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

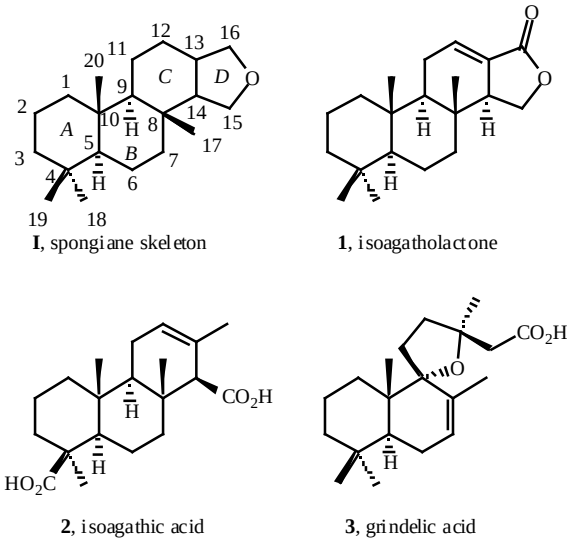
Marine terpenoids are typical constituents of the secondary metabolite composition of marine flora and fauna. These isoprenoid-derived compounds are common in almost all marine phyla and show a wide range of novel structures. Although most of them are also present in terrestrial organisms, the occurrence 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 choosen as the fundamental parent structure with the numbering pattern as depicted in Fig. **1**.



I, spongiane skeleton **1**, isoagatholactone

2, isoagathic acid **3**, grindelic acid

Fig. (1).

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.

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†*An invited review in the series of bioactive compounds.*

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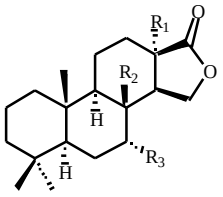
Sponges are exposed to a variety of dangers in their environment and this has led to the development of chemical defense mechanisms against predation. Nudibranchs feed on a variety of sponges and are able of storing selected metabolites, even transform them, for their own self defense. Thus, sponges and nudibranchs are a rich source of biologically active metabolites, and the spongianes, in particular, have displayed a wide spectrum of interesting biological properties including antifeedant, antifungal, antimicrobial, ichthyotoxicity, antiviral, antitumor, antihypertensive, fragmentation of Golgi complex, as well as anti-inflammatory activity (see Table **1**).

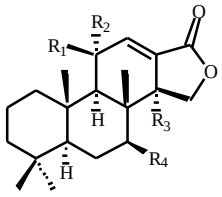
Intact Spongiane Skeleton

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**).



(4)

R_1= H, R_2 = Me, R_3 = OAc
R_1= H, R_2 = CH_2OAc, R_3 = OAc
R_1= H, R_2 = Me, R_3 = OH
R_1= H, R_2 = CHO, R_3 = H
R_1= R_3 = H, R_2 = CH_2OAc
R_1= OH, R_2 = CH_2OAc, R_3 = OAc
R_1= H, R_2 = Me, R_3 = H



(5)

R_1= OH, R_2 = R_3 = R_4 = H
R_1= OAc, R_2 = R_3 = R_4 = H
R_1= OH, R_2 = R_3 = H, R_4 = OH
R_1= H, R_2 = R_4 = OH, R_3 = H
R_1= OAc, R_2 = H, R_3 = OH, R_4 = OAc
R_1= OAc, R_2 = R_4 = H, R_3 = OH
R_1= R_4 = OAc, R_2 = R_3 = H

Fig. (2).

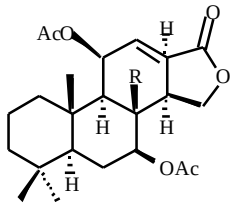
For example, aplyroseol-1 (**4**, R_1= H, R_2= Me, R_3= OAc), was isolated from the dendroceratid sponges *Aplysilla rosea* [12,13], *Dendrilla rosea* [14] *Aplysilla polyrhapis* [15], and *Chelonaplysilla violacea* [16] and also from the nudibranches *Chromodoris obsoleta* [17] and *Chromodoris inopinata* [18]. Anti-tumor activity against the P388 mouse leukaemia cell line *in vivo* showed no significant activity.

The sponge *Aplysilla rosea* also contained the lactone **4** (R_1= H, R_2= CH_2OAc, R_3= OAc). From the tentatively identified mollusk *Ceratosoma brevicaudatum*, it was isolated the simplest member of the series with a functionalised C-17 (**4**, R_1= H, R_2= CHO, R_3= H) [19]. The mollusk resulted to be *Ceratosoma epicuria* [20] and the synthetic compound showed some cytotoxicity against HeLa and HEp-2 cancer cells [21].

Aplyroseol-14 (**4**, R_1= R_3= H, R_2= CH_2OAc) and aplyroseol-16 (**4**, R_1= OH, R_2= CH_2OAc, R_3= OAc) have been isolated more recently also from the sponge *Aplysilla rosea* [24], whereas the cytotoxic γ-lactone spongian-16-one (**4**, R_1= H, R_2= Me, R_3= H) has been found in several species such as *Dictyodendrilla cavernosa* [22], *Chelonaplysilla violacea* [16,23], *Aplysilla var. sulphurea* [24], and also in the mollusks *Chromodoris obsoleta* [17], *C. petechialis* [25], and *C. inopinata* [18]. The structure for aplyroseol-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** (R_1= R_3= H, R_2= CH_2OAc) was renamed as isoaplyroseol-14.

Several members containing the unsaturated γ-lactone ring have shown antimicrobial properties. Compounds **5** (R_1= OH, R_2= R_3= R_4= H; R_1= OAc, R_2= R_3= R_4= H; R_1= OH, R_2= R_3= H, R_4= OH; R_1= H, R_2= R_4= OH, R_3= H) were isolated from the sponge *Spongia officinalis* [27], whose methanol extract is active against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Bacillus sphaericus*. It also inhibits the cell growth of HeLa cells with values of ID_{50} 1-5 μg/mL [11].

Dorisenones A, B and D (**5**, R_1= OAc, R_2= H, R_3= OH, R_4= OAc; R_1= OAc, R_2= R_4= H, R_3= OH; R_1= R_4= OAc, R_2= R_3= H) and dorisenone C (**6**, Δ^{13} R= Me) (Fig. **3**) were isolated from the mollusk *Chromodoris obsoleta* [17], and sponges from the Aegean Sea [28]. These compounds have displayed cytotoxic activities, in particular, dorisenone A has shown strong cytotoxicity against L1210 and KB cancer cells [17].



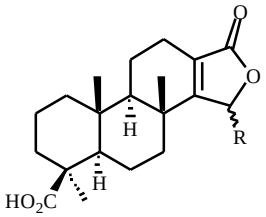
(6)

Δ^{13} R= Me
Δ^{12} R= CHO
R= CHO

Fig. (3).

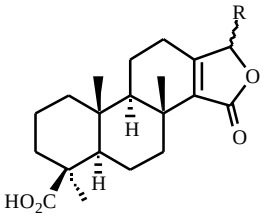
From the african mollusk *Chromodoris hamiltoni* [29], new spongianes having a functionalised C-17 such as compounds **6** (Δ^{12} R= CHO) and **6** (R= CHO) have been isolated. Their biological activity has not yet been investigated.

During the past few years, new spongiane lactones characterised by an acid group at C-19 and like **6** (Δ^{13} R= Me) with a double bond between C-13 and C-14 (Fig. **4**). For example, compound **7** (R= H) was isolated from the sponge *Spongia matamata* along with the hemiacetal lactone **7** (R= α-OMe) and the isomeric lactones **8** [30]. Compound **7** and **8** (R=H) have also been found in the sponge *Coscinoderma mathewsi* along with the lactol **7** (R=OH) [31]. Lactol **7** (R=OH) also called spongiabutenolide A and its hydroxy C-19 derivative, spongiabutenolide B, together with isomeric lactols, spongiabutenolides C-D, having the carbonyl group of the lactone moiety at C-16 have been found in a Philippines marine sponge of the genus *Spongia* [32].



(7)

R= H
R= α-OMe
R= OH



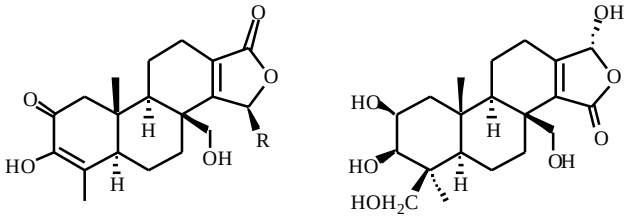
(8)

R= H
R= α-OMe
R= β-OMe

Fig. (4).

Other related metabolites such as zimoclactones A **9** (R=OH), B **9** (R=H) and C **10** (Fig. **5**) have been isolated recently from the

marine sponge *Spongia zimocca* subspecies irregularia [33,34]. Zimoclactone A showed a moderate cytotoxic activity against P388 cell lines.



(**9**)

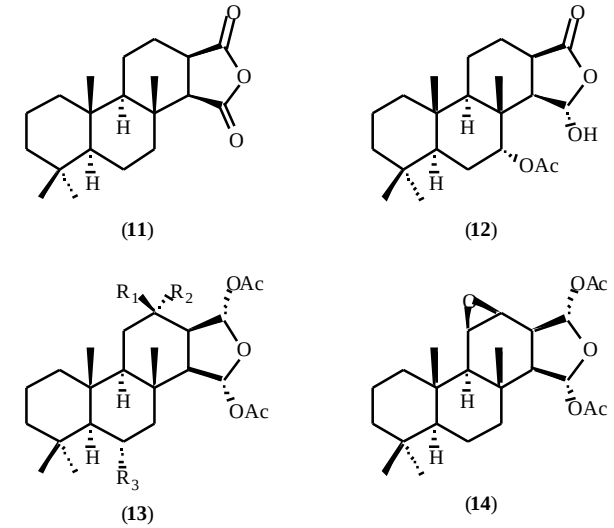
R= OH
R= H

(**10**)

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** (R_1= R_2= R_3= H) was isolated from the sponges *Spongia officinalis* [35], *Chelonaplysilla violacea* [23] and *Aplysilla var. sulphurea* [24]. Aplysillin (**13**, R_1= H, R_2= OAc, R_3= 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.



(**11**)

(**12**)

(**13**)

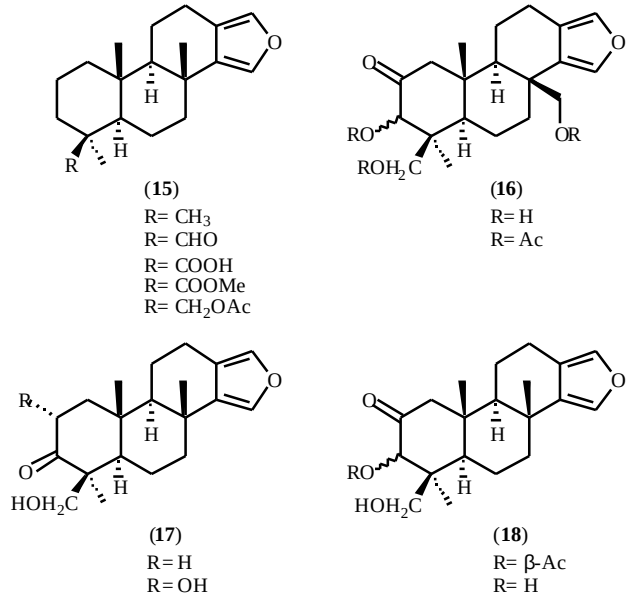
R_1= R_2= R_3= H
R_1= H, R_2= OAc, R_3= H
R_1= OAc, R_2= H, R_3= H
R_1= OH, R_2= H, R_3= H
R_1= H, R_2= OH, R_3= H
R_1= H, R_2= H, R_3= OAc
R_1= OAc, R_2= H, R_3= OAc

(**14**)

Fig. (6).

Compound **13** (R_1= OAc, R_2= H, R_3= H)(12-*epi*-aplysillin) was found in the marine organism *Chromodoris luteorosea*, along with the corresponding hydroxy derivative **13** (R_1= OH, R_2= H, R_3= H) [37], which has also been found in the sponge *Spongia zimocca* [38], together with 12-deacetyl aplysillin **13** (R_1= H, R_2= OH, R_3= 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** (R_1= OAc, R_2= H, R_3= H) has also been found in the nudibranch *Chromodoris geminus*, along with the 7-acetoxy derivatives **13** (R_1= R_2= H, R_3= OAc) and 7α-acetoxy-12-*epi*-aplysillin **13** (R_1= OAc, R_2= H, R_3= 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 obsoleta* 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= CO_2Me) was synthesised during that work by esterification with ethereal



(**15**)

R= CH_3
R= CHO
R= COOH
R= COOMe
R= CH_2OAc

(**16**)

R= H
R= Ac

(**17**)

R= H
R= OH

(**18**)

R= β-Ac
R= H

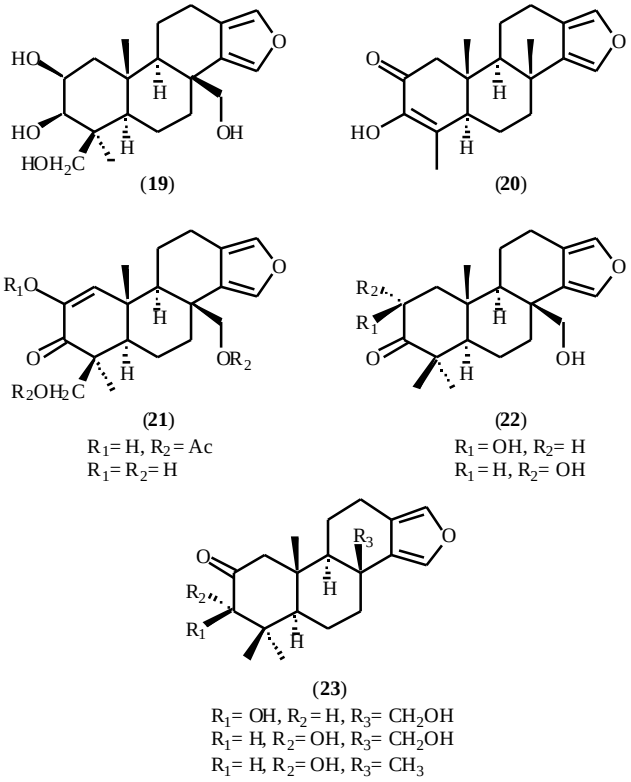
Fig. (7).

diazomethane of **15** (R= CO_2H), and recently has been isolated as a metabolite of an unidentified sponge of the family Demospongiae, together with known **15** (R= CO_2H) and a new furanospongiane, compound **15** (R= CH_2OAc) [40]. During this work the inhibition of DNA polymerase β lyase was demonstrated by compounds **15** (R= CO_2Me, CO_2H and CH_2OAc), being ester **15** (R= CO_2Me) the most active. In addition, compound **15** (R= Me) was also found in the sponge *Hyatella intestinalis* [41], as well as compound **15** (R= CO_2H) has also been isolated from the sponges *Spongia matamata* [30] and *Coscinoderma mathewsi* [31].

Other furanospongianes are characterised by a highly functionalised A-ring, for instance, compounds **16**-**23**. The series of compounds **16** has been isolated from similar species of the genus *Spongia* [9], and their stereochemistry was confirmed by single crystal X-ray analysis, in addition to their absolute configuration measured by circular dichroism. Spongiatriol **16** (R=H) causes falling of blood pressure in hypertensive rats and also reduces the

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 *Rhopaloeides 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



(**19**)

(**20**)

(**21**)
R_1= H, R_2= Ac
R_1= R_2= H

(**22**)
R_1= OH, R_2= H
R_1= H, R_2= OH

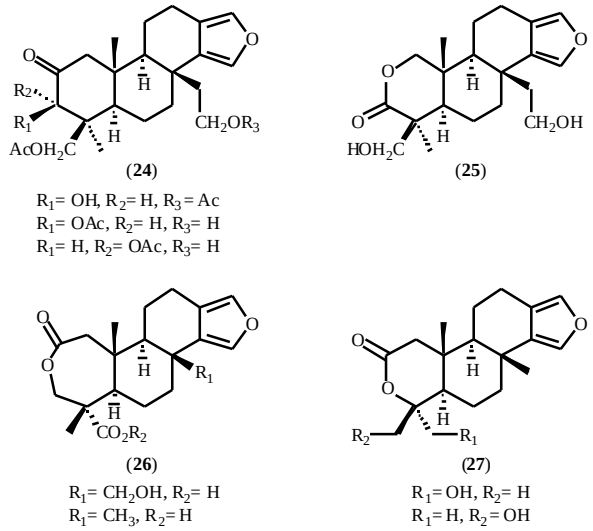
(**23**)
R_1= OH, R_2= H, R_3= CH_2OH
R_1= H, R_2= OH, R_3= CH_2OH
R_1= H, R_2= OH, R_3= CH_3

Fig. (8).

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 furanospongiane acetates, compounds **24** (Fig. **9**), from the mollusk *Glossodoris atromarginata* [49]. They also found the corresponding tetracetate of tetraol **19**. Several of these acetates had been previously found in the related mollusk *Casella atromarginata* [43].

Finally, within the group of furanospongianes 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** (R_1= CH_2OH, R_2= 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.



(**24**)
R_1= OH, R_2= H, R_3= Ac
R_1= OAc, R_2= H, R_3= H
R_1= H, R_2= OAc, R_3= H

(**25**)

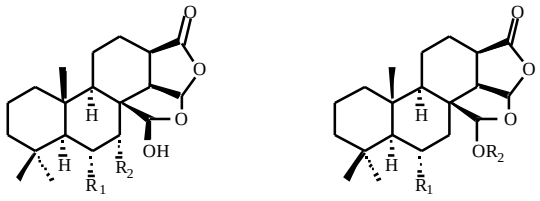
(**26**)
R_1= CH_2OH, R_2= H
R_1= CH_3, R_2= H

(**27**)
R_1= OH, R_2= H
R_1= H, R_2= OH

Fig. (9).

Spongiolactone A **26** (R_1= CH_3, R_2= H) is structurally related and was isolated from *Spongia officinalis* var. *arabica* [50]. Finally, lactones **27** were isolated from the sponge *Spongia zimocca sensu* [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**).



(**28**)

R_1= H, R_2= OCOPr
R_1= H, R_2= OAc
R_1= H, R_2= OH
R_1= OH, R_2= OCOPr
R_1= OAc, R_2= OCOPr
R_1= OCOPr, R_2= OH
R_1= OCOPr, R_2= OAc
R_1= R_2= H
R_1= R_2= OAc

(**29**)

R_1= OCOPr, R_2= H, 17-b
R_1= OAc, R_2= H, 17-b
R_1= OAc, R_2= Ac, 17-a
R_1= OCOPr, R_2= Ac, 17-a
R_1= H, R_2= Ac, 17-b

Fig. (10).

Schmitz and co-workers established the structure **28** (R_1= H, R_2= 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** (R_1= H, R_2= OCOPr) also known as aplyroseol-1 is mildly cytotoxic in *lymphocytic leukemia* PS cells [52]. Taylor and co-workers have also confirmed the absolute stereochemistry of **28** (R_1= H, R_2= OCOPr), except one stereocenter, by X-ray diffraction methods of the p-bromobenzoyl derivative [53]. Aplyroseol-1 (**28**, R_1= H, R_2= OCOPr) and aplyroseol-2 (**28**, R_1= H, R_2= OAc) have been found in the sponges *Igernella notabilis* [52], *Aplysilla rosea* [12] and *Dendrilla rosea* [13], and recently aplyroseol-2 (**28**, R_1= H, R_2= 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 inopinata* [18].

Compound **28** (R_1= H, R_2= OH) was also isolated from *Igernella notabilis* [52], and aplyroseol-3 (**28**, R_1= OH, R_2=

OCOPr), aplyroseol-4 (**28**, R_1= OAc, R_2= OCOPr), aply-roseol-5 (**28**, R_1= OCOPr, R_2= OH) and aplyroseol-6 (**28**, R_1= OCOPr, R_2= OAc) were isolated from *Aplysilla rosea* [12] and also from *Dendrilla rosea* (except aplyroseol-4) [13], though the known aplyroseol-3 (**28**, R_1= OH, R_2= OCOPr) was isolated for the first time from *Aplysilla sp.* [54]. In addition, aplyroseol-1 (**28**, R_1= H, R_2= OCOPr), aplyroseol-5 (**28**, R_1= OCOPr, R_2= OH), and aplyroseol-6 (**28**, R_1= OCOPr, R_2= OAc) are inhibitors of the enzyme phospholipase A_2 (PLA_2), an enzyme involved in inflammation processes [55].

Dendrillol-1 (**28**, R_1= R_2= H) and dendrillol-2 (**28**, R_1= R_2= 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** (R_1= OCOPr, R_2= H, 17-β), **29** (R_1= OAc, R_2= H, 17-β), **29** (R_1= OAc, R_2= Ac, 17-α) and **29** (R_1= OCOPr, R_2= Ac, 17-α). The mollusk was ultimately identified to be *Ceratosoma epicuria* [20]. Dendrillol-1 (**28**, R_1= R_2= H) has proved to have cytotoxic activity on tumor cells.[21] More recently, it has been isolated compound **29** (R_1= H, R_2= Ac, 17-β), called acetyldendrillol-1, from the mollusk *Cadlina luteomarginata* [56], which was missasigned 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 spongiane diterpenes, which was isolated from the sponge *Aplysilla polyrhaphis* in 1989 [15].

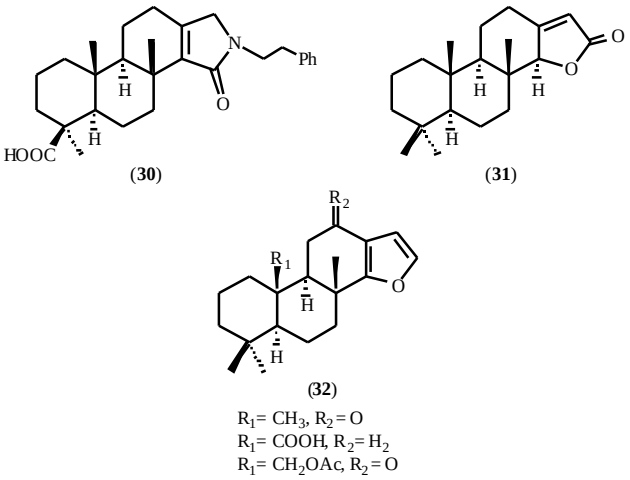


Fig. (11).

Also, it is worth mentioning several structures with a isospongian skeleton, which was named marginatane skeleton. For example, marginatafuran **32** (R_1= COOH, R_2= H_2) 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** (R_1= CH_3, R_2= O), which was isolated from the sponge *Aplysilla glacialis* [60], the 20-acetoxy marginatone **32** (R_1= CH_2OAc, R_2= 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].

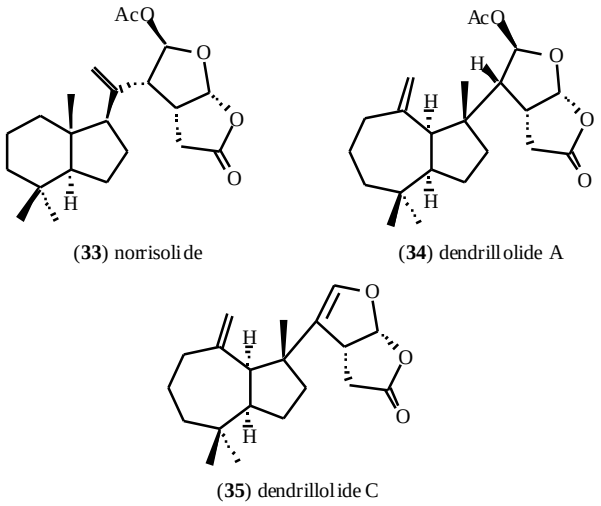


Fig. (12).

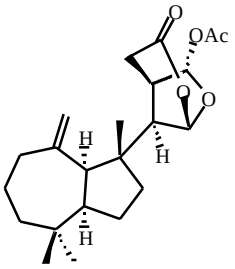
Norrisolide (**33**) has also been found in other marine species (see below) and displays PLA_2 inhibition [55], ichthyotoxicity to *Gambusia affinis* [65], as well as Golgi fragmentation [66].

Dendrillolide A (**34**) has also been found in other marine species (see below) and biologically inactivates PLA_2 at 2 μg/mL [55].

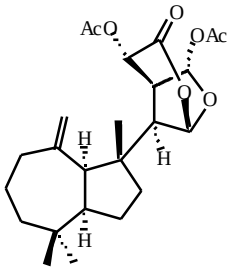
Aplyviolene (**36**) was also isolated from Palauan sponge *Dendrilla* sp. though this structure was initially assigned to dendrillolide A. The X-ray analysis of **36** isolated from the sponge *Chelonaplysilla violacea* confirmed this initial misassignment [23,67,68]; aplyviolacene (**37**) was also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

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

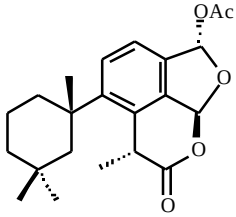
The studies of the constituents of the Mediterranean sponge *Spongionella gracilis* led to the structure elucidation by spectral analysis of gracilin A (**39**) and gracilin B (**40**), which represents the first bis-nor-diterpene observed from a marine sponge, together with two gracilin A derivatives (**41-42**) and spongionellin (**43**) which possess a new carbocyclic skeleton (Fig.**14**) [70-72]. Gracilin A inactivates PLA_2 at 2μg/mL [55].



(**36**) aplyviolene

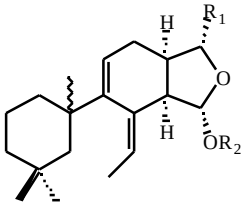


(**37**) aplyviolacene

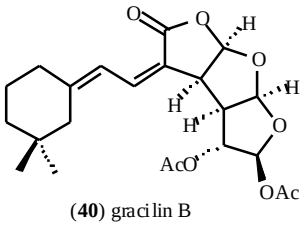


(**38**) aplysulphurin

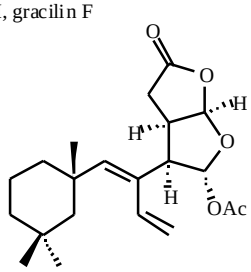
Fig. (13).



(**39**) R_1=OAc R_2= Ac, gracilin A
(**41**) R_1=H R_2= Ac, gracilin E
(**42**) R_1=H R_2= H, gracilin F



(**40**) gracilin B

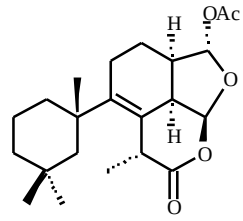


(**43**) spongionellin

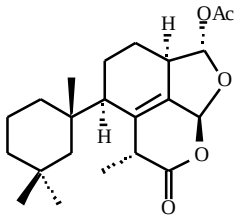
Fig. (14).

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].

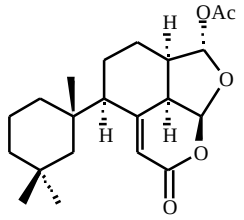
The chemical study of dorid nudibranchs of the genus Chromodoris, in particular, *Chromodoris macfarlandi* yielded five new rearranged spongianes, macfarlandins A-E (**47-50, 37**), whose structures were elucidated from spectral data (Fig. **16**). Macfarlandin E (**37**) has been named aplyviolacene, see above. Only the structure of macfarlandin C (**49**) was determined by a single-crystal X-ray diffraction analysis. Macfarlandin E is identical to aplyviolacene **37** and was marginally active against *Vibrio anguillarum* and *Beneckea harveyi*. Macfarlandin A, B and D showed antimicrobial activity against *Bacillus subtilis* [74,75].



(**44**) tetrahydroaplysulphurin-1

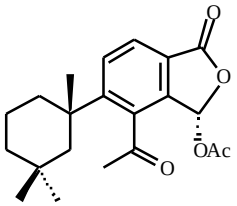


(**45**) tetrahydroaplysulphurin-2

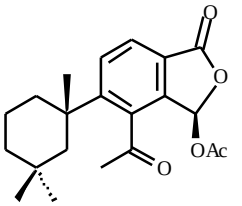


(**46**) tetrahydroaplysulphurin-3

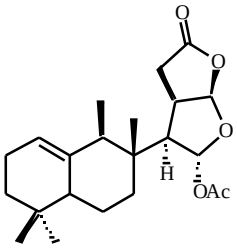
Fig. (15).



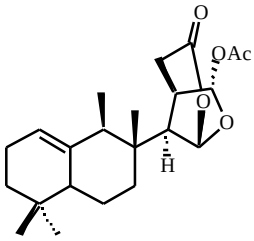
(**47**) macfarlandin A



(**48**) macfarlandin B



(**49**) macfarlandin C



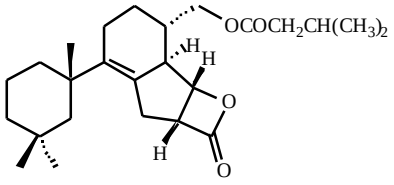
(**50**) macfarlandin D

Fig. (16).

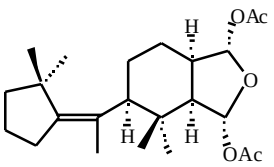
Further chemical studies of the sponge *Spongionella gracilis* led to the discovery of spongiolactone (**51**) (Fig. **17**) whose structure was deduced from chemical and physico-chemical evidence [76]. Also the two minor norditerpenes (**52**) and (**53**) were characterised by spectral data and derivatisation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

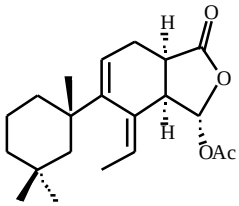
The X-ray analysis of a keto derivative of 9,11-dihydrogracillin A (**54**) confirmed the structure fixing the previous unknown stereochemistry at C-10 [79]. 9,11-dihydrogracillin A (**54**) has also been isolated from the Northeastern Pacific dorid nudibranch *Cadlina luteomarginata* and the sponge *Aplysilla* sp [56].



(**51**) spongiolactone

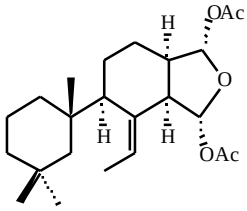


(**52**)

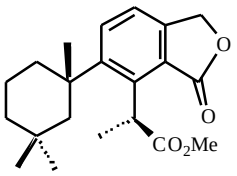


(**53**)

Fig. (17).



(**54**) 9,11-dihydrogracilin A



(**55**) membranolide

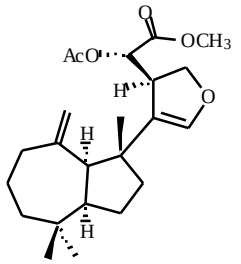
Fig. (18).

The investigation of two Red Sea *Dysidea* sponges yielded ten new rearranged spongianes, shahamins A-J (**56-65**), together with known aplyviolacene (**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].

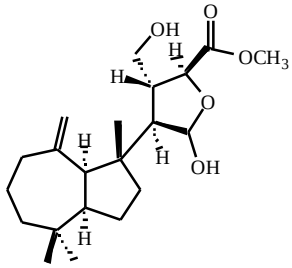
From the Californian sponge *Aplysilla polyrhaphis* were isolated the known compounds norrisolide (**33**), aplyviolene (**36**), macfarlandin E (**37**), shahamin C (**58**), and three novel rearranged diterpenes, polyrhaphins A-C (**66-68**) (Fig. **20**) [15]. Norrisolide (**33**), macfarlandin E (**37**), shahamin C (**58**), and polyrhaphin A (**66**) were also found in the dorid nudibranch *Chormodoris 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 *Thalossoma 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].

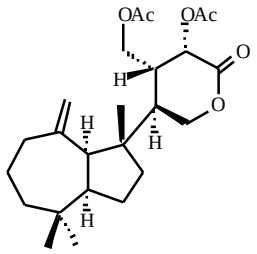
The skin chemistry of the Indian Ocean Nudibranch *Chromodoris cavae* was examined leading to the isolation of chromodorolide A (**73**) (Fig. **22**), a putative repellent which displays both cytotoxic and antimicrobial activities [82]. A few years later, the same authors reported the isolation of chromodorolide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



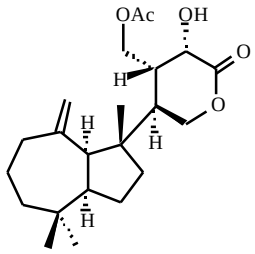
(**56**) shahamin A



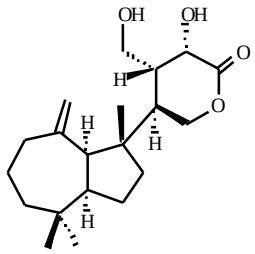
(**57**) shahamin B



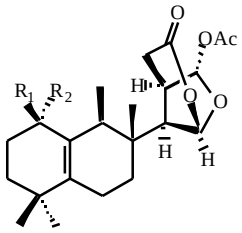
(**58**) shahamin C



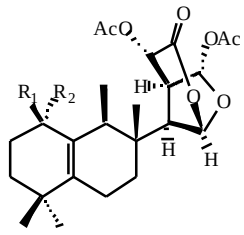
(**59**) shahamin D



(**60**) shahamin E



(**61**) shahamin F R_1=R_2=H
(**62**) shahamin G R_1=H,R_2=OH
(**63**) shahamin H R_1=OH, R_2=H

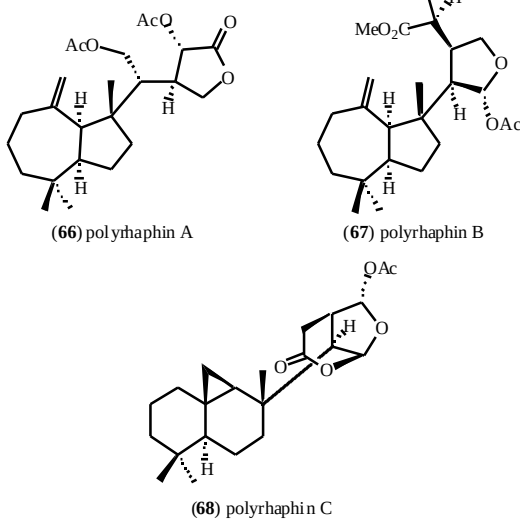


(**64**) shahamin I R_1=R_2=H
(**65**) shahamin J R_1=OH,R_2=H

Fig. (19).

The degraded and rearranged diterpenoid glaciolide (**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].

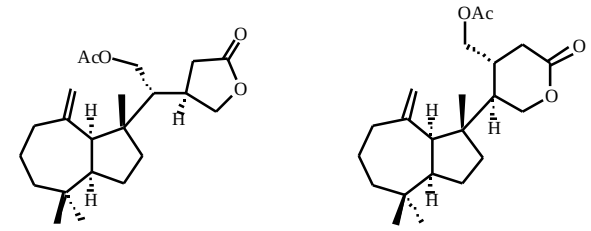
The chemical study of the nudibranch *Chromodoris luteorosea* yielded luteorosin (**76**) (Fig. **23**), along with the known macfarlandin A (**47**). Both compounds presented ichthyotoxic activity [65,85].



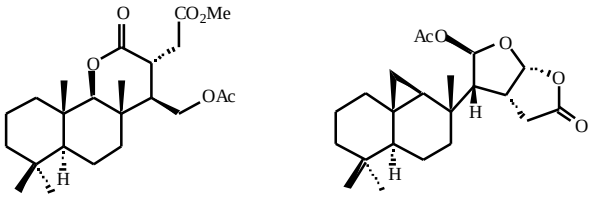
(**66**) polyrhaphin A (**67**) polyrhaphin B

(**68**) polyrhaphin C

Fig. (20).

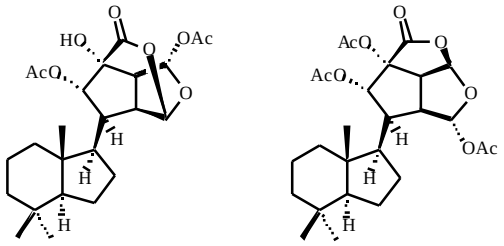


(**69**) 12-desacetoxypolyrhaphin A (**70**) 12-desacetoxyshahamin C

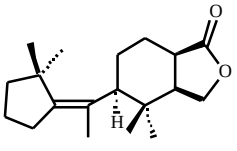


(**71**) dendrillolide D (**72**) dendrillolide E

Fig. (21).



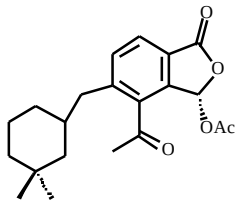
(**73**) chromodorolide A (**74**) chromodorolide B



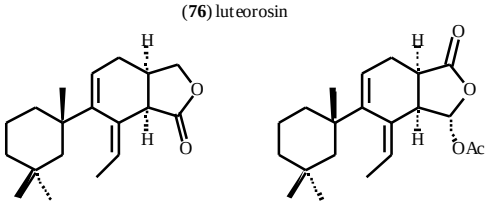
(**75**) glaciolide

Fig. (22).

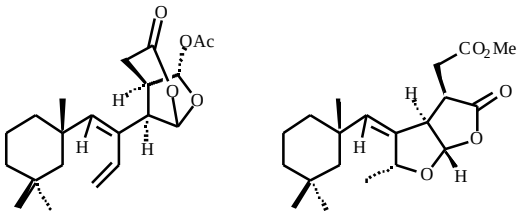
The encrusting sponge *Aplysilla tango* gave five degraded spongian diterpenes, including the known gracilin A (**39**), aplytandiene-1 (**77**), aplytandiene-2 (**78**), aplytan-gene-1 (**79**) and aplytangene-2 (**80**) (Fig. **23**) [86].



(**76**) luteorosin



(**77**) aplytandiene-1 (**78**) aplytandiene-2



(**79**) aplytangene-1 (**80**) aplytangene-2

Fig. (23).

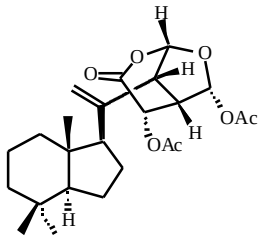
Three new rearranged spongiane-type diterpenes were isolated from a Red Sea *Dysidea* species along with known norrisolide (**33**). Thus, the structures of norrlandin (**81**), seco-norrisolide B (**82**) and seco-norrisolide C (**83**) (Fig. **24**) were elucidated from intensive NMR experiments and 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, chelonaplysins A-C (**84-86**) (Fig. **24**) were identified by interpretation of spectral data and chemical correlation with known compounds. Aplyviolene (**36**), chelonaplysin B (**85**), and chelonaplysin C (**86**) exhibited antimicrobial activity against the bacterium *Bacillus subtilis* [62]. Chelonaplysin C (**86**) is also a consti-tuent of the Cantabrian nudribranch *Chromodoris luteorosea*, presents ichthyotoxicity to *Gambusia affinis* [65] and its structure has been confirmed by a single-crystal X-ray study [88].

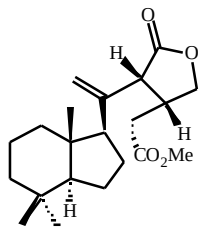
The skin extracts of the Sri Lankan dorid nudibranch *Chromodoris gleniei* contained dendrillolide A (**34**), 12-desacetoxyshahamin C (**70**) and the new shahamin K (**87**) (Fig. **25**) [18].

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].

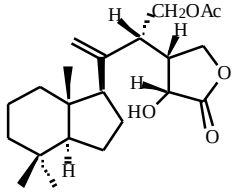
The New Zealand sponge *Chelonaplysilla violacea* contains known norrisolide (**33**), dendrillolide A (**34**), aplyviolene (**36**), chelonaplysin C (**86**), and a series of new rearranged spongianes:



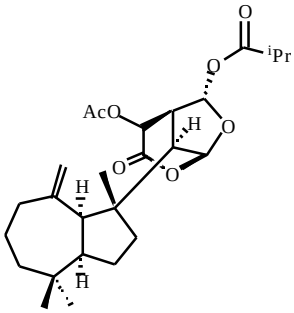
(**81**) norrlandin



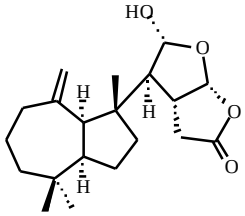
(**82**) seco-norrisolide B



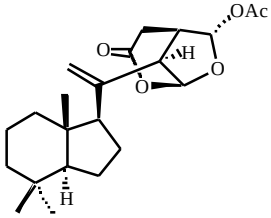
(**83**) seco-norrisolide C



(**84**) chelonaplysin A

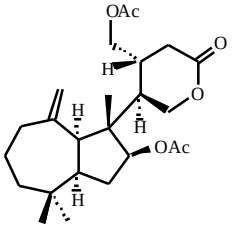


(**85**) chelonaplysin B



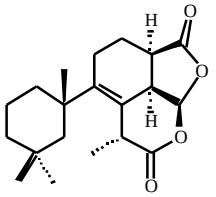
(**86**) chelonaplysin C

Fig. (24).

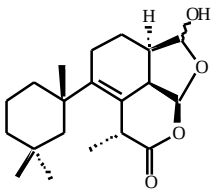


(**87**) shahamin K

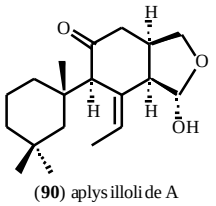
Fig. (25).



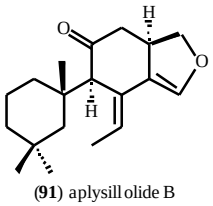
(**88**) cadlinolide A



(**89**) cadlinolide B



(**90**) aplysillolide A

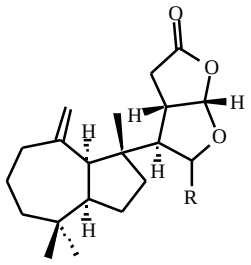


(**91**) aplysillolide B

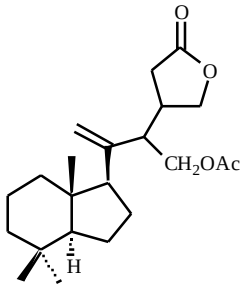
Fig. (26).

cheloviolenes A-F (**92-97**) and chelo-violin (**98**) (Fig. **27**) [16]. 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 ^{1}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].

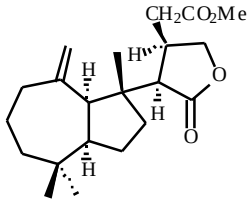
Another investigation on the antarctic sponge *Dendrilla membranosa* led to the isolation of dendrillin (**99**) (Fig. **28**), a spongiane-derived norditerpene related to 9,11-dihydro-gracillin A (**54**). Dendrillin (**99**) displayed no deterrent effect towards the major sponge predator, the sea star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



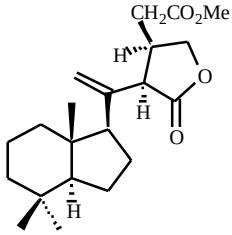
(**92**) R= α-OH, cheloviolene A
(**93**) R= β-OH, cheloviolene B



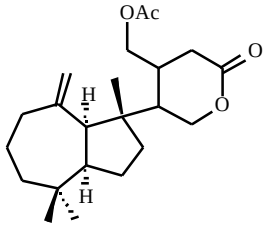
(**94**) cheloviolene C



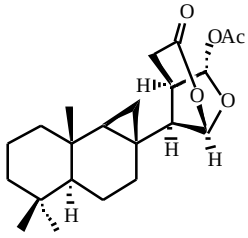
(**95**) cheloviolene D



(**96**) cheloviolene E



(**97**) cheloviolene F



(**98**) cheloviolin

Fig. (27).

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 γ-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 aplypallidoxone 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

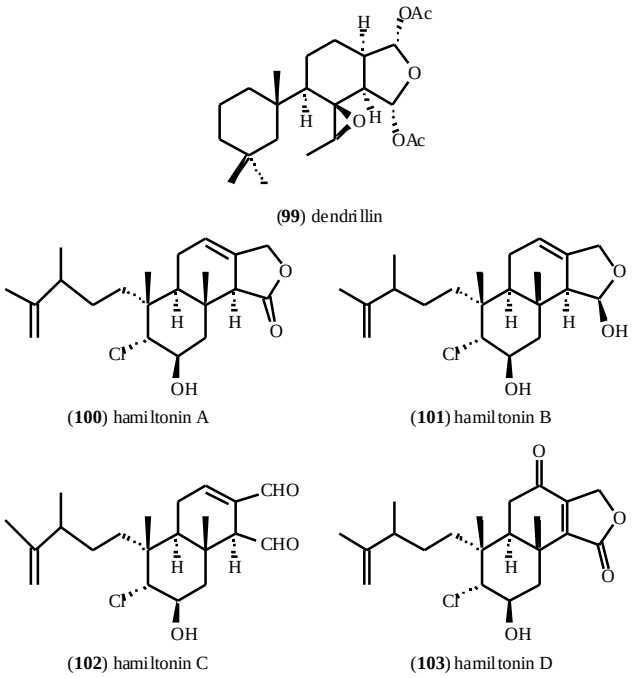


Fig. (28).

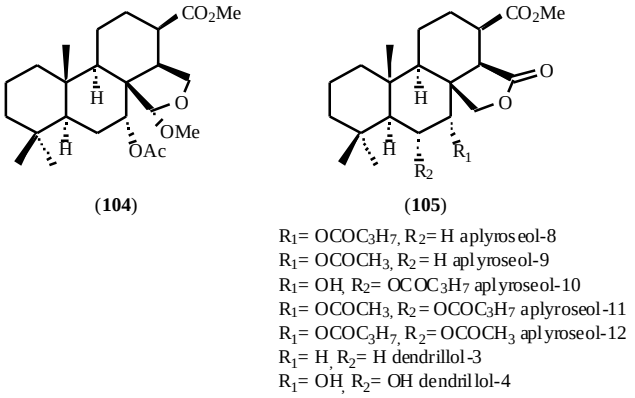


Fig. (29).

rerranged spongiane members. For example, dendrinolide (**111**) (Fig. **31**) which was isolated together with known 9,11-dihydrogracilin A (**54**).

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

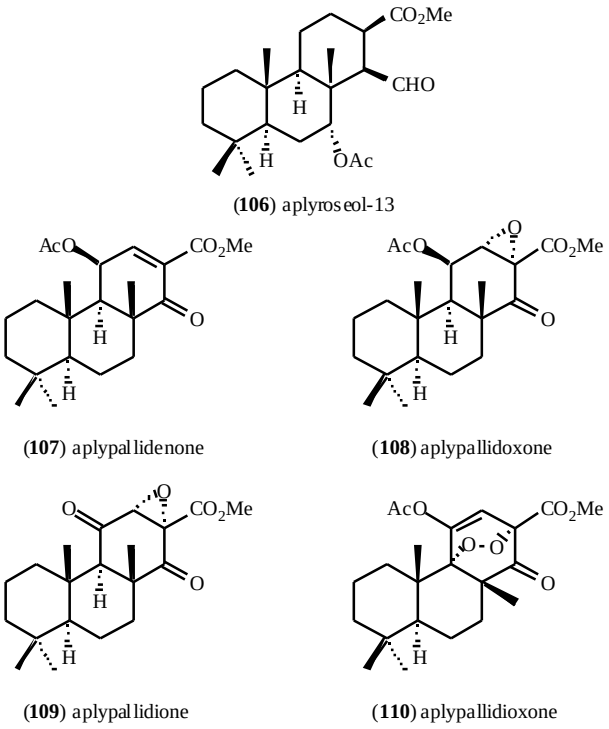


Fig. (30).

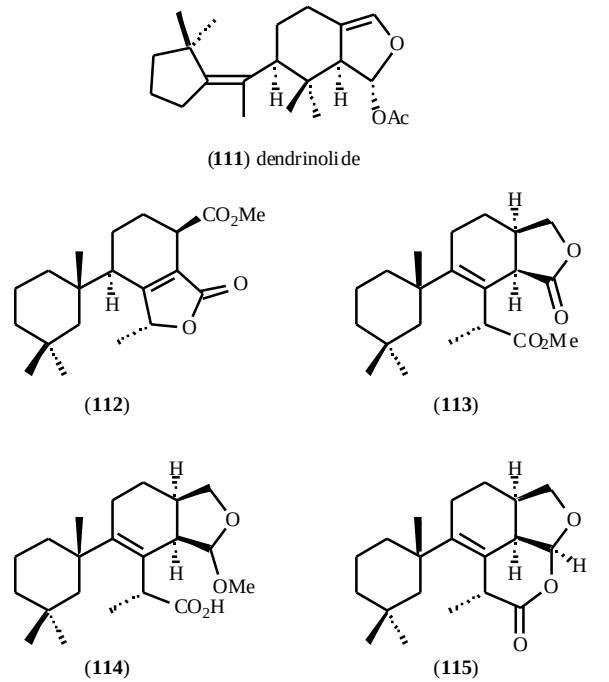
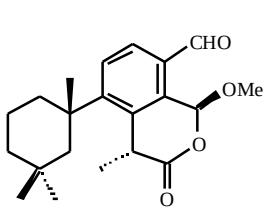


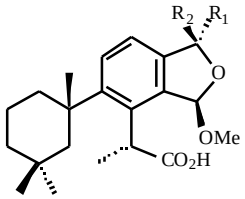
Fig. (31).

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 spongia-nes related to membranolide (**55**). Thus, membranolides B-D (**116-118**) (Fig. **32**) were isolated along with known membranolide (**55**), aplysulphurin (**38**), and tetrahydroaply-sulphurin (**44**). Membranolides C (**117**) and D (**118**) display Gram-negative antibiotic and antifungal activities [94].



(**116**) membranolide B

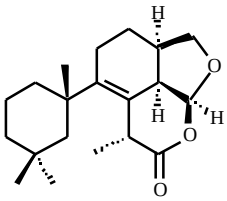


(**117**) R_1= OMe, R_2 = H membranolide C
(**118**) R_1= H, R_2= OMe membranolide D

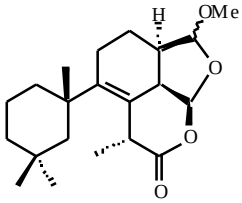
Fig. (32).

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**).

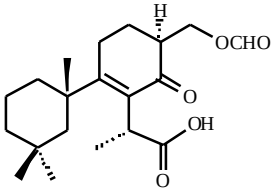
Two of the new metabolites are related to cadlinolide B and were therefore reported as cadlinolides C (**119**) and D (**120**) (Fig. **33**). Pourewanone (**121**) presents a new carbon skeleton, being the first example of a formate compound of marine origin, while compounds **122-124** are lactone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



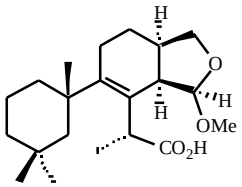
(**119**) cadlinolide C



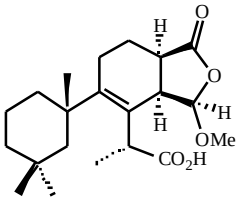
(**120**) cadlinolide D



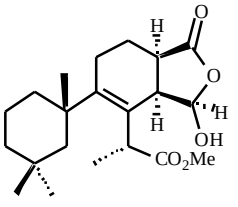
(**121**) pourewanone



(**122**) pourewic acid A



(**123**) 15-methoxypourewic acid B

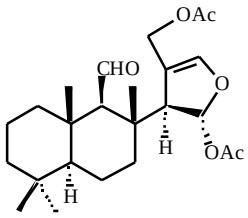


(**124**) methylpourewate B

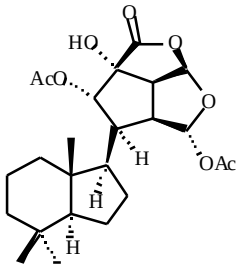
Fig. (33).

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].



(**125**) tyrinnal

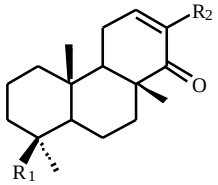


(**126**) chromodorolide C

Fig. (34).

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 sulfurea*, 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].

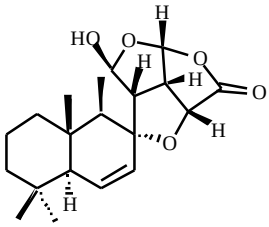
Using an assay to detect inhibitors of the lyase activity of DNA polymerase β, the bioassay-directed fractionation of an extract of an unidentified sponge of the family Demospon-giae led to the isolation of two new and bioactive bis-norditerpenoids, compounds (**127**) and (**128**) (Fig. **35**) [40].



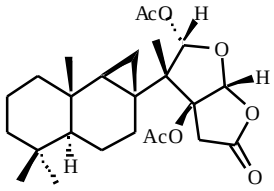
(**127**) R_1= CO_2Me, R_2 = OH
(**128**) R_1= CO_2H, R_2= OH

Fig. (35).

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].



(**129**) omriolide A



(**130**) omriolide B

Fig. (36).

Table 1. Biological Activity Found in Compounds 1-130

Compound	Biological Activity
Isoagatholactone, **1**	Antimicrobial
Aplyroseol-7 (**4**, R_1=H, R_2=Me, R_3=OAc)	Antifeedant and cytotoxic
Spongianal (**4**, R_1=R_3=H, R_2=CHO)	Cytotoxic
Spongian-16-one (**4**, R_1=H, R_2=Me, R_3=H)	Cytotoxic
Lactones **5**	Antimicrobial and cytotoxic
Dorisenone A (**5**,R_1=R_4=OAc,R_2=H,R_3=OH)	Cytotoxic
Dorisenone B (**5**,R_1=OAc,R_2=R_4=H,R_3=OH)	Cytotoxic
Dorisenone C (**6**, Δ^{13} R= Me)	Cytotoxic
Dorisenone D (**5**,R_1=R_4=OAc, R_2=R_3=H)	Cytotoxic
Zimoclactone A, **9** (R=OH)	Cytotoxic
12-epi-aplysillin **13** (R_1=OAc, R_2=R_3=H)	Antifeedant
12-epi-deacetyl-aplysillin **13** (R_1=OH, R_2=R_3=H)	Antifeedant
12-deacetyl-aplysillin **13** (R_1=H, R_2=OH, R_3=H)	Antifeedant
Epoxide **14**	Cytotoxic
Furans **15**	Antifungal and inhibition of DNA polymerase β lyase
Spongiatriol **16** (R=H)	Antihypertensive
Spongiadiols **17** and **18**	Antiviral and cytotoxic
Furanolactone **25**	Cytotoxic
Aplyroseol-1 (**28**, R_1=H, R_2=OCOPr)	Cytotoxic and phospholipase A_2 (PLA_2) inhibition
Aplyroseol-2 (**28**, R_1=H, R_2=OAc)	Cytotoxic
Aplyroseol-5 (**28**, R_1= OCOPr, R_2=OH)	PLA_2 inhibition
Aplyroseol-6 (**28**, R_1= OCOPr, R_2=OAc)	PLA_2 inhibition
Dendrillol-1 (**28**, R_1= R_2=H)	Cytotoxic
Haumanamide **30**	Cytotoxic
Norrisolide **33**	Golgi fragmentation, PLA_2 inhibition, ichthyotoxic
Dendrillolide A **34**	PLA_2 inhibition
Gracilin A **39**	PLA_2 inhibition
Macfarlandins A **47**, B **48** and D **50**	Antimicrobial, ichthyotoxic
Macfarlandin E **37**	Antimicrobial
Aplyviolene **36**	Antimicrobial
9,11-Dihydrogracillin A **54**	Antimicrobial
Membranolide **55**	Antimicrobial
Shahamin C **58**	Antifeedant
Polyrhaphin C **68**	Antifeedant, antimicrobial and ichthyotoxic
Chromodorolide A **73**	Cytotoxic, antimicrobial, antinematocidal
Luteorosin **76**	Ichthyotoxic
Norrlandin **81**	Cytotoxic
Chelonaplysin B **85**	Antimicrobial
Chelonaplysin C **86**	Antimicrobial, ichthyotoxic
Membranolide C **117**	Antimicrobial, antifungal
Membranolide D **118**	Antimicrobial, antifungal
Cadlinolide C **119**	Antiinflammatory
Pourewic acid A **122**	Antiinflammatory
Methylpourewate B **124**	Antiinflammatory
Bis-norditerpenoids **127**, **128**	Inhibition of DNA polymerase β lyase

SYNTHESIS 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.

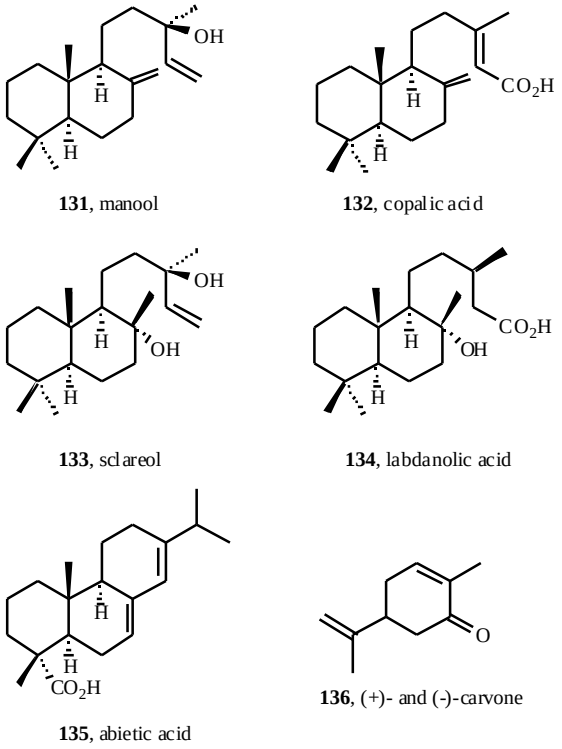
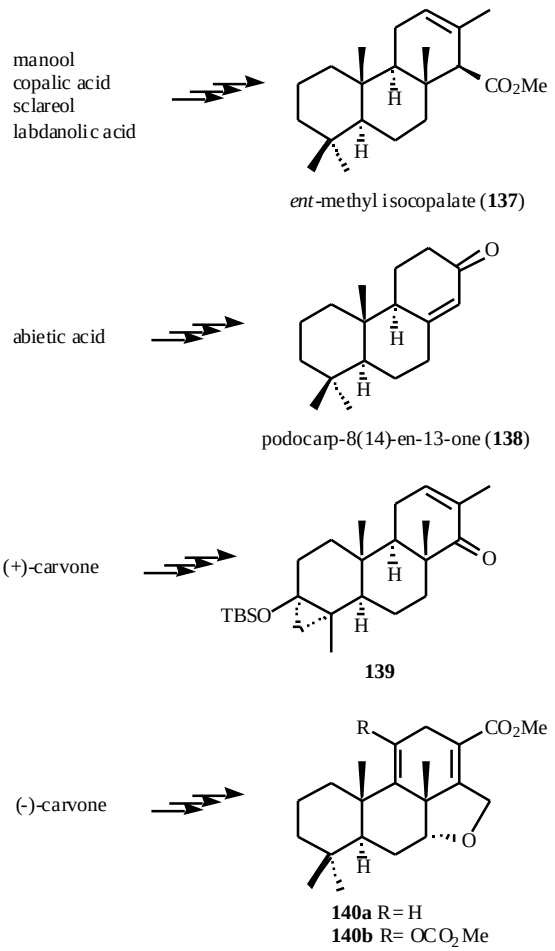


Fig. (37).

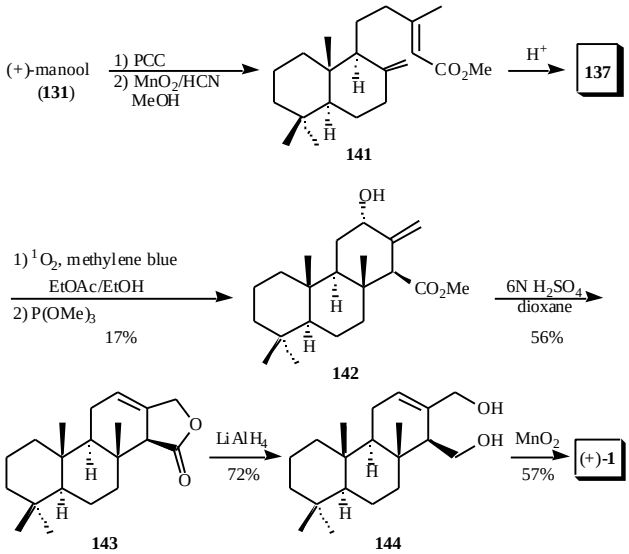
These starting materials were converted into versatile tricyclic intermediates having the characteristic ABC ring system of spongianes (Scheme **1**) such as *ent*-methyl isocopalate (**137**), podocarp-8(14)-en-13-one (**138**) and phenanthrenones (**139-140**). Several strategies have been reported 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



Scheme 1. Precursors of spongiane diterpenoids prepared from natural sources.

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



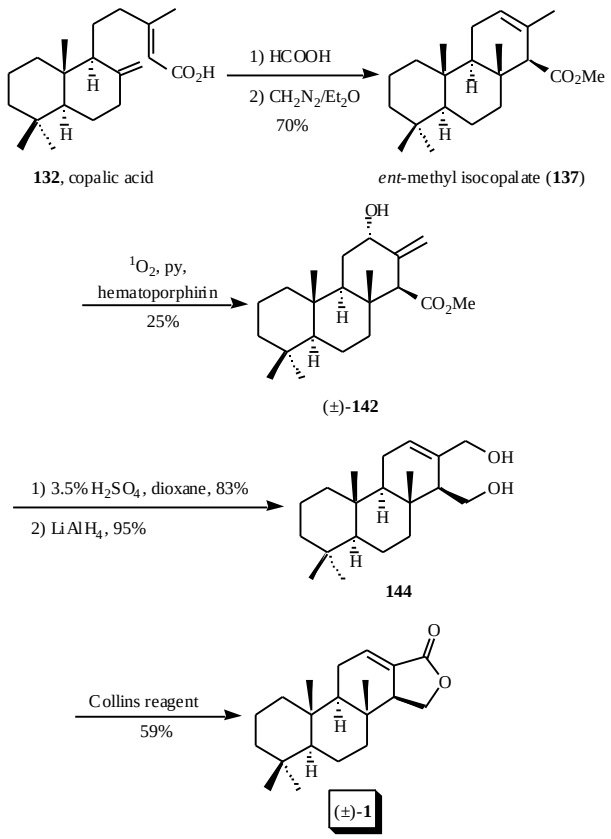
Scheme 2. Rúveda´s synthesis of natural isoagatholactone.

142. 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 MnO_2 gave (+)-isoagatholactone (**1**) in 3.9% yield from **137**.

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 furan ring D led to the synthesis of (-)-12α-hydroxyspongia-13(16),14-diene (**151**) by Rúveda *et al.* using **148** also prepared from methyl isocopalate (Scheme **4**) [104]. This unnatural spongiane was designed as a precursor for other members with different functionality in ring D since it contains, the required stereochemistry at C-12. Compound (+)-**137** was converted into 12,14-isocopa-ladiene (**148**) by $LiAlH_4$ reduction, mesylation, and elimina-tion. Photooxygenation of **148** and reduction produced alcohol **149** which was submitted to a second photooxygena-tion reaction, and the resulting unsaturated cyclic peroxide **150** was treated with ferrous sulfate to afford 12-hydroxy-furan **151**.

Concurrent to this report, Nakano *et al.* described the synthesis of racemic **151** from hydroxy-isocopalane **142** (Scheme **5**), which was prepared as outlined in Scheme **3** from (±)-copalic acid. Epoxidation of **142** followed by treatment with lithium diisopropylamide (LDA) led to β-elimination and lactonization in one-pot to give α,β- unsaturated γ-lactone **153** in 50% yield. When **153** was reduced with diisobutylaluminium hydride, the furan (±)-**151** was obtained in 19% yield. The major drawback of Nakano´s synthesis of **151** is the yield of the photochemical reaction to functionalize C-16 to give **142** (25% yield based on recovered **137**) and the final aromatization, which encouraged further studies to solve these low yielding steps [101,102].



Scheme 3. Nakano´s synthesis of racemic isoagatholactone.

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 MnO_2 to give isoagatholactone (see also Scheme **2**). In this case compound **144** was prepared in 48% yield by allylic oxidation of isocopalol **155** with SeO_2 in EtOH, though Rúveda and colleagues reported that this oxidation on isocopalate **137** and alcohol(isocopalol) **155** led to complex mixtures of products [104].

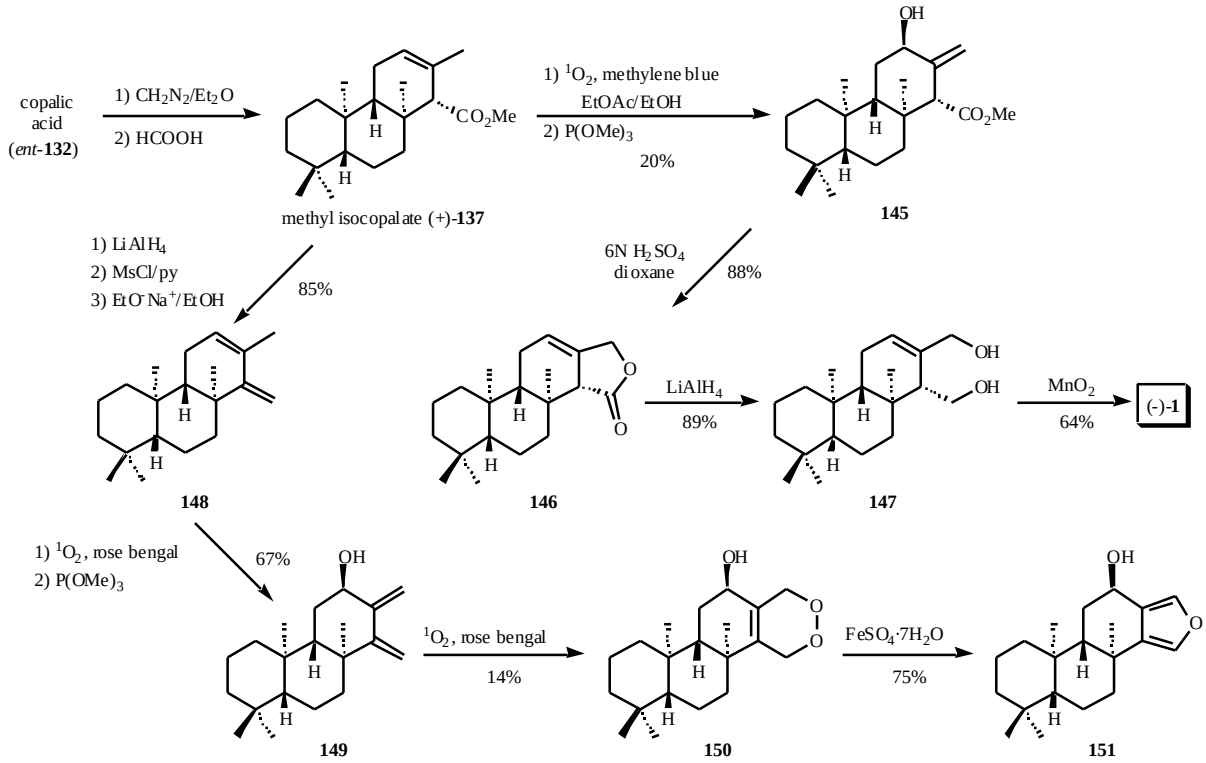
Isocopalol **155** was prepared by acid-catalyzed cycliza-tion of an acetate mixture (**154**) (Scheme **6**) [106]. These authors have used chiral isocopalol **155** and diol **144** for the synthesis of sponge metabolites such as aldehydes **156** and **157** by consecutive oxidations [107]. These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

The same authors also reported the synthesis of a furanoditerpene, methyl spongia-13(16),14-dien-19-oate (**160**), by cyclization of methyl lambertianate (**159**), which can be obtained from lambertianic acid (**158**), a diterpene acid of the Siberian cedar *Pinus sibirica* (Scheme **6**) [105].

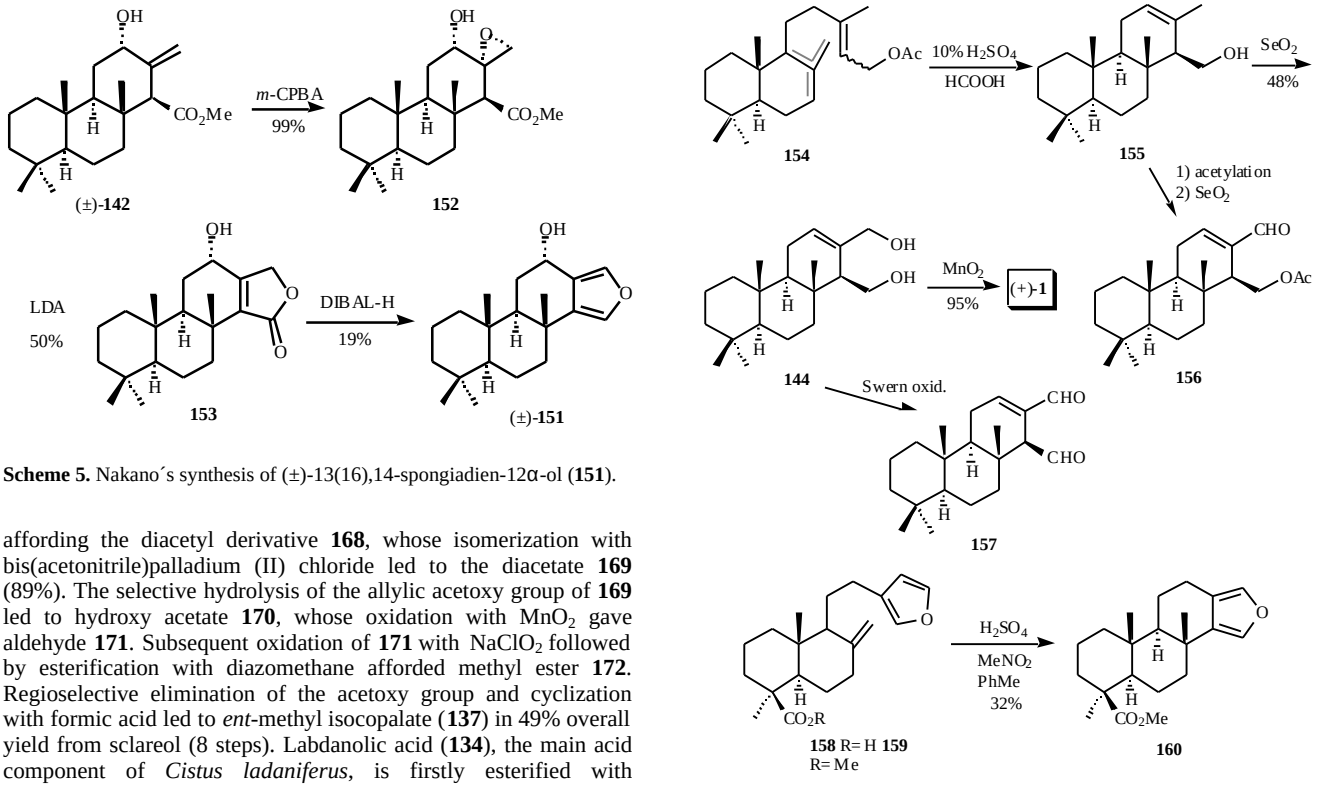
In 1985, Rúveda *et al.* reported the first synthesis of a naturally occurring furanospongiane, albeit in racemic form (Scheme **7**) [109]. (±)-Spongia-13(16),14-diene (**15**, R= CH_3) was prepared from (±)-methyl isocopalate (**137**) *via* the same unsaturated lactone (**143**) used in the synthesis of isoagatholactone (see Scheme **2**). It is worth mentioning that lactone **143** was similarly prepared from alcohol **142**, however, the latter was synthesized in an improved manner (60% overall yield) by epoxidation of **137** and subsequent treatment with aluminium isopropoxide [108]. Racemic lactone **143** was then hydrogenated on Pt to give **161**, which was reduced with $LiAlH_4$, oxidized under Swern conditions and treated with *p*-TsOH to afford the desired furan **15** (R= CH_3) in 20% overall yield. The tetracyclic diterpene (±)-spongian **164**, which is the tetrahydrofuran derivative of **15** (R= CH_3) and possesses precisely the fundamental parent structure **I** (Fig. **1**), was synthesized in this work by hydrogenation of furan **163**. Furan **163** was obtained by allylic rearrangement with simultaneous cyclization of the diol **162**, which was prepared by lithium aluminum hydride reduction of **142**.

A few years later, Nakano *et al.* also described the synthesis of (±)-spongia-13(16),14-diene (**15**, R= CH_3) from the same hydroxy-isocopalane **142** used in the synthesis of (±)-**151** (Scheme **8**) [110], however, that starting material was synthesized from (±)-methyl isocopalate (**137**) using the improved procedure developed by Rúveda *et al.* for the synthesis of related tricyclic diterpenes (aldehydes **156** and **157**) [108]. Thus, epoxidation of methyl isocopalate **137** gave α-epoxide **165** which upon treatment with aluminium isopropoxide afforded hydroxy-isocopalane **142** in 60% overall yield. Lactonization and β-elimination of **142** using H_2SO_4, followed by isomerization with 10% ethanolic potassium hydroxide gave α,β-unsaturated γ-lactone **166**, which was reduced with lithium aluminium hydride to give diol **167**. Oxidation of **167** with pyridinium chlorochromate gave the desired (±)-furanospongian **15** (R= CH_3) in 55% yield (Scheme **8**).

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,



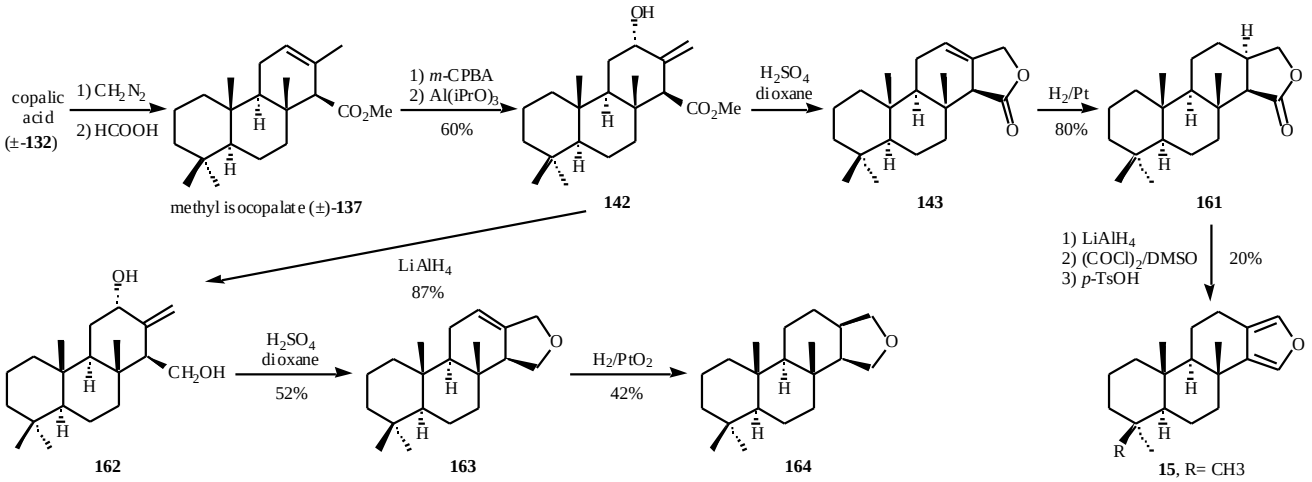
Scheme 4. Rúveda´s synthesis of *ent*-isoagatholactone (-)-(**1**) and *ent*-13(16),14-spongiadien-12a-ol (**151**).



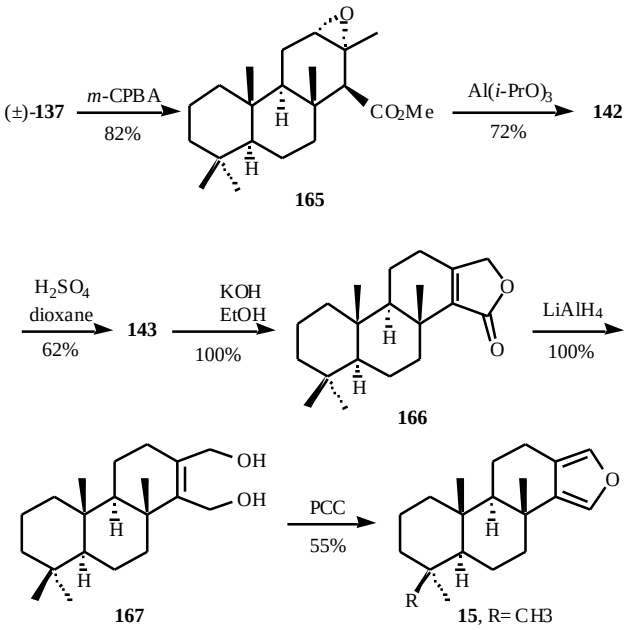
Scheme 5. Nakano´s synthesis of (±)-13(16),14-spongiadien-12α-ol (**151**).

Scheme 6. Vlad´s syntheses of natural isoagatholactone (+)-**1**, aldehydes **156** and **157**, and methyl spongia-13(16),14-dien-19-oate (**160**).

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_2 gave aldehyde **171**. Subsequent oxidation of **171** with $NaClO_2$ 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 *Cistus ladaniferus*, is firstly esterified with diazomethane, and then dehydrated and isomerized with I_2 in refluxing benzene to give methyl labden-15-oate **174**. Ester **174** is



Scheme 7. Rúveda´s syntheses of (±)-spongia-13(16),14-diene (**15**, R= CH3) and (±)-spongian (**164**).



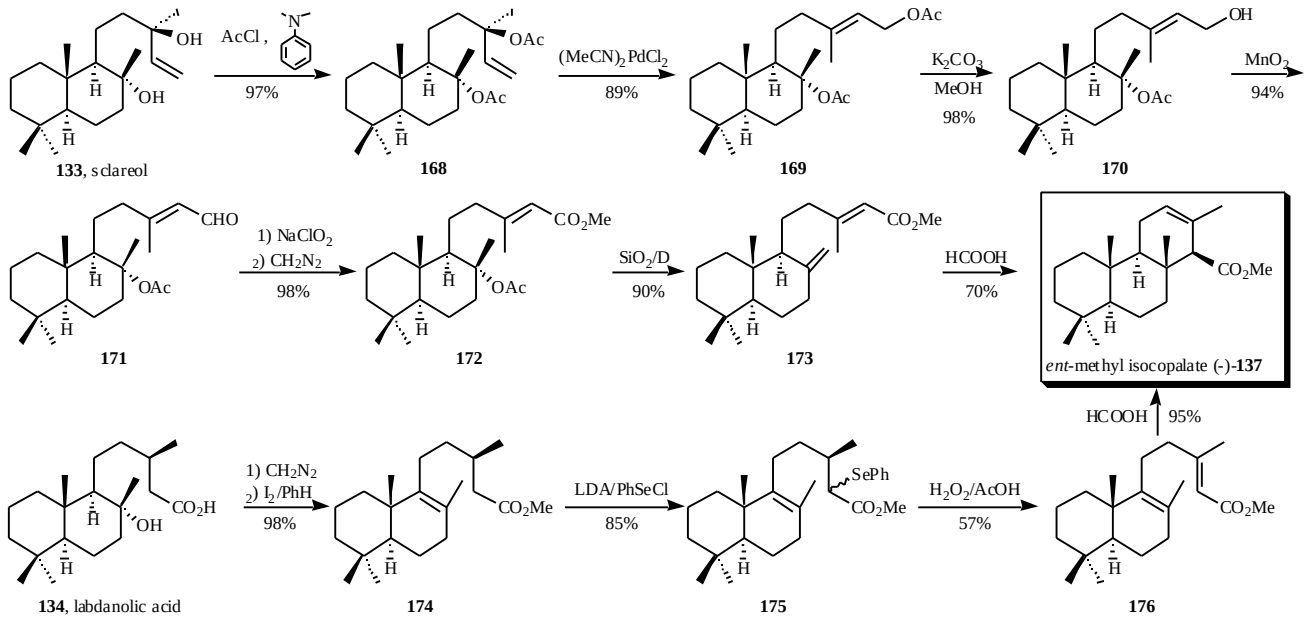
Scheme 8. Nakano´s synthesis of (±)-spongia-13(16),14-diene.

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

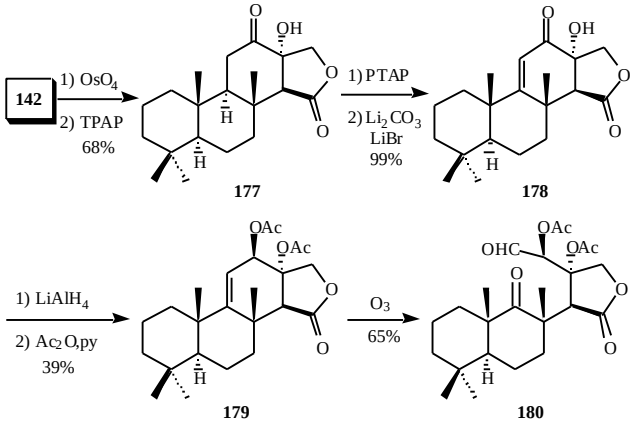
The same authors showed how this material, *ent*-methyl isocopalate (**137**), can be converted into 9,11-secospon-gianes, one of the most widespread subgroups of spongianes (Scheme **10**) [113]. To this end, the introduction of a Δ^{9-11} double bond and subsequent cleavage was investigated. The method 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 OsO_4 followed by oxidation with TPAP gave the ketone **177** in 68% yield. The desired double bond was introduced by bromination with phenyltri-methylammonium perbromide (PTAP) and subsequent elimination with Li_2CO_3/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 ocurring 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 (+)-isoagatholactone (**1**) and (-)-spongia-13(16),14-diene (**15**, R= CH_3) starting from chiral podocarpenone **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 stereocontrolled acetylenic-cation cyclization of acetylenic alcohol **183**, which was prepared from **138** by epoxidation, silica gel catalysed eschenmoser ring-opening reaction and addition of methyllithium. 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 targeted spongianes. In the first approach, the required homologation at C-13 was introduced by carbonylation of triflate **187**, subsequent deprotection in acidic media afforded directly the desired isoagatholactone (+)-**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 ºC in a sealed tube to give lactone **189**, which was transformed into (**15**, R= CH_3) *via* reduction to its corresponding lactol, followed by dehydration and aromatization in acidic media (Scheme **11**). (-)-Furanospongiane **15** (R= CH_3) was thus prepared in eleven steps from **138** in 28% overall yield.



Scheme 9. Urones´ syntheses of *ent*-methyl isocopalate (-)-**137** from sclareol (**133**) and labdanolic acid (**134**).



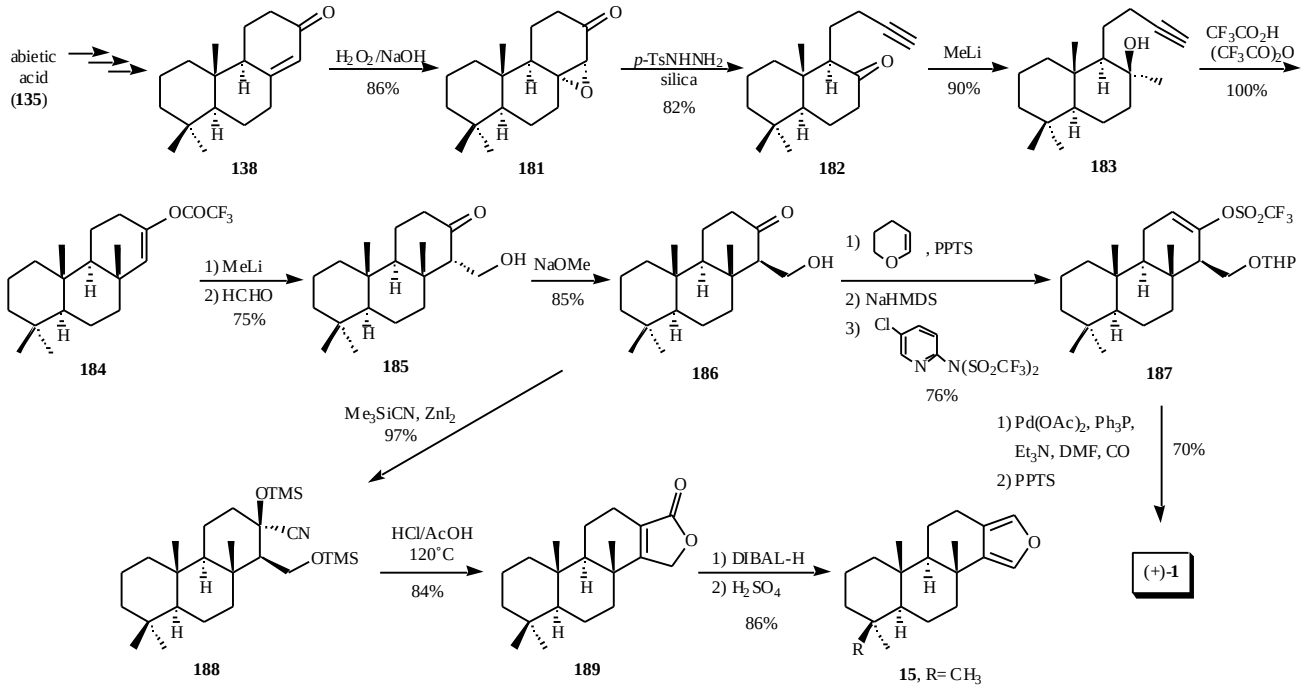
Scheme 10. Urones´ synthesis of 9,11-secospongiane **180**.

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_1= R_2= 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 deacetyla-plyroseol-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 cyanophosphorylation followed by reductive elimination to give nitriles **196**.

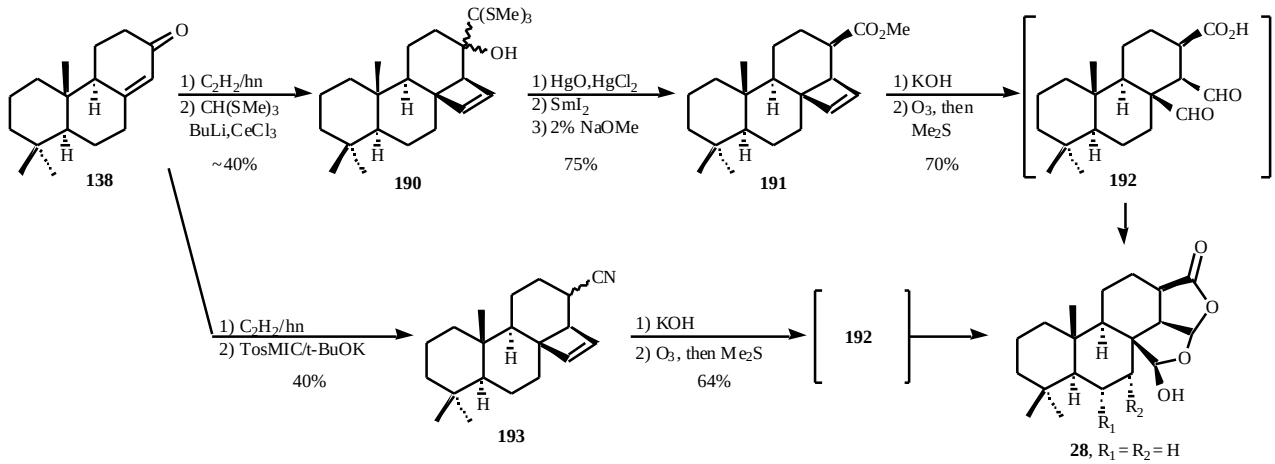
The versatility of intermediate **191** also led to further investigations which culminated with the synthesis of acetyldendrillol-1 **202** and revision of its stereochemistry at C-17, as well as the synthesis of tetracyclic spongianes functionalized at C-17 (Scheme **14**) [57]. The introduction of a cyanophosphorilation step improved the synthesis of **191** which was then converted into the intermediate dialdehyde **201**. Acetylation of compound **201** with AcOH/Ac_2O 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 unpredented 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 spongiane 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-cyclobutenone **197** into spon-gianal **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 = CH_3) starting from (+)-carvone *via* the phenanthrenone **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].



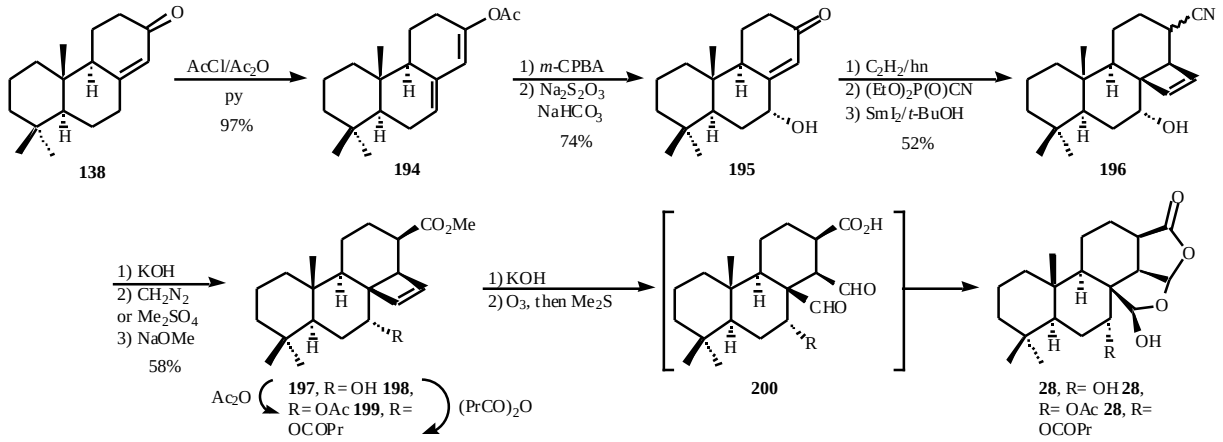
Scheme 11. Arnó´s syntheses of (+)-isoagatholactone (**1**) and (-)-spongia-13(16),14-diene (**15**, R= CH3) from **138**.



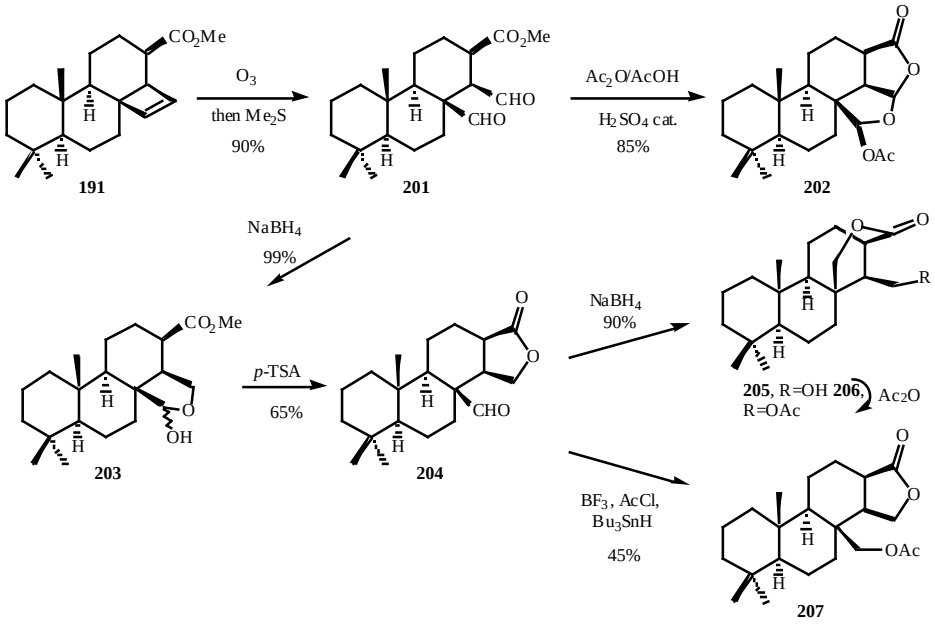
Scheme 12. Arnó´s synthesis of (-)-dendrillol-1 (**28**, R1= R2= H).

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=CH_3) 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 stereo-selectively 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=CH_3) in 75% yield.

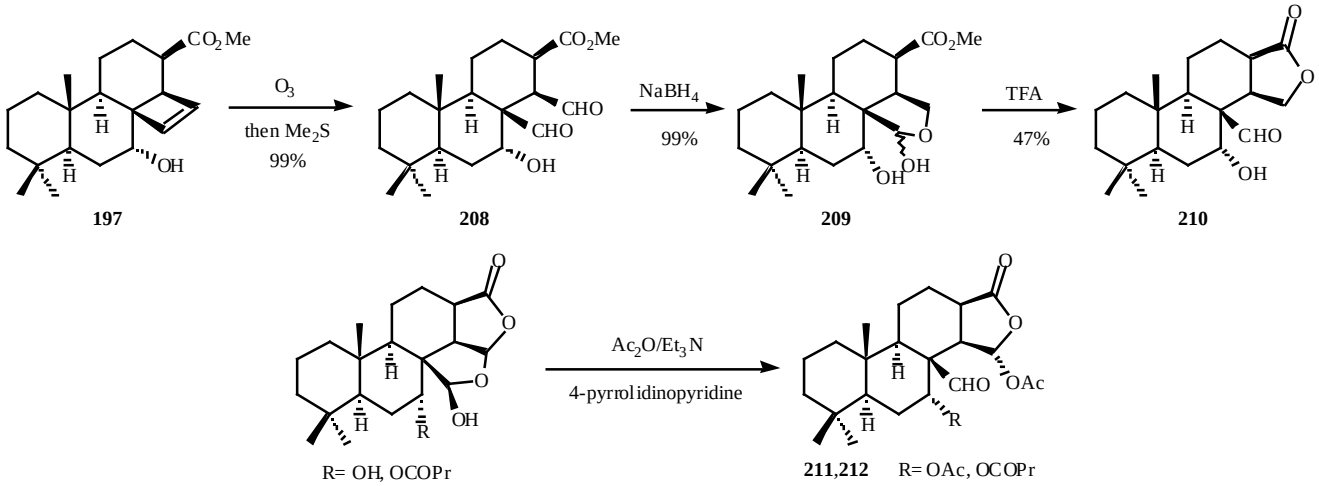
A new strategy towards oxygenated spongianes using (-)-carvone as starting material has recently been described by Abad *et al.* [126] as outlined in Scheme **17**. This synthetic sequence follows a B→AB→ABC→ABCD approach in which carvone is first converted into the decalone **220** (AB system) by alkylation 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 cycloaddition took place at 112ºC for 17 h to give the



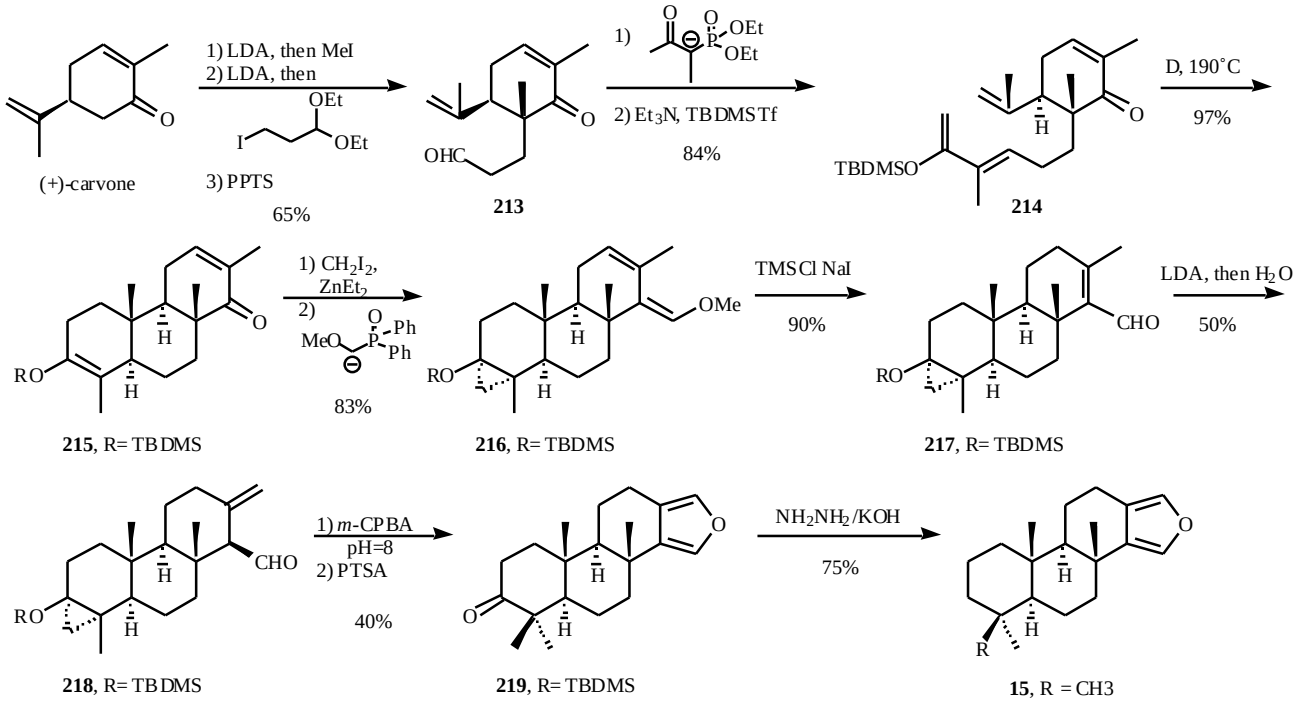
Scheme 13. Arnó´s syntheses of (-)-aplyroseol-1 (**28**, R= OCOPr), (-)-aplyroseol-2 (**28**, R= OAc) and (-)-deacetylaplyroseol-2 (**28**, R= OH).



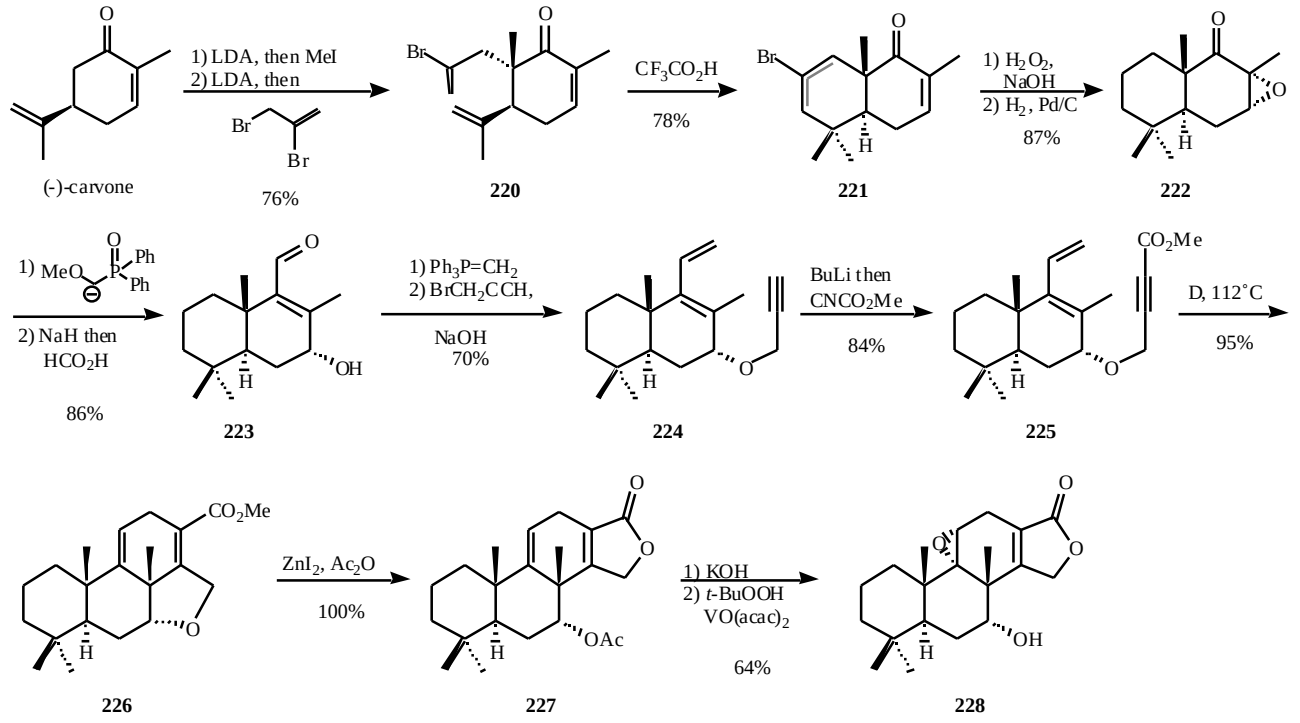
Scheme 14. Arnó´s syntheses of (-)-acetyldendrillol-1 (**202**), (-)-spongian-16-oxo-17-al (**204**), (-)-aplyroseol-14 (**206**) and (-)-isoaplyroseol-14 (**207**).



Scheme 15. González´s synthesis of C7,C17-functionalized spongianes.



Scheme 16. Arnó´s synthesis of (-)-spongia-13(16),14-diene (**15,** R= CH3) from (+)-carvone.

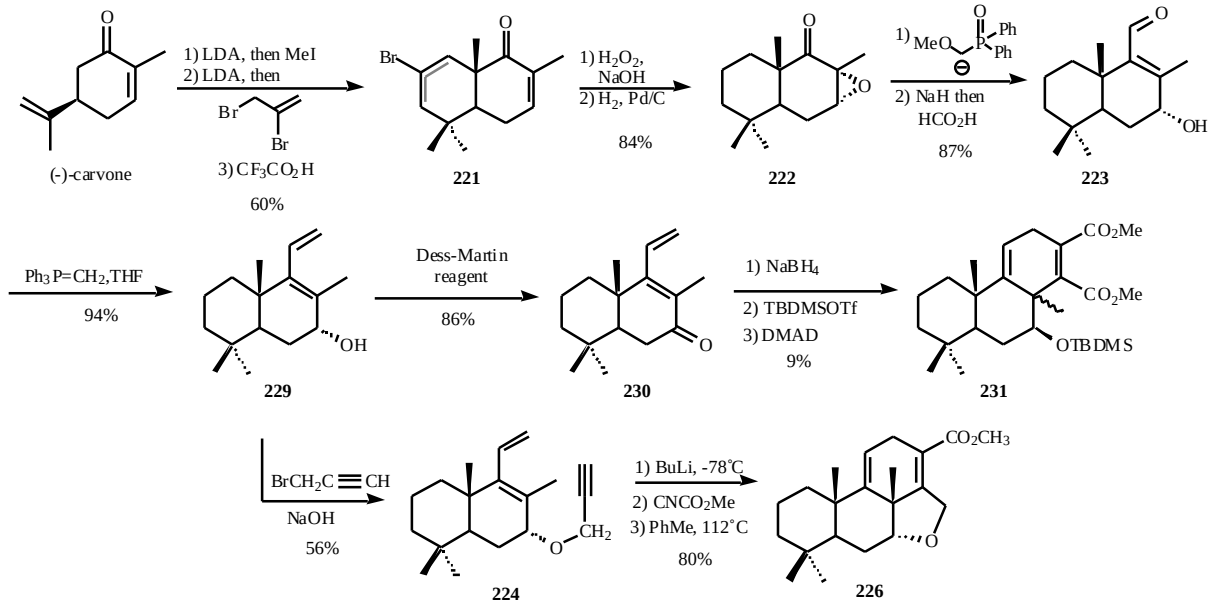


Scheme 17. Abad´s synthesis of C7,C11-functionalized spongianes (**228**) from (-)-carvone.

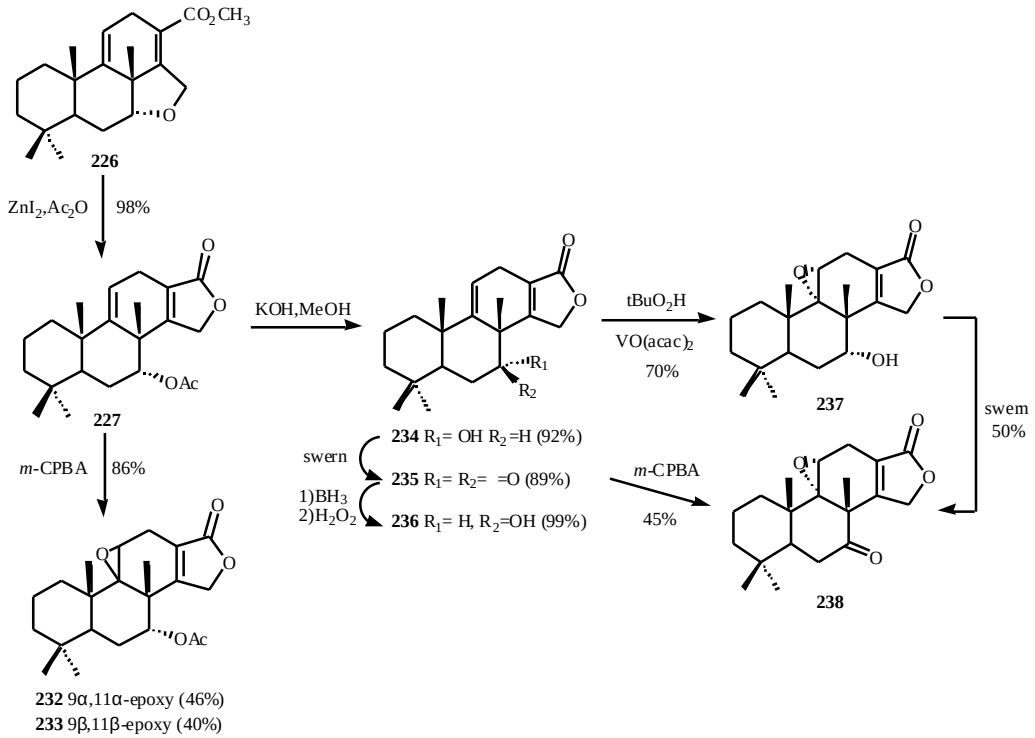
Diels-Alder adduct **226** in 95% yield. This was next elaborated using a regioselective ring-opening of a dihydrofuran ring to give the C7,C11-functionalized spongiane lactone **228** after hydrolysis and epoxidation with *t*-BuOOH and $VO(acac)_2$.

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

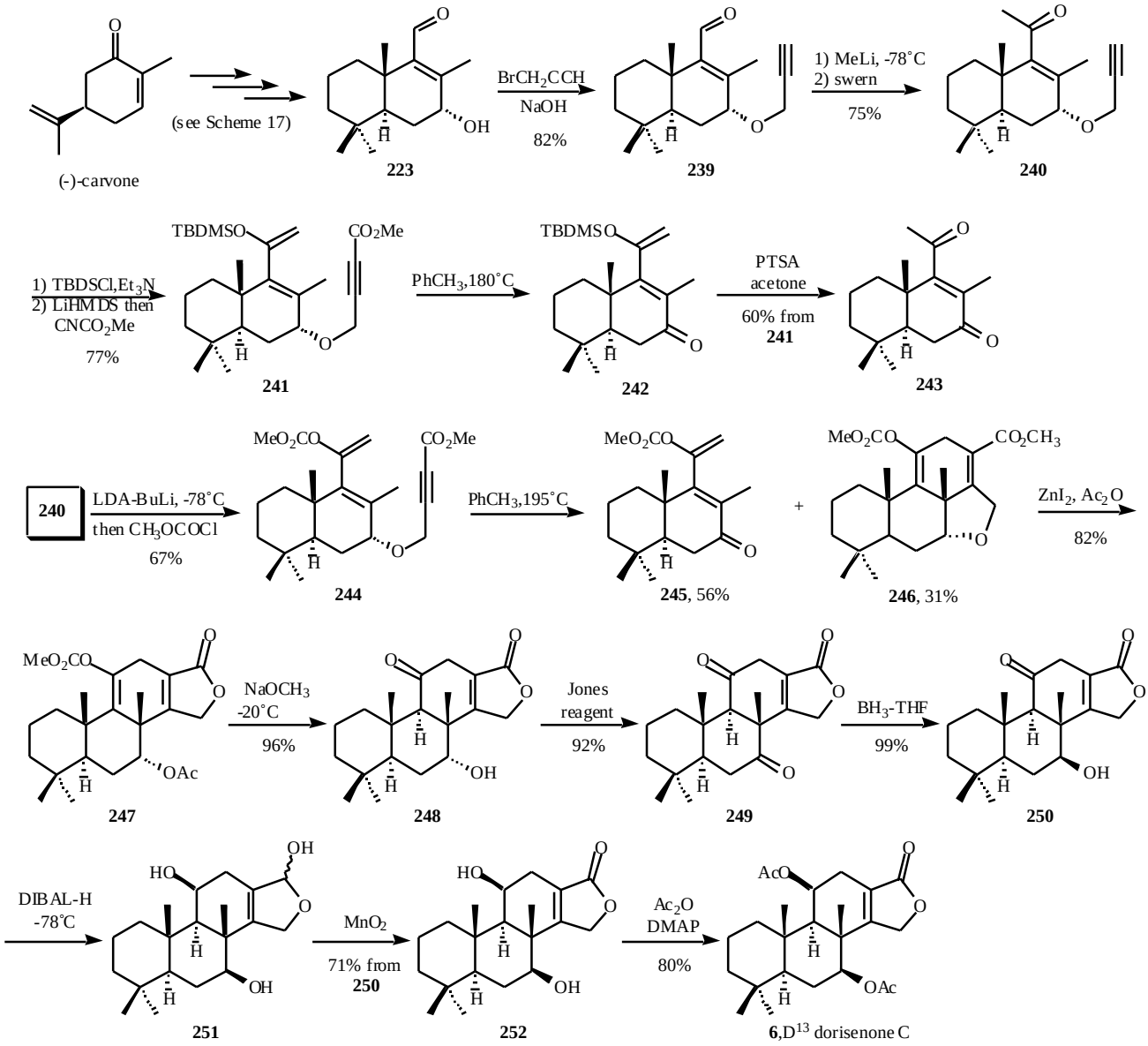
was further elaborated to the Diels-Alder precursor **225** (Scheme **17**). Other Diels-Alder precursors were also synthesized from **223** for intermolecular Diels-Alder reactions but provided low yields using dimethyl acetylene-dicarboxylate (DMAD) as dienophile (Scheme **18**) [127]. The synthesis starts with alquilation with LDA of the α-position of the enone. Further alquilation with an allyl bromide gave **221**. Epoxidation, followed by olefination gave **223**, 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.

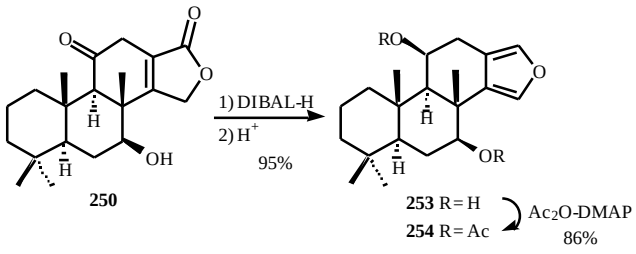


Scheme 20. Abad´s synthesis of dorisenone C (**6**,Δ13 R= Me) from (-)-carvone.

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**, Δ^{13} R= Me) (Fig. **3**) [128].

They have developed a B→AB→ABC→ABCD app-roach starting from *R*-(-)-carvone, in which the known hydroxyaldehyde **223** (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 MnO_2 to give the corresponding lactone **252**. Final diacetylation of **252** gave the synthetic natural product dorisenone C (**6**, Δ^{13} 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**).



250 **253** R = H, **254** R = Ac

Scheme 21. Abad´s synthesis of furanoditerpenes **253-254** from (-)-carvone.

Finally, we describe how recently Ragoussis and co-workers have converted natural (-)-sclareol **133** into the furanoditerpene (-)-marginatone **32** (R_1= CH_3, R_2= O, Fig. **11**) (Scheme **22**) [172]. The authors converted sclareol **133** into (+)-coronarin E **257**, using minor modifications of reported procedures, which by regioselective hydrogenation 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-bicyclohomofarnesal **255** from sclareol **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 (+)-coronanin 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 BF_3 etherate furnished the desired tetracyclic derivative **259** with the marginatane skeleton, on which an allylic oxidation with t-BuOOH gave the target molecule (-)-marginatone **32**, albeit in low yield (33%).

Syntheses by Biomimetic Approaches

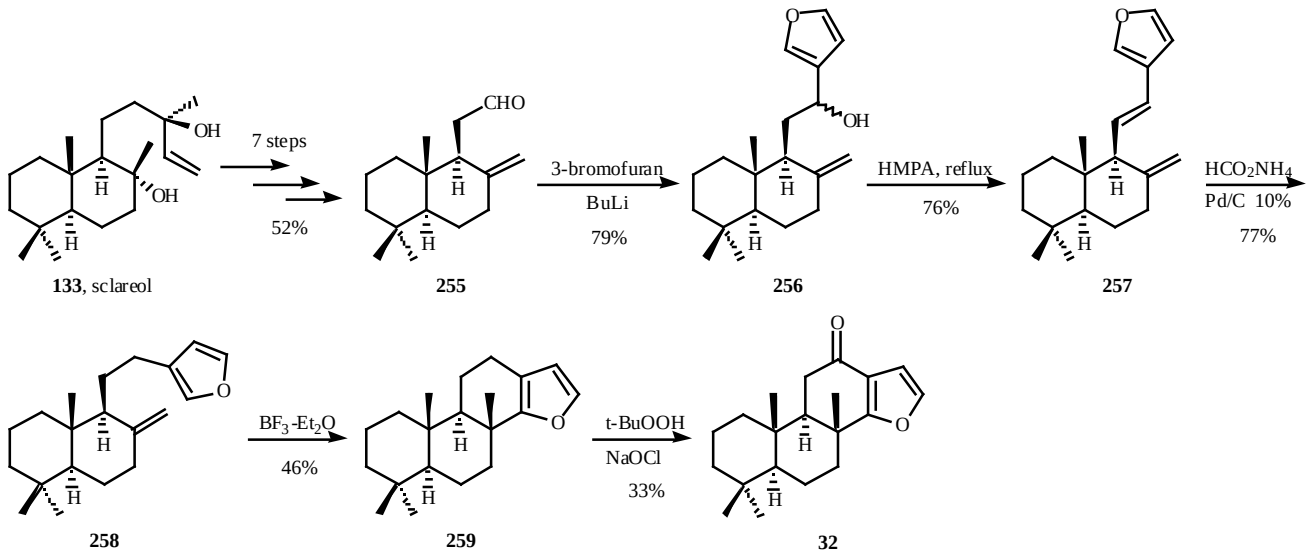
Inspired by Nature, biologists and chemists have made polyene cyclizations a powerful synthetic tool for the one-step construction of polycyclic compounds starting from acyclic polyene precursors. Despite the impressive and economical syntheses achieved over the past 50 years by chemical simulation of 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 isoagatholactone (**1**) by Nakano and Hernández [102] and Ungur *et al.* [105,106]. Compound **155** has also been converted into 12α-hydroxyspongia-13(16),14-diene by Rúveda *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].

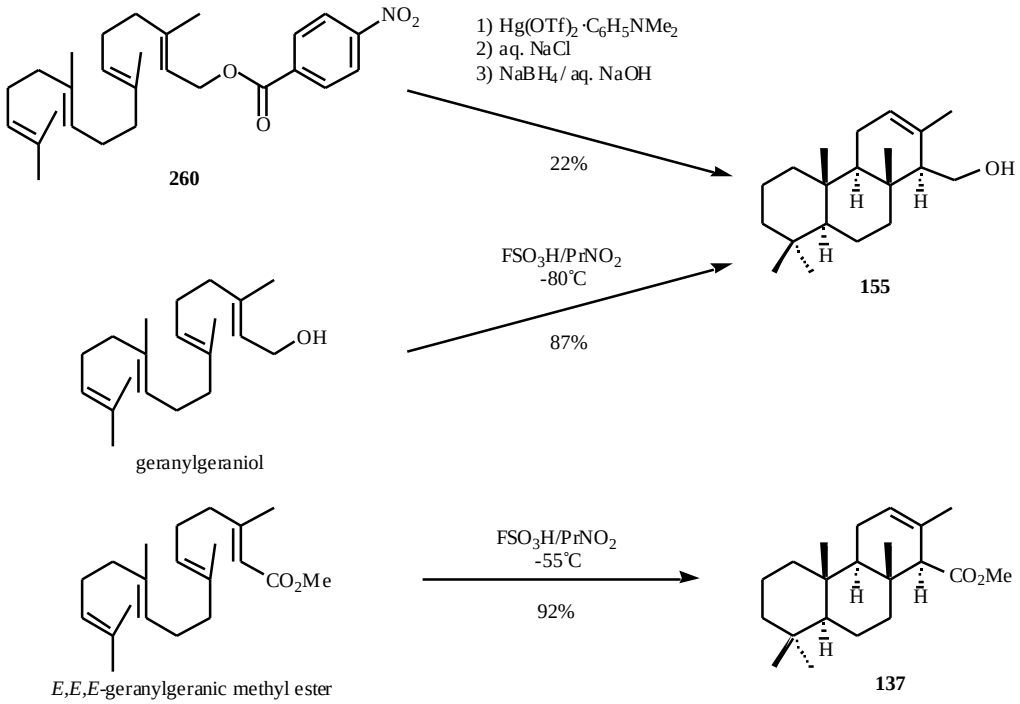
Nishizawa *et al.* also used the mercury (II) reagent to cyclize ambliofuran **261** leading to the tetracyclic isospon-giane **262** in 13% yield (Scheme **24**) [144]. Compound **263**, having the marginatane carbon skeleton [59], was obtained after the demercuration treatment of **262** with sodium borohydride. Ambliofuran **261** had also been cyclized to furanoditerpene **263** in high yield by Sharma *et al.* using $SnCl_4$ 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].

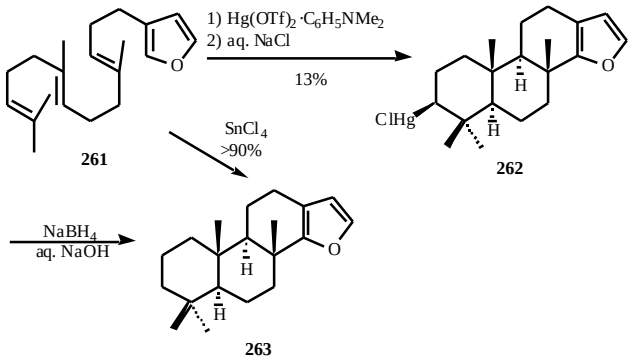


133, sclareol **255** **256** **257** **258** **259** **32**

Scheme 22. Ragoussis´s synthesis of (-)-marginatone **32** from (-)-sclareol.



Scheme 23. Biomimetic syntheses of racemic isocopalol **155** and methyl isocopalate **137**, precursors of spongiane diterpenoids.



Scheme 24. Biomimetic synthesis of isospongiane **263** from ambliofuran **261**.

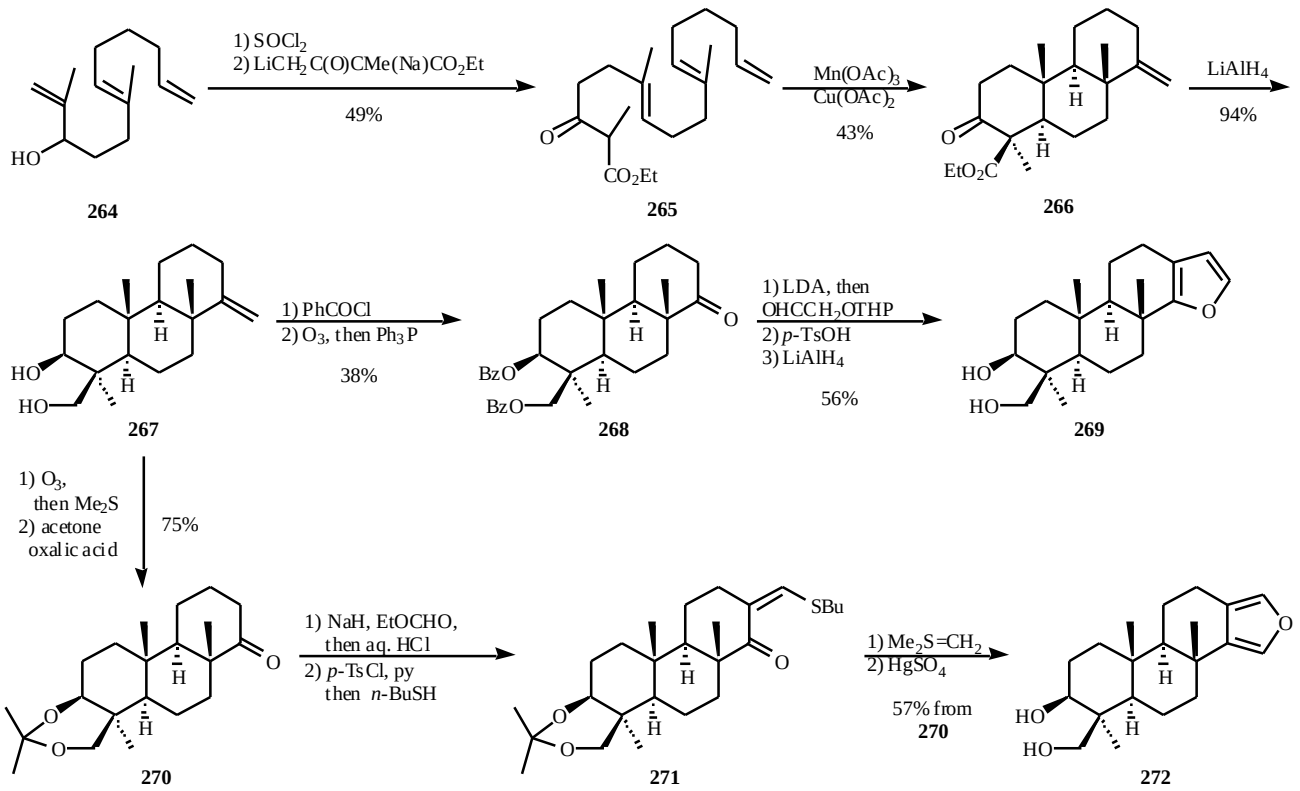
In the early 1990s, Zoretic and co-workers developed a very efficient series of triple and tetra cyclizations leading to *trans*-decalin ring systems. Their strategy [149] was based on the Snider method to cyclize intramolecularly unsaturated β-keto esters with Mn(III) salts [150]. Following the success 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 seq-uences, the construction of the required furan ring D of the spongiane 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 hydroxyacetaldehyde, subsequent hydrolysis with concomitant aromatization and final debenzoylation by reduction.

On the other hand, ozonolysis of diol **267** and protection as its corresponding acetonide, followed by furan ring formation using Spencer´s method gave unnatural furanos-pongiane **272** in 8% overall yield from **264**.

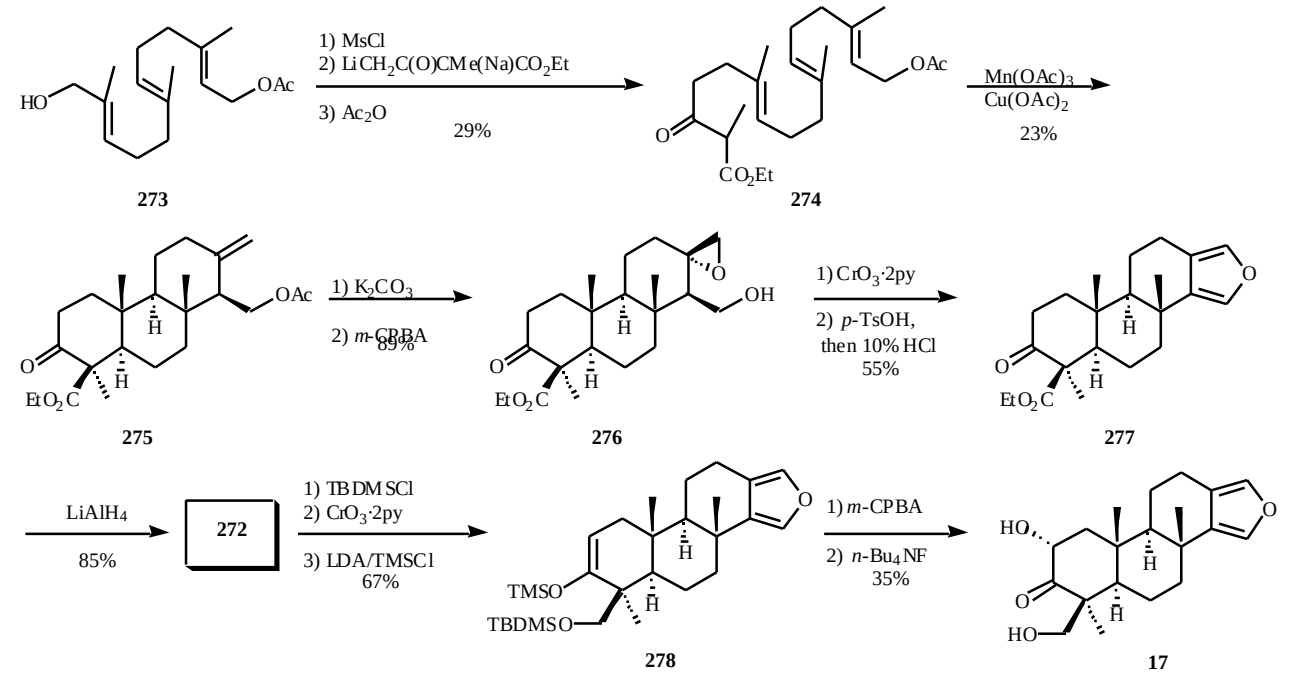
The same authors also reported an alternative route to **272** *via* the tricyclic intermediate **275**, which was prepared from the farnesyl acetate derivative **273** in four steps (Scheme **26**) [153]. Compound **275** possessing all of the carbons in the spongiane skeleton was transformed into spongiane **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 (±)-isospongiadiol **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**.

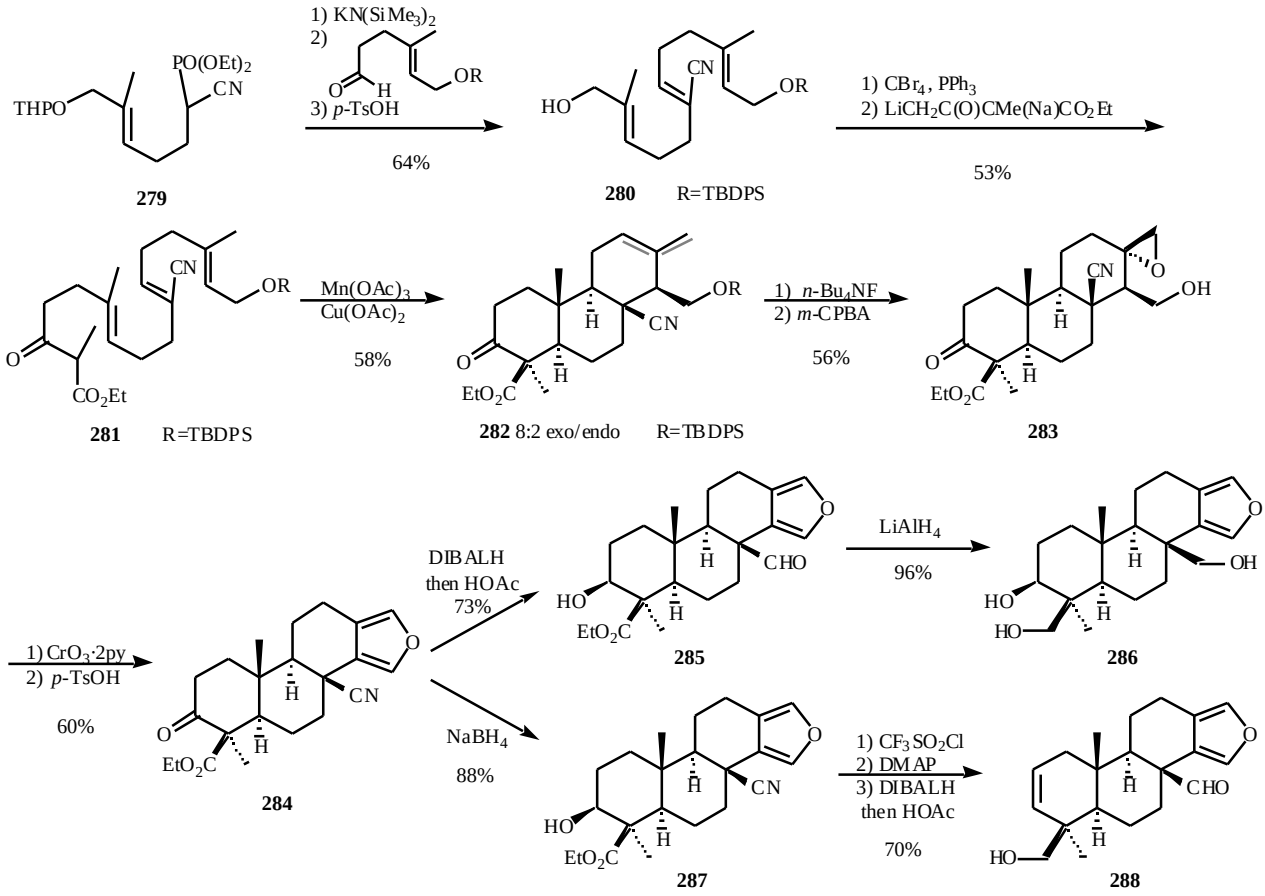
Concurrent to these studies, Pattenden and co-workers applied their expertise in polycyclic ring constructions, based on free radical-mediated cyclizations of polyolefin selenyl esters [156,157], for the total synthesis of (±)-spongian-16-one **4** (6% overall yield) (Scheme **28**) [158,159]. They completed 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 tetrahydropyranyl ether, followed by lithiation and reaction with



Scheme 25. Zoretic´s biomimetic synthesis of isospongiane **269** and spongiane **272** from precursor **265**.



Scheme 26. Zoretic´s biomimetic synthesis of (±)-isospongiadiol **17**.



Scheme 27. Zoretic´s biomimetic synthesis of C17-functionalized furanospongianes.

cyclopropyl methyl ketone led to compound **290**. Ring-opening of the cyclopropane and formation of a *E*-homoallylic bromide using HBr, which was then used as its corresponding iodide **291** to alkylate 2-phenylthio-butyrolactone. Removal of the thioether and subsequent manipulation of the tetrahydropyranyl ether led to selenoate **295**. The treatment of the latter with Bu_3SnH and AIBN in refluxing degassed benzene led, after methylenation, to the tetracycle lactone **296** in 42% yield. Lactone **296** was then converted into **4** by Simmons-Smith cyclopropanation and hydrogenolysis.

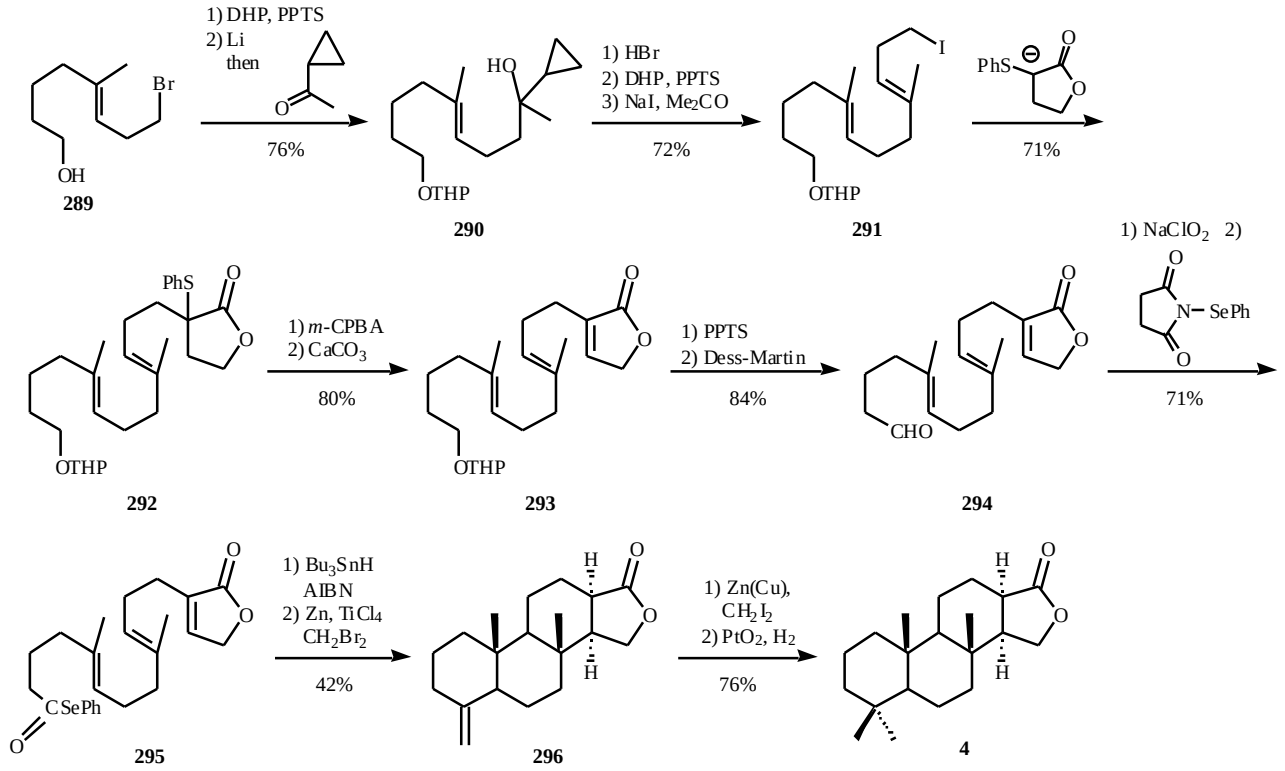
Recently, Demuth and co-workers have developed a radical-type cascade cyclization for the synthesis of (±)-3-hydroxy-spongian-16-one **302**, a precursor of **4** (Scheme **29**) [160]. In their strategy, the photoinduced radical cation of the polyene undergoes water addition in *anti-Markovnikov* sense, followed by cyclization cascades terminated by a 5-*exo*-trig ring closure. The overall reaction sequence mimics the non-oxidative biosynthesis of terpenes. The radical cation precursor **301** was synthesized from farnesyltri-*n*-butylstannane **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 λ_{max}=300nm afforded spongiane **302** in 23% yield after purification. The structure of **302** was unambigously determined by NOE and X-ray analyses.

Other Approaches and Total Syntheses

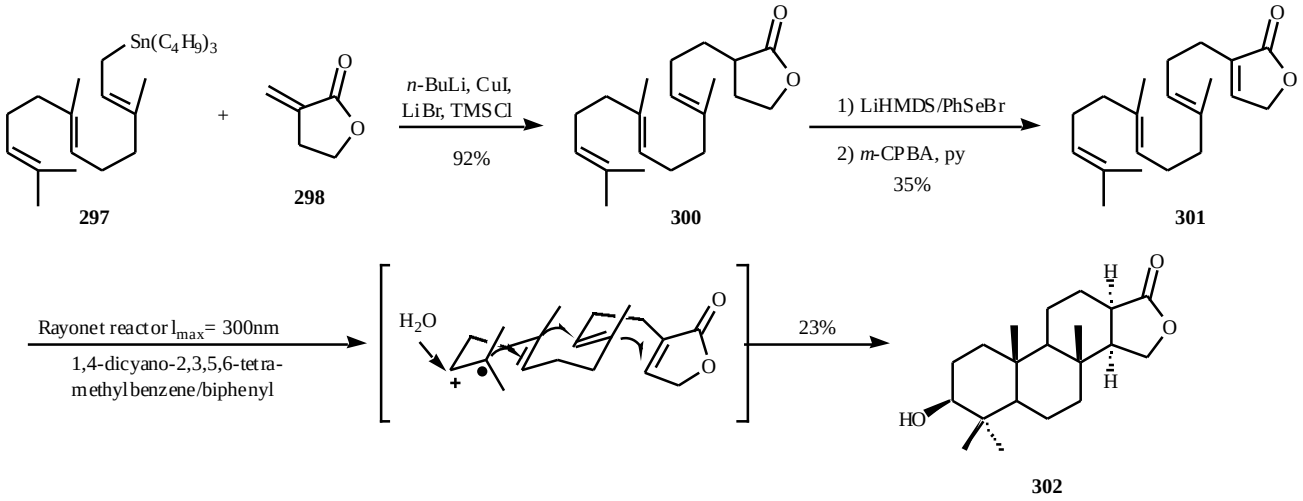
As we mentioned before, the studies towards the synthesis of spongianes are scarce, specially of rearranged metabolites. The synthesis of furanospongiaditerpenoids has been embarked starting from natural products and using biomimetic-like reaction sequences. Both of them have provided in some cases the 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 **316** (Scheme **30**), which later was converted into (±)-spongia-13(16), 14-diene **15** and (±)-spongiadiosphenol **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 28. Pattenden´s biomimetic synthesis of (±)-spongian-16-one **4**.



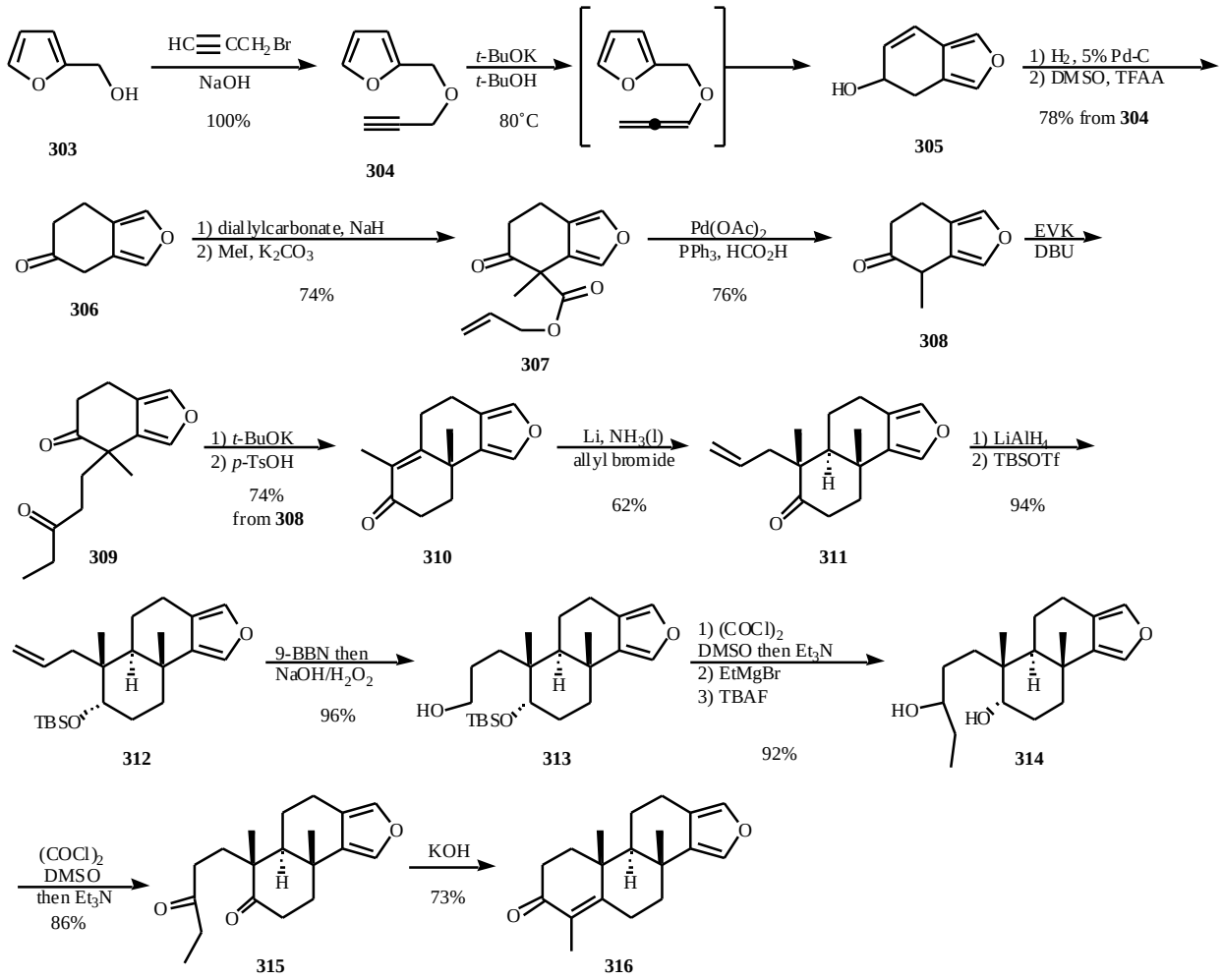
Scheme 29. Demuth´s biomimetic synthesis of (±)-3-hydroxy-spongian-16-one **302**.

spongiadiosphenol **20**, which represents the first total synthesis of a furanospon-giaditerpenoid with a functionalized A-ring (Scheme **31**).

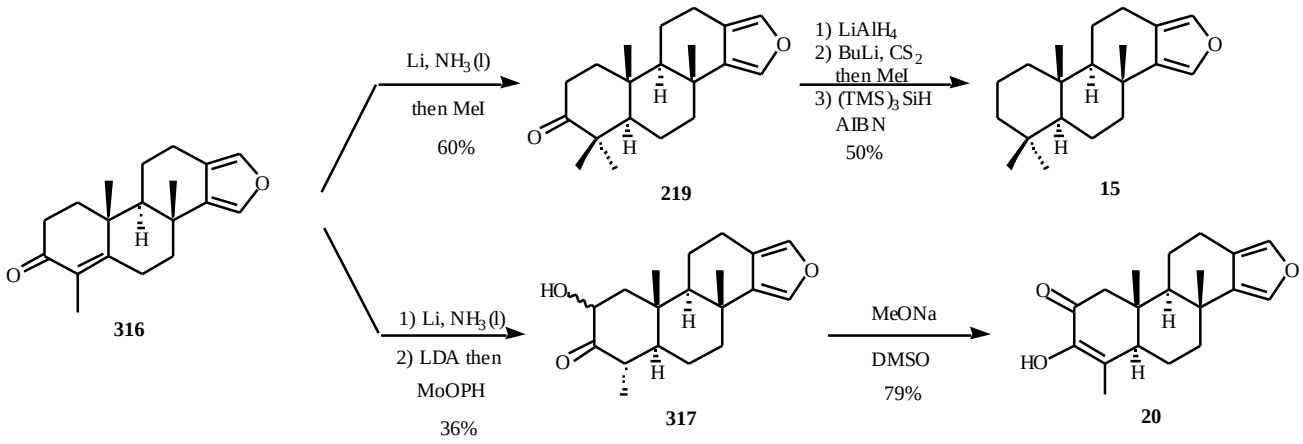
With regard to the synthesis of rearranged spongianes, there are about three synthetic approaches to build up bycyclic systems [163-165] present in those and, to the best of our knowledge, only two enantioselective total syntheses [166,167].

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].



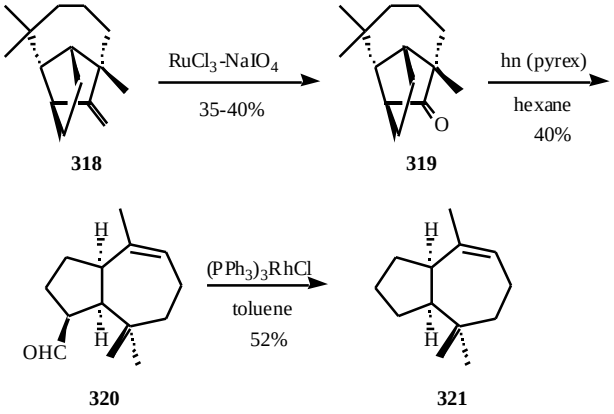
Scheme 30. Kanematsu´s synthesis of spongian precursor **316**.



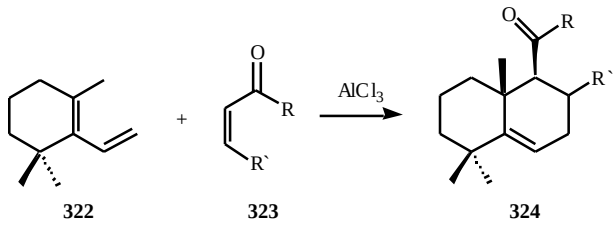
Scheme 31. Kanematsu´s synthesis of (±)-spongia-13(16),14-diene **15** and (±)-spongiadiosphenol **20**.

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].



Scheme 32. Mehta´s synthesis of hydroazulene **321**.



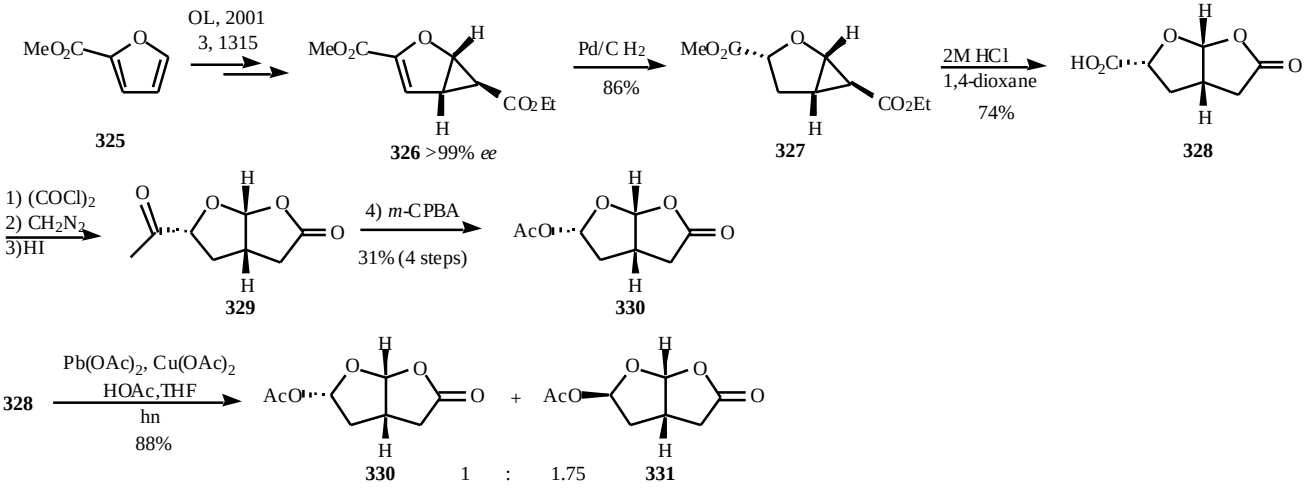
Scheme 33. Bhat´s synthesis of decalins.

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 rerrangement 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 diastereo-selective Baeyer-Villiger oxidation under retention of configuration. Alternatively, **328** could be photochemically decarboxylated with lead tetraacetate 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.

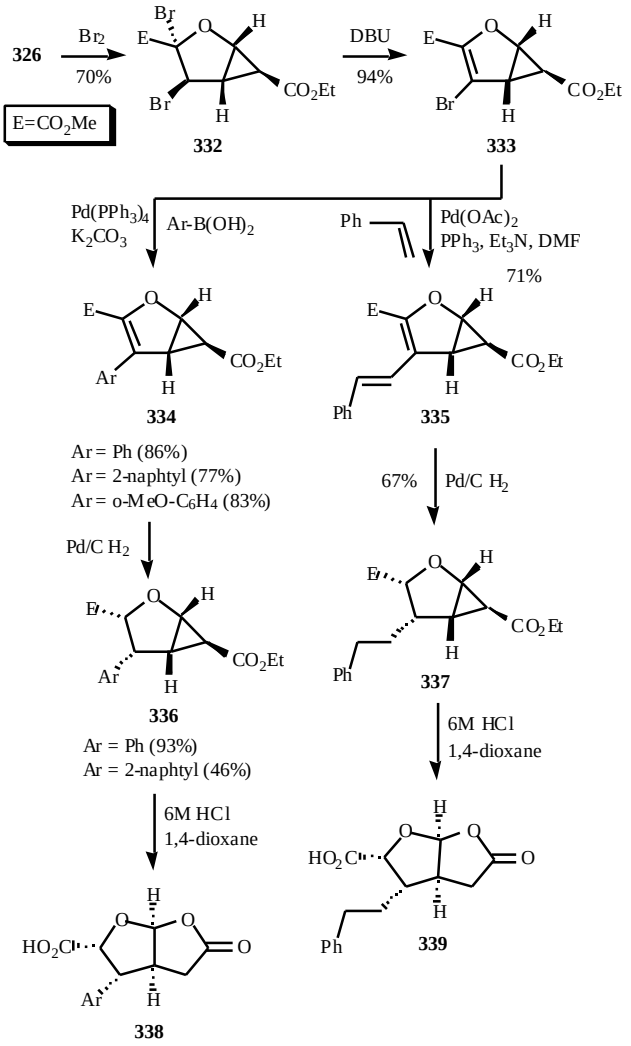
Following this general strategy, the authors next looked for a flexible way to stereoselectively introduce substituents into the 3-position of 5-oxofuro[2,3-b]furans (Scheme **35**).

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 thiocetalization gave compound **341**, which was subjected to the chemical resolution to give enantioenriched ketone (*S*)-**344** in 44% yield. Addition of (*E*)-1-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 bicycle **345** in 80% yield as a mixture of sulfide epimers, whose structure was confirmed by single-crystal X-ray analysis of the corres-ponding 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 α-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**.



Scheme 34. Reiser´s synthesis of 5-oxofuro[2,3-b]furans.



Scheme 35. Reiser´s synthesis of 3-substituted 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 sythesis of norrisolide **33** in 2004. This molecule presents a rare γ-lactone-γ-lactol moiety as side chain which has few synthetic precedents. This group developed initially an enantio-selective synthesis of the side chain starting from D-mannose (Scheme **37**) [168]. The preparation of the side chain begins with the transformation of D-mannose to the known bisacetonide **354** with improved conditions using iodine as catalyst to give **354** in 85% yield. Treatment of **354** with p-toluenesulfonyl chloride and triethylamine afforded the desired glycosyl chloride **355**, which upon elimination with a mixture of sodium naphthalenide in THF gave rise to glycal **356** in 48% overall yield. Compound **356** proved to be labile upon standing and was immediately benzylated to produce vinyl ether **357** in 90% yield. Syringe pump addition of ethyl diazoacetate (0.1M in DCM) into a mixture of **357** (2M in DCM) and rhodium (II) acetate at 25ºC gave the cyclopropanation ester **358** with the desired configuration at C-12 center. The only diastereomers acquired during this reaction were produced at the C-13 center (4:1 ratio in favor of the exo adduct) and both were taken forward.

Exposure of **358** to a dilute ethanolic solution of sulfuric acid induced acetonide deprotection followed by concomitant opening of the cyclopropane ring afforded compound **359** in 78% overall yield. Acetonide **358** can also be converted into the desired fused lactone-lactol in one step using methanesulfonic acid [169]. After oxidative cleavage of diol **359**, the resulting aldehyde was methylated by treatment with MeTi(*i*-OPr)$_3$ formed *in situ* to produce **360** in 63% combined yield. Oxidation of **360** under Swern conditions gave rise to ketone **361** (79%). The best yields for the conversion of **361** to **362** were obtained using methane-sulfonic acid, which at 0ºC produced bicycle **362** as a single isomer in 67% yield. 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.

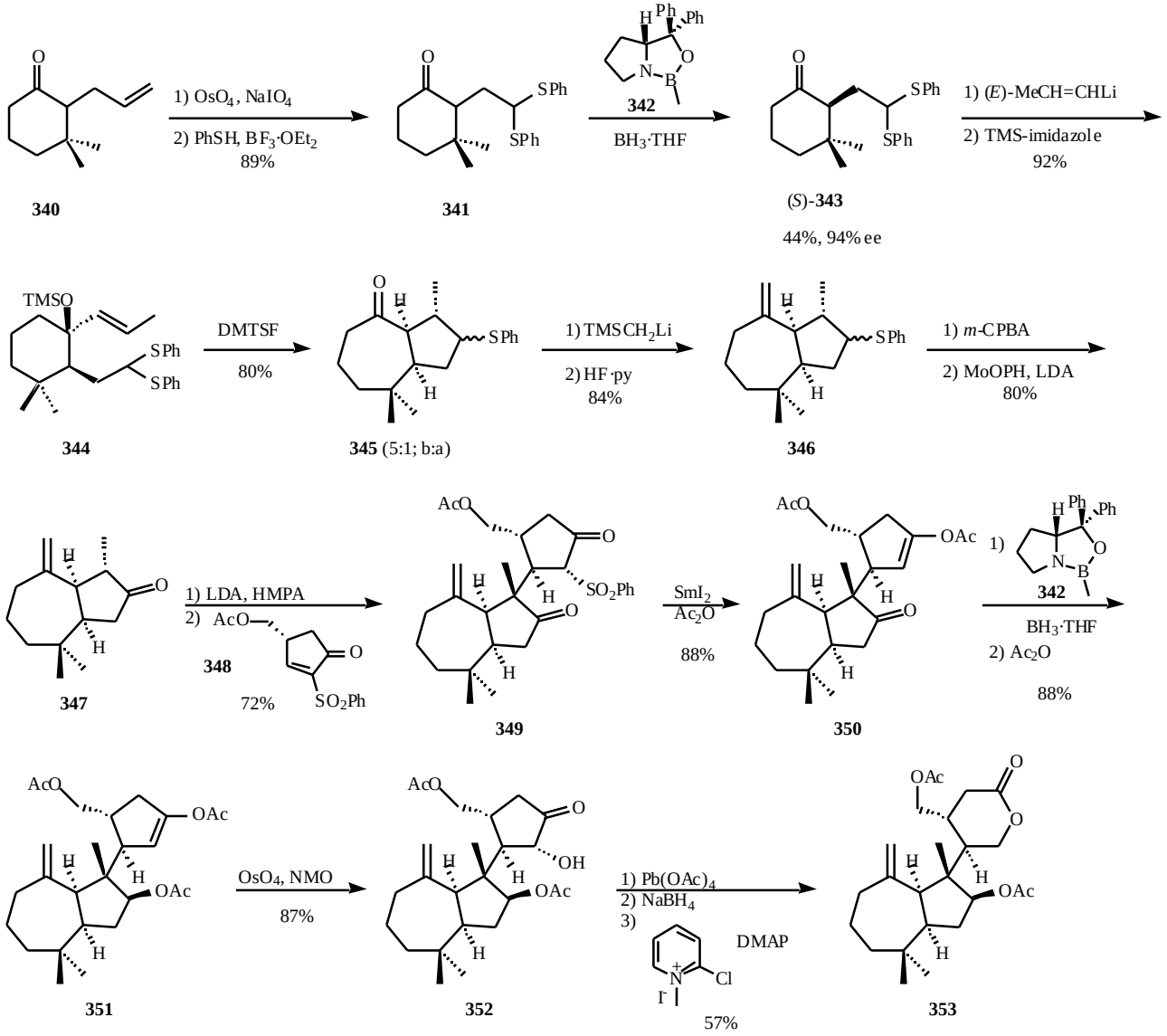
The Theodorakis´s group described the total synthesis of norrisolide **33** in 2004 [167,170]. In their strategy, they did the assembly of the two main fragments, **365** and **366**, through the C9-C10 bond (Scheme **38**). One of the frag-ments, the *trans*-fused hydrindane motif, could be prepared 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 an 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 hydrazone **374**. Finally, treatment of **374** with I_2/Et_3N led to the formation of the desired vinyl iodide **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 **378**. Compound **378** was then converted into the selenide **379**, which underwent oxidation and elimination to give alkene **380** (61% yield from **378**). Osmylation of **380**, followed by oxidative cleavage of the resulting diol, furnished the aldehyde **366** (two steps, 94% yield) as a crystalline solid whose structure was confirmed by X-ray analysis.

The remaining steps in the synthesis of norrisolide **33** are shown in Scheme **41**. Lithiation of the vinyl iodide **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 MeLi 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

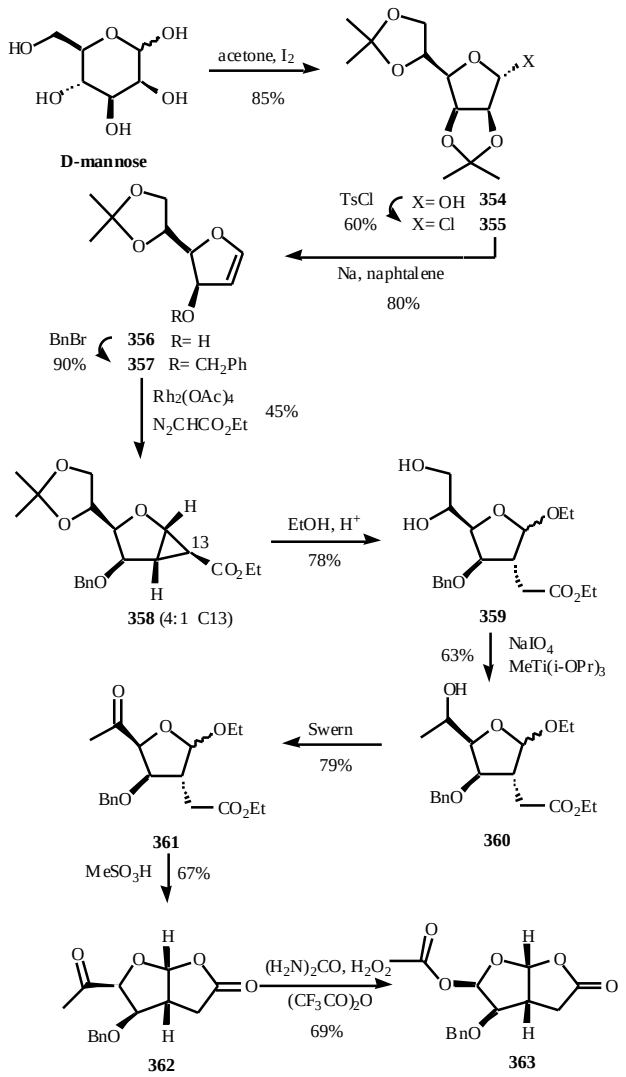


Scheme 36. Overman´s synthesis of (+)-shahamin K **353**.

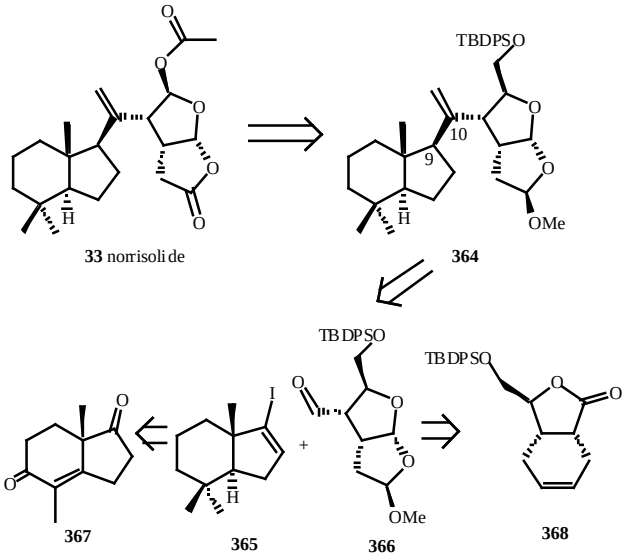
silyl ether and oxidation of the resulting alcohol gave aldehyde **383**, which was subsequently converted into the ketone **384** via treatment with MeMgBr and Dess-Martin oxidation (68% yield). Treatment of **384** with CrO_3 in aqueous acetic acid produced the lactone **385** in 80% yield. Finally, Baeyer–Villiger oxidation of **385** (MCPBA, $NaHCO_3$, 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**, **373** and **385** from previous synthetic studies were evaluated together with **386**-**391** which were also synthesized (Scheme **42**) [66].

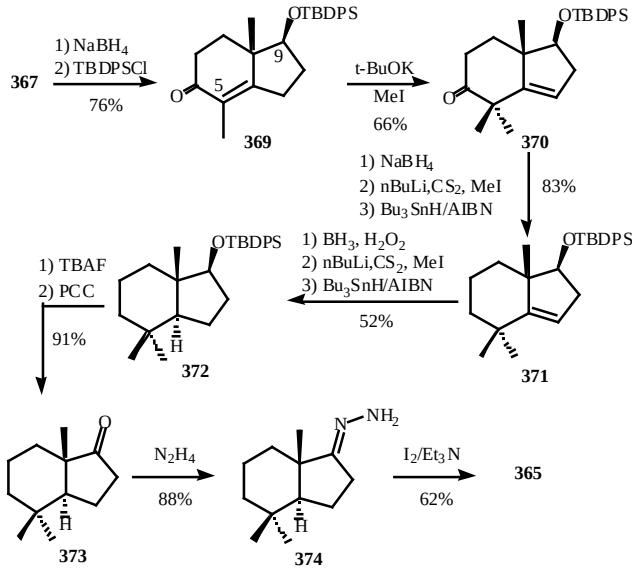
From the structure/function studies it was suggested that the perhydroindane core of norrisolide is critical for binding to the target protein, while the acetate unit is essential for the irreversible vesiculation of the Golgi membranes. Compounds **389**-**391** have no effect on Golgi membranes. This 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 stablizing 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



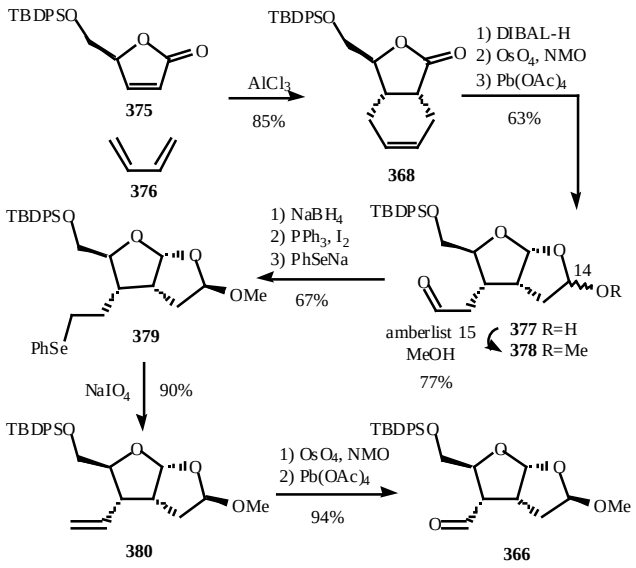
Scheme 37. Theodorakis´ synthesis of norrisolide side chain **363**.



Scheme 38. Theodorakis´ retrosynthesis of norrisolide **33**.



Scheme 39. Theodorakis´ synthesis of fragment **365** of norrisolide **33**.

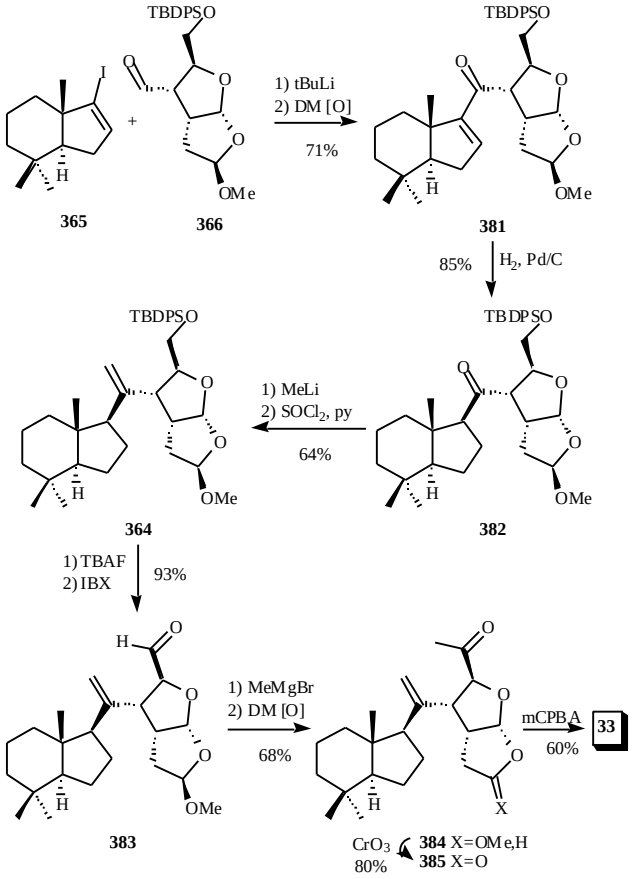


Scheme 40. Theodorakis´ synthesis of fragment **366** of norrisolide **33**.

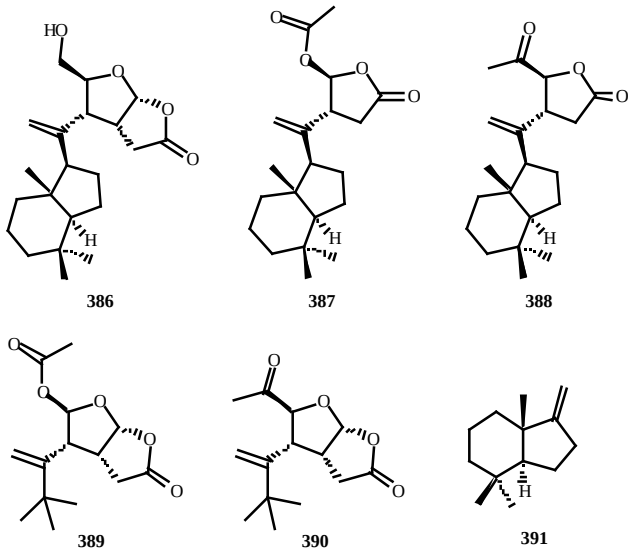
attached to a bisepoxide scaffold (suitable for protein labeling), induced an irreversible vesiculation of the Golgi membranes. On the other hand, compound **395**, lacking the perhydroindane motif, had no effect on Golgi membranes, attesting to the importance of the norrisolide core in Golgi localization 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

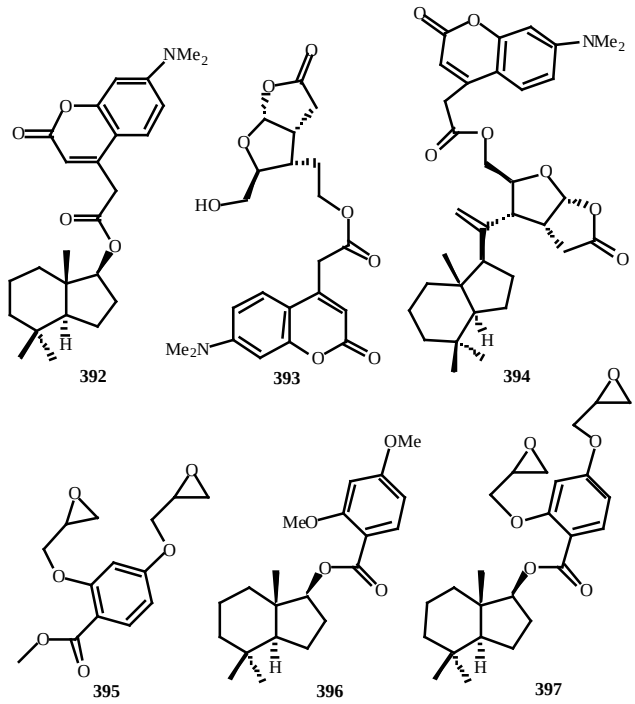


Scheme 41. Theodorakis´ synthesis of norrisolide **33**.



Scheme 42. Theodorakis´ analogues of norrisolide **33**.

found, the synthetic studies represent only one third of the publiccations 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.



Scheme 43. Theodorakis´ norrisolide-based fluorescent probes.

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