and secondary metabolites, all derived from the five carbon isoprene entity (Ruzicka, 1953). Combination and modifications of these isoprene units leads to a multitude of diverse structures with different chemical and biological properties. Terpenoids from higher plants are well studied and ethnopharmacologically applied since centuries. However, it was not until the early to mid 20th century that their marine counterparts were explored. Steroidal terpenoids were the first marine isoprenes to be discovered. Bergmann studied during the 1930s and the following decade sterols from various marine macroorganisms (Bergmann and Johnson, 1933). Later on, one of his students, Leon Ciereszko, was attracted by the odors of gorgonians and catalyzed with his findings research in the field of marine terpenoid chemistry (Ciereszko et al., 1960). To date a large number of marine terpenoid structures are known (Blunt et al., 2005). Terpenes from taxa occurring predominantly or exclusively in the oceans, such as certain algae and invertebrates are, due to their uniqueness, the most interesting structures.

Since the 1970s terpenoids of marine origin have been described in several general reviews devoted to marine natural products (Scheuer, 1973, 1983, 1989; Blunt et al., 2005). Marine terpenoids are also listed in the *Dictionary of Terpenoids* and can be found in annual reviews on the isolation of new $C_{10}$ (Grayson, 2000), $C_{15}$ (Fraga, 2005), $C_{20}$ (Hanson, 2005) and $C_{30}$ (Connolly and Hill, 2005) isoprenoids and sterols. Additionally, there exists a wealth of literature

dealing predominantly with marine isoprenoids covering aspects of marine monoterpenoids (Naylor et al., 1983), marine diterpenoids (Fenical, 1978), algal sesquiterpenoids (Martin and Darias, 1978), marine sesterterpenes (Crews and Naylor, 1985) marine triterpenoid oligoglycosides (Minale et al., 1996) and marine sterols (Djerassi, 1981; Kerr and Baker, 1991; Sica and Musumeci, 2004). Other authors highlighted the presence and significance of terpenoids occurring in marine invertebrates (Faulkner, 1977; Pennock, 1977; Minale, 1978; Tursch et al., 1978; Andersen et al., 1990) or marine plants (De Rosa, 1991; Kladi et al., 2004). A number of reviews dealing with the synthesis of marine terpenoids have been reported (White and Wardrop, 1998; Miyaoka and Yamada, 2002), as well as theoretical considerations concerning the biosynthesis of marine isoprenoids (Zheng et al., 1994; Kashman and Rudi, 2004). However, despite the many structures known and their ecological and pharmacological importance, only few experimental biosynthetic studies on marine terpenoid compounds were performed.

Due to the extensive literature coverage and the vast number of marine terpenoid structures it would be pointless to write an encyclopedic review of marine isoprenes. Instead, the material in this review will first focus briefly on the ecological relevance and pharmacological potential of marine terpenoids, and subsequently intriguing structural features and biosynthetic implications will be pointed out exemplarily. The selected examples represent, in the authors' opinion, interesting milestones in terpenoid chemistry which are combined with results from the marine drug discovery program of the authors' laboratories.

## Ecological significance of marine terpenoid compounds

Marine chemical ecology, dealing with chemically mediated interactions of marine organisms, has been extensively reviewed (Bakus at al., 1986; Hay and Fenical, 1988; Paul, 1992; Pawlik, 1992, 1993; Hay, 1996; Proksch, 1994, 1999; McClintock and Baker, 1997, 2001; Paul and Puglisi, 2004). Secondary metabolites, including terpenes, play an important role in the everlasting competition for space and reproduction, maintenance of an unfouled surface and the deterrence of predation (Coll, 1992; Fusetani, 2004). Diterpenoid cembranes like e.g. flexibilide (Figure 1, **1**) and dihydroflexibilide (**2**) are found in the sea water surrounding the soft coral *Sinularia flexibilis*. These compounds serve as a chemical defense for the animal (Coll et al., 1985). They are toxic to fish, cause tissue necrosis on nearby scleractinian corals, e.g. *Acropora tenuis*, and destroy fertilised eggs of hard corals (Aceret et al., 1995). On the other hand, terpenes derived from other organisms in the neighborhood of soft corals might harm the latter, as in the case of the red alga *Plocamium hamatum* and the soft coral *Sinularia cruciata*. In the field, tissue necrosis on the affected side of the coral was evident and could be traced back and subsequently shown to be caused by chloromertensene (**3**), a highly chlorinated monoterpene of the alga (De Nys et al., 1991; Leone et al., 1995). An interesting example for a sponge–coral interaction is the terpenoid siphonodictidine (**4**), biosynthesized by marine sponges of the genus *Siphonodictyon*. This sessile animal burrows deep into living coral heads and exudes mucus that contains siphonodictidine (**4**). This sesquiterpene is toxic to the coral polyps and serves the sponge to prevent overgrowth by the coral (Sullivan et al., 1983). Consequently, a 1–3 cm bare zone of dead coral skeleton can be observed around the base of each sponge. It has been hypothesized that the secretion of toxin-containing mucus serves the sponge to concentrate the metabolites and furthermore to prevent dilution of the bioactive compound by the surrounding sea water (Jackson and Buss, 1975). Allelopathic effects are not limited to the inter-phyletic level, they occur also within the same class of organisms. At coral reefs of Guam Island, the marine sponge *Cacospongia* sp. is frequently overgrown by a sponge of the genus *Dysidea*. Thacker et al. (1998) demonstrated that the major sesquiterpene 7-deacetoxy-olepupuane (**5**), isolated from the marine sponge *Dysidea* by Garson et al. (1992), is involved in this spatial competition. Additionally, it was shown that the sesquiterpene deterred predation by the spongivorous fish *Pomacanthus imperator*. This example illustrates that terpenoids may have multiple ecological functions. This is also supported by studies with triterpene glycosides from marine sponges, which were found to deter predation, microbial attachment, and fouling by invertebrates and algae (Kubanek et al., 2002).

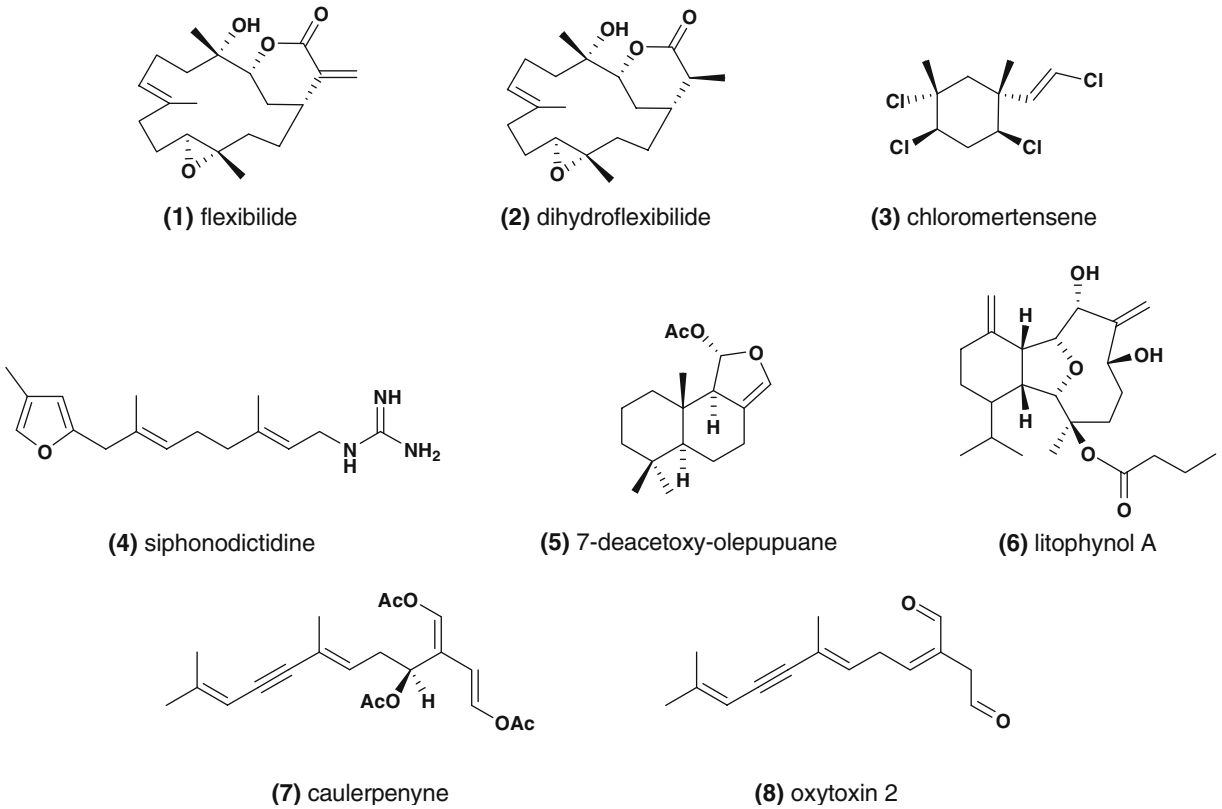



*Figure 1.* Marine terpenes of ecological importance.

In several cases, however chemical defense using terpenoids fails to prevent feeding by specific predators. Marine opisthobranch molluscs are specialized herbivorous (feeding on algae) or carnivorous (feeding on sponges, tunicates, soft corals or other molluscs) predators, and appear to be immune to terpenoid toxins which they are able to incorporate and accumulate from their dietary source. As part of their defensive strategy the toxic metabolites are stored in the body to serve as repellents (Wägele and Klussmann-Kolb, 2005). The chemistry and ecology of sea slugs has been thoroughly reviewed (Avila, 1995) and therefore will be only briefly exemplified in the following chapters of this review.

A mixture of terpenes seems to be the basis for the symbiotic relationship between the soft coral *Litophyton viridis*, known to release a potent ichthyotoxin, and the juvenile damselfish, *Abudefduf leucogaster*, resistant towards the ichtyotoxic terpenes. In case of a threat, the fish rapidly hides within the branches of the coral, and in this way is protected from larger predators. Preliminary data indicated that the ichthyotoxicity may derive from a mixture of terpenes (Tursch, 1982). Indeed, several years later, eunicellin based diterpenes, like e.g. litophynol A (**6**) were isolated from a Japanese *Litophyton* species which showed ichthyotoxic and hemolytic activities (Miyamoto et al., 1994).

An impressive, albeit environmentally disastrous demonstration of the influence of terpenoids on the ecosystem represents the case of the green seaweed *Caulerpa taxifolia*. This green alga is indigenous throughout tropical and subtropical waters (Phillips and Price, 2002). However, due to the beauty and robustness towards cold temperatures of a certain strain of this alga, it is widely used for aquarium decoration. Many aquariums aquired this particular strain, among them the Oceanographic Museum of Monaco, from which it accidentally escaped in the mid 80s into the Mediterranean Sea (Wiedenmann et al., 2001). Since then, the seaweed spread rapidly and invaded large areas of the coastline of several Mediterranean

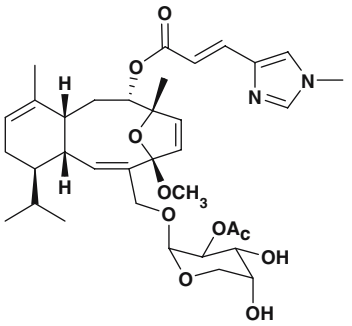
countries (Croatia, France, Italy, Monaco, Spain and Tunisia). *C. taxifolia* is outcompeting and replacing endemic seagrasses and subsequently reduced seriously the biodiversity in those areas (Bellan-Santini et al., 1996). The population of sea-urchins, fishes, amphipods and polychaetes are much affected. The massive spreading is due to the alga's enormous growth rate, and especially to its efficient strategy against predators and fouling organisms by producing toxic terpenoids. *C. taxifolia* contains several terpenoid compounds (Blunt and Munro, 2005), the major metabolite being caulerpenyne (**7**) (Amico et al., 1978; Guerriero et al., 1992). The array of mono- and sesquiterpenes exhibits ichthyotoxic, antibiotic (Paul and Fenical, 1986, 1987), neurotoxic (Brunelli et al., 2000; Mozzachiodi et al., 2001) and cytotoxic (Parent-Massin et al., 1996; Barbier et al., 2001) properties.

Due to the presence of these repellent toxins only a few autochthonous predators feed on the *Caulerpa* genus, that is mainly the two sea slugs *Oxynoe olivacea* and *Lobiger serradifalci* (Thibaut and Meinesz, 2000). Unfortunately, during grazing the slug fragments the alga into small pieces which can subsequently regenerate into new plants. This phenomenon is based on the fact that the alga is a unicellular organism and survival upon injury is assured by a very efficient repair mechanism, in which a terpenoid is involved. After tissue disruption, an esterase converts the major metabolite caulerpenyne (**7**) into oxytoxin 2 (**8**), a compound, originally isolated from molluscs (Cimino et al., 1990; Cutignano et al., 2004). The resulting dialdehyde (**8**) acts as a crosslinking agent through reaction with nucleophilic functional groups of proteins. In this way a gelatinous external wound plug is formed within seconds after injury and protects further cell leakage. The sealed cell fragments contain the full genetic information and are able to establish new colonies (Adolph et al., 2005). Therefore, the native predators appear to be inefficient and might even accelerate the spreading of the alga. With no biocontrol on hand, *C. taxifolia* continues to threat the sensitive balanced aquatic ecosystem of the Mediterranean Sea. Regrettably, this threat is not any more limited to the southern European region. Presumably associated with the worldwide shipping traffic (transit of algae in ballast tanks; attachment to hulls and anchors) and continued use of *C. taxifolia* in aquariums (Frisch and Murray, 2002), the so-called "killer algae" has recently invaded the coasts of southern California (Jousson et al., 2000; Meinesz et al., 2001).

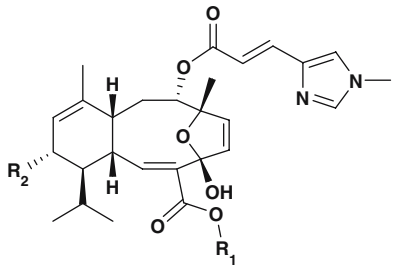
### *Terpenoid drugs leads*

Secondary metabolites produced by marine organisms in order to ensure their survival, may be envisaged as 'optimized' by evolutionary mechanisms, e.g. mutation and natural selection, to specifically influence certain biological target structures, i.e. DNA, enzymes, receptors, membranes. Since some molecular targets are highly conserved (Harris-Warrick, 2000) defensive toxins may also bind to therapeutically relevant target sites. In this way the biological activity of marine terpenes, as illustrated by their ecological role, may also be exploited in terms of pharmacology. Several biologically active terpenoids turned out to possess biomedical potential and are thus already in preclinical or clinical development (Newman and Cragg, 2004).

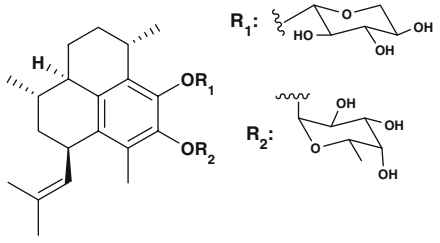
Eleutherobin (Figure 2, **9**) is a microtubuline stabilizing compound in preclinical trials, which competes for the paclitaxel binding site on the microtubule polymer (Long et al., 1998). Aside from paclitaxel, its mode of action is shared with the natural products epothilone A and B and discodermolide. Ojima et al. (1999) proved that these four natural products share a similar 3D structure, and suggested a common pharmacophore, necessary for binding to the paclitaxel site. Eleutherobin (**9**) originates from a soft coral of the genus *Eleutherobia* collected from Australian waters (Lindel et al., 1997) and has been re-isolated along with congeners from another octocoral from the Caribbean (Cinel et al., 2000), which can be kept by aquaculture (Taglialatela-Scafati et al., 2002). The terpene nucleus of eleutherobin is bound to a sugar moiety and linked *via* an ester bond to a partial structure most probably derived from histidine. Total synthesis was achieved in 1997 (Nicolaou et al., 1997) and 1998 (Chen et al., 1999) but a paucity of material currently hinders the development of the compound. The sarcodictyins (**10**) possess a very similar structure and were already described in the 1980s by Pietra et al. (D'Ambrosio et al., 1987, 1988), without recognising the activity of these compounds. They were derived from the Mediterranean stolonifer



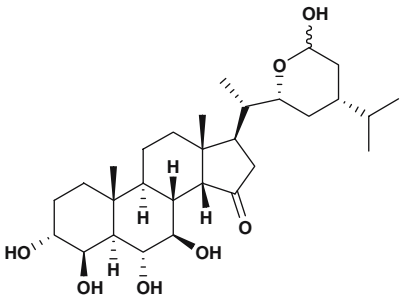
**(9)** eleutherobin



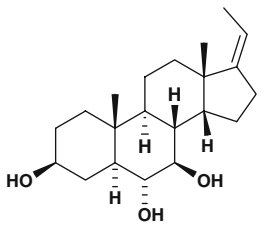
**(10)** sarcodictyin A ($R_1$=Me, $R_2$=H)
sarcodictyin B ($R_1$=Et, $R_2$=H)
sarcodictyin C ($R_1$=Me, $R_2$=OH)
eleuthoside A ($R_1$=2",3"-diacetylarabinose, $R_2$=H)
eleuthoside B ($R_1$=2",4"-diacetylarabinose, $R_2$=H)



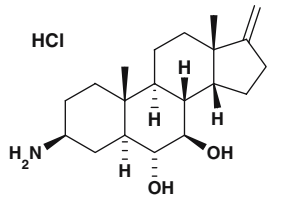
**(11)** pseudopterosin A ($R_1$=xylose, $R_2$=H)
pseudopterosin E ($R_1$=H, $R_2$=fucose)
methopterosin ($R_1$=xylose, $R_2$=Me)



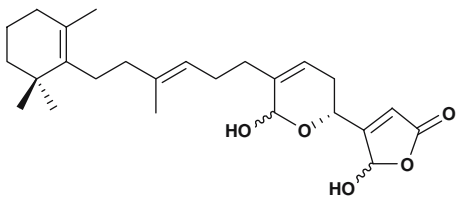
**(12)** contignasterol (IZP-94,005)



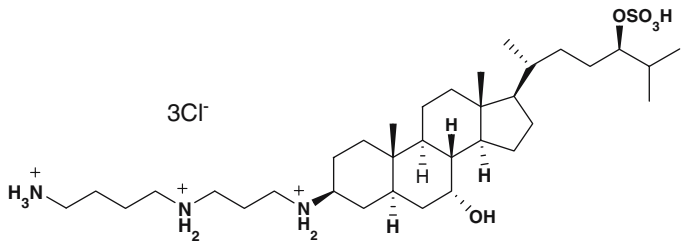
**(13)** IPL 576,092



**(14)** IPL 512,602



**(15)** manoalide



**(16)** squalamine

*Figure 2.* Terpenoid drug leads.

*Sarcodictyon roseum* whereas the glycosylated derivatives eleuthoside A and B (**10**) originate from the South African soft coral *Eleutherobia aurea* (Ketzinel et al., 1996). Recently, the double bond isomer (*Z*)-sarcodictyin A, isolated from the soft coral *Bellonella albiflora* was added to the

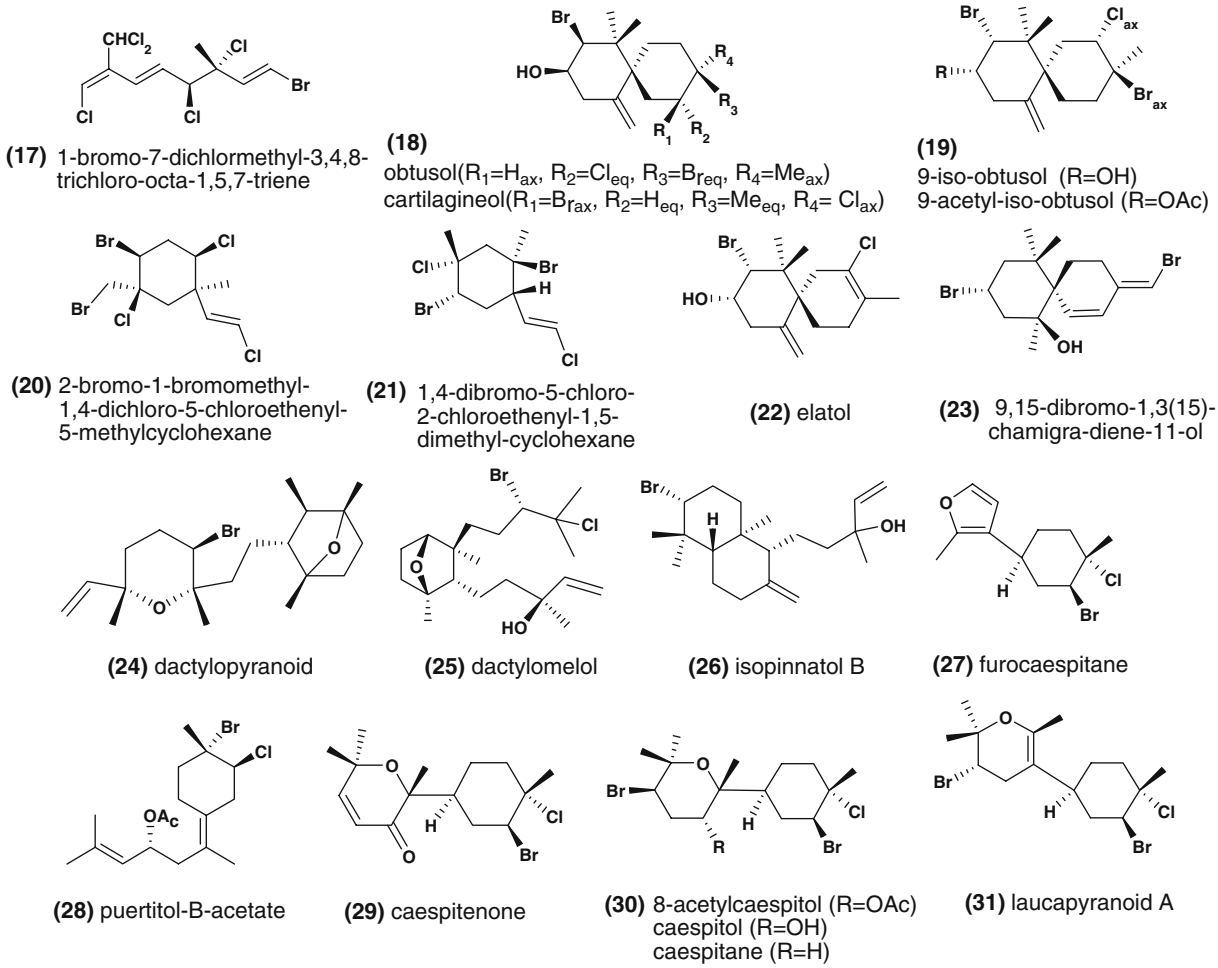



*Figure 3.* Highly halogenated terpenes from marine algae and their predators.

sarcodictyin series (Nakao et al., 2003). In 1997 the tubulin stabilizing activity of sarcodictyin was discovered (Ciomei et al., 1997). Consequently, this compound is now in preclinical development (Newman and Cragg, 2004).

The anti-inflammatory pseudopterosins A-L (**11**) are diterpene glycosides with an amphilectane skeleton and were originally isolated from the gorgonian coral *Pseudopterogorgia elisabethae* by the Fenical group in the late 1980s (Look et al., 1986a; Roussis et al., 1990; Lazerwith et al., 2000). Further research on *Pseudopterogorgia* species resulted in several new pseudopterosin derivatives (M-Z) and *seco*-pseudopterosins (Ata et al., 2003; Rodríguez et al., 2004). Recently it was demonstrated that the symbiotic dinoflagellate *Symbiodinium* sp. in *P. elisabethae* is the true source of the pseudopterosins (Mydlarz et al., 2003). The anti-inflammatory potential of pseudopterosins is superior to that of standard drugs such as indomethacin (Look et al., 1986b). At present, the exact molecular mechanism of action is not yet known, however an interference at several stages of the arachidonic acid cascade as well as an inhibition of the release of eicosanoids has been discussed (Look et al., 1986b; Potts et al., 1992a; Haimes et al., 1995; Mayer et al., 1998; Scherl et al., 1999). A partially purified extract of *P. elisabethae*, containing pseudopterosin E is currently already used as an additive in a cosmetic preparation, a face cream sold by Estée Lauder under the brand name Resilience. The commercial development of pseudopterosins resulted in enormous biomass collections along the coastline of the Bahamas (Faulkner, 2000). Since the demand for

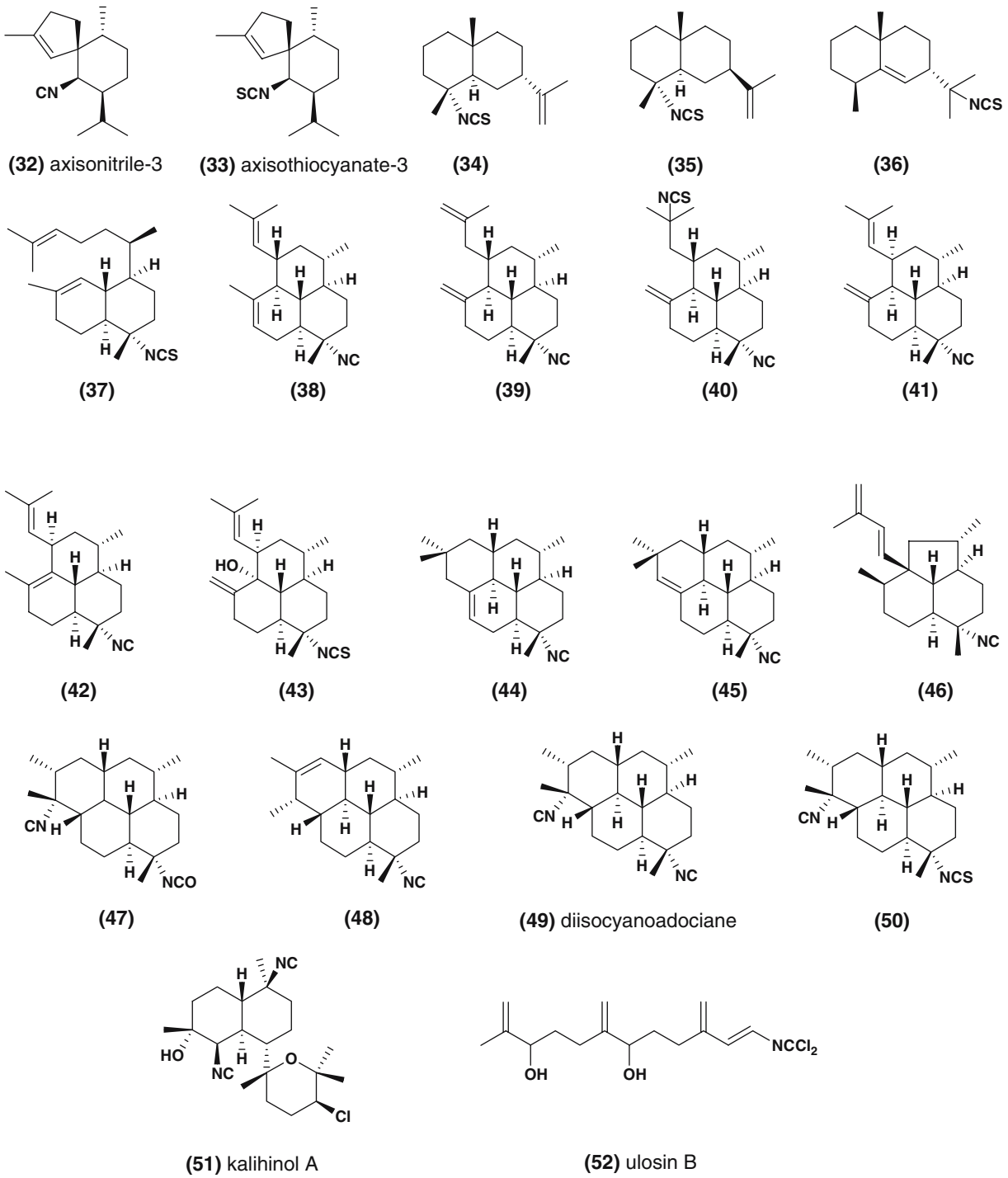



*Figure 4*. Terpenes with isonitrile and related functionalities.

pseudopterosins increased, alternative and more ecologically compatible solutions are needed. Consequently, total syntheses were developed (Lazerwith et al., 2000; Chow et al., 2001; Kocienski et al., 2001). With the aim to overcome the supply difficulties of the pseudoperosins, the Kerr group investigated the

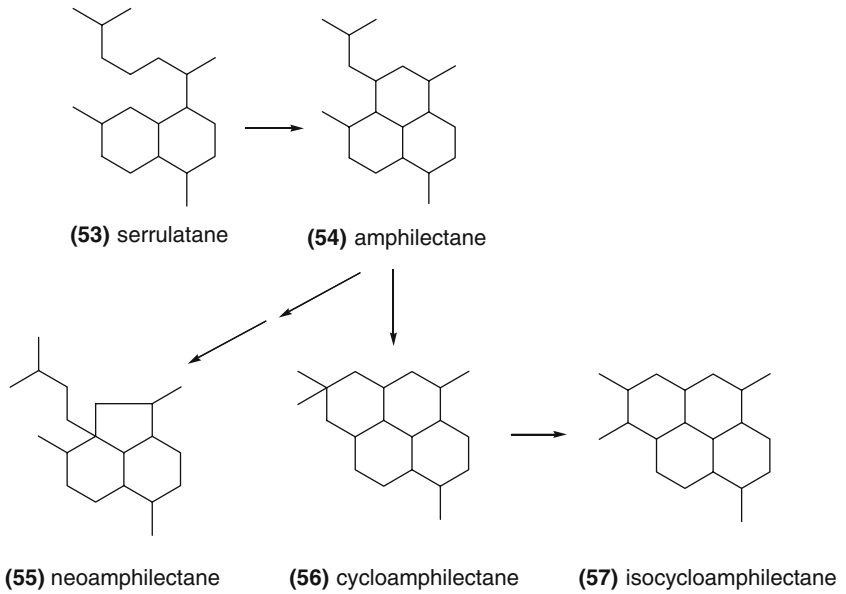



*Figure 5*. Proposed biogenetic relationship between *Cymbastela* metabolites.

biosynthesis of these compounds in order to develop a biotechnological production method. A crude enzyme preparation of *P. elisabethae* transformed the terpene precursor geranylgeranyl pyrophosphate (GGPP) to the pseudopterosin aglycone. Finally the appropriate sugar moiety was attached to this skeleton to form the known natural product (Kohl et al., 2003). Aside from Estée Lauder, the pseudopterosins were also licensed to OsteoArthritis Sciences Inc., who evaluated the semisyn-

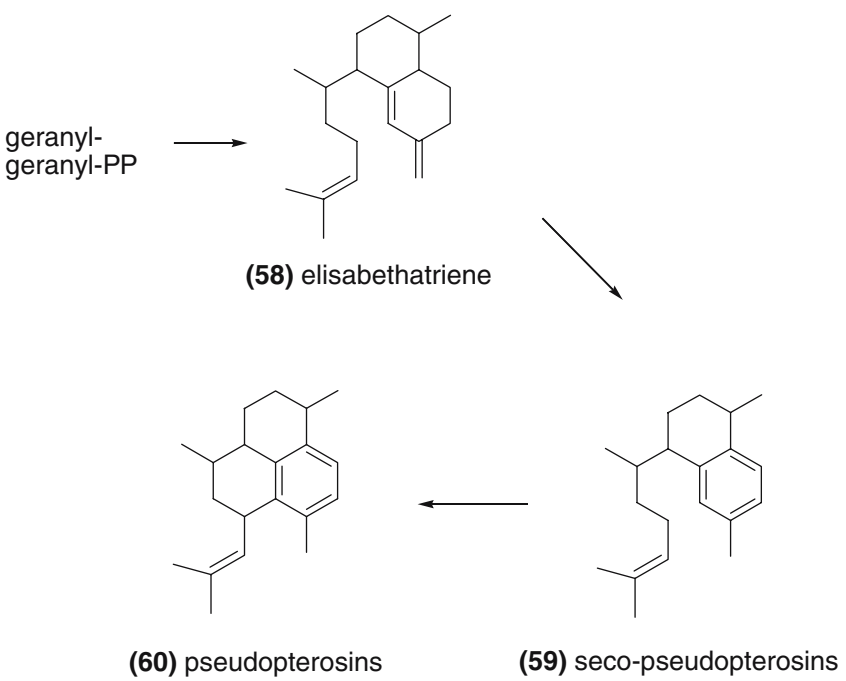
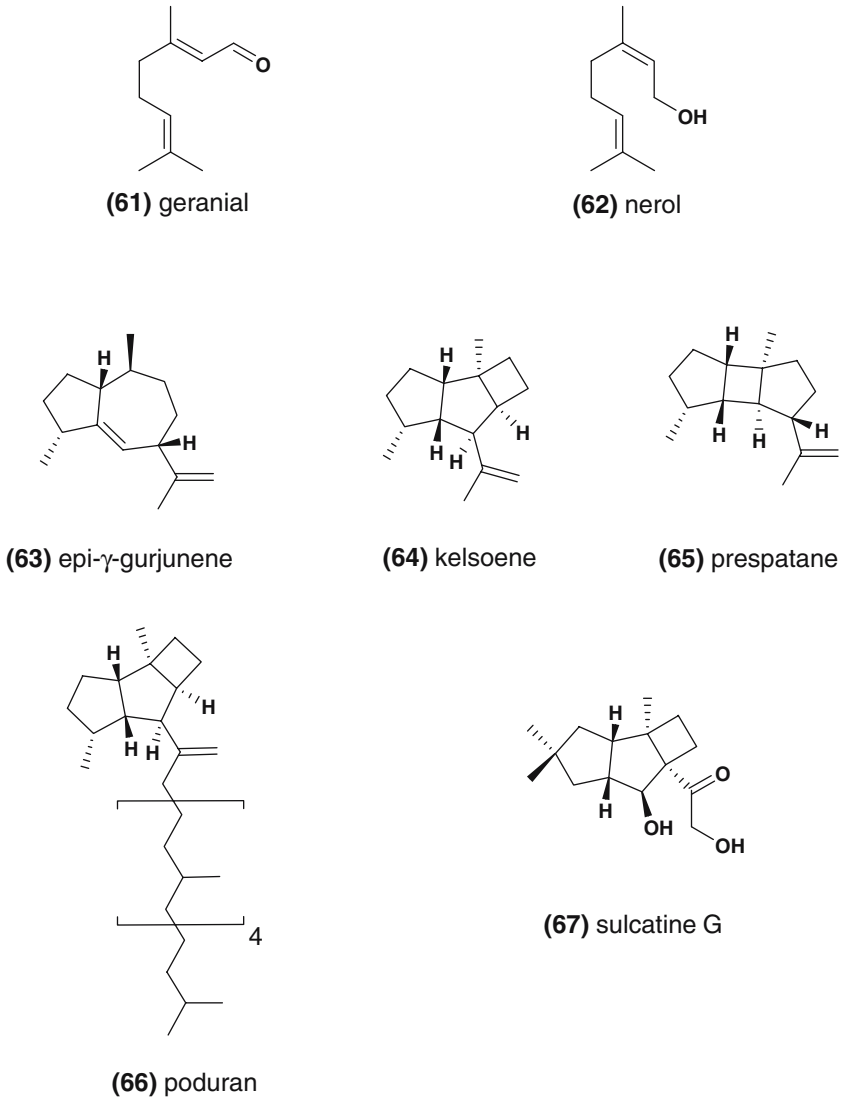



*Figure 6*. Towards the biosynthesis of pseudopterosins.




**(61)** geranial **(62)** nerol

**(63)** epi-γ-gurjunene **(64)** kelsoene **(65)** prespatane

**(66)** poduran **(67)** sulcatine G

*Figure 7.* Marine derived terpenes and their terrestrial counterparts.

thetic pseudopterosin derivative methoptherosin (**11**) (synonyms: PsA methyl ether and OAS1000) in clinical trials as topical anti-inflammatory agent for contact dermatitis (Haimes et al., 1995). Regrettably, the studies were not pursued because the company was declared bankrupt in the late 1990s (Faulkner, 2000).

Marine organisms, above all sponges, contain unusual sterols (Djerassi, 1981; D'Auria et al., 1993; Fujita et al., 2001; Rudi et al., 2001; Volkman, 2003; Gross et al., 2004b), one of which is contignasterol (**12**) from *Petrosia contignata*. This highly oxygenated steroid is remarkable due to the unusual 14$\beta$ proton configuration and the half acetal functionality in the side chain (Burgoyne et al., 1992; Yang and Andersen, 2002). Contignasterol (also referred to as IZP-94,005) and its derivatives exhibit an anti-inflammatory effect. Despite their structural relationship to the classical glucocorticosteroids, these compounds do not share the $PLA_2$-inhibition mechanism (Bramley et al., 1995). The effect is mediated by the inhibition of the release of histamine from leucocytes (Takei et al., 1994; Coulson and O'Donnell, 2000; Kasserra et al., 2004). These compounds were therefore classified as leucocyte-selective anti-inflammatory drugs (LSAIDs). Based

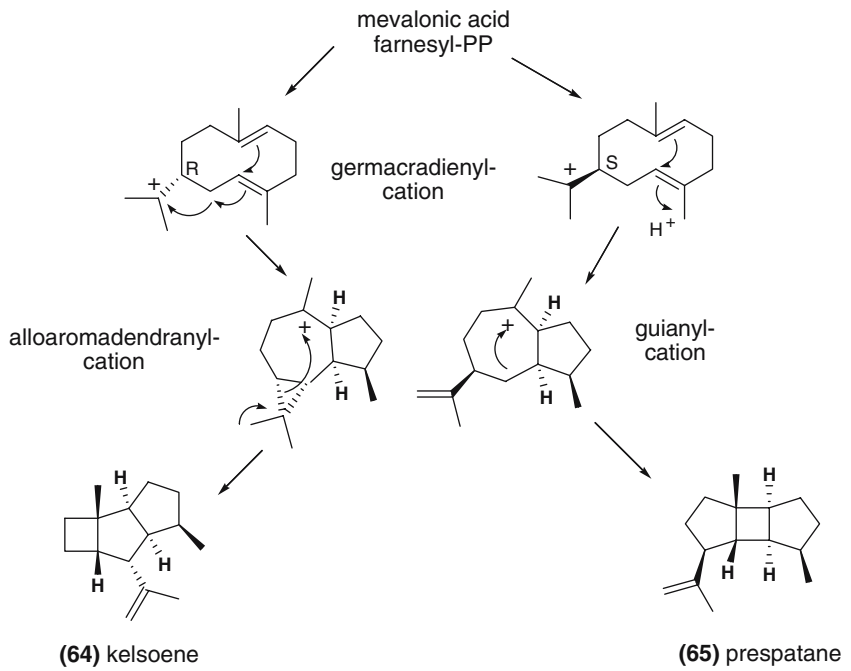



*Figure 8*. Biosynthesis of kelsoene and prespatane in liverworts.

on the promising bioactivity contignasterol was evaluated by InflaZyme Pharmaceuticals Ltd. in conjunction with Aventis Pharma as an anti-asthma agent. Due to the structural complexity and the potential pharmacokinetic instability, the compound was structurally modified and optimized, leading to the development of the derivatives IPL576,092 (**13**) and IPL512,602 (**14**) (Raymond et al., 2001; Shen and Burgoyne, 2002). IPL576,092 (Aventis development Code HMR-4011) recently successfully completed phase II studies for the treatment of asthma. In spite of the positive results IPL576,092 was replaced by the more potent derivative IPL512,602 (Aventis development Code AVE 0547) which is currently under Phase II trial investigations as an anti-asthma agent. Concerning IPL 576,092 it is intended to investigate its potential for the topical treatment of inflammatory diseases of the skin and eye. IPL550,260, another member of the contignasterol family, was evaluated in various models of inflammatory diseases and has already entered Phase I trials. Difficulties in proving the efficacy of IPL512,602 during a Phase IIa study led to the termination of the collaboration between Inflazyme and Aventis (now part of the Sanofi-Aventis group) in 2004. However, Inflayzme has now refocused their research program and intends to continue the development of IPL 512,602 in further clinical studies in asthma by changing the product profile. In the field of academic chemistry this class of compound remains an interesting topic. Lately a hybrid synthesis approach was reported, in which the contignasterol nucleus was linked to the anti-inflammatory compound manoalide (Izzo et al., 2004).

Manoalide (**15**) is also a sponge-derived natural terpenoid (*Luffariella variabilis*), one of the typical sesterterpenes (Figure 11) encountered in these organisms. It was already discovered in the 1980s by Scheuer (De Silva and Scheuer, 1980), and later the potent anti-inflammatory potential was realized simultaneously by the group of Jacobs and Dennis. Both groups demonstrated that the anti-inflammatory effect of manoalide is due to inhibition of phospholipase $A_2$ (De Freitas et al., 1984; Jacobs et al., 1985; Lombardo and Dennis, 1985; Glaser and Jacobs, 1986, 1987; Deems et al., 1987; Glaser et al., 1988; Reynolds et al., 1991; Soriente et al., 1999). Mechanistic studies revealed that manoalide binds irreversibly *via* its two masked aldehyde groups (hemiacetal- and $\gamma$-lactone ring) to several lysine residues on the interfacial binding site of $PLA_2$. Thus it prevents the hydrolysis of membrane-bound phospholipids which, inversely, would lead to the

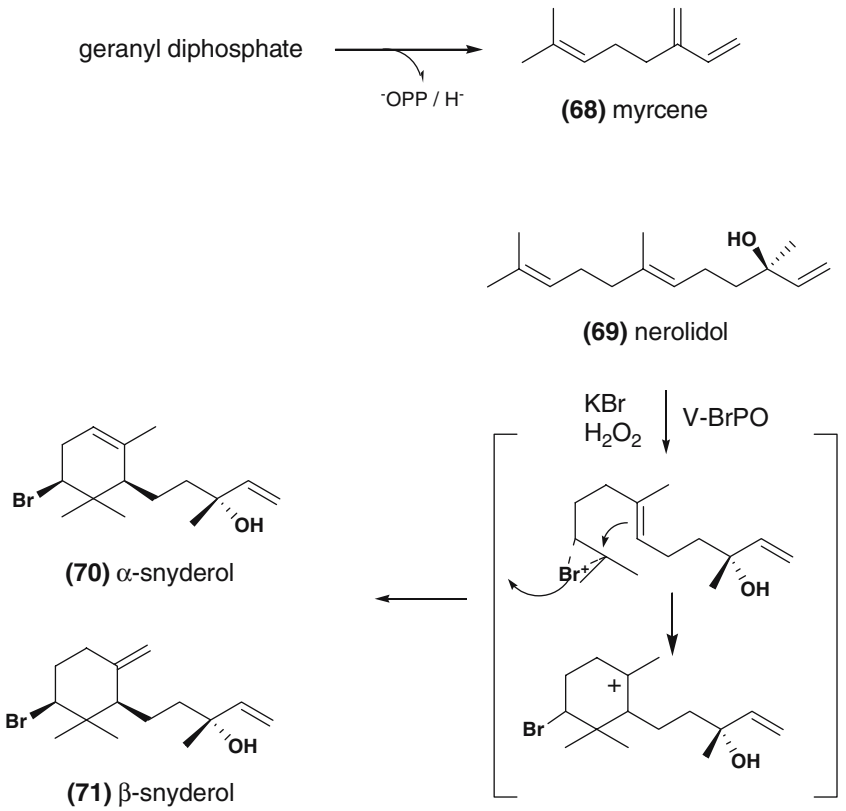



*Figure 9*. Biosynthesis of the algal monoterpene myrcene and the sesquiterpenes α- and β-snyderol.

start of the arachidonic acid cascade causing pain and inflammation (Glaser et al., 1988; Potts et al., 1992a, b; Ortiz et al., 1993). Manoalide 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 $PLA_2$. Synthetic efforts to improve the activity of this type of anti-inflammatory compound are still ongoing (De Rosa et al., 2000; Izzo et al., 2004).

Squalamine (**16**) is a water soluble cationic amino sterol occuring in the liver and stomach tissues of the dogfish shark (*Squalus acanthias*). The structure was published in 1993 and initially reported to be a potent antimicrobial agent with antibacterial, antifungal and anti-protozoic properties (Moore et al., 1993; Wehrli et al., 1993). Subsequent studies demonstrated that the compound inhibits angiogenesis and tumor growth in various models (Sills et al., 1998), thus making squalamine a good candidate for drug development as an innovative anticancer agent. Licensed to Maganin Pharmaceuticals (today Genaera), the compound has advanced into Phase II clinical trials as an anticancer agent against non-small cell lung cancer and ovarian cancer. For the latter indication, in 2001 the FDA granted squalamine orphan drug status. However, it did not perform satisfactorily as a single agent in the initial trials. Further studies showed a synergistic effect in combination with carboplatin and paclitaxel (Bhargava et al., 2001; Hao et al., 2003; Herbst et al., 2003). Squalamine seems to act through a multitude of different mechanisms in order to exert its effects. It inhibits growth factor signaling including VEGF, integrin expression, and reverses cytoskeletal formation, thereby resulting in endothelial cell inactivation, apoptosis and vessel regression (Akhter et al., 1999; Li et al., 2002; Pietras and Weinberg, 2005). The importance of squalamine is ever increasing as the anti-neovascular effect may also be useful for the treatment of wet age-related macular degeneration (AMD) (Genaidy et al., 2002; Ciulla et al., 2003). Patients

with wet AMD pathologically develop many, very fragile new blood vessels under the retina causing bleeding and damage to surrounding tissue, ultimately leading to the rapid deterioration of central vision. Squalamine could be an interesting option in the treatment of this ophthalmic disease, since the current possibilities are limited. Consequently, Phase I/II clinical trials with squalamine lactate (intended brand name is Evizon) for wet AMD were started in 2002 and are ongoing. Due to its promising applications as well as the fact that the compound cannot be obtained in large quantities from natural sources, lively activity in the field of total synthesis of squalamine or congeners has been encouraged (Brunel and Letourneux, 2003).

*Structural features of marine terpenes*

Some, but not all, marine terpenes are distinguished by characteristic structural features. Certain structural classes, e.g. chamigrene (Figure 3, **18**, **19**, **22**, **23**), amphilectane (Figure 5, **54**), cembrane (Figure 10) skeletons, and unusual functional groups such as isonitrile, isothiocyanate, isocyanate, dichloroimine (Figure 4), and halogenated (Figure 3) functionalities occur predominantly in marine metabolites. In most cases however, these structural features are not uniquely marine.

Highly brominated and chlorinated terpenes are frequently produced by marine red algae. In one of our studies several specimens of the sea hare *Aplysia dactylomela* (Mollusca), which is known to feed on such algae and to store and enrich secondary metabolites from its diet, were investigated. These animals contained many different structural types of terpenes, as they occur in algae (Wessels et al., 2000). Halogenated monoterpenes, as shown in Figure 3, may originate from red alga of the genus *Plocamium*, occurring either as acyclic regular monoterpenes (**17**) or as irregular monocyclic structures (**20**, **21**). Halogenated chamigrene derivatives (**18**, **19**, **22**, **23**) are regular sesquiterpenes with a spiro centre and typically occur in algae of the genus *Laurencia*, as are the further sesqui- and diterpenoid structures depicted in Figure 3. Most of these compounds were formerly obtained from the respective algae. In some cases however, the acetyl moiety was not present in the algal metabolite, i.e. acetyl-isoobtusol (**19**), puertitol-B-acetate (**28**), acetyl-caespitol (**30**). It may thus be suggested that sea hares modify metabolites that they sequester from their food source. Further, caespitenone[1] (**29**), which was for the first time encountered in this study of *A. dactylomela*, is an oxidation product of the algal metabolite caespitol (**30**), and may be produced by the animal through oxidation of the diet derived natural product. Dactylopyranoid (**24**) is a unique compound, to date only encountered in the animal *A. dactylomela*. This irregular and brominated diterpene is, however, structurally also similar to *Laurencia* metabolites (Wessels et al., 2000).

Apart from halogens, isonitrile and related functionalities are a characteristic feature of terpenes from the marine environment, with most of these being encountered in sponges and nudibranchs that feed on them (Garson and Simpson, 2004). *Acanthella klethra* and *Cymbastela hooperi*, two sponges that were of interest for us due to their antiplasmodial activity, were found to produce numerous sesqui- and diterpenes with these unusual functionalities. The sponge *A. klethra* yielded axisonitrile-3 (Figure 4, **32**), an unusual and irregular terpene. Isonitrile containing metabolites such as axisonitrile-3 are frequently accompanied by compounds with an isothiocyanate functionality, i.e. the corresponding isothiocyanate of axisonitrile-3 (**33**) and eudesmane type compounds **34**–**36** in *A. klethra* (Figure 4) (Angerhofer et al., 1992; Wright et al., 1996). *C. hooperi* was distinguished by the presence of diterpenes substituted with isonitrile and isothiocyanate functionalities. One of the isocycloamphilectane diterpenes (**47**) present in *C. hooperi* deserves special attention due to the isocyanate functionality, which is extremely rare in nature (Van Soest et al., 1996; König et al., 1996, Linden et al., 1996).

Many of these metabolites were found to have antiplasmodial activity (Wright et al., 1996), with the activity of axisonitrile-3 (**32**) being very pro-

[1] According to the taxonomy of the source organism and the enone functionality, the trivial name caespitenone was assigned to a pseudoguaiane sesquiterpene isolated in 1980 from the liverwort *Porella caespitans* (Asakawa et al., 1980). Later on, this structure was revised to have an africane based terpenoid skeleton (Tori et al., 1993). Terpene **29** was regrettably also given the trivial name caespitenone (Wessels et al., 2000), due to its enone function and the close resemblance to caespitol (**30**), a sequiterpene which was originally isolated from the marine red alga *Laurencia caespitosa*. Here we only refer to the marine derived caespitenone.

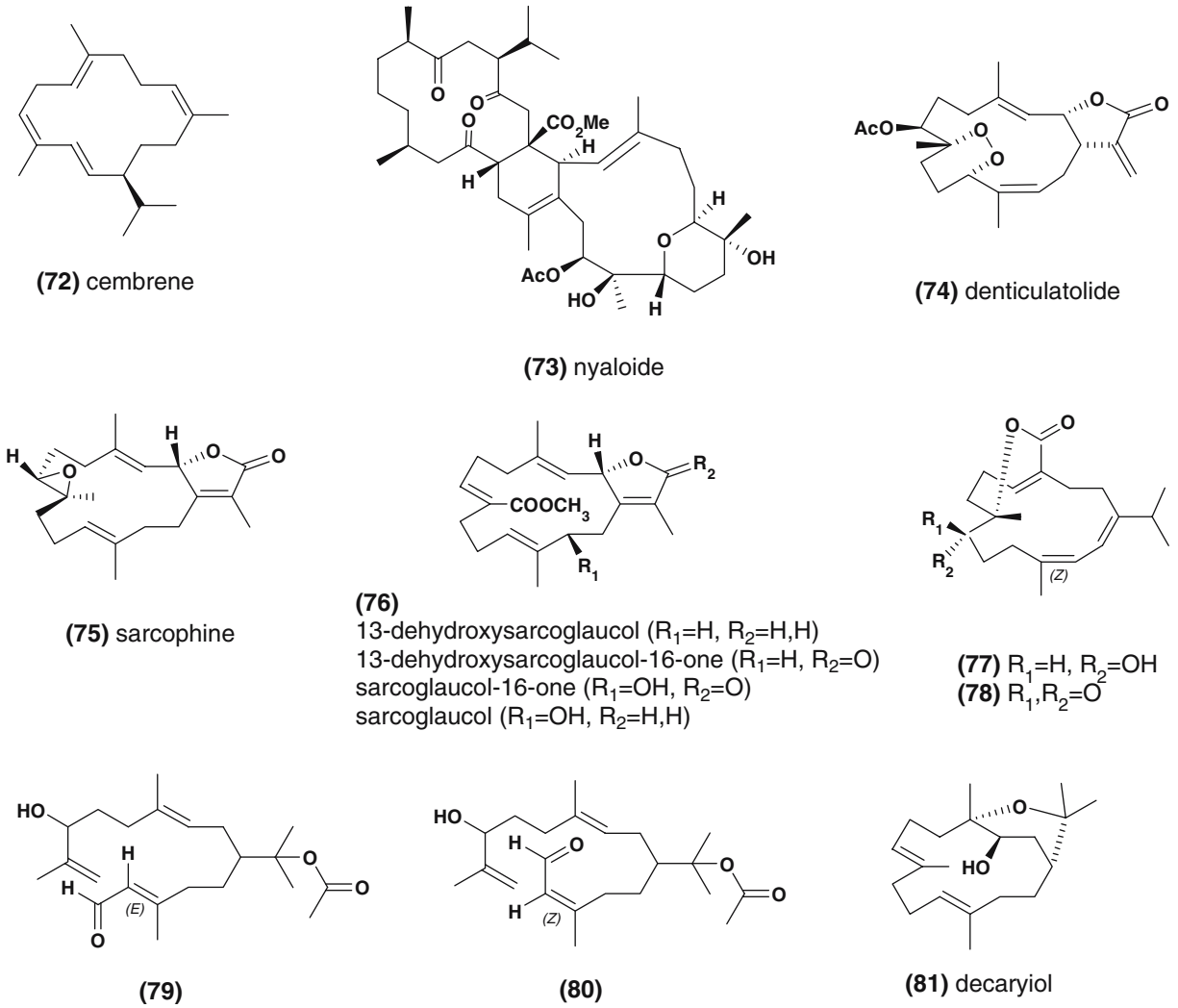
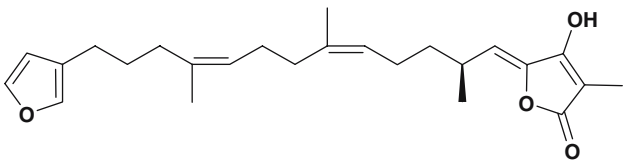


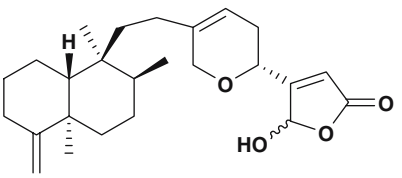

*Figure 10.* Cembranoid structures from marine soft corals.

nounced with an $IC_{50}$ towards *Plasmodium falciparum* of 16.5 ng/ml and no associated cytotoxicity (Angerhofer et al., 1992). The most potent antiplasmodial activity of all *Cymbastela* metabolites was found for diisocyanoadociane (**49**) with an $IC_{50}$ value of 4.9 ng/ml towards *Plasmodium falciparum*. This activity is more pronounced than that of axisonitrile-3 (**32**), but unfortunately is also accompanied by some cytotoxicity. Both compounds interfere with the detoxification of heme, a degradation product of haemoglobin digestion within infected erythrocytes. Axisonitrile-3 (**32**) forms a binary complex with the iron in protoporphyrin IX, whereas diisocyanoadociane gives rise to a ternary complex. In this way, heme accumulates and exerts its toxicity towards the malaria parasite (Wright et al., 2001). Kalihinanes, like e.g. kalihinol A (**51**) are diterpenoid sponge metabolites with isonitrile function and were also shown to have antimalarial properties (Miyaoka et al., 1998); most likely they share the same mode of action.

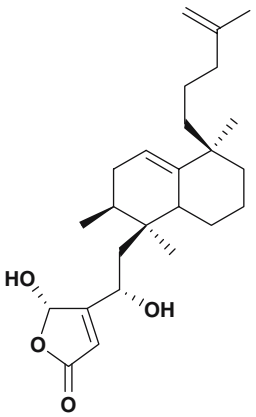
The carbon skeleton of *Cymbastela* diterpenes and kalihinanes was proposed to be biosynthetically derived from serrulatane type compounds (Figure 5, **53**) (Garson and Simpson, 2004; König et al., 1996). Indeed, a bicyclic serrulatane type metabolite (Figure 4, **37**) was identified in *C. hooperi* and in other sponges, and may be proposed as the biosynthetic precursor of further cyclized terpenes. Amphilectanes (Figure 5, **54**)



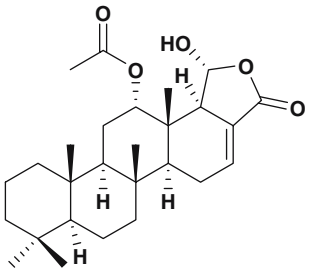
**(82)** 8*Z*,13*Z*,18*S*,20*Z*-strobilinin



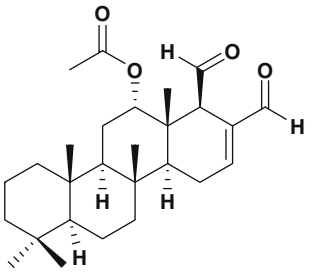
**(83)** cacospongionolide B



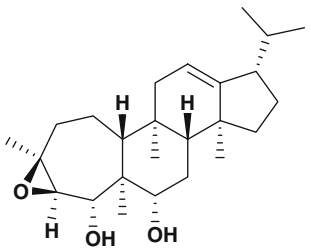
**(84)** dysidiolide



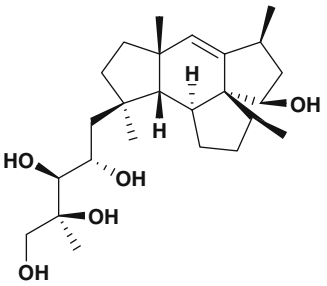
**(85)** scalarin



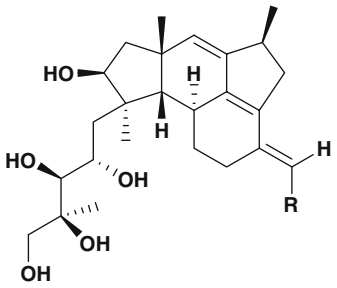
**(86)** scalaradial



**(87)** aspergilloxide



**(88)** mangicolA



**(89)** neomangicol A (R=Cl)
neomangicol B (R=Br)

*Figure 11.* Marine derived sesterterpenes.

can thus be envisaged as cyclization products of serrulatane precursors (**53**), cycloamphilectanes (**56**) derive from amphilectanes (**54**) through a further ring closure, and the irregular isocycloamphilectanes (**57**) are formed after migration of a methyl group from cycloamphilectanes (**56**). The new neoamphilectane (**55**) skeleton in *C. hooperi* is biosynthetically related to serrulatane (**53**) and amphilectane (**54**), however its formation requires an extensive rebuild of the carbon skeleton (Figure 5). The biosynthetic relationship of the *Cymbastela* metabolites, as proposed in Figure 5 is exclusively based on the co-occurrence of these structural types in the same sponge. There is, however some evidence concerning the biosynthesis of these structural types although the supporting data come from a phylogenetically quite different marine animal, i.e. the coral *Pseudopterogorgia elisabethae*. Pseudopterosins (Figure 2, **11**; Figure 6, **60**) in this gorgonian coral are

amphilectane type (Figure 5, **54**) natural products which are formed *via* the serrulatane elisabethatriene (Figure 6, **58**). Isolation and characterization of elisabethatriene diterpene cyclase has been achieved, making this the first biosynthetic enzyme derived from a marine invertebrate or its microbial symbiont, respectively. This enzyme shares important characteristics with corresponding terrestrial diterpene cyclases, e.g. pH optimum and dependency of the synthase activity on divalent metal ion concentrations ($Mg^{2+}$) (Coleman and Kerr, 2000; Ata et al., 2003; Kohl and Kerr, 2004; Ferns and Kerr, 2005).

The biogenetic origin of the isonitrile and related functional groups in terpenes poses some intriguing questions (for a recent review see, Garson and Simpson, 2004). Incorporation studies with labeled inorganic cyanide showed, in several cases, the presence of labeled carbon and nitrogen in the isonitrile, isothiocyanate, and formamide groups of the natural product (Simpson and Garson, 1998, 1999, 2004). Cyanide is also incorporated in the dichloroimine functionality, a rare functional group to date exclusively known from marine terpenes (Brust and Garson, 2003; Simpson et al., 2004) e.g. present in ulosin B (Figure 4, **52**) (Kehraus et al., 2001). The biological origin of cyanide remains obscure, since it is only found in trace amounts in sea water. The most intriguing hypothesis to date is that it might be produced by symbiotic microorganisms in sponges, e.g. bacteria including cyanobacteria, and is, in this way made available for the secondary metabolite biosynthesis of the host.

Many terpenes are easily recognized as being derived from marine organisms by their characteristic structural features, e.g. extensive halogenation. There are, however, also numerous cases where marine and terrestrial terpenes have identical or very similar structures. *Flustra foliacea* colonies, distinguished by a pleasant smell of lemon when collected freshly, produce a small amount of essential oil, apart from their characteristic indole alkaloids. Steam distillation and subsequent GC-MS analysis showed the major components to be geranial (Figure 7, **61**) and nerol (**62**) (Peters et al., 2004a), compounds predominantly known from terrestrial plants.

Also, apart from isonitrile substituted diterpenes (Figure 4), the tropical sponge *Cymbastela hooperi* contained simple sesquiterpenes (Figure 7), i.e. the guaiane derivative epi-$\gamma$-gurjunene (**63**), kelsoene (**64**) and prespatane (**65**). Kelsoene (**64**) was, at the time of its first isolation from this sponge, a new carbon skeleton (Wright et al., 1996; König and Wright, 1997), but became later also known from liverworts and an insect species (Nabeta et al., 2000; Fietz-Razavian et al., 2001; Mehta and Sreenivas, 2003). Additionally, poduran (**66**), a tetraterpene bearing the same tricarbocyclic skeleton as kelsoene has been reported from the springtail *Podura aquatica* (Schulz et al., 1997). Sulcatine G (**67**) from basidiomycetes is also structurally related to kelsoene (**64**), the biosynthesis of the latter however must proceed differently (Mehta and Sreenivas, 2002) (Figure 8). Since the guaiane derivative **63**, kelsoene (**64**) and prespatane (**65**) were isolated from the same sponge sample, it appeared feasible to envisage the bicyclic guaiane (**63**) as being involved in kelsoene (**64**) and/or prespatane (**65**) biosynthesis. In case of the terrestrial liverwort *Ptychanthus striatus* this was proven experimentally. Studies with labeled precursors led to the deduction that kelsoene (**64**) is formed from farnesylpyrophosphate through a germacradienyl and alloaromadendrane cation (Figure 8) (Nabeta et al., 2000). This biosynthetic pathway may also occur in sponges, i.e. *Cymbastela hooperi*, to date, however no such biosynthetic studies on sponge terpenoids have been done.

## Selected topics on marine terpenoid classes

### *Marine mono- and sesquiterpenes [$C_{10}$,$C_{15}$]: biosynthesis of algal metabolites*

The biosynthesis of marine algal metabolites has hardly been investigated. One of the few studies reported is that of Wise and Croteau who suggested that the acyclic monoterpene myrcene (Figure 9, **68**) is a likely precursor of halogenated compounds in the red alga *Ochtodes secundiramea*. Myrcene synthase was isolated from the cultured marine alga and represents the first enzyme of this type from any marine organism. This enzyme is rather similar to monoterpene synthases from terrestrial sources, one of the major differences being that the algal myrcene synthase is not capable of isomerising geranyl to linalyl diphosphate (Wise et al., 2002).

Butler and co-workers shed some light on the terpene halogenating process. Vanadium-containing bromoperoxidases (V-BrPO) were isolated from diverse marine red algae. Upon incubation with the terpenoid precursor nerolidol (**69**), these enzymes were able to produce the brominated cyclic terpenes $\alpha$- and $\beta$-snyderol (**70**, **71**), which are known as algae-derived natural products (Figure 9). Halogenation and cyclization occurred enantiospecifically. It is suspected that the bromoperoxidase mediates the oxidation of bromide to a bromonium ion or a biological equivalent thereof, which is thought to then initiate the cyclization and halogenation of the terpene precursor. The yields of natural products in these *in vitro* experiments were very low and by-products not encountered in nature are also found as reaction products. Products formed are also strongly dependent on reaction conditions (Butler and Carter-Franklin, 2004; Carter-Franklin and Butler, 2004). It is thus not unequivocally clear whether the enzymatic halogenation of marine terpenes is related to vanadium containing haloperoxidases.

### *Marine diterpenes [$C_{20}$]: structural types and biological activity of cembranoids*

Cembrene (Figure 10, **72**), a diterpene with a 14-membered ring, was first isolated from the pine tree *Pinus albicaulis* (classified according to the valid taxonomic system at that time as subgenus *Haploxylon*, group *Cembrae*) and became the eponym for this compound class (Haagen-Smit et al., 1951; Dauben et al., 1965). Later on, many other cembranes were isolated from plants, insects, alligators (Mattern et al., 1997) and especially from marine organisms. Thus, cembranes are indisputably not uniquely marine, but their striking presence in soft corals outnumbers the occasional occurrence in other taxa. Cembranoids are also interesting in terms of pharmacological research. They show significant biological activity, including antimicrobial, Ca-antagonistic and anti-inflammatoric properties. The antitumoral effect of cembranes is, however the most important activity of this class of natural products.

The ability of soft corals to produce a wide array of diversified cembranoid structures is remarkable. Cembranoids are often highly functionalized, possessing peroxy (**74**) (Uchio et al., 1985), epoxide (**75**) (Bernstein et al., 1974), lactone (**77**) or ether ring systems (**81**) and forming complex dimers (**73**) (Feller et al., 2004). The high functionalization often poses many stereochemical questions. For most cembranes, however only the relative stereochemistry was established. Hence, we recently investigated the absolute stereochemistry of the cytotoxic cembrane sarcophine (**75**) and three new congeners of sarcoglaucol (**76**), by application of Mosher's method in combination with CD spectroscopy (Gross et al., 2003, 2004a).

Some unusual variations of the cembranoid skeleton were lately encountered by us in cembranes **77** and **78**, which possess a diene moiety with a *Z*,*E* configuration, in contrast to the more common *E*,*E*-configuration. The configuration of **77** and **78** was resolved using $^{1}H$–$^{1}H$ coupling constants in combination with the deduction of the dihedral angles between coupling protons from minimized models (Gross et al., 2004a). Considering the biosynthesis of such cembranes, an alteration of the geometry of the last double bond in GGPP must be proposed before cyclization occurs. Analogous to the biosynthesis of cyclic monoterpenes, isomerization and cyclization might be carried out by the same enzyme (Gross et al., 2004a). Since nearly all cembranes obtained thus far show an *E* configuration for the respective double bonds, isomerization of GGPP seems to occur rarely requiring an unusual enzymatic activity in the soft coral. To date, however the only known diterpene cyclase from marine invertebrates is the aforementioned enzyme from the gorgonian *Pseudopterogorgia elisabetae* (Kohl and Kerr, 2004).

Another unusual structural variation are the seco-cembranes, where cleavage of the macrocycle must has take place. Two examples (**79**, **80**) of this rare cembranoid class were isolated by us along with the cembranoid decaryiol (**81**), from a Fijian soft coral of the genus *Nephthea* (Gross et al., 2003). Decaryiol (**81**) demonstrated significant cytotoxicity (e.g. $IC_{50}$ 0.15 $\mu$g/ml towards MCF7 cells lines) in this study and was found to be a cell cycle specific inhibitor of cell growth.

### *Marine sesterterpenes [$C_{25}$]: frequently encountered structures in marine organisms*

Sesterterpenes are the smallest and therefore rarest group of all subclasses of terpenoids. Several

reviews on this topic give detailed information on the chemistry and bioactivities of sesterterpenoids (Crews and Naylor, 1985; Hanson, 1996). Especially striking is the frequent occurrence of sesterterpenes (Figure 11) in marine organisms. Sponges must be considered as one of the prime sources of these $C_{25}$ terpenoid compounds, even though they are not exclusively encountered in the marine environment.

Sesterterpenes show a series of interesting pharmacological properties, including cytotoxicity, antimicrobial activity and platelet aggregation inhibition, however the anti-inflammatory activity is outstanding and a dominating feature in this compound class (Keyzers and Davies-Coleman, 2005). Even though sesterterpenoid structures occur mainly in marine organisms, they can also be found in the wax of insects (Rios and Colunga, 1965), higher plants (Toyoda et al., 1969) and terrestrial fungi (Lauer et al., 1989). Although they are by definition strictly $C_{25}$ compounds, there are a large number of nor- and alkylated derivatives.

The skeletons range from acyclic to tetracarbocyclic structures (Figure 11). The acyclic forms are mostly provided by marine sponges of various genera, e.g. strobilinin-derivative **82** from *Ircinia oros* (Höller et al., 1997), and comprise usually furanyl, $\gamma$-lactone or tetronic acid moieties. These linear sesterterpenes co-occur frequently with closely related $C_{21}$ compounds and it is proposed that they arise biogenetically by oxidative cleavage of the tetronic acids (González González et al., 1983). Pharmacologically, the most important marine monocarbocyclic sesterterpenoid is the above already mentioned manoalide (Figure 2, **15**). Cacospongionolide B (**83**), a bicarbocyclic representative of the $C_{25}$ terpenes (De Rosa et al., 1995), is like manoalide (**15**), a potent anti-inflammatory agent and also inhibits $PLA_2$. Due to the same pharmacological target and their structural resemblance, the cacospongionolides were in the past considered to be more stable congeners of manoalide (De Rosa et al., 1998). However, recent synthetic studies with cacospongionolides led to derivatives lacking the masked aldehyde functionalities, but still demonstrating $PLA_2$ activity. Therefore, the authors suggested that in the case of cacospongionolides the binding to $PLA_2$ is rather based on a certain three-dimensional structure than on the hithero proposed manoalide-like mode of action (Cheung et al., 2004). Aside from the $PLA_2$ activity, cacospongionolide B was in the interim also shown to be anti-inflammatory due to its ability to suppress the expression of inflammatory enzymes and tumor necrosis factor-$\alpha$ by inhibition of NF-$\kappa$B activation (Posadas et al., 2003). Dysidiolide (**84**) (Gunasekera et al., 1996), a further bicarbocyclic sesterterpene, has been the subject of extensive research due to its antitumor activity, mediated by inhibition of the cdc25A protein phosphatase (Brohm et al., 2002). Tetracarbocyclic $C_{25}$ terpenoid structures are in the majority of cases based on the scalarane skeleton, e.g. scalarin (**85**), one of the most common types of marine sesterterpenoids, particularly prevalent in sponges (Fattorusso et al., 1972). Scalaranes were also located in nudibranchs and might originate from *de novo* biosynthesis (Kubanek et al., 1997) or from sponges as a dietary source (Gavagnin et al., 2004). A bioactive example of the scalarane subclass is the anti-inflammatory scalaradial (**86**), obtained from the marine sponge *Cacospongia mollior* (Cimino et al., 1974). Scalaradial was shown to be a potent inhibitor of $PLA_2$ (De Carvalho and Jacobs, 1991).

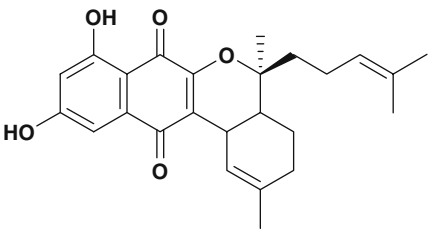
Aside from these classical sesterterpenoid skeletons several structurally exceptional and unique sesterterpenoids have recently been isolated from marine-derived fungi, e.g. aspergilloxide (**87**), a novel tetracyclic epoxide-diol sesterterpene, the first member of the new class of asperane-sesterterpenes (Cueto et al., 2002). Of interest are also the mangicols (**88**) and neomangicols (**89**), provided by a marine *Fusarium* species (Renner et al., 1998, 2000). These tetracarbocyclic $C_{25}$-isoprenoids represent new rearranged carbon skeletons. Based on $^{13}C$ acetate labeling studies, a biosynthetic pathway for these irregular terpenes *via* geranylfarnesyl diphosphate was proposed (Renner et al., 2000).

### *Prenylated marine metabolites*

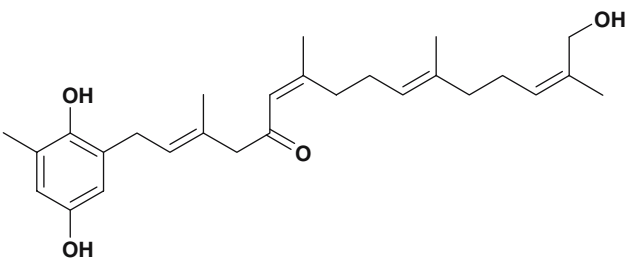
Many marine natural products contain terpene units attached to a core structure originating from another biosynthetic pathway. Among others, prenylated naphthoquinones (**90**) (Pathirana et al., 1992), hydroquinones (**91**) (Fisch et al., 2003) or alkaloids (Figure 12) can be observed.

In one of our studies the North Sea bryozoan *Flustra foliacea* was found to contain numerous prenylated indole alkaloids (Figure 12, **92**–**95**). A most unusual feature, apart from the rarely encountered sulfonamide group in one of the

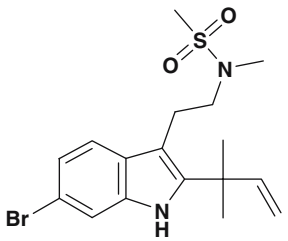
compounds (**92**), was the reverse attachment of the terpene residues, i.e. via C-3 and not C-1 of the $C_5$ unit (Peters et al., 2002, 2004a). Two compounds, flustramine D (**93**) and dihydroflustramine C (**94**), were found to inhibit acylhomoserin mediated quorum sensing, while other compounds were



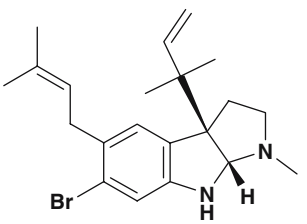

**(90)** marinone



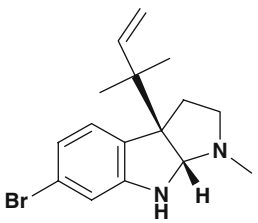

**(91)**



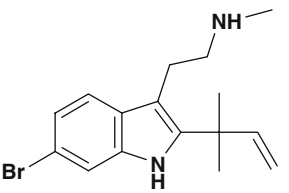

**(92)** N-(2-[6-bromo-2-(1,1-dimethyl-2-propenyl)-1*H*-indol-3-yl]ethyl)-N-methylmethanesulfonamide



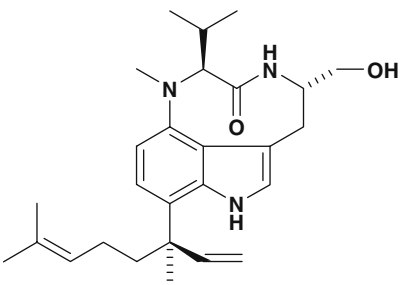

**(93)** flustramine D




**(94)** dihydroflustramine C




**(95)** deformylflustrabromine




**(96)** lyngbyatoxin A

*Figure 12.* Marine terpenoids of mixed biogenesis.

biocidal (Peters et al., 2003). Both effects might contribute to the avoidance of biofouling on the surface of the animal. Pharmacologically it is of interest that one of the indole alkaloids, i.e. deformylflustrabromine (**95**) showed affinity to nicotinic acetylcholine receptors, with selectivity for certain subtypes of this ion channel (Peters et al., 2004b). Functional assays with receptors expressed in frog oocytes revealed deformylflustrabromine to be able to specifically enhance the activity of the neurotransmitter acetylcholine (Sala et al., 2005).

Another interesting example of prenylated indole alkaloids are the lyngbyatoxins (**96**), produced by the cyanobacterium *Lyngbya majuscula* (Cardellina II et al., 1979; Aimi et al., 1990). The lyngbyatoxins catched the attention of researchers because they cause a severe skin dermatitis ("swimmers' itch" or "seaweed dermatitis") through activation of protein kinase C. Similar to the above mentioned indole alkaloids (**92**–**95**), a reverse prenylation occurs, however at a different position of the aromatic indole skeleton. The appropriate prenyltransferase has been identified recently and will give some insight into the mechanism of reverse prenylation reactions (Edwards and Gerwick, 2004).

## Biosynthesis of marine terpenes: an important topic for future research

The structures of marine terpenoids range from identical and very closely related to those of terrestrial terpenes, to compounds with unusual skeletons and substitutions, uniquely found or predominantly present in marine organisms.

Only very few significant and detailed biosynthetic studies on marine terpenoids have been done, focussing mainly on marine molluscs and a few cultivated organisms, e.g. fungi (Renner et al., 2000) and diatoms (Schwender et al., 1996; Cvejic and Rohmer, 2000; Massé et al., 2004). In several studies, it was amply demonstrated that apart from sequestering terpenes from their diet, marine mollusc biosynthesize terpenes *de novo*, including degraded sesterterpenes, from mevalonic acid (Gavagnin et al., 2001; Kubanek et al., 1997; Fontana et al., 2003a, b).

The first study concerning the biosynthesis of marine terpenoids *via* the MVA (Mevalonic acid) or the alternative MEP (methylerythritol-4-phosphate) pathway was done in the cultivated marine diatoms *Phaeodactylum tricornutum* and *Nitzschia ovalis*, and revealed the same dichotomy of isoprenoid metabolism as found in higher plants (Schwender et al., 1996; Cvejic and Rohmer, 2000). Concerning sesterterpenes, the first investigations in terms of their biosynthesis were done employing the marine diatoms *Haslea ostrearia* and *Rhizosolenia setigera*, which produce this class of $C_{25}$ compounds *via* the MEP and MVA pathway, respectively. Which pathway is used seems to be an individual feature of the producing organism (Massé et al., 2004). The chemical structure of sesterterpenes in sponges (Figure 11), however, is rather different to those of diatom derived compounds, and no studies on invertebrate sesterterpenes have been conducted. Concerning the sponge diterpene diisocyanoadociane (Figure 4, **49**) studies with labeled mevalonic acid were inconclusive, even though the label was incorporated in carotenoids, leaving the question which pathways may be involved in invertebrate terpenoid biosynthesis wide open (Garson and Simpson, 2004). Also, despite the multitude of terpenes, partly with unusual ring structures in red algae, there is, as yet, no experimental evidence for their biosynthesis (Wise, 2003).

The first terpene cyclases are beginning to be described (Wise et al., 2002; Kohl and Kerr, 2004), as are the enzymes which may be responsible for the in part excessive halogenation of marine terpenes (Carter-Franklin and Butler, 2004). As yet, genetic information underlying marine terpenoid biosynthesis is missing completely, and thus the prerequisite for any homology based biosynthetic studies.

The scarcity of information on the biosynthetic formation of marine terpenes may be explained by the difficulty to cultivate most marine organisms. Additionally, biosynthetic investigations are a complicated and challenging task, due to the fact that many marine organisms harbor a massive amount of different kinds of symbiotic or otherwise associated microorganisms (Friedrich et al., 1999, 2001; Lesser et al., 2004; Piel, 2004). Experimentally, it was shown that terpenes in the sponge *Dysidea herbacea* are located within the sponge cells, whereas peptides are to be found in cyanobacterial symbionts of these animals (Unson and Faulkner, 1993; Flowers et al., 1998; Flatt et al., 2005). Even though the storage site of nat-

ural products is no proof of where or by which partner they are produced, it is a strong indication for the biosynthetic origin of some of these secondary metabolites. In the case of the anti-inflammatory pseudopterosins it was recently demonstrated that the symbiotic dinoflagellate *Symbiodinium* sp. in *P. elisabethae* is the true source of the pseudopterosins (Mydlarz et al., 2003). These pioneering results show that further studies shedding light on the tissue/cell specific localization of marine terpenes are necessary, as well as biochemical studies with cultured macro- and microorganisms. Once some insight into the genetic basis of marine terpenoid biosynthesis has been gained, molecular biology methods will be another lever with which to further our understanding of marine terpenoid production. It would also be of great importance to understand how terpene metabolism influences these symbiotic life forms, and what the specific ecological function of individual compounds might be.

## Conclusions

Hopefully some of the mentioned terpenoids under clinical investigation will soon reach the pharmaceutical market and improve the treatment of human diseases. Taken into account the immense biodiversity of the oceans, especially regarding microorganisms, certainly more bioactive isoprenoids will follow. Employment of dereplication strategies using liquid chromatography coupled with mass spectrometry (LC-MS), innovative bioassays, improved separation and detection, e.g. diode array detection (DAD), evaporative light scattering detection (ELSD) and MS techniques as well as ultra high field NMR spectrometers will facilitate the future drug discovery process. In case of problems with supply of sufficient amounts of bioactive compounds for clinical and pharmacological studies, creative syntheses or biotechnological solutions are required. With growing knowledge about biosynthetic pathways, this problem may be overcome. The ultimate goal to redesign the genetic information by modulation and recombination in a transgenic organism could also be within reach and will allow creation of novel terpenoids with improved biological activities. Imaginable is the control of stereochemistry, substitution pattern (halogenation), change of the backbone or different ring closures. Gene mining offers another great approach to exhaustively assess the full biosynthetic potential of marine organisms and subsequently uncover even more and novel isoprenoid compounds of medical importance in the future.

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