Spongiane Diterpenoids†

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Abstract: In this review we cover the structures, occurrence, biological activities and synthesis of all the spongianes and rearranged spongianes since their discovery in 1974. We have given special attention to structure revisions and biological properties of these polycyclic terpenoids of exclusive marine origin. However, an important part of the review describes the synthetic efforts in the field. Thus, this part has been subdivided into syntheses from other natural products, syntheses by biomimetic approaches and other approaches including enantioselective total syntheses.

INTRODUCTION

Marine terpenoids are typical constituents of the secondary metabolite composition of marine flora and fauna. These isoprenoid-derived compounds are common in almost all marine phyla and show a wide range of novel structures. Although most of them are also present in terrestrial organisms, the occurrence of a few skeletons is restricted to certain marine species. In this review we focus our attention to diterpenoids characterized by polycyclic structures having either the spongiane (I, C_{20}) (Fig. 1) carbon framework or several degraded or rearranged spongiane-derived skeletons.

Spongiane diterpenoids are bioactive natural products isolated exclusively from sponges and marine shell-less mollusks (nudibranchs), which are believed to be able of sequestering the spongian-derived metabolites from the sponges, soft corals, hydroids and other sessile marine invertebrates on which they feed. Most of these compounds play a key role as eco-physiological mediators and are of interest for potential applications as therapeutic agents.

Spongianes having the characteristic carbon skeleton I (Fig. 1) have been reviewed up to 1990 and listed in the Dictionary of terpenoids [1]. During the last two decades, many new members of this family of natural products have been isolated and described in specific reviews on naturally occurring diterpenoids by Professor Hanson [2], and the excellent reviewing work on marine natural products by Professor Faulkner [3,4], now continued by the team of Professor Blunt [5,6], all of which have mainly covered the isolation and structural aspects of spongianes. A recent review on the chemistry of diterpenes isolated from marine opisthobranchs, has also included articles on isolation and structure determination of spongianes up to 1999 [7]. The latter also covered some synthetic studies of this class of substances. To the best of our knowledge, there is only one more report dealing with the initial studies towards the synthesis of spongianes [8]. We now provide full coverage of recent advances in the field including a comprehensive description of the synthetic approaches and syntheses reported in the literature on spongianes up to march 2006.

STRUCTURE, OCCURRENCE AND BIOLOGICAL ACTIVITY

The semisystematic naming of this family of diterpenoids was introduced in 1979 following the isolation of the first members of the family from sponges of the genus *Spongia* [9]. Thus, in accordance with the IUPAC recommendations the saturated hydrocarbon I, named ‘spongian’, was chosen as the fundamental parent structure with the numbering pattern as depicted in Fig. 1.

![Fig. 1](image-url)

The first known member of the spongiane family, isoagatholactone (1), was discovered by Minale et al. from the sponge *Spongia officinalis* about thirty years ago, being the first natural compound with the carbon framework of isoagathic acid (2). Structure (1) was assigned based on spectroscopic data and chemical correlation with natural grindelic acid (3) [10].

To date, there are nearly 200 known compounds belonging to this family of marine natural products, including those with a spongiane-derived skeleton. Most of them present a high degree of oxidation in their carbon skeleton, particularly at positions C-17 and C-19 as well as on all the rings A-D. Given the variety of chemical structures found in the spongiane family, we could group them according to the degree of oxidation as well as the degree of carbocyclic rearrangement of the parent 6,6,6,5-tetracyclic ring system. Thus, we have integrated most of them into two main groups: compounds having the intact spongiane skeleton and compounds either with an incomplete skeleton or resulting from an hypothetical rearrangement process, which has been proposed several times from a biosynthetic point of view.
Sponges are exposed to a variety of dangers in their environment and this has led to the development of chemical defense mechanisms against predation. Nudibranchs feed on a variety of sponges and are able of storing selected metabolites, even transform them, for their own self defense. Thus, sponges and nudibranchs are a rich source of biologically active metabolites, and the sponges, in particular, have displayed a wide spectrum of interesting biological properties including antifeedant, antifungal, antimicrobial, ichthyotoxic, antiviral, antitumor, antihypertensive, fragmentation of Golgi complex, as well as anti-inflammatory activity (see Table 1).

**Intact Spongiane Skeleton**

The first subgroup contains compounds derived formally from the antimicrobial isoagatholactone (1) [11], and therefore characterized by the functionalization present in ring D, a γ-lactone ring D, in this case (Fig. 2).

![Fig. (2)](image)

For example, alyproseol-1 (4, R1 = H, R2 = Me, R3 = OAc) was isolated from the dendrocerecid sponges *Aphysilla rosea* [12,13], *Dendrilla rosea* [14] *Aplysilla polyrhapis* [15], and *Chelonaplysilla violacea* [16] and also from the nudibranches *Chromodoris obsoleta* [17] and *Chromodoris inopinata* [18]. Anti-tumor activity against the P388 mouse leukaemia cell line in vivo showed no significant activity.

The sponge *Aphysilla rosea* also contained the lactone 4 (R1 = H, R2 = CH2OAc, R3 = OAc). From the tentatively identified mollusk *Ceratosoma brevicaudatum*, it was isolated the simplest member of the series with a functionalised C-17 (4, R1 = H, R2 = CHO, R3 = H) [19]. The mollusk resulted to be *Ceratosoma epicurium* [20] and the synthetic compound showed some cytotoxicity against HeLa and HeP-2 cancer cells [21].

Alyproseol-14 (4, R1 = R2 = H, R3 = CH2OAc) and alyproseol-16 (4, R1 = OH, R2 = CH2OAc, R3 = OAc) have been isolated more recently also from the sponge *Aphysilla rosea* [24], whereas the cytotoxic γ-lactone spongian-16-one (4, R1 = H, R2 = Me, R3 = H) has been found in several species such as *Dictyodendrilla carnosa* [22], *Chelonaplysilla violacea* [16,23], *Aphysilla var. sulphurea* [24], and also in the mollusks *Chromodoris obsoleta* [17], *C. petechialis* [25], and *C. inopinata* [18]. The structure for alyproseol-14 was corrected a few years later by spectroscopic means, chemical synthesis (see synthesis section) and also by X-ray diffraction analysis [26]. Thus, structure 4 (R1 = R2 = H, R3 = CH2OAc) was renamed as isoalyproseol-14.

Several members containing the unsaturated γ-lactone ring have shown antimicrobial properties. Compounds 5 (R1 = OH, R2 = R3 = OAc) have been isolated recently from the
marine sponge *Spongia zimocca* subspecies irregularia [33,34]. Zimoc lactone A showed a moderate cytotoxic activity against P388
cell lines.

![Diagram](image)

**Fig. (5).**

In this first subgroup, we can also include examples where the D-ring system is an anhydride, a lactol, or a double hemiacetal
functionality which is acetylated (Fig. 6). For example, compound 11 was isolated from the sponge *Dictyodendrilla cavernosa* and is
the first anhydride isolated from a marine sponge [22]. Lactol 12 also called *aplyroseol-15*, was isolated from *Aplysilla rosea* and is
characterised by an oxidation pattern between a lactone and an anhydride [24].

Compound 13 (R₁= R₂= R₃= H) was isolated from the sponges *Spongia officinalis* [35], *Chelonaplysilla violacea* [23] and
*Aplysilla var. sulphurea* [24]. Aplysillin (13, R₁= H, R₂= OAc,
R₃= H) has been found in the sponge *Aplysilla rosea* [36], though later other studies demonstrated that the sponge was Darwinella sp.
[14], and also in the sponge *Spongia officinalis* [27]. The molecule was inactive in a number of antimicrobial assays.

![Diagram](image)

**Fig. (6).**

Compound 13 (R₁= OAc, R₂= H, R₃= H) (12-epi-aplysillin) was found in the marine organism *Chromodoris luteoarea*, along with
the corresponding hydroxy derivative 13 (R₁= OH, R₂= H, R₃= H)
[37], which has also been found in the sponge *Spongia zimocca*
[38], together with 12-deacetyl aplysillin 13 (R₁= H, R₂= OH, R₃= H). They have shown antifeedant properties and therefore they are
suggested to be part of the chemical defense of these organisms. 12-
epi-aplysillin 13 (R₁= OAc, R₂= H, R₃= H) has also been found in the nudibranch *Chromodoris geminus*, along with the 7-acetoxy
derivatives 13 (R₁= R₂= H, R₃= OAc) and 7α-acetoxy-12-epi-
aplysillin 13 (R₁= OAc, R₂= H, R₃= OAc) [18]. More recently, a
new member of this group has been isolated and is characterised by a β-epoxide between the positions C-11 and C-12, compound 14.
This metabolite was isolated from the mollusk *Chromodoris obsola*
and presents a strong cytotoxicity against L1210 and KB
cancer cells [17].

This group, also includes a number of furanospongianes which
presents a furan ring D instead of the γ-lactone ring D (Fig. 7-9).
There are several examples which are charac-terised by different
substituents at C-19, compounds 15. These molecules were isolated
from the sponge *Spongia officinalis* and this dichloromethane
extract displayed antifungal activity [39]. Compound 15 (R= CO₂Me) was synthesised during that work by esterification with
ethereal

![Diagram](image)

**Fig. (7).**
heart rate of anesthetised cats [42]. Compounds 16 and other acetate derivatives have been isolated from the nudibranch Casella atromarginata as well [43]. However, compounds 17 and 18 were found in the sponge Hyatella intestinalis [41]. The two epimers of compound 18 (R=H), 3α and 3β, named spongiadiol and epispongiadiol, respectively, were also isolated from Australian Spongia species [9], and together with the compound 17 (R=OH), named isospongiadiol and found in Caribbean Spongia species [44], are active against herpes simplex virus type 1 and P388 cancer cells. They have also shown induction of apoptosis in human melanoma cells [45]. This series of compounds are also present in the sponge of the genus Rhopaloecides odorabile and it was demonstrated that the environmental conditions generates a considerable chemical variation [46].

From a Great Barrier Reef sponge of the genus Spongia, two new metabolites were isolated, compounds 19 and 20 (Fig. 8). Both were inactive in antitumor tests against P388 cancer cells [47]. Compounds 21 were isolated from the nudibranch Casella atromarginata [43], whereas compounds 22 and 23 were found in other Australian Spongia species [48].

More recently, Fontana and co-workers isolated several furanosponge acetates, compounds 24 (Fig. 9), from the mollusk Glossodoris atromarginata [49]. They also found the corresponding tetracete of tetroal 19. Several of these acetates had been previously found in the related mollusk Casella atromarginata [43].

Finally, within the group of furanosponge acetates it is worth to mention several metabolites characterised by a lactone ring forming the A-ring, compounds 25-27. For example, compounds 25 and 26 (R₁=CH₂OH, R₂=H) were isolated from a Great Barrier Reef sponge of the genus Spongia [47], in particular, compound 25 has shown certain cytotoxicity against P388 cancer cells.

Spongialactone A 26 (R₁=CH₃, R₂=H) is structurally related and was isolated from Spongia officinalis var. arabica [50]. Finally, lactones 27 were isolated from the sponge Spongia zimocca sensu var. [51], which was erroneously identified as Spongia matamata [30].

The last subgroup is composed by pentacyclic compounds, such as 28-29, having and additional ring E, which is a peculiar group of highly oxygenated metabolites (Fig. 10).

Schmitz and co-workers established the structure 28 (R₁=H, R₂=OCOPr) by X-ray analysis and suggested that the oxygenated positions of these compounds might act as a complexing moiety for cations and such complexation might play a role in the biological activity of these compounds. Compound 28 (R₁=H, R₂=OCOPr) also known as aplyroseol-1 is mildly cytotoxic in lymphomia leukemia PS cells [52]. Taylor and co-workers have also confirmed the absolute stereochemistry of 28 (R₁=H, R₂=OCOPr), except one stereocenter, by X-ray diffraction methods of the p-bromobenzoyl derivative [53]. Aplyroseol-1 (28, R₁=H, R₂=OCOPr) and aplyroseol-2 (28, R₁=H, R₂=OAc) have been found in the sponges Igernella notabilis [52], Aplysilla rosea [12] and Dendrilla rosea [13], and recently aplyroseol-2 (28, R₁=H, R₂=OAc) was isolated from the mollusk Chromodoris obsoleta showing cytotoxic activity (but no relevant anti-tumor activity in vivo) [17], as well as from Chromodoris insopinita [18].

Compound 28 (R₁=H, R₂=OCOPr) was also isolated from Igernella notabilis [52], and aplyroseol-3 (28, R₁=OH, R₂=OAc) was
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OCOPr), aplyroseol-4 (R1 = OAc, R2 = OCOPr), aplyroseol-5 (R1 = OCOPr, R2 = OH) and aplyroseol-6 (R1 = OCOPr, R2 = OAc) were isolated from Aplysilla rosea [12] and also from Dendrilla rosea (except aplyroseol-4) [13], though the known aplyroseol-3 (R1 = OH, R2 = OCOPr) was isolated for the first time from Aplysilla sp. [54]. In addition, aplyroseol-1 (R1 = H, R2 = OCOPr), aplyroseol-5 (28, R1 = OCOPr, R2 = OH), and aplyroseol-6 (28, R1 = OCOPr, R2 = OAc) are inhibitors of the enzyme phospholipase A2 (PLA2), an enzyme involved in inflammation processes [55].

Dendrillol-1 (28, R1 = R2 = H) and dendrillol-2 (28, R1 = R2 = OAc) were isolated from Dendrilla rosea [13], and the former was also found later in the mollusk identified as Ceratosoma brevicaudatum [19], along with compounds 29 (R1 = OCOPr, R2 = H, 17-β), 29 (R1 = OAc, R2 = H, 17-β), 29 (R1 = OAc, R2 = Ac, 17-α) and 29 (R1 = OCOPr, R2 = Ac, 17-α). The mollusk was ultimately identified to be Ceratosoma epicurium [20]. Dendrillol-1 (28, R1 = R2 = H) has proved to have cytotoxic activity on tumor cells. [21] More recently, it has been isolated compound 29 (R1 = H, R2 = Ac, 17-β), called acetyldendrillol-1, from the mollusk Cadlina luteomarginata [56], which was misassigned a 17-α configuration during its isolation [57].

Finally, several compounds with a derived intact spongian structure merit mention. For example, haumanamide 30 (Fig. 11), based on a nitrogenous amide was isolated from a Pohnpei Spongia sp. [58], which is active against KB cancer cells and LoVO (colon cancer). Polyrhaphin D 31 is also a novel isospongian diterpene in which a 2,3-fused tetrahydrofuran ring replaces the 3,4-fused tetrahydrofuran ring normally found in spongian diterpenes, which was isolated from the sponge Aplysilla polyrhaphis in 1989 [15].

![Fig. (11)](image-url)

Also, it is worth mentioning several structures with a isospongian skeleton, which was named marginatane skeleton. For example, marginatafuran 32 (R1 = COOH, R2 = H2) is a furanoditerpene isolated from the dorid nudibranch Cadlina luteomarginata, whose structure was solved by X-ray diffraction analysis [59]. This compound has also been found later in sponges of the genus Aplysilla [56], together with a derivative of marginatone 32 (R1 = CH3, R2 = O), which was isolated from the sponge Aplysilla glacialis [60], the 20-acetoxy marginatone 32 (R1 = CH2OAc, R2 = O) was isolated, however, from the skin extracts of the nudibranch Cadlina luteomarginata [56].

Degraded or Rearranged Spongiane Skeleton

The second main group is formed by a number of norspongianes, secospongianes and other compounds with a rearranged carbon skeleton.

Norrisolide (33) is the first known member of rearranged spongiane diterpenes. It was firstly isolated by Faulkner and Clardy from the dorid nudibranch Chromodoris norrisi and its structure was determined by single-crystal X-ray diffraction analysis [61]. Structurally, norrisolide belongs to a family of natural products that share a fused γ-lactone-γ-lactol ring system attached to a hydrophobic bicyclic core and includes dendrillolide A (34), initially assigned to dendrillolide B and dendrillolide C (35) (Fig. 12), for example, which were found in the Palauan sponge Dendrilla sp., later reidentified as Chelonaplysilla sp. [62], along with norrisolide (33) as a minor constituent and dendrillolide B whose structure is still unknown [63,64].

![Fig. (12)](image-url)

Norrisolide (33) has also been found in other marine species (see below) and displays PLA2 inhibition [55], ichthyotoxicity to Gambusia affinis [65], as well as Golgi fragmentation [66].

Dendrillolide A (34) has also been found in other marine species (see below) and biologically inactivates PLA2 at 2 μg/mL [55].

Aplyviolene (36) was also isolated from Palauan sponge Dendrilla sp. though this structure was initially assigned to dendrillolide A. The X-ray analysis of 36 isolated from the sponge Chelonaplysilla violacea confirmed this initial misassignment [23,67,68]; aphyviolene (37) was also found in this sponge (Fig. 13).

The chemical investigation of the sponge Aplysilla sulphurea yielded as major component aphyphilurine (38) (Fig. 13) and a small amount of aphyphiluride whose structure was not elucidated. The structure 38 was confirmed by a single-crystal X-ray determination [13].

The studies of the constituents of the Mediterranean sponge Spongionella gracilis led to the structure elucidation by spectral analysis of gracilin A (39) and gracilin B (40), which represents the first bis-nor-diterpene observed from a marine sponge, together with two gracilin A derivatives (41-42) and spongionellin (43) which possess a new carbocyclic skeleton (Fig. 14) [70-72]. Gracilin A inactivates PLA2 at 2μg/mL [55].
The sponges *Darwinella* sp. and *Darwinella oxeata* contain the known rearranged spongiane aplysulphurin 38 and the new compounds tetrahydroaplysulphurins-1 (44), -2 (45), and -3 (46) (Fig. 15) [14]. The structure of tetrahydro-aplysulphurin-1 (44) was confirmed by X-ray studies [73], and also it has been isolated from the dorid nudibranch *Cadlina luteomarginata* [60].

Further chemical studies of the sponge *Spongionella gracilis* led to the discovery of spongialactone (51) (Fig. 17) whose structure was deduced from chemical and physico-chemical evidence [76]. Also the two minor norditerpenes (52) and (53) were characterised by spectral data and derivatisation reactions [77].

From the antarctic sponge *Dendrilla membranosa* two new rearranged spongianes were isolated and identified by spectral data and chemical correlations. 9,11-dihydrogracillin A (54) and membranolide (55) (Fig. 18) showed growth inhibition of *Bacillus subtilis*, also membranolide was mildly active against *S. aureus* [78].

The X-ray analysis of a keto derivative of 9,11-dihydro-gracillin A (54) confirmed the structure fixing the previous unknown stereochemistry at C-10 [79]. 9,11-dihydrogracillin A (54) has also been isolated from the Northeastern Pacific dorid nudibranch *Cadlina luteomarginata* and the sponge *Aplysilla* sp [56].
The investigation of two Red Sea Dysidea sponges yielded ten new rearranged spongianes, shahamins A-J (56-65), together with known aplyviolene (37). Structures of all compounds were elucidated from spectral data, mass spectra, and by comparison with other related known diterpenes (Fig. 19) [80,81]. Shahamin F (61) has also been found in the nudibranch Chromodoris annulata [18].

From the Californian sponge Aplysilla polyrhaphis were isolated the known compounds norrisolide (33), aplyviolene (36), macfarlandin E (37), shahamin C (58), and three novel rearranged diterpenes, polyrhaphins A-C (66-68) (Fig. 20) [15]. Norrisolide (33), macfarlandin E (37), shahamin C (58), and polyrhaphin A (66) were also found in the dorid nudibranch Chromodoris norrisi collected in the same locality as Aplysilla polyrhaphis, which is the presumed dietary source. Shahamin C (58), and polyrhaphin C (68) inhibited feeding by the Gulf of California rainbow wrasse Thalassoma lucasanum. Polyrhaphin C (68) also showed antimicrobial activity against Staphylococcus aureus and Bacillus subtilis while aplyviolene (36) was also active against B. subtilis. Polyrhaphin C (68) has also been isolated from the Cantabrian nudibranch Chromodoris luteorosea and displayed ichthyotoxic activity to Gambusia affinis [65].

A reinvestigation of the Palauan sponge Dendrilla sp. led to the isolation of four novel rearranged spongiane diterpenes (69-72) (Fig. 21) in addition to known norrisolide (33), dendrillolide A (34), and dendrillolide C (35). The structure of the four novel metabolites were determined by interpretation of spectral data [64].

The skin chemistry of the Indian Ocean Nudibranch Chromodoris cavae was examined leading to the isolation of chromodorolide A (73) (Fig. 22), a putative repellent which displays both cytotoxic and antimicrobial activities [82]. A few years later, the same authors reported the isolation of chromodorolide B (74) from the same nudibranch [83].

The degraded and rearranged diterpenoid gluciolide (75) (Fig. 22) was isolated from the dorid nudibranch Cadlina luteomarginata and the sponge Aplysilla glacialis. The structure was solved by extensive spectroscopic analysis and chemical derivatisation [60,84].

The chemical study of the nudibranch Chromodoris luteorosea yielded luteorosin (76) (Fig. 23), along with the known macfarlandin A (47). Both compounds presented ichthyotoxic activity [65,85].
The encrusting sponge *Aplysilla tango* gave five degraded spongian diterpenes, including the known gracilin A (39), aplytandiene-1 (77), aplytandiene-2 (78), aplytan-gene-1 (79) and aplytangene-2 (80) (Fig. 23) [86].

Three new rearranged spongiane-type diterpenes were isolated from a Red Sea *Dysidea* species along with known norrisolide (33). Thus, the structures of norrlandin (81), seco-norrisolide B (82) and seco-norrisolide C (83) (Fig. 24) were elucidated from intensive NMR experiments and both norrisolide (33) and norrlandin (81) displayed cytotoxic activities [87].

The Pohnpeian sponge *Chelonaplysilla* sp. contains the known spongiane-derived diterpenes norrisolide (33), dendrillolide A (34), dendrillolide D (71), aplyviolene (36), and 12-desacetoxyshahamin C (70). Three novel rearranged spongiane-type diterpenes, chelona-plysin A-C (84-86) (Fig. 24) were identified by interpretation of spectral data and chemical correlation with known compounds. Aplyviolene (36), chelona-plysin B (85), and chelona-plysin C (86) exhibited antimicrobial activity against the bacterium *Bacillus subtilis* [62]. Chelona-plysin C (86) is also a constituent of the Cantabrian nudibranch *Chromodoris luteorosea*, presents ichthyotoxicity to *Gambusia affinis* [65] and its structure has been confirmed by a single-crystal X-ray study [88].

The skin extracts of the Sri Lankan dorid nudibranch *Chromodoris gleniei* contained dendrillolide A (34), 12-desacetoxyshahamin C (70) and the new shahamin K (87) (Fig. 25) [18].

The sponge *Aplysilla glacialis* gave four new rearranged and/or degraded “spongian” terpenoids: cadlinolide A (88), cadlinolide B (89), aplysillolide A (90), and aplysillolide B (91) (Fig. 26). The structures were determined by extensive spectroscopic analysis and chemical interconversions, the structure of cadlinolide A (88) was further confirmed by X-ray diffraction analysis [60].

The New Zealand sponge *Chelonaplysilla violacea* contains known norrisolide (33), dendrillolide A (34), aplyviolene (36), chelonaplysin C (86), and a series of new rearranged spongianes:
cheloviolenes A-F (92-97) and cheloviolin (98). The structures were established by analysis of the spectroscopic data. This study indicated that the structure assignment for chelonaplysin B (85) was incorrect, since its 'H NMR spectrum was identical to that of cheloviolene A (92). Separate proof for the structure of cheloviolene A (92) was obtained by a single-crystal X-ray determination [89].

Another investigation on the antarctic sponge *Dendrilla membranosa* led to the isolation of dendrillin (99) (Fig. 28), a spongiane-derived norditerpene related to 9,11-dihydro-gracillin A (54). Dendrillin (99) displayed no deterrent effect towards the major sponge predator, the sea star *Perknaster fuscus* [90].

The chemical study of the South African nudibranch *Chromodoris hamiltoni* led to the isolation of the chlorinated homo-diterpenes hamiltonins A-D (100-103) (Fig. 28), which possess an unusual 3-homo-4,5-seco-spongiane carbon framework [69]. Hamiltonins A (100) and B (101) showed no significant activity in antimicrobial and cytotoxicity bioassays.

The chemical investigation of skin extracts of North-eastern Pacific nudibranch *Cadlina luteomarginata* led to the isolation of the novel seco-spongian (104) (Fig. 29) [56]. A number of seco-spongianes were isolated from *Aplysilla rosea* and are characterised by an \( \gamma \)-lactone between C15 and C17 [24]. Thus, aplyroseols -8 to -12 and dendrillol-3 and dendrillol-4 present the structure as drawn in 105, typical of *ent-isocopalanes* (Fig. 29). Aplyroseol-13 (106) was also isolated from this sponge and possess a carbon skeleton similar to several norditerpenoids isolated from the sponge *Aplysilla pallida*: aplypallidenone (107),
aplypallidoxone (108), aplypallidione (109), and aplypalli-dioxone (110) (Fig. 30). The structures were elucidated by spectroscopic studies and the crystal structures of aplypallidenone and aplypallidioxone were determined by X-ray diffraction methods [91].

Further studies on the Antarctic sponge *Dendrilla membranosa* by different research groups have led to the isolation of novel rearranged spongiane members. For example, dendrinolide (111) (Fig. 31) which was isolated together with known 9,11-dihydrogracilin A (39).

This structure was elucidated by interpretation of spectral data and comparison with data for similar compounds [92].

Other researchers found in the same sponge, the new compounds 112-115 (Fig. 31). Compound 112 is a nor-diterpene related to known gracilin A (39) and its structure containing a γ-methyl butenolide moiety, was determined by spectroscopic data interpretation. Compound 113 is a rearranged diterpene related to known tetrahydroaplysul-phurin-1 (44). Compound 114 is very similar to 113, the main difference between them is the substitution of the carbonyl group of the lactone ring of 113 for a hemiketal carbon. Finally, compound 115 can be seen as a derivative of 114 by the loss of methanol as a consequence of an intramolecular displacement of the hemiketalic methoxy group by the free carboxylic acid to give the corresponding δ-lactone [93].
Also another research group working with *Dendrilla membranosa* were able to discover new rearranged spongianes related to membranolide (55). Thus, membranolides B-D (116-118) (Fig. 32) were isolated along with known membranolide (55), aplysulphurin (38), and tetrahydroaplysulphurin (44). Membranolides C (117) and D (118) display Gram-negative antibiotic and antifungal activities [94].

![membranolide B](image1)

(116) membranolide B

![membranolide C](image2)

(117) R_1 = OMe, R_2 = H membranolide C

![membranolide D](image3)

(118) R_1 = H, R_2 = OMe membranolide D

In the course of a NMR-directed sponge extract screening program, an extract of *Chelonaplysilla violacea* was found to contain compounds of interest. After intensive isolation work, eight new spongiane diterpenes were identified, including the known tetrahydroaplysulphurin-1 (44) and cadlinolide B (89).

Two of the new metabolites are related to cadlinolide B and were therefore reported as cadlinolide C (119) and D (120) (Fig. 33). Pourewanone (121) presents a new carbon skeleton, being the first example of a formate compound of marine origin, while compounds 122-124 are lactone seco-acid derivatives of cadlinolide B (Fig. 33) [95].

![pourewanone](image4)

(121) pourewanone

![pourewic acid A](image5)

(122) pourewic acid A

![15-methoxypourewic acid B](image6)

(123) 15-methoxypourewic acid B

![methylpourewate B](image7)

(124) methylpourewate B

Pourewic acid A (122) was inactive in both leukaemia cell line and in antimicrobial tests. Pourewic acid A (122), methylpourewate B (124) and cadlinolide C (119) showed moderate anti-inflammatory activity. Pourewic acid A (122) has been found simultaneously in the sponge *Dendrilla membranosa*, see compound 114, however, the reported optical rotation was of opposite sign. Similarly, also cadlinolide C (119) has been found in the sponge *Dendrilla membranosa*, see compound 115.

The first chemical study of patagonian nudibranchs, in particular the dorid nudibranch *Tyrinna nobilis* has led to the isolation of a new seco-11,12-spongiane, named tyrinnal (125) (Fig. 34) [96].

![tyrinnal](image8)

(125) tyrinnal

![chromodorolide C](image9)

(126) chromodorolide C

The small scale extract of an *Aplysillid* sponge exhibited potent cytotoxicity. The isolation of the bioactive substances of the whole sponge, tentatively identified as *Aplysilla sulfaurea*, led to the isolation of known chromodorolide diterpenes chromodorolide A (73) and B (74), which were reported from the nudibranch *Chromodoris cavae*, along with the new derivative chromodorolide C (126) (Fig. 34). All chromodorolides displayed significant cytotoxicity against P388 cell line but not useful at low concentrations (1 µg/mL). Chromodorolide A (73) also showed nematocidal activity against the free-living larval stages of the parasitic nematodes *Haemonchus contortus* and *Trichostrongylus colubriformis* [97].

Using an assay to detect inhibitors of the lyase activity of DNA polymerase β, the bioassay-directed fractionation of an extract of an unidentified sponge of the family Demospongiae led to the isolation of two new and bioactive bis-norditerpenoids, compounds (127) and (128) (Fig. 35) [40].

![extract](image10)

(127) R_1 = CO_2Me, R_2 = OH

(128) R_1 = CO_2H, R_2 = OH

Two new rearranged spongiane diterpenes named omriolide A (129) and omriolide B (130) (Fig. 36) have been isolated from the southern Kenyan sponge *Dictyodendrilla aff. retiara* [98]. Omriolide A (129) possesses a unique trioxatricyclodecane ring system. The structures of both diterpenes were elucidated by interpretation of MS results and NMR data. Both omriolide A and B lacked cytotoxicity against several tumor lines as well as any activity on the Golgi membrane, on which norrisolide (33) was found to be highly active [66].

Two new rearranged spongiane diterpenes named omriolide A (129) and omriolide B (130) (Fig. 36) have been isolated from the southern Kenyan sponge *Dictyodendrilla aff. retiara* [98]. Omriolide A (129) possesses a unique trioxatricyclodecane ring system. The structures of both diterpenes were elucidated by interpretation of MS results and NMR data. Both omriolide A and B lacked cytotoxicity against several tumor lines as well as any activity on the Golgi membrane, on which norrisolide (33) was found to be highly active [66].
### Table 1. Biological Activity Found in Compounds 1-130

<table>
<thead>
<tr>
<th>Compound</th>
<th>Biological Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoagatholactone, 1</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>Aplyroseol-7 (4, R₃=H, R₄=Me, R₅=OAc)</td>
<td>Antifeedant and cytotoxic</td>
</tr>
<tr>
<td>Spongianal (4, R₃=R₄=H, R₅=CHO)</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>Spongian-16-one (4, R₃=H, R₅=Me, R₆=H)</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>Lactones 5</td>
<td>Antimicrobial and cytotoxic</td>
</tr>
<tr>
<td>Dorisenone A (5,R₃=R₄=OAc; R₅=H; R₆=OH)</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>Dorisenone B (5,R₃=OAc; R₄=R₅=H; R₆=OH)</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>Dorisenone C (6, Δ¹ R= Me)</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>Dorisenone D (5,R₃=R₄=OAc; R₅=R₆=H)</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>Zimoclactone A, 9 (R=OH)</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>12-epi-aplysillin 13 (R₃=OAc; R₄=R₅=H)</td>
<td>Antifeedant</td>
</tr>
<tr>
<td>12-epi-deacetyl-aplysillin 13 (R₃=OH, R₄=R₅=H)</td>
<td>Antifeedant</td>
</tr>
<tr>
<td>12-deacetyl-aplysillin 13 (R₃=H, R₄=OH, R₅=H)</td>
<td>Antifeedant</td>
</tr>
<tr>
<td>Epoxide 14</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>Furans 15</td>
<td>Antifungal and inhibition of DNA polymerase β lyase</td>
</tr>
<tr>
<td>Spongiosiol 16 (R=H)</td>
<td>Antihypertensive</td>
</tr>
<tr>
<td>Spongiodiols 17 and 18</td>
<td>Antiviral and cytotoxic</td>
</tr>
<tr>
<td>Furanolactone 25</td>
<td>Cytotoxic</td>
</tr>
<tr>
<td>Aplyroseol-1 (28, R₃=H, R₅=OCOPr)</td>
<td>Cytotoxic and phospholipase A₂ (PLA₂) inhibition</td>
</tr>
</tbody>
</table>

### SYNTHESES OF SPONGIANE DITERPENOIDS

Several syntheses have appeared within the last twenty five years and we will classify them in three main groups. We will also include the synthetic studies developed so far, thus, we will describe the syntheses from other natural products, syntheses using biomimetic approaches and finally other approaches including the total synthesis of rearranged spongianes.

Generally, despite the interesting molecular architectures and biological properties of spongianes, there have been relatively few synthetic studies towards their synthesis. In the 1980s, most of the
synthetic studies towards spongiane-type diterpenes addressed mainly the synthesis of isoaga-tholactone and the preparation of simple furanospongianes.

In the next decade, syntheses of several pentacyclic spongianes were accomplished together with the development of biomimetic-like strategies for the synthesis of more complex furanospongianes and isoagatholactone derivatives. Over the last three or four years, some structure-activity studies have emerged together with several approaches towards more complex oxygenated spongianes.

Syntheses from Other Natural Products

Manool (131), copalic acid (132), sclareol (133), labdanolic acid (134), abietic acid (135), and carvones (136) (Fig. 37) have been used for the preparation of optically-active spongianes. Naturally occurring racemic labda-8(20),13, dien-15-oic acid (copalic acid) has also been used for preparing racemic compounds.

These starting materials were converted into versatile tricyclic intermediates having the characteristic ABC ring system of spongianes (Scheme 1) such as ent-methyl isocopalate (137), podocarp-8(14)-en-13-one (138) and phenanthrenones (139-140). Several strategies have been reported to build up the necessary ring D from those key intermediates, preferably as a furan ring or a γ-lactone ring. The choice of podocarpenone 138 as starting material assures the absolute stereochemistry at C-5, C-9 and C-10. Moreover, the election of methyl isocopalate-137 phenanthrenones 139-140 also assures the stereochemistry of the additional methyl group at C-8 of the ring system.

In 1981, Rúveda et al. reported the first synthesis of a natural spongiane diterpene [99]. (+)-Isoagatholactone (1) was synthesized from tricyclic ester 137 prepared from (+)-manool (131) in three synthetic steps (Scheme 2). Two successive oxidations of manool followed by acid-catalyzed cyclization of methyl copalate 141 gave the known intermediate 137 [100], also obtained from grindelic acid (3) by Minale et al. during the structure elucidation of (+)-1 [10]. The required functionalization of the allylic methyl group was achieved by sensitized photooxygenation to give allylic alcohol

\[ \text{Scheme 1. Precursors of spongiane diterpenoids prepared from natural sources.} \]

\[ \text{Scheme 2. Rúveda’s synthesis of natural isoagatholactone.} \]
The allylic rearrangement of 142 with simultaneous lactonization to give lactone 143, followed by reductive opening of the lactone ring gave the known degradation product of isoagatholactone, diol 144 [10]. Finally, allylic oxidation with MnO₂ gave (+)-isoagatholactone (1) in 3.9% yield from racemic methyl isocopalate 137 [102].

Contemporaneous studies by Nakano et al. described soon after the synthesis of racemic isoagatholactone using a similar strategy in which the reaction conditions were different as well as the starting material, which was racemic copalic acid (Scheme 3) [101]. Thus, (+)-isoagatholactone (1) was prepared in 11.6% yield from racemic methyl isocopalate 137 [102].

Unnatural (+)-isoagatholactone has also been prepared by Rúveda et al. using the same sequence of steps starting from methyl isocopalate (+)-137 readily prepared from copalic acid (Scheme 4) [103,104]. The interest in spongiane-type diterpenes possessing a material, which was racemic copalic acid (Scheme 132) 3.5% H₂SO₄, dioxane, 83%

In 1984, another synthesis of natural isoagatholactone (+)-(1) was reported by Vlad and Ungur (Scheme 6) [105]. The route is identical to that of Rúveda since the same diol 144 was oxidized by MnO₂ to give isoagatholactone (see also Scheme 2). In this case compound 144 was prepared in 48% yield by allylic oxidation of isocopalate 155 with SeO₂ in EtOH, though Rúveda and colleagues reported that this oxidation on isocopalate 137 and alcohol(isocopalate) 155 led to complex mixtures of products [104].

Isocopalate 155 was prepared by acid-catalyzed cyclization of an acetate mixture (154) (Scheme 6) [106]. These authors have used chiral isocopalate 155 and diol 144 for the synthesis of sponge metabolites such as aldehydes 156 and 157 by consecutive oxidations [107]. These aldehydes have also been prepared in racemic form starting from (±)-137 (methyl isocopalate) via the racemic diol (±)-144 [108].

More recently, Urones et al. reported the preparation of the useful intermediate in spongiane synthesis, ent-methyl isocopalate (137), from sclareol [111] (133) and labdanolic acid [112] (134), two abundant bicyclic natural products (Scheme 9). Thus, sclareol (133), a major terpenic constituent of Salvia sclarea, was acetylated quantitatively with acetyl chloride and N,N-dimethylaniline,
affording the diacetyl derivative 168, whose isomerization with bis(acetonitrile)palladium (II) chloride led to the diacetate 169 (89%). The selective hydrolysis of the allylic acetoxy group of 169 led to hydroxy acetate 170, whose oxidation with MnO\textsubscript{2} gave aldehyde 171. Subsequent oxidation of 171 with NaClO\textsubscript{2} followed by esterification with diazomethane afforded methyl ester 172. Regioselective elimination of the acetoxy group and cyclization with formic acid led to ent-methyl isocopalate (137) in 49% overall yield from sclareol (8 steps). Labdanolic acid (134), the main acid component of \textit{Cistus ladaniferus}, is firstly esterified with diazomethane, and then dehydrated and isomerized with I\textsubscript{2} in refluxing benzene to give methyl labden-15-oate 174. Ester 174 is
bond was introduced by bromination with phenyltri-methyl-
with TPAP gave the ketone
Scheme 7. Rúveda’s syntheses of (±)-spongia-13(16),14-diene (15, R= CH3) and (±)-spongian (164).

Scheme 8. Nakano’s synthesis of (±)-spongia-13(16),14-diene.

converted into unsaturated ester 176 by elimination of phenyl-
selenic acid from 175, and then cyclized with formic acid to afford ent-methyl isocopalate (137) in 45% overall yield from labdanolic acid (5 steps).

The same authors showed how this material, ent-methyl isocopalate (137), can be converted into 9,11-secosop-gianes, one of the most widespread subgroups of spongianes (Scheme 10) [113]. To this end, the introduction of a Δ 15 double bond and subsequent cleavage was investigated. The method failed with tricyclic derivatives of 137, no cleavage conditions were successful. The strategy was then applied to other tetracyclic derivatives and led to the synthesis of secospongiane 180. The precursor of secospongiane 180 was the known hydroxy-isocopalane 142, which was again synthesized using Rúveda’s method as outlined in Scheme 7 [108]. Treatment of 142 with OsO4 followed by oxidation with TPAF gave the ketone 177 in 68% yield. The desired double bond was introduced by bromination with phenyltri-methyl-
ammonium perbromide (PTAP) and subsequent elimination with Li2CO3/LiBr to give the α,β-unsaturated ketone 178. Reduction of 178 and acetylation gave the compound 179 which was subjected to ozonolysis to afford the highly functionalized secospongiane 180 in 65% yield.

The readily available abietic acid (135) together with other naturally occurring resin acids isolated from conifer oleoresins are common starting materials for the synthesis of natural products and numerous diterpene derivatives [114,115]. (+)-Podocarp-8(14)-en-
13-one 138 (Scheme 11) is a versatile chiral starting material easily prepared from commercially available (-)-abietic acid or colophony [116]. Recently, the enantioselective biomimetic synthesis of this chiral building block has been described [117]. In the course of synthetic studies on the chemical conversion of podocarpane diterpenoids into biologically active compounds, Arnó et al. achieved an efficient synthesis of natural (+)-isagatholactone (1) and (-)-spongia-13(16),14-diene (15, R= CH3) starting from chiral podocarpene 138 [118]. Compound 138 was converted in six steps into the common intermediate 186 (40% overall yield), appropriately functionalized for the elaboration of the D-ring system (Scheme 11).

The necessary 8β-methyl group was introduced by stereoc cone controlled acetylenic-cation cyclization of acetylenic alcohol 183, which was prepared from 138 by epoxidation, silica gel catalysed eschenmoser ring-opening reaction and addition of methylolithium. The instability of enol trifluoro-acetate 184 (~70% overall yield from 138) to hydrolysis required in situ incorporation of the hydroxymethyl side chain to give hydroxy ketone 185 which was isomerized at C-14, to afford compound 186, upon treatment with methanolic sodium methoxide. This intermediate was used in two separate approaches to complete the D ring of target spongianes. In the first approach, the required homologation at C-13 was introduced by carbynylation of triflate 187, subsequent deprotection in acidic media afforded directly the desired isagatholactone (+)-1 (20% overall yield from 138). On the other hand, addition of trimethylsilyl cyanide provided the carbon at C-13, compound 188. Subsequent hydrolysis with concomitant deprotection, lactonization, and dehydration occurred by treatment with a mixture of hydrochloric acid and acetic acid at 120 °C in a sealed tube to give lactone 189, which was transformed into (15, R= CH3) via reduction to its corresponding lactol, followed by dehydration and aromatization in acidic media (Scheme 11). (−)-Furanospongiane 15 (R= CH3) was thus prepared in eleven steps from 138 in 28% overall yield.
In the early 1990s, the same research group described the first enantioselective synthesis of pentacyclic spongianes [119,120]. To date the synthetic routes reported for these natural products are based on this one. Chiral podocarpenone 138 was converted into the cyclobutene-ester 191 by photo-chemical reaction with acetylene, nucleophilic carboxylation and reductive dehydroxylation as indicated in Scheme 12. Compound 191 was hydrolized under alkaline conditions and then cleaved with ozone to afford (-)-dendrillol-1 28 (R= H), the simplest member of the pentacyclic spongianes. This synthetic sequence was later shortened by reductive cyanation with tosylmethyl isocyanide (TosMIC) to give nitriles 193, which were subjected to alkaline hydrolysis in ethylene glycol ethyl ether and ozonolysis. The key feature of the strategy is the cleavage of a cyclobutene ring to form a latent acid-dialdehyde unit, compound 192, which spontaneously underwent internal lactone-hemiacetal formation. Based on this synthetic plan, the same authors have prepared related C7-oxygenated congeners [121] (aplyroseol-1 (28, R= OCOPr), aplyroseol-2 (28, R= OAc) and deacetyl- aplyroseol-2 (28, R= OH)) upon stereoselective introduction of a hydroxy function at the 7-position in the starting material 138 (Scheme 13). Formation of the dienyl acetate of 194 followed by oxidation with m-chloroperbenzoic acid gave the hydroxy enone 195 in 74% yield which was elaborated to give hydroxy ester 197, precursor of the pentacyclic diterpenes. It is worth mentioning that the homologation at C-13 was conducted more efficiently by cyanophosphorilation followed by reductive elimination to give nitriles 196.

The versatility of intermediate 191 also led to further investigations which culminated with the synthesis of acetyldendrillol-1 202 and revision of its stereochemistry at C-17, as well as the synthesis of tetracyclic spongianes functionalized at C-17 (Scheme 14) [57]. The introduction of a cyanophosphorilation step improved the synthesis of 191 which was then converted into the intermediate dialdehyde 201. Acetylation of compound 201 with AcOH/Na2O and sulfuric acid (1%) at 65 ºC gave exclusively natural acetate 202, while reduction followed by lactonization led to (-)-spongian-16-oxo-17-al 204 (Scheme 14). This compound was next converted into (-)-aplyroseol-14 206, having an unprecedented δ-lactone unit for spongianes, and its structural isomer 207 which permitted the structural reassignment of this natural product [122]. This fact was also confirmed by X-ray crystallography of compound 206 [26].

Recently, the same laboratory reported a couple of structure-activity relationship studies of the spongianes prepared in the group including the synthesis and biological evaluation of novel C7,C17-functionalized spongianes (Scheme 15) [21,123]. Some of these new sponge derivatives possess an α-acetoxy group at C-15 and were obtained from pentacyclic samples using an optimized hemiacetal-ring opening under basic conditions. The synthetic protocol developed for the synthesis of 204 was also used to convert hydroxy-cyclobutene 197 into spongianal 210, 211 and 212 which were evaluated against HeLa and HEP-2 cancer cells being compound 212 the most active.

Arnó et al. have also achieved the total synthesis of (-)-spongia-13(16),14-diene (15, R = CH3) starting from (+)-carvone via the phenanthrene 215, which contains the two necessary methyls groups at C-8 and C-10, and an useful carbonyl group at C-14 for the final assembly of the D ring (Scheme 16) [124].
The strategy is based on a C→ABC→ABCD ring annulation sequence in which the key step for the preparation of the tricyclic ABC-ring system present there was an intramolecular Diels-Alder (IMDA) reaction [125]. The whole sequence takes 13 steps to furnish the furanospongiane (15, R=CH₃) in 9% overall yield.

Carvone is first alkylated twice to introduce a three carbon side-chain which is then elongated using a wittig-type reaction to give 213. Formation of the silylenolether of 214, which upon IMDA reaction in toluene at 190 ºC during 7 days provided stereoselectively compound 215 in 95% overall yield. The tricyclic system 215 is already an useful intermediate for the synthesis of norspongianes and other spongianes functionalized in ring A as well as other terpenes containing the same ABC-ring system. Cyclopronation of the enol double bond followed by homologation of the carbonyl group at C-14 led to enol ether 216. After completing the desired carbon framework, functionalization at C-16 was carried out by isomerization of the double bond in 217, then careful epoxidation followed by treatment with p-TSA gave the furanoketone 219. Compound 219 is a potential precursor of other furanospongianes functionalized in ring A. Finally, Wolff-Kishner reduction of 219 afforded (15, R=CH₃) in 75% yield.

A new strategy towards oxygenated spongianes using (-)-carvone as starting material has recently been described by Abad et al. [126] as outlined in Scheme 17. This synthetic sequence follows a B→AB→ABC→ABCD approach in which carvone is first converted into the decalone 220 (AB system) by alkylation and cyclization in acidic media. The construction of the C ring needed an intramolecular Diels-Alder reaction (IMDA) reaction to give Diels-Alder adduct 226. Therefore, decalone 220 was transformed into the IMDA precursor 225 by homologation at C-9, epoxide opening, wittig reaction and introduction of the dienophile moiety. The desired cyclodaddition took place at 112ºC for 17 h to give the...
Scheme 13. Arnó’s syntheses of (-)-aplyroseol-1 (28, R = OCOPr), (-)-aplyroseol-2 (28, R = OAc) and (-)-deacetylaplyroseol-2 (28, R = OH).

Scheme 14. Arnó’s syntheses of (-)-acetyldendrillol-1 (202), (-)-spongian-16-oxo-17-al (204), (-)-aplyroseol-14 (206) and (-)-isoaplyroseol-14 (207).

Scheme 15. González’s synthesis of C7,C17-functionalized spongianes.
Diels-Alder adduct 226 in 95% yield. This was next elaborated using a regioselective ring-opening of a dihydrofuran ring to give the C7,C11-functionalized spongiane lactone 228 after hydrolysis and epoxidation with \( \text{t-BuOOH} \) and \( \text{VO(acac)}_2 \). Based on this synthetic plan, Abad and co-workers continued the development of several studies for the synthesis of spongiane diterpenes related to natural dories-nones (see Fig. 3). Therefore, following the same strategy B→AB→ABC→ABCD for the ring-system construction they used the key epoxydecalone 222, which
was further elaborated to the Diels-Alder precursor 225 (Scheme 17). Other Diels-Alder precursors were also synthesized from 223 for intermolecular Diels-Alder reactions but provided low yields using dimethyl acetylene-dicarboxylate (DMAD) as dienophile (Scheme 18) [127]. The synthesis starts with alquilation with LDA of the α-position of the enone. Further alquilation with an allyl bromide gave 229, another olefination led to 229 which after Dess-Martin oxidation, sodium borohydride reduction and protection with TBDMS and reaction with DMAD gave mixture of 231 in low yield. Alternatively, 229 is propargylated with allyl propargyl bromide.

Introduction of the methoxycarboxylate and final reaction in toluene at 112 ºC gave the desired Diels-Alder diene 226. Thus, by using an IMDA reaction the compound 226 was formed and used to further introduce the required functionalities and the construction of the D ring system (Scheme 19). The regioselective ring-opening of the dihydrofuran ring of 226 gave initially the corresponding 7-acetoxy-15-iodo-derivative, which rapidly underwent lactonization to afford the γ-lactone 227 in nearly quantitative yield. The structure of 227 was initially assigned on the basis of a detailed spectroscopic NMR study, and final proof of the structure was obtained by single-crystal X-ray diffraction analysis.

Scheme 18. Abad’s synthesis of advanced intermediates for the preparation of C7,C11-functionalized spongianes from (-)-carvone.

Scheme 19. Abad’s synthesis of C7,C11-functionalized spongianes (232,233,237,238) from (-)-carvone.
Unfortunately, all attempts to introduce the required oxygenated function present in natural dorisenones at C-11 were unsuccessful. Following the above mentioned extensive synthetic studies for the preparation of dorisenone diterpenes of the spongiane family, Abad and co-workers have recently adapted their synthetic sequences for the synthesis of dorisenone C (6, Δ13 R = Me) (Fig. 3) [128]. They have developed a B→AB→ABC→ABCD approach starting from R-(-)-carvone, in which the known hydroxyaldehyde (AB rings) (Scheme 18) is the key intermediate for the preparation of different Diels-Alder precursors, since the key step for the formation of the C ring is an intramolecular Diels-Alder reaction (Scheme 20). Firstly, the Diels-Alder precursor 241 was prepared from 223 following standard reaction conditions used previously by the same group. Unfortunately, this precursor did not produce the desired Diels-Alder adduct but a product of retro-hetero-ene rearrangement of the propargylic ether moiety instead. Thus, the enone 242 was formed in good yield. To avoid the sterically demanding group of the diene moiety, the preparation of the dienol carbonate 244 was undertaken and thus it was envisaged the reduction of the retro-hetero-ene rearrangement product. In fact, the strategy did work but the product of the rearrangement 245 was still the main product of the intramolecular Diels-Alder reaction. Though in moderate yield the desired compound 246 was obtained and the sequence proceeded with it. Opening of the dihydrofuran ring of 246 gave rise to product 247 as a result of in situ lactonization. The cleavage of the ester groups and oxidation gave diketone 249 which was reduced with borane-THF complex to give alcohol 250. Further reduction with DIBAL-H gave triols 251 in which the lactol moiety was reoxidized with MnO2 to give the corresponding lactone 252. Final diacetylation of 252 gave the synthetic natural product dorisenone C (6, Δ13 R = Me, Fig. 3) whose data were in complete agreement with those reported earlier for the natural product and hence establishing the absolute configuration of the natural product.

During these synthetic studies several unnatural furanoditerpenes were also prepared from lactone 250 by reduction and dehydration to give the furan ring present in 253 and 254 (Scheme 21).
Finally, we describe how recently Ragoussis and co-workers have converted natural (-)-sclareol 133 into the furanoditerpene (-)-marginatone 32 (R₁= CH₃, R₂= O, Fig. 11) (Scheme 22) [172]. The authors converted scclareol 133 into (+)-coronarin E 257, using minor modifications of reported procedures, which by regioselective hydrogenic oxidation and stereocontrolled-intramolecular electrophilic cyclization gave the tetracyclic marginatane-type diterpene 259. Subsequent allylic oxidation of 259 afforded the synthetic (-)-marginatone 32 whose spectroscopic data were identical to those reported for the natural product. The synthesis starts with the preparation of the ambergris odorant, (-)-γ-bicyclonomafarnesal 255 from scclareol 133 in 7 steps and 52% overall yield. The coupling of 255 with 3-lithiofuran led to a mixture of two diastereomeric alcohols in 78% overall yield. Dehydration of this mixture in refluxing HMPA gave (+)-coronarin E 257 in high yield (76%) (Scheme 22). Partial reduction of the side chain double bond of 257 gave (+)-dihydrocoronarin E 258 and a subsequent intramolecular electrophilic cyclization with BF₃ etherate furnished the desired tetracyclic derivative 259 with the marginatane skeleton, on which an allylic oxidation with t-ButOOH gave the target molecule (-)-marginatone 32, albeit in low yield (33%).

Syntheses by Biomimetic Approaches

Inspired by Nature, biologists and chemists have made polyene cyclizations a powerful synthetic tool for the one-step construction of polycyclic compounds starting from acyclic polyene precursors. Despite the impressive and economical syntheses achieved over the past 50 years by chemical simulation of polycyclic terpenoid biosynthesis [129,130], this area of research still remains a growing field of investigation. The biosynthetic transformations have been mimicked by cation-olefin and radical cyclization reactions, and more recently by radical-cation cyclization cascades.

The first subgroup, commonly known as electrophilic cyclizations of polyenes, has been intensively studied for the synthesis of steroids and a wide variety of polycyclic ring systems, and is well documented in the literature [131,132]. Indeed, their importance has increased over the past three decades due to the development of new routes to polyolefinic precursors, methods of asymmetric synthesis, and different conditions for the key cyclization step [133-139].

In the early 1980s, Nishizawa’s research group described the biomimetic cyclization of a geranylgeraniol derivative 260 to the racemic tricyclic alcohol 155 (Scheme 23) [140,141], which had been previously converted into isogatholalcone (1) by Nakano and Hernández [102] and Ungur et al. [105,106]. Compound 155 has also been converted into 12α-hydroxyisospongia-13(16),14-diene by Rüveda et al. [104]. The cyclization takes place using as the electrophile a mercury (II) triflate-N,N-dimethylaniline complex, which after reductive demercuration leads to alcohol 155 (22%) together with two bicyclic diterpenoids. Contemporary synthetic studies by Ungur et al. also described the biomimetic synthesis of 155 by superacid cyclization of geranylgeraniol with fluorosulfonic acid [142]. The same group also reported the synthesis of racemic methyl isocopalate 137 by using similar conditions a few years later (Scheme 23) [143].

Nishizawa et al. also used the mercury (II) reagent to cyclize ambliofuran 261 leading to the tetracyclic isopson-gane 262 in 13% yield (Scheme 24) [144]. Compound 263, having the marginatone carbon skeleton [59], was obtained after the demercuration treatment of 262 with sodium borohydride. Ambliofuran 261 had also been cyclized to furanoditerpene 263 in high yield by Sharma et al. using SnCl₂ as electrophile initiator (Scheme 24) [145].

Since the first investigations in the 1960s by Breslow et al. [146,147], biomimetic radical-mediated cyclization reactions have become an excellent synthetic method for the synthesis of polycyclic natural products under mild conditions and with high stereochemical control [148].
In the early 1990s, Zoretic and co-workers developed a very efficient series of triple and tetra cyclizations leading to trans-decalin ring systems. Their strategy [149] was based on the Snider method to cyclize intramolecular unsaturated β-keto esters with Mn(III) salts [150]. Following the success of this approach they reported, in 1995, the first biomimetic-like synthesis of spongianes diterpenes, particularly furanospongianes (Scheme 25) [151]. In their synthesis, an oxidative free-radical cyclization of polyene 265 with a 2:1 mixture of Mn(OAc)₃ and Cu(OAc)₂ provided stereoselectively the tricyclic intermediate 266 in 43% yield. Subsequent functional group manipulation and homologation at C-13 of 266 allowed, in two independent synthetic sequences, the construction of the required furan ring D of the spongian and marginatane carbon skeletons. Thus, starting from allylic alcohol 264, the necessary cyclization precursor 265 was obtained by treatment with allyl chloride followed by alkylation with ethyl-2-methyl-acetoacetate in 49% overall yield. After securing the stereochemistry of 266 by means of meticulous NMR studies [152], isospongiane 269 was prepared by reduction, benzoylation, ozonolysis, alkylation with a THP-protected hydroxylacetaldehyde, subsequent hydrolysis with concomitant aromatization and final debenzylation by reduction.

On the other hand, ozonolysis of diol 267 and protection as its corresponding acetone, followed by furan ring formation using Spencer’s method gave unnatural furanospongiane 272 in 8% overall yield from 264.

The same authors also reported an alternative route to 272 via the tricyclic intermediate 275, which was prepared from the farnesyl acetate derivative 273 in four steps (Scheme 26) [153]. Compound 275 possessing all of the carbons in the spongiane skeleton was transformed into spongiane 272 in five steps as detailed in Scheme 26. Thus, hydrolysis, epoxidation, collins oxidation, aromatization with p-TsOH and final reduction gave diol 272 in 2.8% overall yield from 273. The synthetic sequence leading to diol 272 was later optimized (15% overall yield from 273) allowing the synthesis of (±)-isospongadiol 17 upon manipulation of the A-ring functionalization in 272 [154].

A few years later, Zoretic’s group reported an analogous stereoselective radical cascade cyclization introducing an α,β-unsaturated cyano group in the cyclization precursor (Scheme 27) [155]. This modification allows the synthesis of furanospongianes functionalized at C-17, such as 285-288, through the advanced intermediate 284. Compound 284 was prepared in four steps from tricyclic system 282 exo, which was synthesized by intramolecular radical cyclization of polyene 281.

Concurrent to these studies, Pattenden and co-workers applied their expertise in polycyclic ring constructions, based on free radical-mediated cyclizations of polyolefin selenyl esters [156,157], for the total synthesis of (±)-spongian-16-one 4 (6% overall yield) (Scheme 28) [158,159]. They completed the synthesis in a concise fashion via the cyclization precursor 295, which was prepared from alcohol 289 as shown in Scheme 28. Protection of 289 as tetrahydropryanyl ether, followed by lithiation and reaction with
Scheme 25. Zoretic’s biomimetic synthesis of isospongiane 269 and spongiane 272 from precursor 265.

spongianes are scarce, specially of rearranged metabolites. Other Approaches and Total Syntheses

NOE and X-ray analyses. The radical cation precursor reaction sequence mimics the non-oxidative biosynthesis of ter-exo-cascades terminated by a 5-water addition in strategy, the photoinduced radical cation of the polyene undergoes spongian-16-one type cascade cyclization for the synthesis of (±)-3-hydroxy-tetracycle lactone in refluxing degassed benzene led, after methylenation, to the selenoate subsequent manipulation of the tetrahydropyranyl ether led to alkylate 2-phenylthio-butyrolactone. Removal of the thioether and HBr, which was then used as its corresponding iodide the cyclopropane and formation of a cyclopropyl methyl ketone led to compound 292. Removal of the allyl ester gave ketone 295. The radical cation precursor 301 was synthesized from far-nesytri-n-butyllaminate 297, which reacted with the methylenbutyrolactone 298 via a Michael addition. Following the introduction of the double bond in 300, irradiation of 301 in a Rayonet reactor with \( \lambda_{max}=300\)nm afforded spongiane 302 in 23% yield after purification. The structure of 302 was unambiguously determined by NOE and X-ray analyses.

**Other Approaches and Total Syntheses**

As we mentioned before, the studies towards the synthesis of spongianes are scarce, specially of rearranged metabolites. The synthesis of furanospongadipterpneoids has been embarked starting from natural products and using biomimetic-like reaction sequences. Both of them have provided in some cases the synthesis of spongianes with a functionalized A-ring. Also, in the mid 1990s, Kanematsu’s group carried out synthetic studies for the construction of an appropriate furanohydrophenanthrene ring system (Scheme 301), which later was converted into (±)-spongia-13(16), 14-diene 15 and (±)-spongiodiosphenol 20 (Scheme 31) [161,162].

The route to the tetracyclic compound 316, the key intermediate for the synthesis of 15 and 20, starts with the conversion of furfuryl alcohol 303 into a progargyl ether 304, which underwent a furan ring transfer reaction to give the bicyclic alcohol 305. Hydrogenation of 305 followed by Swern oxidation afforded the ketone 306. The ketone 306 was converted into the allylic β-keto ester followed by methylation with iodomethane to afford 307. Removal of the allyl ester gave ketone 308 which was next annulated with ethyl vinyl ketone to give the tricyclic furan 310. The construction of the ring A was effected by reductive alkylation to introduce an allyl group which was then converted into an adequate side-chain ketone, compound 315, ready for the final annulation to give the tetracyclic intermediate 316. The stereochemical structure of 316 was assured by NOE effects between the two angular methyl groups.

The synthesis of spongiane 15 was successfully completed forming the gem-dimethyl moiety by reductive methylation of 316 to give ketone 219 and removal of the carbonyl group at C-3. In parallel studies, compound 316 was reduced, hydroxylated to give ketone 317 and then oxidized to afford the desired (±)-

**Scheme 27.** Zoretic’s biomimetic synthesis of C17-functionalized furanospongianes.
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spongiadiosphenol 20, which represents the first total synthesis of a furanospon-giaditerpenoid with a functionalized A-ring (Scheme 31).

With regard to the synthesis of rearranged spongianes, there are about three synthetic approaches to build up bycyclic systems [163-165] present in those and, to the best of our knowledge, only two enantioselective total syntheses [166,167].

Mehta and Thomas reported in 1992 how the abundant, commercially available (+)-longifolene 318 can be degraded to a hydroazulene moiety, compound 321, present in rearranged spongianes [163]. Catalytic ruthenium oxidation of 318 led to the formation of longicamphenilone 319 in 35-40%. Irradiation of 319 with a 450 W Hg lamp through a pyrex filter resulted in the expected Norrish-type I cleavage to the bicyclic aldehyde 320 in about 40%. Reductive decarbonylation using the Wilkinson catalyst furnished the bicyclic hydroazulenic hydrocarbon (+)-321 in 52% yield (Scheme 32).

Bhat and co-workers reported a common Lewis acid catalyzed Diels-Alder reaction to form decalin systems, present in spongianes and other terpenoids (Scheme 33) [164].


Scheme 29. Demuth’s biomimetic synthesis of (±)-3-hydroxy-spongian-16-one 302.
The last approach described for the synthesis of spongianes features a synthetic route for the preparation of the cis-fused 5-oxofuro[2,3-b]furan unit present in some rearranged spongianes. Reiser and co-workers reported a short and enantio-selective synthesis of the above mentioned unit starting from methyl 2-furoate (Scheme 34) [165].
under retention of configuration. Alternatively, 328 could be photochemically decarboxylated with lead tetracetate under copper (II) catalysis following a radical pathway to directly yield a mixture of 330 and epi-330 (331), which could be easily separated by chromatography.

Following this general strategy, the authors next looked for a flexible way to stereoselectively introduce substituents into the 3-position of 5-oxofuro[2,3-b]furans (Scheme 35).

To date, to the best of our knowledge, there has been reported only two enantioselective total syntheses of diterpenes with rearranged spongiane skeleton. Firstly, in 2001, Overman et al. described the first enantioselective synthesis of a spongian-derived metabolite, (+)-shahamin K 353 (Scheme 36) [166], a rearranged spongiane having a cis-hydroazulene unit and an attached highly oxidized six-carbon fragment.

One of the key steps of the synthesis was a Prins-Pinacol reaction that produced the core of the carbon framework, the cis-hydroazulene system. The synthesis starts with the conversion of cyclohexanone 340 into the cyclization precursor 344 introducing a kinetic resolution step with (R)-oxazaborolidine 342. Thus, oxidative cleavage of the double bond in 340, followed by thio-cetolation gave compound 341, which was subjected to the chemical resolution to give enantioenriched ketone (S)-344 in 44% yield. Addition of (E)-propenyllithium to (S)-343 followed by silylation gave the silyl ether 344 in high yield. The treatment of 344 with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) initiated the Prins-pinacol reaction to give the bicyclic 345 in 80% yield as a mixture of sulfide epimers, whose structure was confirmed by single-crystal X-ray analysis of the corresponding sulfone. Installation of the exocyclic methylene group, followed by oxidative desulfonylation provided ketone 347, whose thermodynamic lithium enolate reacted with enantiopure sulfone 348 to give compound 349, as a single isomer in 72% yield. To transform the cyclopentanone ring in the side chain to the required pyranone unit, keto sulfone 349 was reduced with SmI$_2$ and the resulting enolate was acetylated to give enol acetate 350 in 88% yield. Reduction of the ketone of this intermediate with (R)-oxazaborolidine 342 and borane complex, followed by acetylation gave acetate 351 in 88% yield. Chemoselective dihydroxylation of the enol acetate in 351 gave the 6-hydroxy ketone 352 in 87% yield. Cleavage of the hydroxy-ketone in 352 with Pb(OAc)$_4$ followed by reduction of the resulting aldehyde with NaBH$_4$ and lactonization using the Mukaiyama reagent provided (+)-shahamin K 353.

The synthesis starts with a copper-bisoxazoline-catalyzed, enantioselective cyclopropanation of methyl 2-furoate 325 to cyclopropane 326, a versatile building block toward a broad variety of derivatives, which could be subsequently converted into 5-oxofuro[2,3-b]furans. In fact, hydrogenation of 326 gave exclusively compound 327 as a single stereoisomer in 86% yield. Subsequent rearrangement to 328 using 2 M HCl in dioxane gave rise to the parent 5-oxofuro[2,3-b]furan framework in only three steps from inexpensive methyl 2-furoate 325, and in enantiomerically pure form. Conversion of the carboxylic acid to the acetoxy derivative 330, being typical in many spongiane diterpenoids, was accomplished in a four-step sequence from 328 via its methyl ketone 329, which underwent diastereoselective Baeyer-Villiger oxidation

Scheme 32. Mehta’s synthesis of hydroazulene 321.

Scheme 33. Bhat’s synthesis of decalins.

Scheme 34. Reiser’s synthesis of 5-oxofuro[2,3-b]furans.
The second enantioselective total synthesis of a rearranged spongian diterpene was achieved recently by Theodorakis et al. [167]. They completed the syntheses of norrisolide 33 in 2004 [167, 170]. In their strategy, they did the assembly of the two main fragments, 365 and 366, through the C9-C10 bond (Scheme 38). One of the fragments, the trans-fused hydrindane motif, could be prepared starting from the enantiomERICALLY enriched enone 367. The other fragment was prepared from the lactone 368, which contains the desired cis stereochemistry at the C11 and C12 centers.

The synthesis began with the preparation of enone 367, which was available through L-phenylalanine-mediated asymmetric Robinson annulation (55-65% yield, >95% ee after a single recrystallization). Selective reduction at the more reactive C9 carbonyl group, followed by protection of the resulting alcohol afforded the silyl ether 369 in 76% yield for the two steps (Scheme 39). Methyl alkylation of the extended enolate of 369 at the C5 center produced ketone 370 (66%) the reduction and radical deoxygenation of which led to the alkene 371 in 83% yield (from 370). The best results for the conversion of alkene 371 into the trans-fused bicycle 372 were obtained by hydroxylation of the double bond and subsequent reduction of the resulting alcohol (52% yield from 371). Fluoride-induced desilylation of 372 followed by PCC oxidation provided the ketone 373 in 91% yield. The treatment of 373 with hydrazine then produced the hydrazine 374. Finally, treatment of 374 with I$_2$/Et$_3$N led to the formation of the desired vinyl iodoide 365 (62% yield).

The preparation of the fragment 366 is highlighted in Scheme 40. The C11 and C12 centers were connected by a Diels-Alder reaction between butenolide 375 and butadiene (376). Under Lewis acid catalysis this cycloaddition proceeded exclusively from the opposite face to that with the bulky TBDPS group to afford 368 as a single isomer (85% yield). Reduction of the lactone, followed by oxidative cleavage of the alkene produced the fused lactol 377 in 63% yield as a 1:1 mixture of isomers at C14. These isomers were separated after conversion into the corresponding methyl ether 363. The stage was now set for the crucial Baeyer-Villiger oxidation. After testing several conditions, the conversion of 362 to 363 was ultimately achieved using urea-hydrogen peroxide and trifluoroacetic anhydride and gave rise to the desired material in 69% yield as a single isomer.

The Theodorakis’s group described the total synthesis of norrisolide 33 in 2004 [167, 170]. They completed the syntheses of the two main fragments, 365 and 366, through the C9-C10 bond (Scheme 38). One of the fragments, the trans-fused hydrindane motif, could be prepared starting from the enantiomERICALLY enriched enone 367. The other fragment was prepared from the lactone 368, which contains the desired cis stereochemistry at the C11 and C12 centers.

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The remaining steps in the synthesis of norrisolide 33 are shown in Scheme 41. Lithiation of the vinyl iodoide 365, followed by addition of the aldehyde 366 and oxidation of the resulting alcohol, afforded the enone 381 in 71% yield. Hydrogenation of the double bond proceeded exclusively from the more accessible α face of the bicyclic core to form the ketone 382 in 75% yield. After much experimentation, the conversion of ketone 382 into alkene 364 was achieved by methylation with MeI and treatment of the resulting alcohol with SOCl$_2$ in the presence of pyridine (two steps, 64% yield).

With the alkene 364 in hand, the stage was now set to final functionalization of the bicycle (Scheme 41). Deprotection of the
silyl ether and oxidation of the resulting alcohol gave aldehyde 383, which was subsequently converted into the ketone 384 via treatment with MeMgBr and Dess-Martin oxidation (68% yield). Treatment of 384 with CrO₃ in aqueous acetic acid produced the lactone 385 in 80% yield. Finally, Baeyer–Villiger oxidation of 385 (MCPBA, NaHCO₃, 60% yield) led to insertion of the oxygen atom as desired with complete retention of configuration to produce norrisolide 33.

After completion of their total synthesis of norrisolide, this group has also explored the biological activities of some analogs of the parent molecule. Thus, the molecules 362, 363, 277, and 385 from previous synthetic studies were evaluated together with 386-391 which were also synthesized (Scheme 42) [66].

From the structure/function studies it was suggested that the perhydroindane core of norrisolide is essential for binding to the target protein, while the acetate unit is essential for the irreversible vesiculation of the Golgi membranes. Compounds 389-391 have no effect on Golgi membranes. This group has also studied the chemical origins of the norrisolide-induced Golgi vesiculation [171]. To this end, the researchers studied the effect of fluorescent probes 392-397 (Scheme 43) on the Golgi complex. While 393 had no effect on the Golgi apparatus, compound 392 was found to induce extensive Golgi fragmentation. However, in contrast to norrisolide 33, this fragmentation was reversed upon washing. Competition experiments showed that compound 392 and 394 and norrisolide bind to the same receptor, which indicates that the perhydroindane core of norrisolide is essential and necessary for such a binding. In the absence of the acetate group of norrisolide, this binding induces a reversible Golgi vesiculation, indicating that this group plays an essential role in the irreversibility of the fragmentation either by stabilizing the binding or by creating a covalent bond with its target protein. Compound 396, containing the core fragment of the natural product, induced a similar vesiculation that was, however, reversible upon washing. In contrast, compound 397, in which the perhydroindane core was

\[ \text{Scheme 36. Overman's synthesis of (+)-shahamin K 353.} \]
attached to a bisepoxide scaffold (suitable for protein labeling), induced an irreversible vesiculation of the Golgi membranes. On the other hand, compound 395, lacking the perhydroindane motif, had no effect on Golgi membranes, attesting to the importance of the norrisolide core in Golgi localization and structure. Moreover, compound 397 induces an identical phenotype to that of norrisolide, suggesting that it may be used to isolate the biological target of this natural product.

CONCLUSION

The scientific investigations of the spongiane family of diterpenoids has been an active field during the last two decades producing nearly 100 publications on isolation and structural characterisation of its members, including several preliminary biological studies. However, in spite of their biological properties and the challenging variety of chemical entities that have been
found, the synthetic studies represent only one third of the publications in the field. Until quite recently researchers had not initiated any structure/function studies, and therefore this area also remains largely unexplored. The work listed in the review justifies the potential for discovery of novel pharmaceutical agents and biological probes in this area of research.

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