Total syntheses and synthetic studies of spongiane diterpenes

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1. Introduction

Spongiane diterpenoids are bioactive natural products isolated exclusively from sponges and marine shell-less mollusks (nudibranchs), which are believed to be capable 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 Hanson,2 and the excellent reviewing work on marine natural products by Faulkner,3,4 now continued by the team of Blunt,5 all of which have covered mainly 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 1999.6 The latter survey 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 toward the synthesis of spongianes.9

Abbreviations: AcCl, acetyl chloride; Ac₂O, acetic anhydride; AIBN, azobisisobutyronitrile; BuLi, butyllithium; Dibal-H, diisobutylaluminum hydride; DHP, dihydropyrane; DMAD, dimethyl acetylenedicarboxylate; DMAP, 4-(N,N-dimethylamino)pyridine; DMF, dimethylformamide; DMSO, dimethylsulfoxide; EiN, triethylamine; EVK, ethyl vinyl ketone; HMPA, hexamethylphosphorotriamide; IBX, 2-iodoxybenzoic acid; LDA, lithium diisopropylamide; LiHMDS, lithium hexamethyldisilylamide; MsCl, mesyl chloride; MCPBA, m-chloroperbenzoic acid; NaHMDS, sodium hexamethyldisilam-ide; NMO, 4-methylmorpholine N-oxide; PCC, pyridinium chlorochromate; PPTS, pyridinium p-toluene sulfonate; p-TSA, p-toluene sulfonic acid; PhH, benzene; PhMe, toluene; Py, pyridine; TBDMSOTf, tert-butyl dimethylsilyl trifluoromethanesulfonate; TBDPSCI, tert-butyl diphenylsilyl chloride; TBAF, tetra-n-butylammonium fluoride; TFA, trifluoroacetic acid; TMSCl, trimethylsilyl chloride; TPAP, tetrapropylammonium perruthenate.

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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 September 2007.

2. Structure, occurrence, and biological activity

The semisystematic naming of this family of diterpenoids was introduced in 1979 after the isolation of the first members of the family from sponges of the genus *Spongia*. Thus, in accordance with the IUPAC recommendations the saturated hydrocarbon 1, named ‘spongian’, was chosen as the fundamental parent structure with the numbering pattern as depicted in Figure 1.10

The first known member of the spongiane family, isoagatholactone (1), was discovered by Minale et al. from the sponge *Spongia officinalis* about 30 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).11

To date, there are nearly 200 known compounds belonging to this family of marine natural products, including those with a spongian-derived skeleton.12 Most of them present a high degree of oxidation in their carbon skeleton, particularly at positions C17 and C19, as well as on all the rings A–D. Given the variety of chemical structures found in the spongian 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.

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 capable of storing selected metabolites, even transforming 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, ichthyotoxic, antiviral, antitumor, antihypertensive, fragmentation of Golgi complex, as well as anti-inflammatory activity.12,13

3. Syntheses of spongiane diterpenes

Several syntheses have appeared within the last 25 years and we will classify them in three main groups. We will also include the synthetic studies developed so far and, 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 the spongianes, there have been relatively few synthetic studies toward their synthesis. In the 1980s, most of the synthetic studies toward spongiane-type diterpenes addressed mainly the synthesis of isoagatholactone and the preparation of simple furanospongianes.

In the next decade, the 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 toward the more complex oxygenated spongianes.

3.1. Syntheses from other natural products

Manool (4), copalic acid (5), sclareol (6), labdanolic acid (7), abietic acid (8), and carvones (9) (Fig. 2) have been used for the preparation of optically active spongianes. Naturally occurring racemic labda-8(20),13,16-dien-15-oic acid (copalic acid) has also been used for preparing racemic compounds.

These starting materials were converted into versatile tricyclic intermediates having the characteristic ABC-ring system of spongianes (Scheme 1) such as *ent*-methyl isocopalate (10), podocarp-8(14)-en-13-one (11), and phenanthrenones (12,13). Several strategies have been reported to build up the necessary ring D from these key intermediates, preferably as a furan or γ-lactone ring. The choice of podocarpene 11 as starting material assures the absolute stereochemistry at C5, C9, and
Moreover, the selection of methyl isocopalate 10 and phenanthrenones 12,13 also assures the stereochemistry of the additional methyl group at C8 of the ring system.

\[
\begin{align*}
\text{manool} & \rightarrow \text{copal acid} \\
\text{scareol} & \rightarrow \text{labdanolic acid}
\end{align*}
\]

\[
\begin{align*}
\text{abiatic acid} & \rightarrow \text{podocarp-8(14)-en-13-one (11)} \\
(-)-\text{carvone} & \rightarrow \text{TBSO}
\end{align*}
\]

\[
\begin{align*}
(+)-\text{methyl isocopalate (10)} & \rightarrow \text{ent-10} \\
\text{(-)-carvone} & \rightarrow \text{13a (R = H)} \quad \text{13b (R = OCO2Me)}
\end{align*}
\]

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

In 1981, Rúveda et al. reported the first synthesis of a natural spongiane diterpene.\(^{14}\) (+)-Isoagatholactone (1) was synthesized from tricyclic ester 10 prepared from (+)-manool (4) in three synthetic steps (Scheme 2). Two successive oxidations of manool followed by acid-catalyzed cyclization of methyl copalate 14 gave the known intermediate 10,\(^{15}\) also obtained from grindelic acid (3) by Minale et al. during the structural elucidation of (+)-1.\(^{11}\)

\[
\begin{align*}
(+)-\text{manool} & \rightarrow 10 \\
\text{1) PCC} \\
\text{2) MnO2/HCN} \\
\text{MeOH} & \rightarrow 10
\end{align*}
\]

\[
\begin{align*}
1) O_2, \text{methylene blue} \\
\text{EtOAc/EtOH} & \rightarrow 10 \\
2) \text{P(O)}(\text{OMe})_3 & \rightarrow 10
\end{align*}
\]

\[
\begin{align*}
1) 3.5\% \text{H}_2\text{SO}_4, \text{dioxane} & \rightarrow 10 \\
\text{2) LiAlH}_4 & \rightarrow 10
\end{align*}
\]

The required functionalization of the allylic methyl group was achieved by sensitized photooxygenation to give allylic alcohol 15. The allylic rearrangement of 15 with simultaneous lactonization to give lactone 16, followed by reductive opening of the lactone ring, gave the known degradation product of isoagatholactone, diol 17.\(^{11}\)

Finally, allylic oxidation with MnO2 gave (+)-isoagatholactone (1) in 3.9% yield from 10.

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).\(^{16}\) Thus, (±)-isoagatholactone (1) was prepared in 11.6% yield from racemic methyl isocopalate 10.\(^{17}\)

Unnatural (−)-isoagatholactone has also been prepared by Rúveda et al. using the same sequence of steps starting from methyl isocopalate (+)-10, readily prepared from copalic acid (Scheme 4).\(^{18,19}\) Thus, sensitized photooxygenation gave alcohol 18, which was subjected to allylic rearrangement with simultaneous lactonization, using sulfuric acid, to give lactone 20. Then, reductive opening of the lactone ring, gave diol 21, which was oxidized with MnO2 to give (−)-isoagatholactone.

The interest in spongiane-type diterpenes possessing a furan ring D led to the synthesis of (−)-12α-hydroxyspongial-13(16),14-diene (24) by Rúveda et al. using 19, also prepared from methyl isocopalate (Scheme 4).\(^{19}\) This unnatural spongiane was designed as a precursor for other members with a different functionality in ring D, since it contains, the required stereochemistry at C12. Compound (+)-10 was converted into 12,14-isocopaladiene (19) by LiAlH4 reduction, mesylation, and elimination. Photooxygenation of 19 and reduction produced alcohol 22, which was submitted to a second photooxygenation reaction, and the resulting unsaturated cyclic peroxide 23 was treated with ferrous sulfate to afford 12-hydroxyfuran 24.

Concurrent to this report, Nakano et al. described the synthesis of racemic 24 from hydroxy-isocopalane 15 (Scheme 5), which

\[
\begin{align*}
\text{5, copal acid} & \rightarrow 10 \\
\text{1) HCOOH} \\
\text{2) CH}_2\text{N}_2/\text{Et}_2\text{O} & \rightarrow 10
\end{align*}
\]

\[
\begin{align*}
\text{1) 3.5\% \text{H}_2\text{SO}_4, \text{dioxane} & \rightarrow 10 \\
\text{2) LiAlH}_4 & \rightarrow 10
\end{align*}
\]

Scheme 2. Rúveda’s synthesis of natural isoagatholactone.

Scheme 3. Nakano’s synthesis of racemic isoagatholactone.
was prepared as outlined in Scheme 3 from ((−)-copalic acid. Epoxidation of 15 gave epoxide 25 in quantitative yield, then, treatment with lithium diisopropylamide (LDA) led to β-elimination and lactonization in one pot to give α,β-unsaturated γ-lactone 26 in 50% yield. When 26 was reduced with diisobutylaluminium hydride, the furan (+(−))-24 was obtained in 19% yield. The major drawback of Nakano’s synthesis of 24 is the yield of the photochemical reaction to functionalize C16 to give 15 (25% yield, based on recovered 10) and the final aromatization, which encouraged further studies to solve these low-yielding steps.16,17

In 1984, another synthesis of natural isoagatholactone (+(−))-1 (Scheme 5) was reported by Vlad and Ungur (Scheme 5).20 The route is identical to that of Rüveda, since the same diol 17 was oxidized by MnO2 to give isoagatholactone (see also Scheme 2). In this case, compound 17 was prepared in 48% yield by allylic oxidation of isocopalol 28 with SeO2 in EtOH, although Rüveda et al. reported that this oxidation on isocopalate 10 and alcohol (isocopalol) 28 led to complex mixtures of products.19

Isocopalol 28 was prepared by Vlad et al. using an acid-catalyzed cyclization of an acetate mixture (27) (Scheme 6). These authors have used chiral isocopal 28 and diol 17 for the synthesis of sponge metabolites such as aldehydes 29 and 30 by consecutive oxidations.22 The aldehydes have also been prepared in racemic form starting from (+(−))-10 (methyl isocopalate) via the racemic diol (+(−))-17.23

The same authors have also reported the synthesis of a furanoditerpene, methyl spongia-13(16),14-dien-19-oate (33), by cyclization of methyl lambertianate (32), which can be obtained from lambertianic acid (31), a diterpene acid of the Siberian cedar Pinus sibirica (Scheme 6).20

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In 1985, Rúveda et al. reported the first synthesis of a naturally occurring furanospongiane, albeit in racemic form (Scheme 7). \(^{24}\) (±)-Spongia-13(16),14-diene (38) was prepared from (±)-methyl isocopalate (10) via the same unsaturated lactone (16) used in the synthesis of isoagatholactone (see Scheme 2). It is worth mentioning that lactone 16 was similarly prepared from alcohol 15, but the latter was synthesized in an improved manner (60% overall yield) by epoxidation of 10 and subsequent treatment with aluminium isopropoxide. \(^{25}\) Racemic lactone 16 was then hydrogenated on Pt to give 34, which was reduced with LiAlH\(_4\), oxidized under Swern conditions and treated with p-TsOH to afford the desired furan 38 in 20% overall yield. The tetracyclic diterpene, (±)-spongian 37, which is the tetrahydrofuran derivative of 38 and possesses precisely the fundamental parent structure I (Fig. 1), was synthesized in this work by hydrogenation of furan 36. Furan 36 was obtained by allylic rearrangement with simultaneous cyclization of the diol 35, which was prepared by lithium aluminium hydride reduction of 15.

A few years later, Nakano et al. also described the synthesis of (±)-spongia-13(16),14-diene (38) from the same hydroxy-isocopalane 15 used in the synthesis of (±)-1 (Scheme 8). \(^{25}\) The starting material was, however, synthesized from (±)-methyl isocopalate (10) using the improved procedure developed by Rúveda et al. for the synthesis of related tricyclic diterpenes (aldehydes 29 and 30). \(^{24}\) Thus, epoxidation of methyl isocopalate 10 gave α-epoxide 39, which, upon treatment with aluminium isopropoxide, afforded hydroxy-isocopalane 15 in 60% overall yield. Lactonization and β-elimination of 15 using \(\text{H}_2\text{SO}_4\), followed by isomerization with 10% ethanolic potassium hydrogen sulphate, gave α,β-unsaturated γ-lactone 40, which was reduced with lithium aluminium hydride to give diol 41. Oxidation of 41 with pyridinium chlorochromate (PCC) gave the desired (±)-furanspongian 38 in 55% yield (Scheme 8).

More recently, Urones et al. reported the preparation of the useful intermediate in spongian synthesis, ent-methyl isocopalate (10), from sclareol \(^{26}\) (6) and labdanolic acid \(^{27}\) (7), two abundant bicyclic natural products (Scheme 9). Thus, sclareol (6), a major terpenic constituent of \(Salvia scarea\), was acetylated quantitatively with acetyl chloride and \(N,N\)-dimethylaniline, affording the diacetyl derivative 42, the isomerization of which with bis(acetonitrile)palladium(II) chloride led to the diacetate 43 (89%). The selective hydrolysis of the allylic acetoxy group of 43 led to hydroxy acetate 44, the oxidation of which with \(\text{MnO}_2\) gave aldehyde 45. Subsequent oxidation of 45 with \(\text{NaClO}_2\) followed by esterification with diazomethane afforded methyl ester 46. Regioselective elimination of the acetoxy group and cyclization with formic acid led to ent-methyl isocopalate (10) in 49% overall yield from sclareol (eight steps). Labdanolic acid (7), 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 48. Ester 48 is converted into unsaturated ester 50 by elimination of phenylelenic acid from 49, and then cyclized with formic acid to afford ent-methyl isocopalate (10) in 45% overall yield from labdanolic acid.

The same authors showed how this material, ent-methyl isocopalate (10), can be converted into 9,11-secospongianes, one of the most widespread subgroups of spongianes (Scheme 10). \(^{28}\) To this end, the introduction of a \(\text{CO}_2\text{Me}\) double bond and subsequent cleavage was investigated. The method failed with tricyclic derivatives of 10, and no cleavage conditions were successful. The strategy was then applied to other tetracyclic derivatives and led to the synthesis of sescophangiane 54. The precursor of sescophangiane 54 was the known hydroxy-
isocopalane 15, which was again synthesized using Rúveda’s method as outlined in Scheme 7.23 Treatment of 15 with OsO4 followed by oxidation with tetrapropylammonium per ruthenate (TPAP) gave the ketone 51 in 68% yield. The desired double bond was introduced by bromination with phenyltrimethy lammonium perbromide (PTAP) and subsequent elimination with Li2CO3/LiBr to give the α,β-unsaturated ketone 52. Reduction of 52 and acetylation gave the compound 53, which was subjected to ozonolysis to afford the highly functionalized secospongiane 54 in 65% yield.

The readily available abietic acid (8) together with other naturally occurring resin acids isolated from conifer oleoresins are common starting materials for the synthesis of natural products and numerous diterpene derivatives.29,30 (+)-Podocarp-8(14)-en-13-one 11 (Scheme 11) is a versatile chiral starting material easily prepared from commercially available (+)-abietic acid or colophony.31 Recently, the enantioselective biomimetic synthesis of this chiral building block has been described.32

In the course of synthetic studies on the chemical conversion

Scheme 9. Urones’ syntheses of ent-methyl isocopalate (→)-10 from sclareol (6) and labdanolic acid (7).

Scheme 10. Urones’ synthesis of 9,11-secospongiane 54.

Scheme 11. Arno’s syntheses of (+)-isoagatholactone (1) and (→)-spongia-13(16),14-diene (38) from 11.
of podocarpene diterpenoids into biologically active compounds, Arno et al. achieved an efficient synthesis of natural (+)-isoagatholactone (1) and (-)-spongia-13(16),14-diene (38), starting from chiral podocarpenone 11. Compound 11 was converted in six steps into the common intermediate 60 (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 57, which was prepared from 11 by epoxidation to give 55, followed by silica gel-catalyzed Eschenmoser ring-opening reaction to afford ketone 56, and addition of methyllithium. The instability of enol trifluoroacetate 58 (~70% overall yield from 11) to hydrolysis required in situ incorporation of the hydroxymethyl side chain to give hydroxy ketone 59, which was isomerized at C14, to afford compound 60, upon treatment with methanolic sodium methoxide. This intermediate was used in two separate approaches to complete the D ring of the targeted spongia-13(16),14-diene.

In the early 1990s, the same research group described the first enantioselective synthesis of pentacyclic spongianes. To date, the synthetic routes reported for these natural products are based on this method. Chiral podocarpenone 11 was converted into the cyclobutene ester 65, via compound 64, by photochemical reaction with acetylene, nucleophilic carboxylation, and reductive dehydroxylation, as indicated in Scheme 12. Compound 65 was hydrolyzed under alkaline conditions and then cleaved with ozone to afford (−)-dendrillol-1 68 (R=H), the simplest member of the pentacyclic spongianes. This synthetic sequence was later shortened by reductive cyanation with tosylmethyl isocyanide (TosMIC) to give nitriles 67, which were subjected to alkaline hydrolysis in ethylene glycol ethyl ether and ozonolysis. The key feature of the strategy is the cleavage of the cyclobutene ring to form a latent acid-dialdehyde unit, compound 66, which spontaneously underwent internal lactone-hemiacetal formation. Based on this synthetic plan, the same authors have prepared related C7-oxygenated congeners 68 (aplyroseol-1 (68, R=OCOPr), aplyroseol-2 (68, R=OAc) and deacetylaplyroseol-2 (68, R=OH)) upon stereoselective introduction of a hydroxy function at the 7-position in the starting material 11 (Scheme 13). Formation of the dienyl acetate of 69 followed by oxidation with m-chloroperbenzoic acid gave the hydroxy enone 70, in 74% yield, which was elaborated to give hydroxy ester 72, precursor of the pentacyclic...
diterpenes. It is worthy of note that the homologation at C13 was conducted more efficiently by cyanophosphorylation followed by reductive elimination to give nitriles 71.

The versatility of intermediate 65 also led to further investigations, which culminated with the synthesis of acetyldendrillol-1 76 and revision of its stereochemistry at C17, as well as the synthesis of tetracyclic spongianes functionalized at C17 (Scheme 14). The introduction of a cyanophosphorylation step improved the synthesis of 65, which was then converted into the intermediate dialdehyde 75. Acetylation of compound 75 with AcOH/Ac₂O and sulfuric acid (1%) at 65 °C gave exclusively the natural acetate 76, while reduction followed by lactonization led to (−)-spongian-16-oxo-17-al 78 (Scheme 14). This compound was next converted into (−)-aplyroseol-14 80, having an unprecedented δ-lactone unit for spongianes, and its structural isomer 81, which permitted the structural reassignment of this natural product.38 This structure was also confirmed by X-ray crystallography of compound 80.39

Recently, the same laboratory reported some 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).40,41 Some of these new spongiane derivatives possess an α-acetoxy group at C15 and were obtained from pentacyclic samples using an optimized hemiacetal-ring opening under basic conditions. The synthetic protocol developed for the synthesis of 78 was also used to convert hydroxy-cyclobutenone 72 into spongianals 84, 85, and 86, which were evaluated against HeLa and HEP-2 cancer cells, compound 86 being the most active.

Arnó et al. have also achieved the total synthesis of (−)-spongia-13(16),14-diene (38) starting from (+)-carvone via the phenanthrene 89, which contains the two necessary methyl groups at C8 and C10, and a useful carbonyl group at C14 for the final assembly of the D ring (Scheme 16).42

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 was an intramolecular Diels–Alder (IMDA) reaction. The whole sequence takes 13 steps to furnish the furanospongiane 38 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 87. Formation of the silyl enol ether of 88, followed by IMDA reaction in toluene at 190 °C during 7 days, provided stereoselectively compound 89 in 95% overall yield.

Scheme 14. Arnó's syntheses of (−)-acetyldendrillol-1 (76), (−)-spongian-16-oxo-17-al (78), (−)-aplyroseol-14 (80) and (−)-isoplyroseol-14 (81).

Scheme 15. González's synthesis of C7,C17-functionalized spongianes.
The tricyclic system \(89\) is already a 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. Cyclopropanation of the enol double bond followed by homologation of the carbonyl group at C14 led to enol ether \(90\). After completing the desired carbon framework, functionalization at C16 was carried out by isomerization of the double bond in \(91\) to give aldehyde \(92\), and then careful epoxidation followed by treatment with \(p\)-TSA gave the furano ketone \(93\). Compound \(93\) is a potential precursor of other furanospongianes functionalized in ring A and has recently been isolated from natural sources.\(^{43}\) Finally, Wolff–Kishner reduction of \(93\) afforded \(38\) in 75% yield.

A new strategy toward oxygenated spongianes using \((-\rangle\)-carvone as starting material has recently been described by Abad et al., as outlined in Scheme 17.\(^{44}\) This synthetic sequence follows a \(B\rightarrow AB\rightarrow ABC\rightarrow ABCD\) approach in which carvone is first converted into the decalone \(95\) (AB system) by alklylation to give enone \(94\), and cyclization in acidic media. The construction of the C ring needed an intramolecular Diels–Alder reaction (IMDA) reaction to give the Diels–Alder adduct \(100\). Therefore, decalone \(95\) was transformed into the IMDA precursor \(99\) by homologation at C9, epoxide opening, Wittig reaction, and introduction of the dienophile moiety. The desired cycloaddition took place at 112°C for 17 h to give the Diels–Alder adduct \(100\) in 95% yield. This was next elaborated using a regioselective ring opening of a dihydrofuran ring to give the C7,C11-functionalized spongiane lactone \(102\) after hydrolysis and epoxidation with tert-BuOOH and VO(acac)\(_2\).

Based on this synthetic plan, Abad et al. continued the development of several studies for the synthesis of spongiane diterpenes related to natural dorisenones. Therefore, following the same strategy \(B\rightarrow AB\rightarrow ABC\rightarrow ABCD\) for the ring-system construction they used the key epoxydecalone \(96\), which was further elaborated to the Diels–Alder precursor \(99\) (Scheme 17). Other Diels–Alder precursors were also available.

\[\text{Scheme 16. Arno's synthesis of } (-\rangle\text{-spongia-13(16),14-diene (38) from } (+\rangle\text{-carvone.}\]

\[\text{Scheme 17. Abad's synthesis of C7,C11-functionalized spongianes (102) from } (-\rangle\text{-carvone.}\]
synthesized from 96 for intermolecular Diels—Alder reactions but provided low yields using dimethyl acetylenedicarboxylate (DMAD) as dienophile (Scheme 18). The synthesis starts with alkylation with LDA of the α-position of the enone. Further alkylation with an allyl bromide and acidic cyclization gave 95. Epoxidation, followed by olefination, gave 97, and another olefination led to 103, which after Dess—Martin oxidation gave enone 104, then, sodium borohydride reduction and protection with TBDMS and reaction with dimethyl acetylenedicarboxylate (DMAD) gave a mixture of 105 in low yield. Alternatively, 103 is propargylated with allyl propargyl bromide. Introduction of the methoxycarboxylate and final reaction in toluene at 112 °C gave the desired Diels—Alder diene 100. Thus, by using an IMDA reaction the compound 100 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 100 gave initially the corresponding 7-acetoxy-15-iodo-derivative, which rapidly underwent lactonization to afford the γ-lactone 101 in nearly quantitative yield. The structure of 101 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. Unfortunately, all attempts to introduce the required oxygenated function present in natural dorisenones at C11 were unsuccessful. An oxygenated function was introduced leading to epoxides 102, 110–112, but epoxide opening as desired was unsuccessful.

Following the above-mentioned extensive synthetic studies for the preparation of dorisenone diterpenes of the spongiane family, Abad et al. have recently adapted their synthetic sequences for the synthesis of dorisenone C (127) (Scheme 20). They have developed a B → AB → ABC → ABCD approach starting from R-(-)-carvone, in which the known hydroxy-aldehyde 97 (AB rings) (Scheme 18) is the key

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 (102, 110, 111, and 112) from (−)-carvone.
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 115 was prepared from 97 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-heteroene rearrangement of the propargylic ether moiety. Thus, after desilylation of 116 the enone 117 was formed in good yield. To avoid the sterically demanding group of the diene moiety, the preparation of the dienol carbonate 118 was undertaken and the reduction of the retro-heteroene rearrangement product was envisaged. In fact, the strategy did work, but the product of the rearrangement 119 was still the main product of the intramolecular Diels–Alder reaction. Although in moderate yield, the desired compound 120 was obtained and the sequence proceeded. Opening of the dihydrofuran ring of 120 gave rise to the product 121 as a result of in situ lactonization. The cleavage of the ester groups gave diketone 123, which was reduced with a borane–THF complex to give alcohol 124. Further reduction with DIBAL-H gave the triols 125 in which the lactol moiety was re-oxidized with MnO2 to give the corresponding lactone 126. Final diacetylation of 126 gave the synthetic natural product dorisenone C (127), the data for which, were in complete agreement with those reported earlier for the natural product and hence established the absolute configuration of the natural product. During these synthetic studies several unnatural furanoditerpenes were also prepared from lactone 124 by reduction and dehydration to give the furan ring present in 128 and 129 (Scheme 21).

Finally, we describe how, recently, Ragoussis et al. have converted natural (−)-sclareol 6 into the furanoditerpene, (−)-marginatone (135) (Scheme 22). The authors converted sclareol 6 into (−)-coronarin E 132, using minor modifications of reported procedures, which by regioselective hydrogenation and stereocontrolled-intramolecular electrophilic cyclization gave the tetracyclic marginatane-type diterpene 134. Subsequent allylic oxidation of 134 afforded the synthetic (−)-marginatone 135, the spectroscopic data of which were identical to those reported for the natural product. The synthesis starts with the preparation of the ambergis odorant, (−)-γ-bicyclohomofarnesal 130, from sclareol 6 in seven steps and

Scheme 20. Abad’s synthesis of dorisenone C (127) from (−)-carvone.

52% overall yield. The coupling of 130 with 3-lithiofuran led to a mixture of two diastereomeric alcohols 131 in 78% overall yield. Dehydration of this mixture in refluxing HMPA gave (+)-coronarin E 132 in high yield (76%) (Scheme 22). Reduction of the side-chain double bond of 132 gave (+)-dihydrocoronarin E 133 and subsequent intramolecular electrophilic cyclization furnished the tetracyclic derivative 134. Allylic oxidation with tert-BuOOH of 134 gave the target molecule, (−)-marginatone 135, albeit in low yield (33%).

3.2. 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, 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. Indeed, their importance has increased over the past three decades, due to the development of new routes to polylefinic precursors, methods of asymmetric synthesis, and different conditions for the key cyclization step.

In the early 1980s, Nishizawa’s research group described the biomimetic cyclization of a geranylgeraniol derivative 136 to the racemic tricyclic alcohol 28 (Scheme 23), which had been previously converted into isoagatholactone (1) by Nakano and Hernández and Ungur et al. Compound 28 has also been converted into 12z-hydroxyspongial-13(16),14-diene by Ruveda et al. The cyclization takes place using as the electrophile a mercury(II) triflate–N,N-dimethyl-aniline complex, which after reductive demercuration leads to alcohol 28 (22%), together with two bicyclic diterpenoids.

Contemporary synthetic studies by Ungur et al. also described the biomimetic synthesis of 28 by superacid cyclization of geranylgeraniol 137 with fluorosulfonic acid. A few years later, the same group also reported the synthesis of...
racemic methyl isocopalate 10, from 138, using similar conditions (Scheme 23).62

Nishizawa et al. also used the mercury(II) reagent to cyclize ambiofuran 139, leading to the tetracyclic isospongiane 140 in 13% yield (Scheme 24).63 Compound 134, having the marginatane carbon skeleton, was obtained after the demercuration treatment of 140 with sodium borohydride. Ambiofuran 139 had also been cyclized to furanohydride. Ambiofuran 139 had also been cyclized to furanohydride. Ambiofuran 139 had also been cyclized to furanohydride.

In the early 1990s, Zoretic et al. developed a very efficient series of triple and tetra cyclizations, leading to trans-decalin ring systems. Their strategy was based on the Snider method of polycyclic natural products under mild conditions and with high stereocchemical control.67 Following the success of this approach, they reported, in 1995, the first biomimetic-like synthesis of spongiane diterpenes, particularly furanospingianes (Scheme 25).70 In their synthesis, an oxidative free-radical cyclization of polyene 142 with a 2:1 mixture of Mn(OAc)₃ and Cu(OAc)₂ provided stereoselectively the tricyclic intermediate 143 in 43% yield. Subsequent functional-group manipulation and homologation at C13 of 143 allowed, in two independent synthetic sequences, the construction of the required furan ring D of the spongiane and marginatane carbon skeletons. Thus, starting from allylic alcohol 141, the necessary cyclization precursor 142 was obtained by treatment with allyl chloride followed by alkylation with ethyl 2-methylacetooacetate in 49% overall yield. After securing the stereochemistry of 143 by means of meticulous NMR studies,71 isospongiane 146 was prepared by reduction, benzylation, and ozonolysis leading to ketone 145, which was alkylated with a THP-protected hydroxyacetaldehyde and hydrolyzed with concomitant aromatization and final debenzylation by reduction.

On the other hand, ozonolysis of diol 144 and protection as its corresponding acetone, compound 147, followed by furan ring formation using Spencer’s method, gave unnatural furanospongiane 149, via enone 148, in 8% overall yield from 141.

The same authors also reported an alternative route to 149 via the tricyclic intermediate 152, which was prepared from the farnesyl acetate derivative 150 in four steps, using a radical cascade of polyolefin 151 (Scheme 26).72 Compound 152, possessing all of the carbons in the spongiane skeleton, was transformed into spongiane 149 in five steps, as detailed in Scheme 26. Thus, hydrolysis, and epoxidation gave epoxide 153, subsequent Collins oxidation and aromatization with p-TsOH gave furan 154. Final reduction with LiAlH₄ gave diol 149 in 2.8% overall yield from 150. The synthetic sequence leading to diol 149 was later optimized (15% overall yield from 150), allowing the synthesis of (±)-isospongiodiol 156, via silyl enol ether 155, upon manipulation of the A-ring functionalization in 149.73

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.
They started from phosphonate 157, which was subjected to Horner–Emmons olefination to give polyene 158. This modification allows the synthesis of furanospongianes functionalized at C17, such as 163–166, through the advanced intermediate 162. Compound 162 was prepared in four steps from tricyclic system exo 160, which was synthesized by an intramolecular radical cyclization of polyene 159.

Concurrent to these studies, Pattenden et al. applied their expertise in polycyclic ring constructions, based on free-radical-mediated cyclizations of polyolefin selenyl esters, for the total synthesis of (±)-spongian-16-one 175 (6% overall yield).

Recently, Demuth et al. have developed a radical-type cascade cyclization for the synthesis of (±)-3-hydroxy-spongian-16-one 180, a precursor of 175 (Scheme 29). In their strategy, the photoinduced radical cation of the polyene reaction with cyclopropyl methyl ketone, led to compound 168. The next step was ring opening of the cyclopropane and formation of an E-homoallylic bromide using HBr, which was then used as its corresponding iodide 169 to alkylate 2-phenylthiobutyrolactone giving thioether 170. Removal of the thioether in 170 and subsequent manipulation of the tetrahydropyranyl ether led to selenoate 173. Treatment of the latter with Bu3SnH and AIBN in refluxing degassed benzene led, after methylenation, to the tetracycle lactone 174 in 42% yield. Lactone 174 was then converted into 175 by Simmons–Smith cyclopropanation and hydrogenolysis.

Scheme 26. Zoretic’s biomimetic synthesis of (±)-isospongiadiol 156.

Scheme 27. Zoretic’s biomimetic synthesis of C17-functionalized furanospongianes.
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 179 was synthesized from farnesyltri-n-butylstannane 176, which reacted with the methylen-butyrolactone 177 via a Michael addition. Following the introduction of the double bond in 178, irradiation of 179 in a Rayonet reactor with \( \lambda_{\text{max}} = 300 \) nm afforded spongiane 180 in 23% yield after purification. The structure of 180 was unambiguously determined by NOE and X-ray analyses.

### 3.3. Other approaches and total syntheses

As mentioned previously, the studies toward the synthesis of spongians are scarce, especially of rearranged metabolites. The synthesis of furanospongadipterpenoids has been embarked upon starting from natural products and using biomimetic-like reaction sequences, both of which have provided in some cases the synthesis of spongians with a functionalized A-ring. Additionally, in the mid 1990s, Kanematsu’s group carried out synthetic studies for the construction of an appropriate furanohydrophenanthrene ring system 194 (Scheme 30), which later was converted into (+)-spongia-13(16),14-diene 38 and (+)-spongadiosphenol 196 (Scheme 31).80,81

The route to the tetracyclic compound 194, the key intermediate for the synthesis of 38 and 196, starts with the conversion of furfuryl alcohol 181 into a propargyl ether 182, which underwent a furan ring transfer reaction to give the bicyclic alcohol 183. Hydrogenation of 183 followed by Swern oxidation afforded the ketone 184. The ketone 184 was converted into the allylic \( \beta \)-keto ester followed by methylation with iodomethane to afford 185. Removal of the allyl ester gave ketone 186, which was next annulated with ethyl vinyl ketone, via diketone 187, to give the tricyclic furan 188. The construction of the ring A was effected by reductive alkylation to introduce an allyl group, compound 189, which was then converted into an adequate side-chain ketone, compound 193, ready for the final annulation to afford the tetracyclic intermediate 194. The stereochemical structure of 194 was assured by NOE effects between the two angular methyl groups.

The synthesis of spongiane 38 was successfully completed by forming the gem-dimethyl moiety by reductive methylation of 194 to give ketone 93 and removal of the carbonyl group at C3. In parallel studies, compound 194 was reduced,
hydroxylated to give ketone 195 and then oxidized to afford the desired \((\pm\)-spongiadiosphenol\) 196, which represents the first total synthesis of a furanospongiane diterpene with a functionalized A-ring (Scheme 31).

With regard to the synthesis of rearranged spongianes, there are about three reported synthetic approaches to build up the bicyclic systems\(^{82,84}\) present and, to the best of our knowledge, only two published enantioselective total syntheses.\(^{85,86}\) Mehta and Thomas reported in 1992 how the abundant, commercially available \((\pm\)-longifolene\) 197 can be degraded to a hydroazulene moiety, compound 200, present in rearranged spongianes (Scheme 32).\(^{82}\) Catalytic ruthenium oxidation of 197 led to the formation of longicamphenilone 198 in 35\(^\text{-}\)40\% yield. Irradiation of 198 with a 450 W Hg lamp through a Pyrex filter resulted in the expected Norrish-type I cleavage to the bicyclic aldehyde 199 in about 40\% yield. Reductive decarbonylation using the Wilkinson catalyst furnished the bicyclic hydroazulenic hydrocarbon \((\pm\)-200 in 52\% yield (Scheme 32).
Bhat et al. reported a common Lewis acid-catalyzed Diels—Alder reaction to form decalin systems, present in spongianes and other terpenoids (Scheme 33).83

Diene 201 reacts with a series of dienophiles 202, in the presence of AlCl₃, to give a number of decalins 203, which can be further elaborated to build up the spongian skeleton.

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 et al. reported a short and enantioselective synthesis of this furofuran unit starting from methyl 2-furoate (Scheme 34).84

The synthesis starts with a copper-bisoxazoline-catalyzed, enantioselective cyclopropanation of methyl 2-furoate 204 to cyclopropane 205, 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 205 gave exclusively compound 206 as a single stereoisomer in 86% yield. Subsequent rearrangement to 207 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 204, and in enantiomerically pure form. Conversion of the carboxylic acid into the acetoxy derivative 209, typical in many spongian diterpenoids, was accomplished in a four-step sequence from 207 via its methyl ketone 208, which underwent diastereoselective Baeyer—Villiger oxidation under retention of configuration. Alternatively, 207 could be photochemically decarbonylated with lead tetraacetate under copper(II) catalysis following a radical pathway to directly yield a mixture of 209 and epi-209 (210), which could be separated by chromatography.

To date, to the best of our knowledge, there has been reported only two enantioselective total syntheses of diterpenes with a rearranged spongian skeleton.

Firstly, in 2001, Overman et al. described the first enantioselective synthesis of a rearranged spongiane, (+)-shahamin K 224 (Scheme 35),85 a spongian-derived metabolite 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 211 into the cyclization precursor 215 introducing a kinetic resolution step with (R)-oxazaborolidine 213. Thus, oxidative cleavage of the double bond in 211, followed by thiocetalization, gave compound 212, which was subjected to the chemical resolution to give enantiomerically pure ketone (S)-214 in 44% yield. Addition of (E)-1-propenyl lithium to (S)-214 followed by silylation gave the silyl ether 215 in high yield. Treatment of 215 with dimethyl(methylthio)sulfonyl tetrafluoroborate (DMTSF) initiated the Prins-pinacol reaction to give the bicycle 216 in 80% yield as a mixture of sulfide epimers, the structure of which was confirmed by single-crystal X-ray analysis of the corresponding sulfone. Installation of the exocyclic methylene group, followed by oxidative desulfenylation, provided ketone 218, the thermodynamic lithium enolate of which reacted with enantiopure sulfone 219 to give compound 220, as a single isomer in 72% yield. To transform the cyclopentanone ring in the side chain of the required pyranone unit, keto sulfone 220 was reduced with SmI₂ and the resulting enolate was acetylated to give enol acetate 221 in 88% yield. Reduction of the ketone of this intermediate with (R)-oxazaborolidine 213 and borane—THF complex, followed by acetylation, gave acetate 222 in 88% yield. Chemoselective dihydroxylation of the enol acetate in 222 gave the α-hydroxy ketone 223 in 87% yield. Cleavage of the hydroxy ketone in 223 with Pb(OAc)₄ followed by reduction of the resulting aldehyde with NaBH₄ and lactonization using the Mukaiyama reagent, provided (+)-shahamin K 224.

The second enantioselective total synthesis of a rearranged spongian diterpene was achieved recently by Theodorakis et al.,86 who completed the synthesis of norrisolide 235 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 enantioselective synthesis of the side chain, starting from β-mannose (Scheme 36).
The preparation of the side chain begins with the transformation of α-mannose to the known bisacetonide 225 with improved conditions using iodine as catalyst to give 225 in 85% yield. Treatment of 225 with p-toluenesulfonyl chloride and triethylamine afforded the desired glycosyl chloride 226, which, upon elimination with a mixture of sodium naphthalenide in THF, gave rise to glycal 227 in 48% overall yield. Compound 227 proved to be labile upon standing and was immediately benzylated to produce vinyl ether 228 in 90% yield. Syringe-pump addition of ethyl diazoacetate (0.1 M in DCM) into a mixture of other fragment was prepared from the lactone 239 starting from the enantiomerically enriched enone 240, which contained the desired cis stereochemistry at the C11 and C12 centers. The synthesis began with the preparation of enone 239, which was available through an L-phenylalanine-mediated asymmetric Robinson annulation (55% 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 241 in 76% yield for the two steps (Scheme 38). Methyl alkylation of the extended enolate of 241 at the C5 center produced ketone 242 (66%), the reduction and radical deoxygenation of which led to the alkene 243 in 83% yield (from 242). The best results for the conversion of alkene 243 into the trans-fused bicyclic 244 were obtained by hydroxylation of the double bond and subsequent reduction of the resulting alcohol (52% yield from 243). Fluoride-induced desilylation of 244 followed by PCC oxidation provided the ketone 245 in 91% yield. Treatment of 245 with hydrazine then produced the hydrazone was ultimately achieved using urea—hydrogen peroxide and trifluoroacetic anhydride and gave rise to the desired material in 69% yield as a single isomer.

Theodorakis’s group described the total synthesis of norrisolide 235 in 2004. In their strategy, they achieved the assembly of the two main fragments, 237 and 238, through the C9–C10 bond to give alkene 236 (Scheme 37). One of the fragments, the trans-fused hydrindane motif, could be prepared starting from the enantiomerically enriched enone 239. The other fragment was prepared from the lactone 240, which contained the desired cis stereochemistry at the C11 and C12 centers.

Scheme 35. Overman’s synthesis of (+)-shahamin K 224.
Finally, treatment of 246 with I₂/Et₃N led to the formation of the desired vinyl iodide 237 (62% yield).

The preparation of the fragment 238 is highlighted in Scheme 39. The C11 and C12 centers were connected by a Diels—Alder reaction between butenolide 247 and butadiene (248). Under Lewis acid catalysis, this cycloaddition proceeded exclusively from the opposite face to that with the bulky TBDPS group to afford 240 as a single isomer (85% yield). Reduction of the lactone, followed by oxidative cleavage of the alkene, produced the fused lactol 249 in 63% yield as a 1:1 mixture of isomers at C14. These isomers were separated after conversion into the corresponding methyl ether 250. Compound 250 was then converted into the selenide 251, which underwent oxidation and elimination to give alkene 252 (61% yield from 250). Osmylation of 252, followed by oxidative cleavage of the resulting diol, furnished the aldehyde 238 (two steps, 94% yield) as a crystalline solid, the structure of which was confirmed by X-ray analysis.

The remaining steps in the synthesis of norrisolide 235 are shown in Scheme 40. Lithiation of the vinyl iodide 237, followed by addition of the aldehyde 238 and Dess—Martin (DM) oxidation of the resulting alcohol, afforded the enone 253 in 71% yield. Hydrogenation of the double bond proceeded exclusively from the more accessible α face of the bicyclic core to form the ketone 254 in 75% yield. After much experimentation, the conversion of ketone 254 into alkene 236 was achieved by methylation with MeLi and treatment
of the resulting alcohol with \( \text{SOCl}_2 \) in the presence of pyridine (two steps, 64% yield). With the alkene 236 in hand, the stage was now set for the final functionalization of the bicycle (Scheme 40). Deprotection of the silyl ether and oxidation of the resulting alcohol gave aldehyde 255, which was subsequently converted into the ketone 256 via treatment with \( \text{MeMgBr} \) and Dess–Martin (DM) oxidation (68% yield). Treatment of 256 with \( \text{CrO}_3 \) in aqueous acetic acid produced the lactone 257 in 80% yield. Finally, Baeyer–Villiger oxidation of 257 (MCPBA, NaHCO\(_3\), 60% yield) led to insertion of the oxygen atom, as desired, with complete retention of configuration to produce norrisolide 235.

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 233, 234, 245, and 257 from their previous synthetic studies were evaluated together with 258–263, which were also synthesized (Scheme 41).

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 261–263 have no effect on Golgi membranes. The same group has also studied the chemical origins of the norrisolide-induced Golgi vesiculation. To this end, the researchers studied the effect of fluorescent probes 264–269 (Scheme 42) on the Golgi complex. While 265 had no effect on the Golgi apparatus, compound 264 was found to induce extensive Golgi fragmentation. In contrast to norrisolide 235, however, this fragmentation was reversed upon washing.

Competition experiments showed that compounds 264 and 266 and norrisolide bind to the same receptor, which indicates that the perhydroindane core of norrisolide is essential and necessary for such a binding. In the absence of the acetate group of norrisolide, this binding induces a reversible Golgi vesiculation, indicating that this group plays an essential role in the irreversibility of the fragmentation, either by stabilizing the binding or by creating a covalent bond with its target protein. Compound 268, containing the core fragment of the natural product, induced a similar vesiculation that was, however, reversible upon washing. In contrast, compound 269, in which the perhydroindane core was attached to a bisepoxide scaffold (suitable for protein labeling), induced an irreversible vesiculation of the Golgi membranes. On the other hand, compound 267, lacking the perhydroindane motif, had no effect on the Golgi membranes, attesting to the importance of the norrisolide core in Golgi localization and structure. Moreover, compound 269 induces an identical phenotype to that of norrisolide, suggesting that it may be used to isolate the biological target of this natural product.
4. Conclusions

The scientific investigations of the spongian family of diterpenoids have been an active field during the last two decades, producing nearly 100 publications on the isolation and structural characterization of its members, including several preliminary biological studies. In spite of their biological properties and the challenging variety of chemical entities that have been found, however, the synthetic studies represent only one-third of the publications in the field. Until quite recently, researchers had not initiated any structure/function studies, and therefore this area also remains largely unexplored.

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References and notes

Miguel A. González was born in Valencia, Spain, in 1972. He received his B.S. degree in Chemistry in 1995 and a M.Sc. (Honours) degree in Chemistry from the University of Valencia, in 1997. He then remained at the same University to undertake Ph.D. studies, under the direction of Professor Manuel Arnó and Professor Ramón J. Zaragozá, on the *Synthesis of Terpenes with Spongiane, Scopadulane and Estrane skeletons*. Upon completion of his Ph.D. in 2001, he undertook postdoctoral research first in the group of Professor Gerald Pattenden at the University of Nottingham (UK), on the synthesis of Phorboxazole, and then in the group of Professor Emmanuel A. Theodorakis at the University of California, San Diego (USA), on the synthesis of norzoanthamine. After three years of postdoctoral research abroad, he returned to Spain to work with a ‘Ramón y Cajal’ research contract at the University of Valencia. The synthesis of bioactive marine natural products is his major interest.