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Total syntheses and synthetic studies of spongiane diterpenes

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Contents

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,[5–7] 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.[8] 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; Ac_2O, acetic anhydride; AIBN, azobisisobutyronitrile; BuLi, buthyllithium; DIBAL-H, diisobutylaluminum hydride; DHP, dihydropyrane; DMAD, dimethyl acetylenedicarboxylate; DMAP, 4-(*N*,*N*-dimethylamino)pyridine; DMF, dimethylformamide; DMSO, dimethylsulfoxide; Et_3N, triethylamine; EVK, ethyl vinyl ketone; HMPA, hexamethyl phosphorotriamide; IBX, 2-iodoxybenzoic acid; LDA, lithium diisopropylamide; LiHMDS, lithium hexamethyldisilylamide; MsCl, mesyl chloride; MCPBA, *m*-chloroperbenzoic acid; NaHMDS, sodium hexamethyldisilylamide; NMO, 4-methylmorpholine *N*-oxide; PCC, pyridinium chlorochromate; PPTS, pyridinium *p*-toluenesulfonate; *p*-TSA, *p*-toluenesulfonic acid; PhH, benzene; PhMe, toluene; Py, pyridine; TBDMSOTf, *tert*-butyl dimethylsilyl trifluoromethanosulfonate; TBDPSCl, *tert*-butyldiphenylsilyl chloride; TBAF, tetra-*n*-butylammonium fluoride; TFA, trifluoroacetic acid; TMSCl, trimethylsilyl chloride; TPAP, tetrapropylammonium perruthenate.

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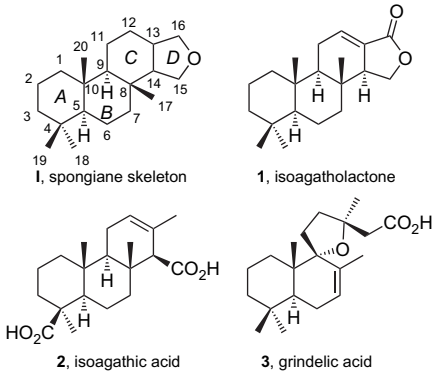


Figure 1.

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 **I**, 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 spongiane-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 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.

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,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 podocarpenone **11** as starting material assures the absolute stereochemistry at C5, C9, and

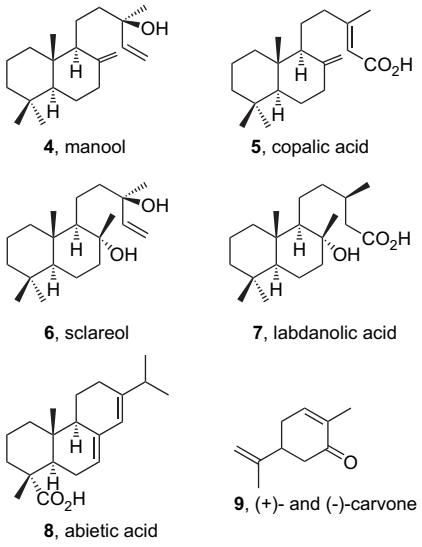
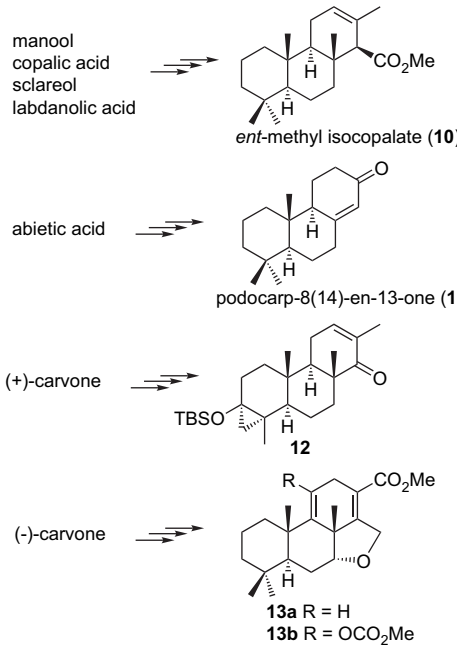


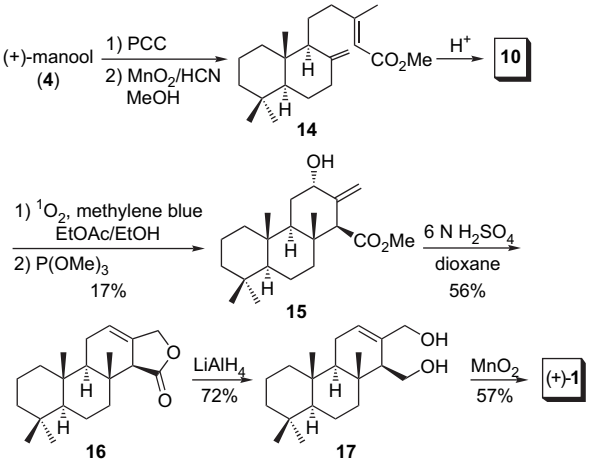
Figure 2.

C10. 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.



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]



Scheme 2. Rúveda's synthesis of natural isoagatholactone.

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]

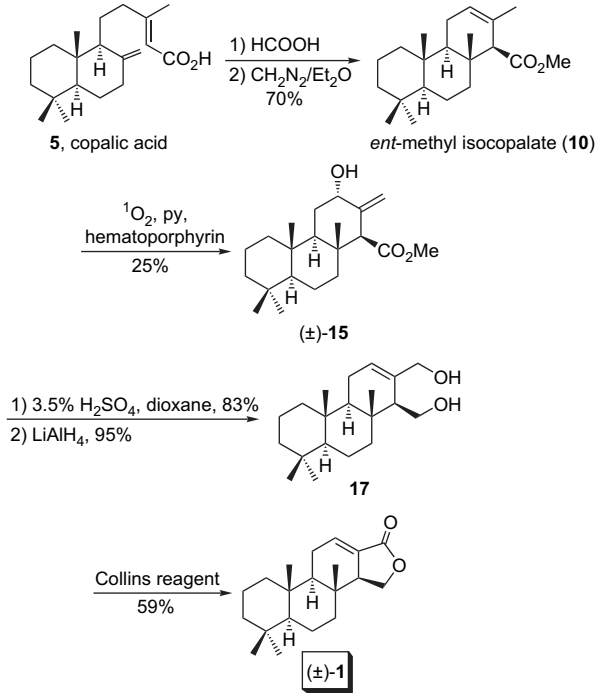
Finally, allylic oxidation with MnO_2 gave (+)-isoagatholactone (**1**) in 3.9% yield from **10**.

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]

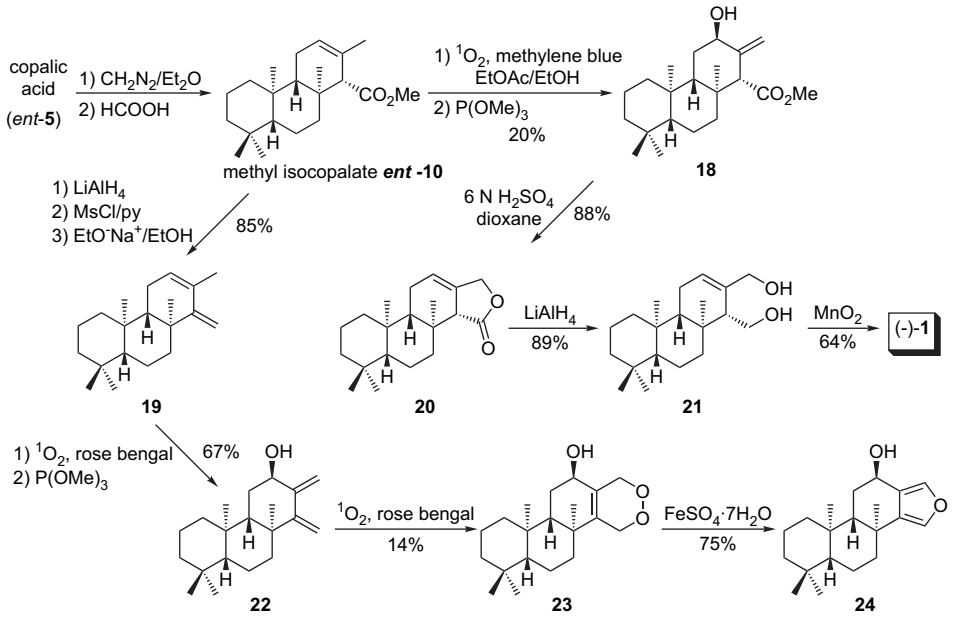
Unnatural (−)-isoagatholactone has also been prepared by Rúveda et al. using the same sequence of steps starting from methyl isocopalate (+)-**10**, readily prepared from copalic acid (Scheme 4).[18,19] Thus, sensitized photooxygenation gave alcohol **18**, which was subjected to allylic rearrangement with simultaneous lactonization, using sulfuric acid, to give lactone **20**. Then, reductive opening of the lactone ring, gave diol **21**, which was oxidized with MnO_2 to give (−)-isoagatholactone.

The interest in spongiane-type diterpenes possessing a furan ring D led to the synthesis of (−)-12α-hydroxyspongia-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 $LiAlH_4$ 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

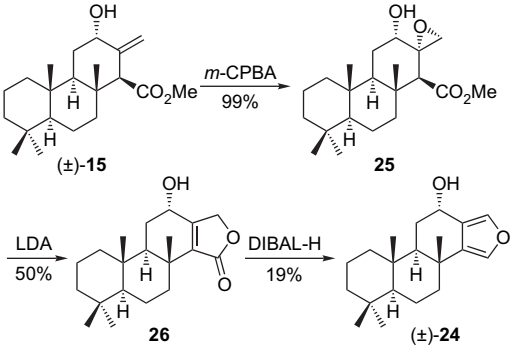


Scheme 3. Nakano's synthesis of racemic isoagatholactone.



Scheme 4. Rúveda's synthesis of *ent*-isoagatholactone (−)-(**1**) and *ent*-13(16),14-spongiadien-12α-ol (**24**).

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]

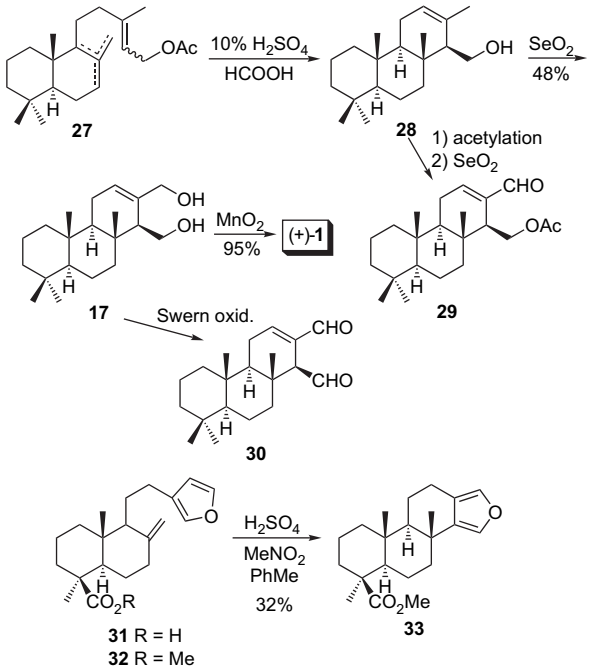


Scheme 5. Nakano's synthesis of (±)-13(16),14-spongiadien-12α-ol (**24**).

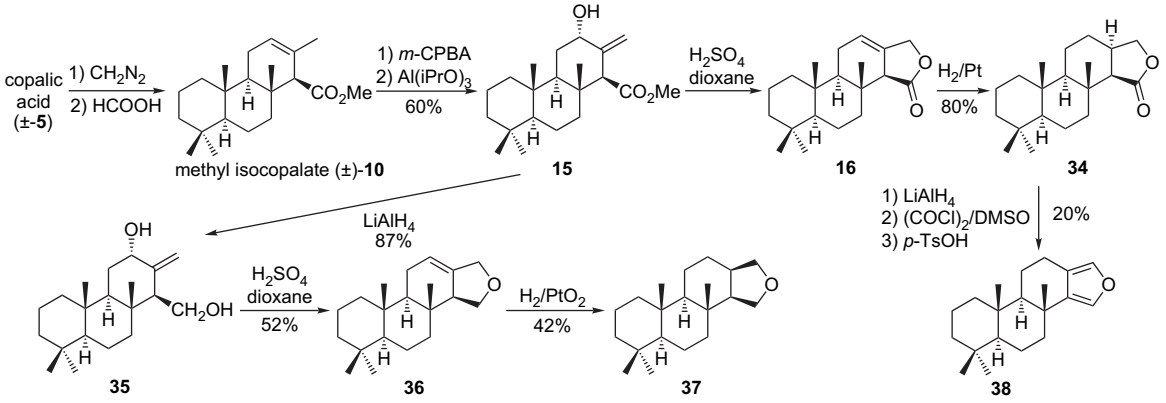
In 1984, another synthesis of natural isoagatholactone (+)-(**1**) was reported by Vlad and Ungur (Scheme 6).[20] The route is identical to that of Rúveda, since the same diol **17** was oxidized by MnO_2 to give isoagatholactone (see also Scheme 2). In this case, compound **17** was prepared in 48% yield by allylic oxidation of isocopalol **28** with SeO_2 in EtOH, although Rúveda 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).[21] These authors have used chiral isocopalol **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]



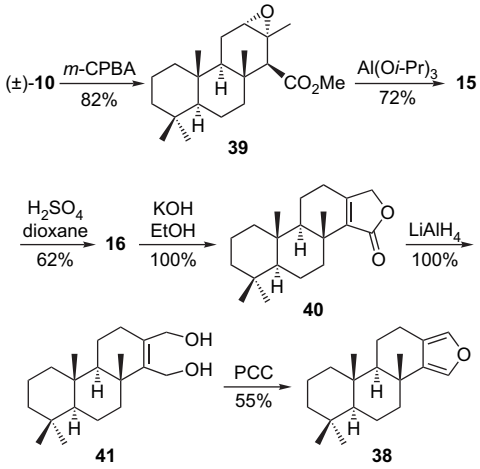
Scheme 6. Vlad's syntheses of natural isoagatholactone (+)-**1**, aldehydes **29** and **30**, and methyl spongia-13(16),14-dien-19-oate (**33**).



Scheme 7. Rúveda's synthesis of (±)-spongian (**37**) and (±)-spongia-13(16),14-diene (**38**).

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.[23] 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 aluminum hydride reduction of **15**.

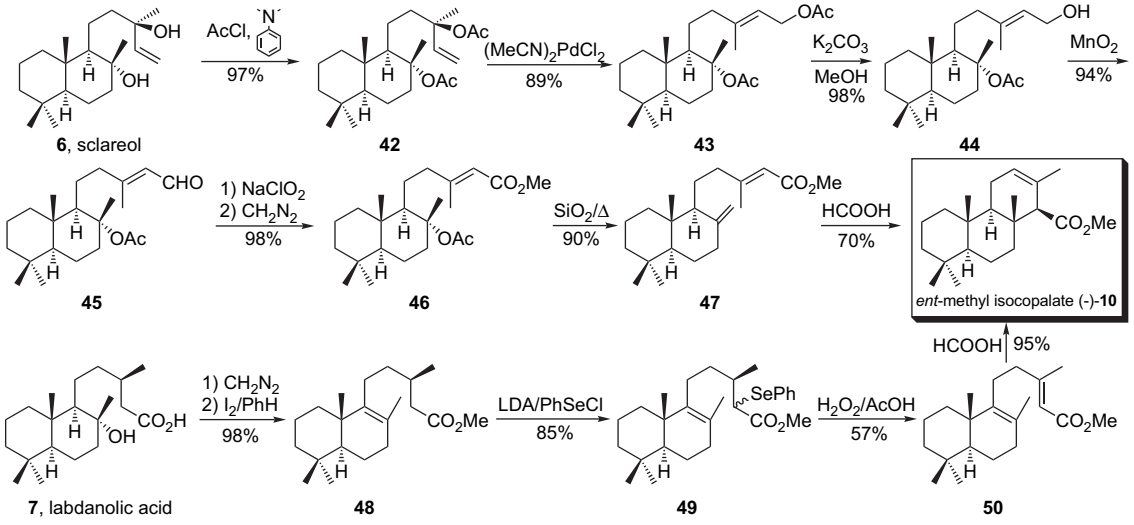
A few years later, Nakano et al. also described the synthesis of (±)-spongia-13(16),14-diene (**38**) from the same hydroxy-isocopalane **15** used in the synthesis of (±)-**1** (Scheme 8).[25] The starting material was, however, synthesized from (±)-methyl isocopalate (**10**) using the improved procedure developed by Rúveda et al. for the synthesis of related tricyclic diterpenes (aldehydes **29** and **30**).[23] 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 H_2SO_4, followed by isomerization with 10% ethanolic potassium hydroxide, 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 (±)-furanospongian **38** in 55% yield (Scheme 8).



Scheme 8. Nakano's synthesis of (±)-spongia-13(16),14-diene, (**38**).

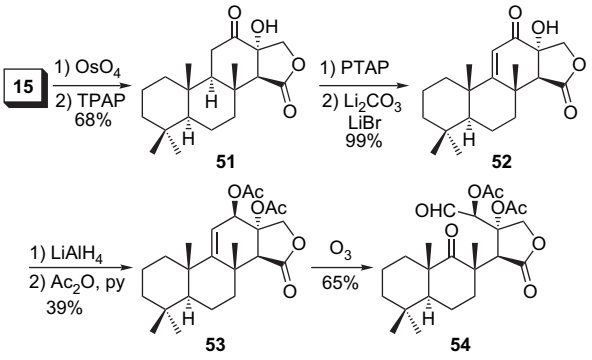
More recently, Urones et al. reported the preparation of the useful intermediate in spongiane synthesis, *ent*-methyl isocopalate (**10**), from sclareol[26] (**6**) and labdanolic acid[27] (**7**), two abundant bicyclic natural products (Scheme 9). Thus, sclareol (**6**), a major terpenic constituent of *Salvia sclarea*, 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 MnO_2 gave aldehyde **45**. Subsequent oxidation of **45** with $NaClO_2$ 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 phenylselenic 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 $\Delta^{9,11}$ 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 secospongiane **54**. The precursor of secospongiane **54** was the known hydroxy-



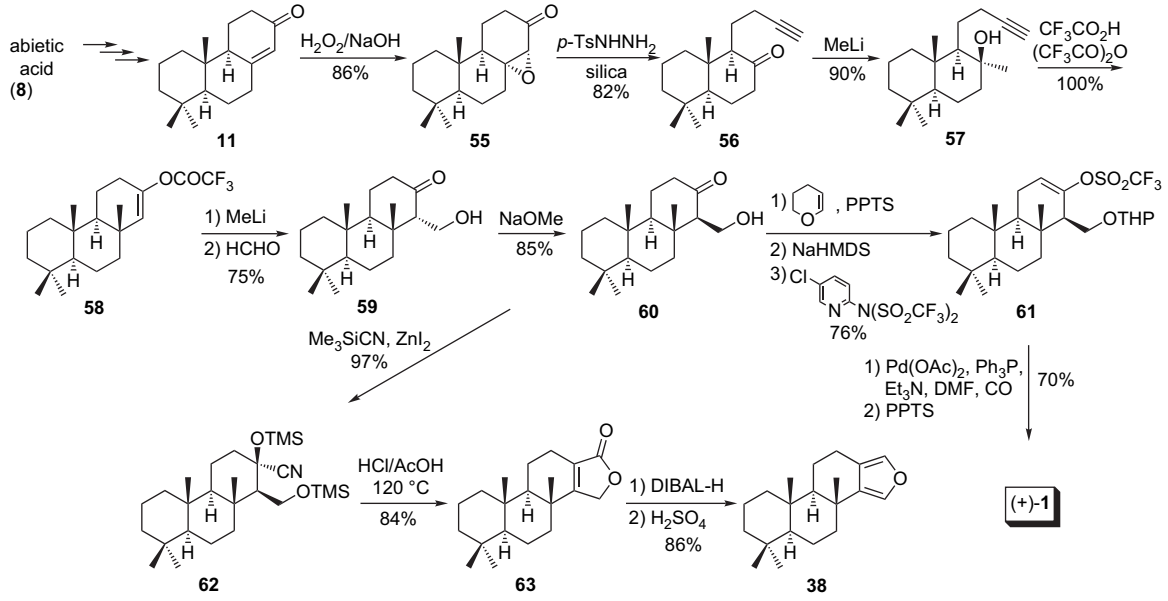
Scheme 9. Urones' syntheses of *ent*-methyl isocopalate (−)-**10** from sclareol (**6**) and labdanolic acid (**7**).

isocopalane **15**, which was again synthesized using Rúveda's method as outlined in Scheme 7.[23] Treatment of **15** with OsO_4 followed by oxidation with tetrapropylammonium perruthenate (TPAP) gave the ketone **51** in 68% yield. The desired double bond was introduced by bromination with phenyltrimethylammonium perbromide (PTAP) and subsequent elimination with Li_2CO_3/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.



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

The readily available abietic acid (**8**) 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.[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

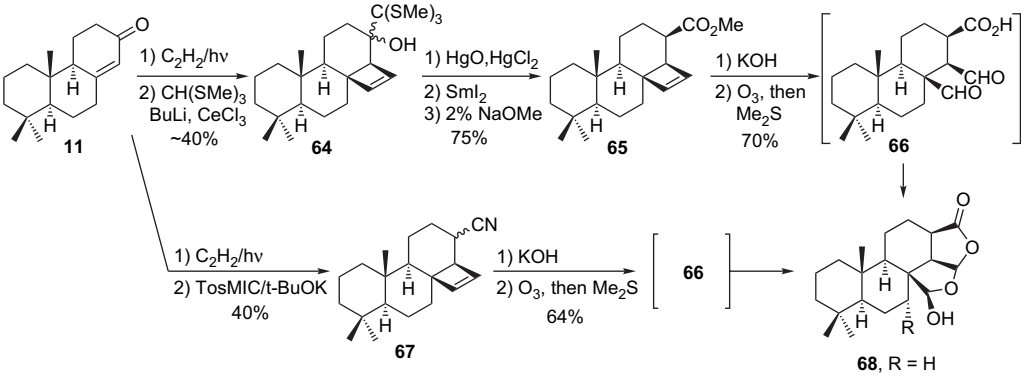


Scheme 11. Arnó's syntheses of (+)-isoagatholactone (**1**) and (−)-spongia-13(16),14-diene (**38**) from **11**.

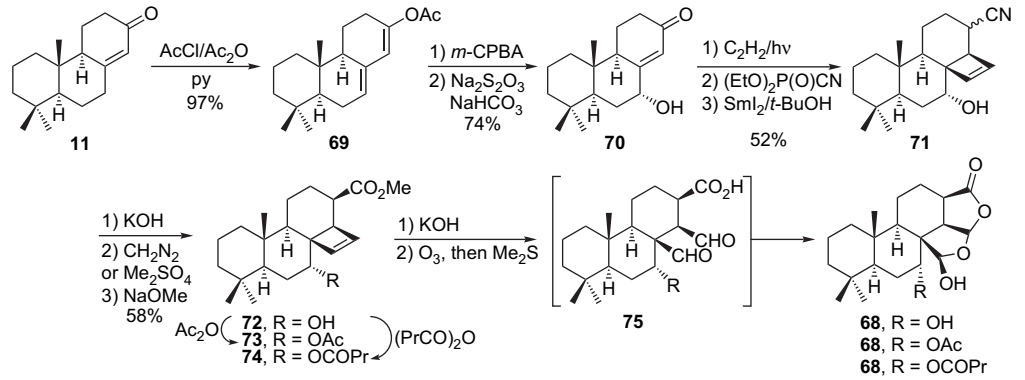
of podocarpane diterpenoids into biologically active compounds, Arnó et al. achieved an efficient synthesis of natural (+)-isoagatholactone (**1**) and (−)-spongia-13(16),14-diene (**38**), starting from chiral podocarpenone **11**.[33] Compound **11** was converted in six steps into the common intermediate **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 spongianes. In the first approach, the required homologation at C13 was introduced by carbonylation of triflate **61**, and subsequent deprotection in acidic media afforded directly the desired isoagatholactone (+)-**1** (20% overall yield from **11**). On the other hand, addition of trimethylsilyl cyanide provided the carbon at C13, compound **62**. Subsequent hydrolysis with concomitant deprotection, lactonization, and dehydration occurred by treatment with a mixture of hydrochloric acid and acetic acid at 120 °C in a sealed tube to give lactone **63**, which was transformed into **38** via reduction to its corresponding lactol, followed by dehydration and aromatization in acidic media (Scheme 11). (−)-Furanospongiane **38** was thus prepared in 11 steps from **11** in 28% overall yield.

In the early 1990s, the same research group described the first enantioselective synthesis of pentacyclic spongianes.[34,35] 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[36] (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



Scheme 12. Arnó's syntheses of (−)-dendrillol-1 (**68**, R=H).



Scheme 13. Arnó's syntheses of (−)-aplyroseol-1 (**68**, R=OCOPr), (−)-aplyroseol-2 (**68**, R=OAc) and (−)-deacetylaplyroseol-2 (**68**, R=OH).

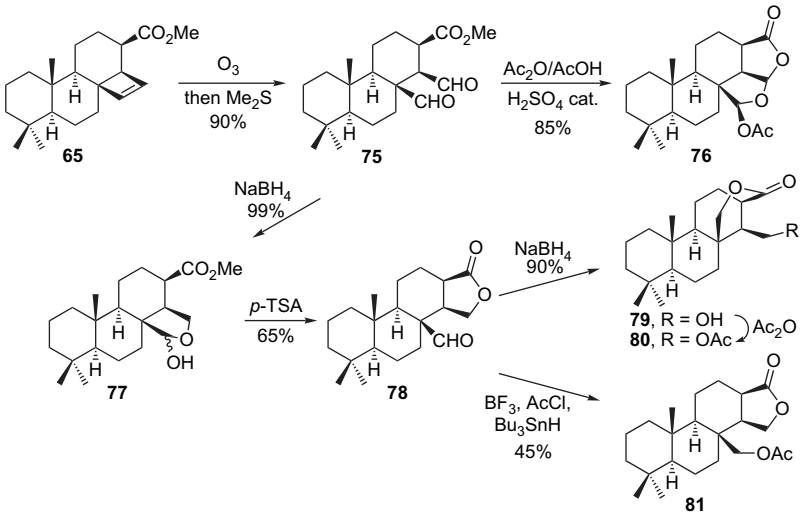
diterpenes. It is worthy of note that the homologation at C13 was conducted more efficiently by cyanophosphorylation followed by reductive elimination to give nitriles **71**.

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).[37] 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/Ac_2O 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]

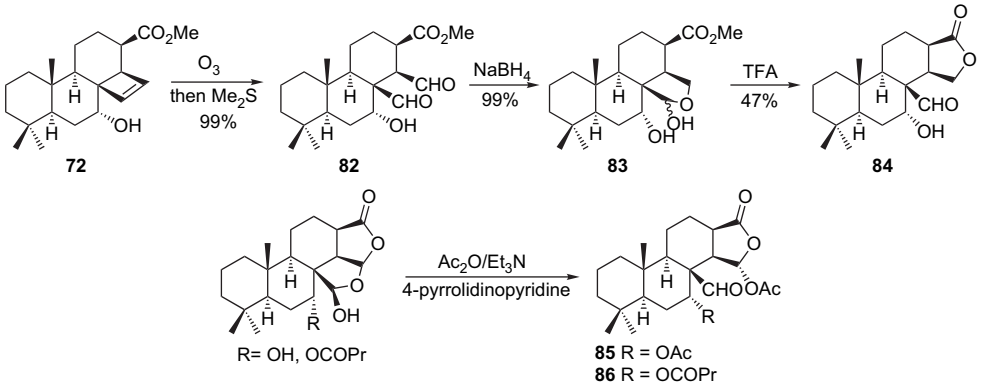
Recently, the same laboratory reported some structure–activity relationship studies of the spongianes prepared in the group including the synthesis and biological evaluation of novel C7,C17-functionalized spongianes (Scheme 15).[40,41] Some of these new spongiane derivatives possess an α-acetoxy group 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 phenanthrenone **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]

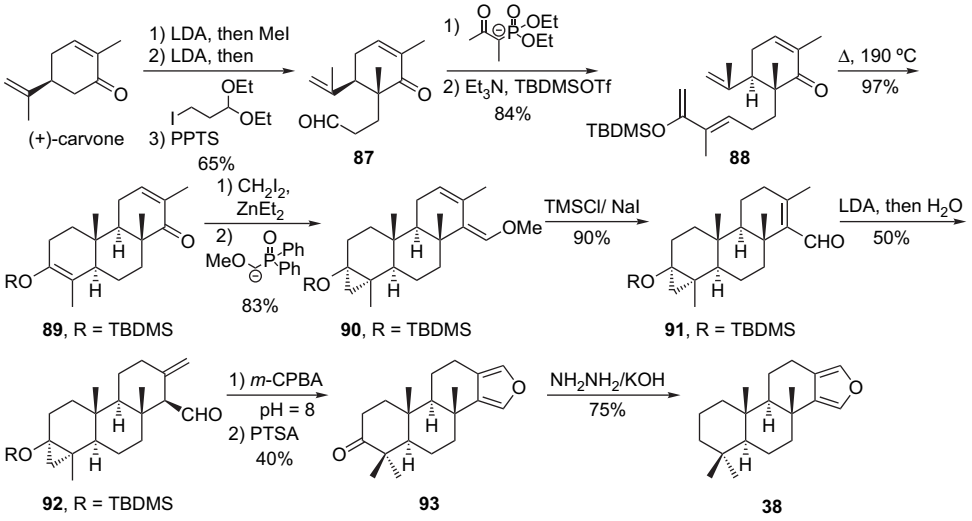
The strategy is based on a C→ABC→ABCD ring annulation sequence in which the key step for the preparation of the tricyclic ABC-ring system was an intramolecular Diels–Alder (IMDA) reaction. The whole sequence takes 13 steps to furnish the furanospongiane **38** in 9% overall yield. Carvone is first alkylated 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.

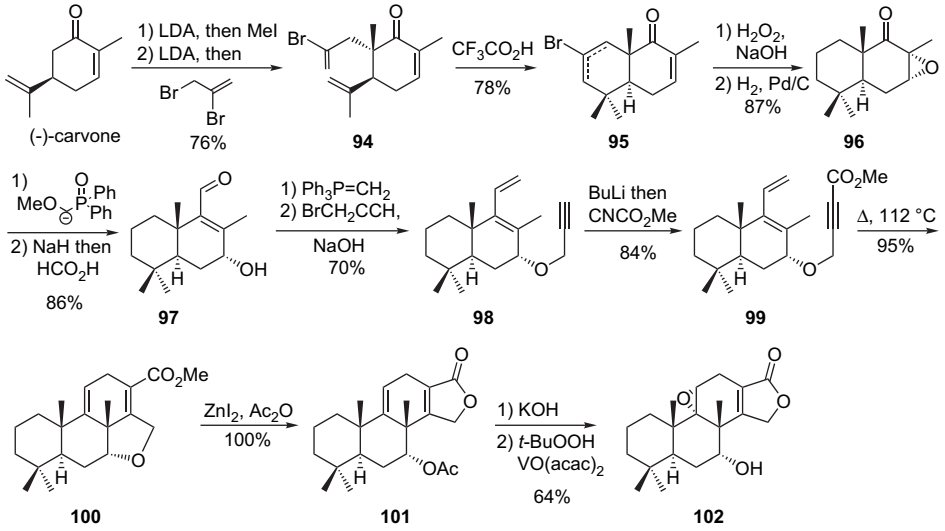


Scheme 16. Arnó's synthesis of (−)-spongia-13(16),14-diene (**38**) from (+)-carvone.

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 (−)-carvone as starting material has recently been described by Abad et al., as outlined in Scheme 17.[44] This synthetic sequence follows a B→AB→ABC→ABCD approach in which carvone is first converted into the decalone **95** (AB system) by alkylation 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 $VO(acac)_2$.

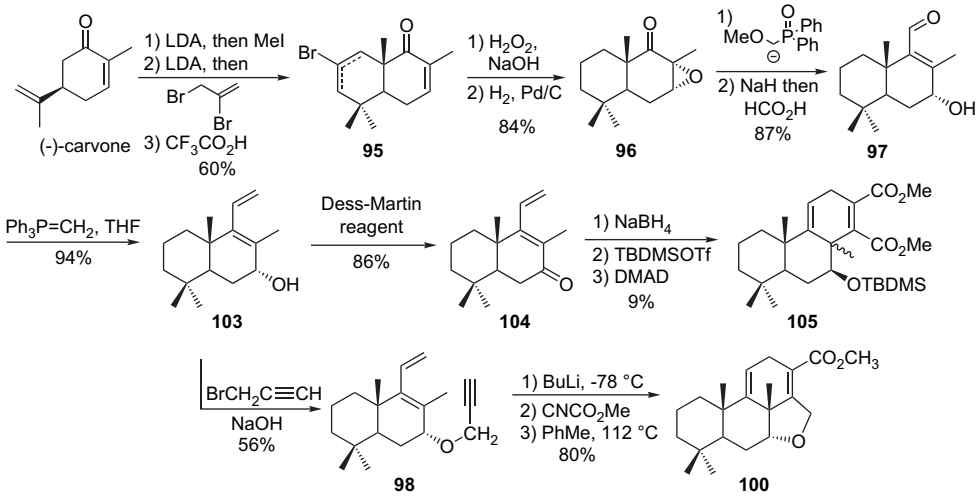
Based on this synthetic plan, Abad et al. continued the development of several studies for the synthesis of spongiane diterpenes related to natural dorisenones. Therefore, following the same strategy B→AB→ABC→ABCD for the ring-system construction they used the key epoxydecalone **96**, which was further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



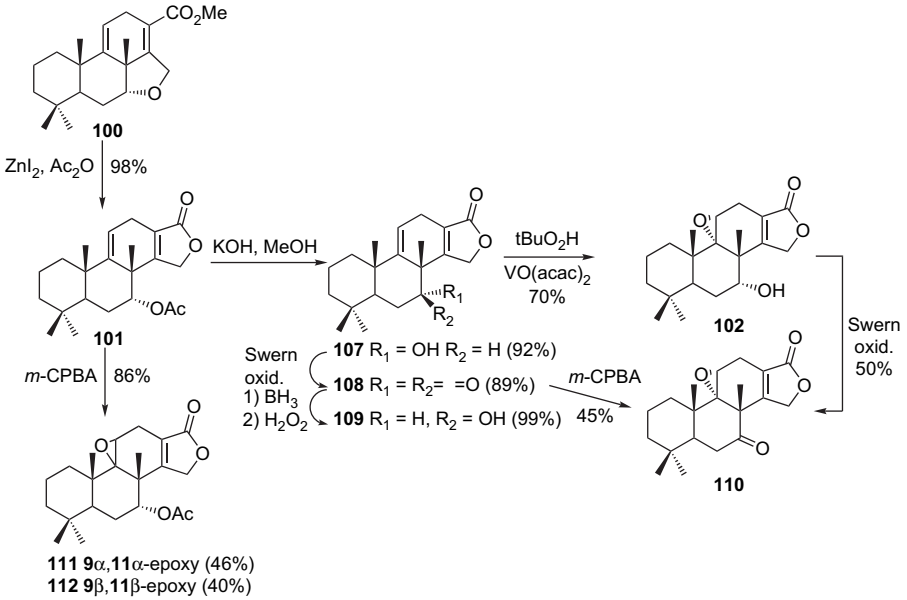
Scheme 17. Abad's synthesis of C7,C11-functionalized spongianes (**102**) from (−)-carvone.

synthesized from **96** for intermolecular Diels–Alder reactions but provided low yields using dimethyl acetylenedicarboxylate (DMAD) as dienophile (Scheme 18).[45] 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.

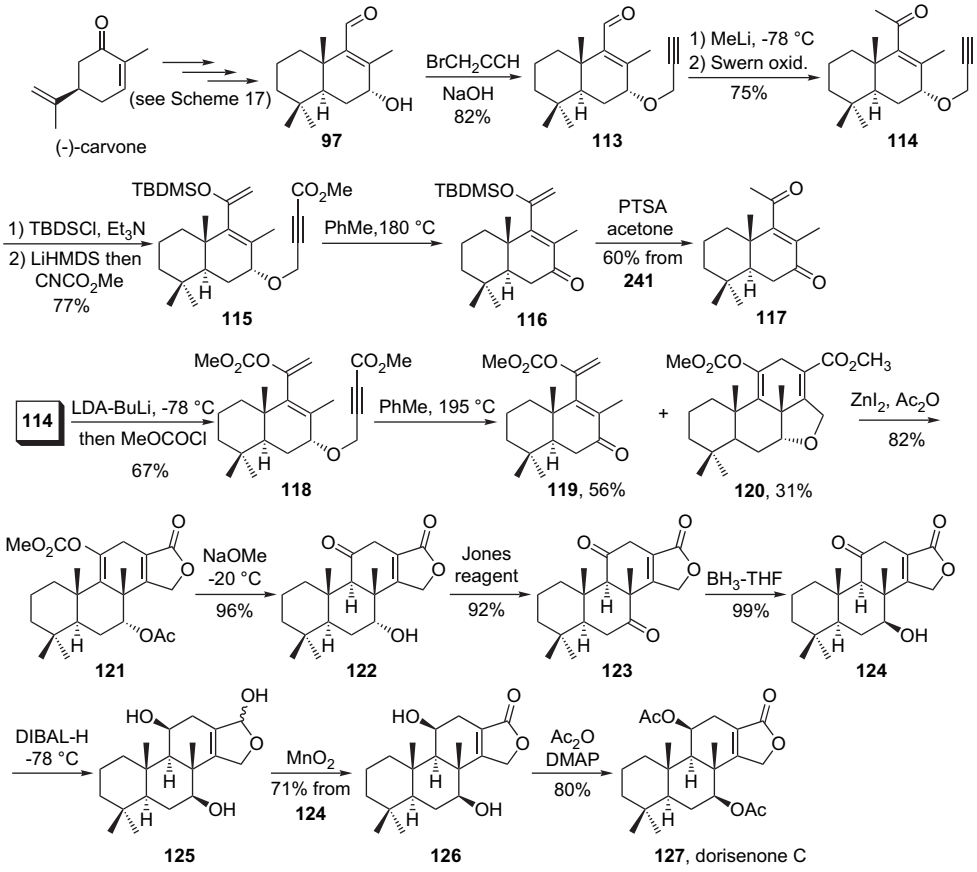
Following the above-mentioned extensive synthetic studies for the preparation of dorisenone diterpenes of the spongiane family, Abad et al. have recently adapted their synthetic sequences for the synthesis of dorisenone C (**127**) (Scheme 20).[46] They have developed a B→AB→ABC→ABCD approach starting 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.



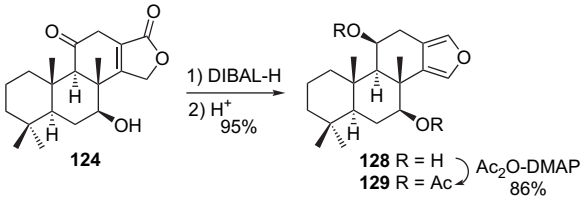
Scheme 19. Abad's synthesis of C7,C11-functionalized spongianes (**102**, **110**, **111**, and **112**) from (−)-carvone.



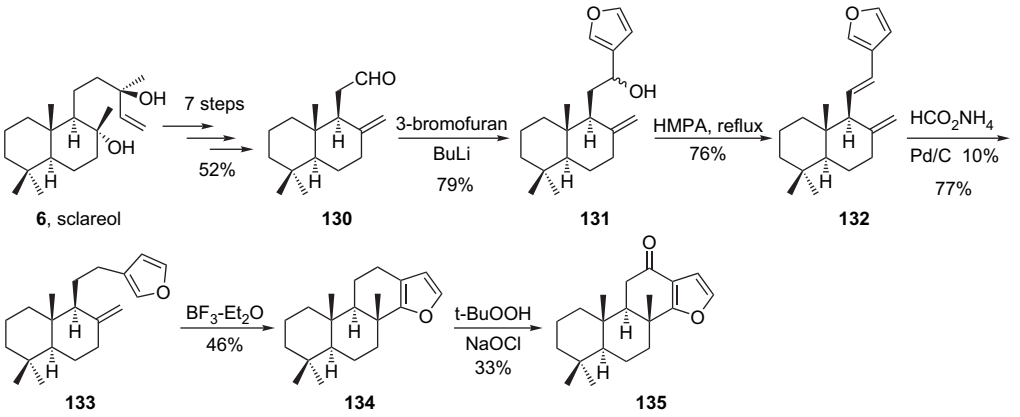
Scheme 20. Abad's synthesis of dorisenone C (**127**) from (−)-carvone.

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-hetero-ene rearrangement of the propargylic ether moiety. Thus, after desililation 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-hetero-ene 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 **122**, and subsequent oxidation 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 MnO_2 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).[47] 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 ambergris odorant, (−)-γ-bicyclohomofarnesal **130**, from sclareol **6** in seven steps and



Scheme 21. Abad's synthesis of furanoditerpenes **128**, **129** from (−)-carvone.



Scheme 22. Ragoussis's synthesis of (−)-marginatone **135** from (−)-sclareol.

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 (+)-coronanin 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%).

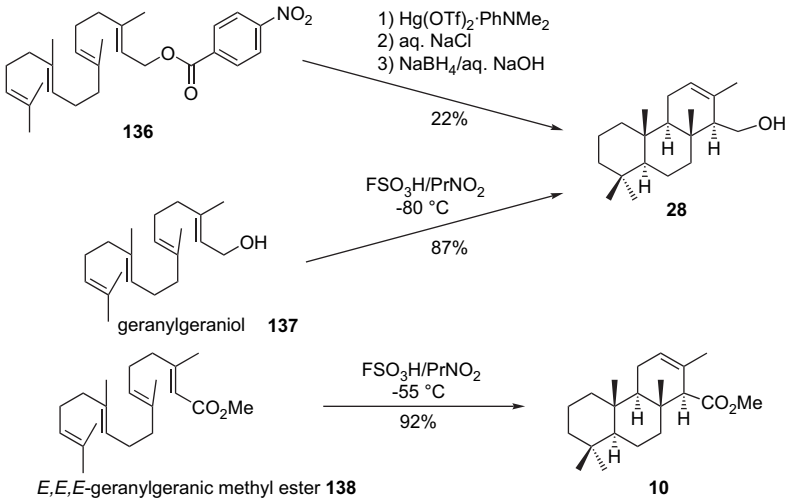
3.2. Syntheses by biomimetic approaches

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,[48,49] 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.[50,51] 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.[52–58]

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),[59,60] which had been previously converted into isoagatholactone (**1**) by Nakano and Hernández[17] and Ungur et al.[20,21] Compound **28** has also been converted into 12α-hydroxyspongia-13(16),14-diene by Rúveda et al.[19] The cyclization takes place using as the electrophile a mercury(II) triflate-*N*,*N*-dimethylaniline complex, which after reductive demercuration leads to alcohol **28** (22%), together with two bicyclic diterpenoids.

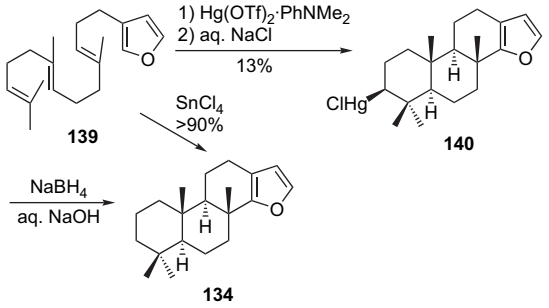
Contemporary synthetic studies by Ungur et al. also described the biomimetic synthesis of **28** by superacid cyclization of geranylgeraniol **137** with fluorosulfonic acid.[61] A few years later, the same group also reported the synthesis of



Scheme 23. Biomimetic syntheses of racemic isocopalol **28** and methyl isocopalate **10**, precursors of spongiane diterpenoids.

racemic methyl isocopalate **10**, from **138**, using similar conditions (Scheme 23).[62]

Nishizawa et al. also used the mercury(II) reagent to cyclize ambliofuran **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. Ambliofuran **139** had also been cyclized to furanoditerpene **134** in high yield by Sharma et al. using $SnCl_4$ as electrophile initiator (Scheme 24).[64]



Scheme 24. Biomimetic synthesis of isospongiane **134** from ambliofuran **139**.

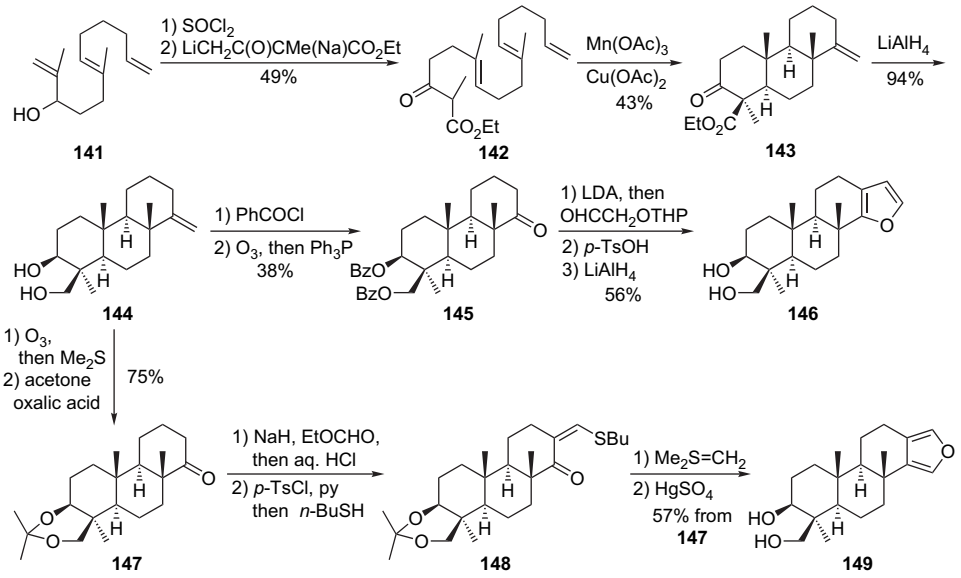
Since the first investigations in the 1960s by Breslow et al.,[65,66] biomimetic radical-mediated cyclization reactions have become an excellent synthetic method for the synthesis of polycyclic natural products under mild conditions and with high stereochemical control.[67]

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[68] was based on the Snider method to cyclize intramolecularly unsaturated β-keto esters with Mn(III) salts.[69] Following the success of this approach, they reported, in 1995, the first biomimetic-like synthesis of spongiane diterpenes, particularly furanospongianes (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-methylacetoacetate in 49% overall yield. After securing the stereochemistry of **143** by means of meticulous NMR studies,[71] isospongiane **146** was prepared by reduction, benzoylation, and ozonolysis leading to ketone **145**, which was alkylated with a THP-protected hydroxyacetaldehyde and hydrolyzed with concomitant aromatization and final debenzoylation by reduction.

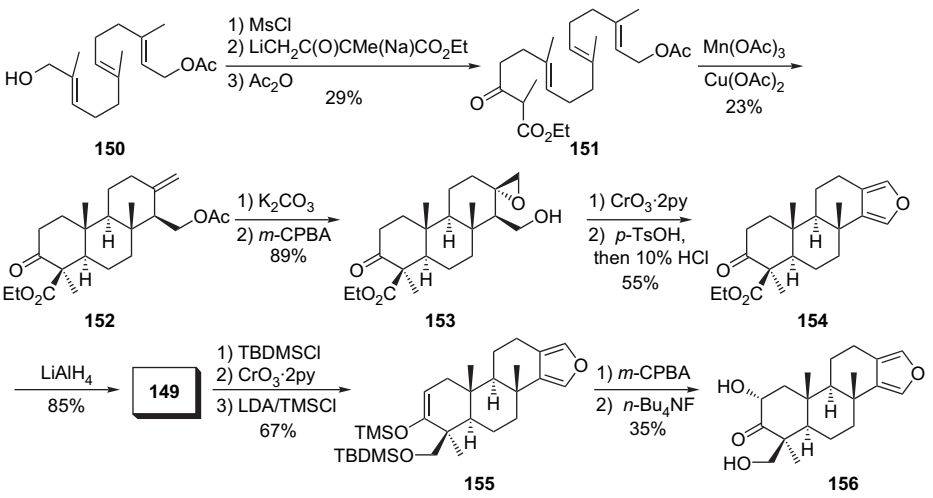
On the other hand, ozonolysis of diol **144** and protection as its corresponding acetonide, compound **147**, followed by furan ring formation using Spencer's method, gave unnatural furanospongiane **149**, via enone **148**, in 8% overall yield from **141**.

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 $LiAlH_4$ 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 (±)-isospongiadiol **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



Scheme 25. Zoretic's biomimetic synthesis of isospongiane **146** and spongiane **149** from precursor **144**.

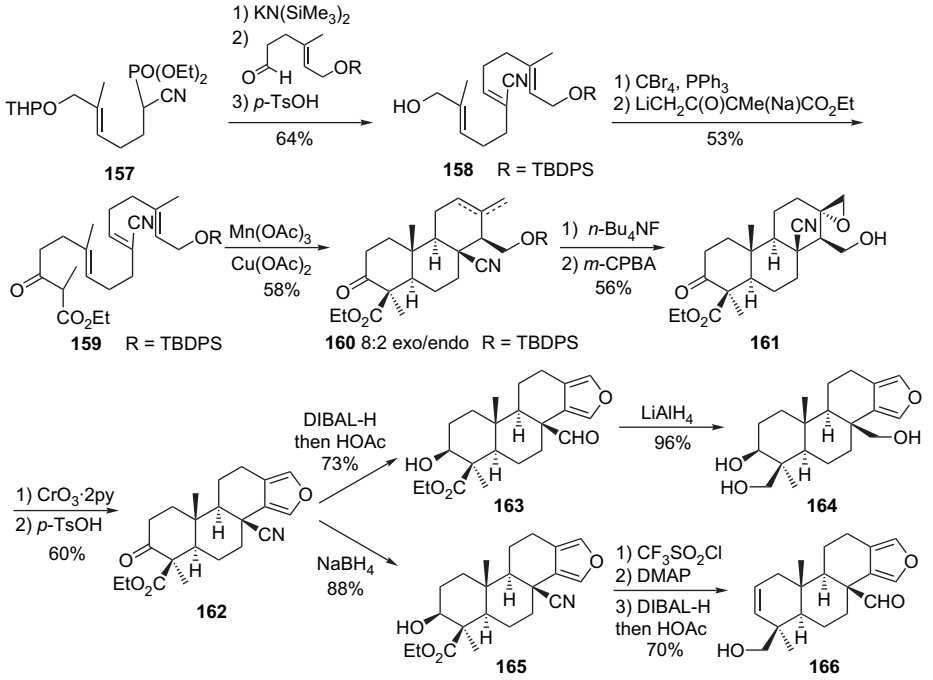


Scheme 26. Zoretic's biomimetic synthesis of (±)-isospongiadiol **156**.

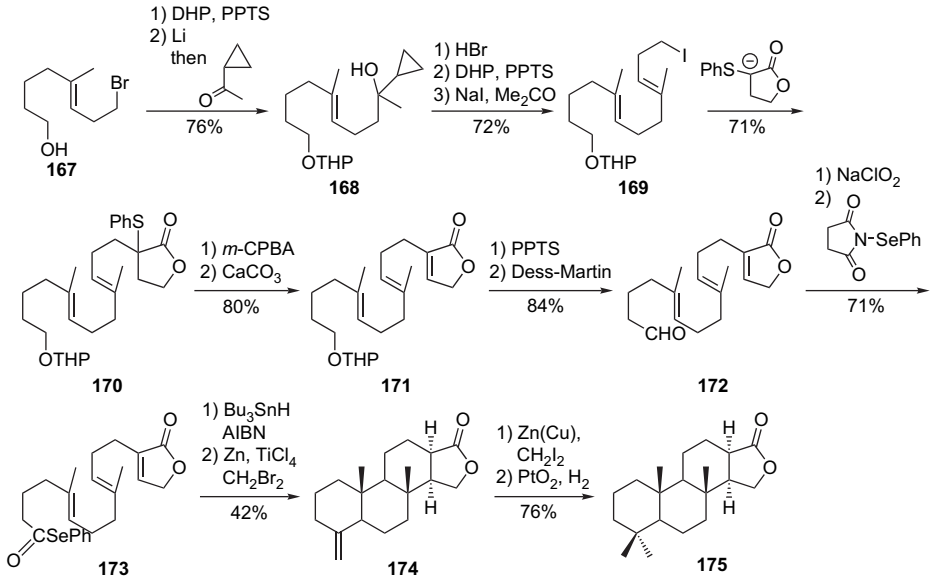
(Scheme 27).[74] They started from phosphonate **157**, which was subjected to Horner–Emmons olefination to give polyene **158**. This modification allows the synthesis of furanospongianes functionalized at C17, such as **163**–**166**, through the advanced intermediate **162**. Compound **162** was 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,[75,76] for the total synthesis of (±)-spongian-16-one **175** (6% overall yield) (Scheme 28).[77,78] They completed the synthesis in a concise fashion via the cyclization precursor **173**, which was prepared from alcohol **167**, as shown in Scheme 28. Protection of **167** as tetrahydropyranyl ether, followed by lithiation and 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 Bu_3SnH 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.

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).[79] In their strategy, the photoinduced radical cation of the polyene



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



Scheme 28. Pattenden's biomimetic synthesis of (±)-spongian-16-one **175**.

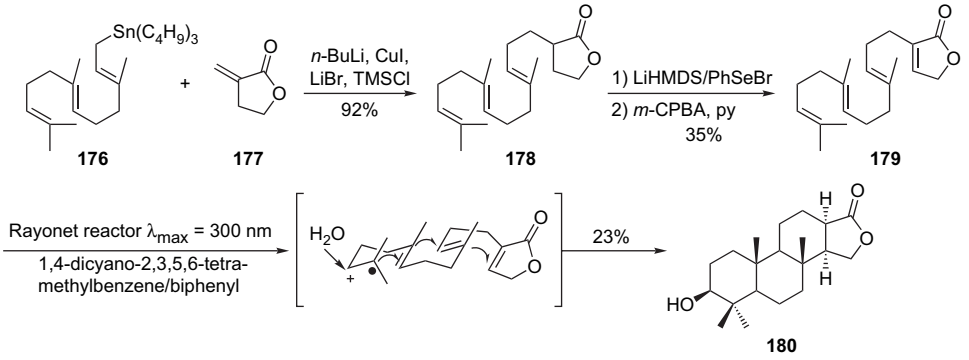
undergoes water addition in *anti-Markovnikov* sense, followed by cyclization cascades terminated by a 5-*exo-trig* ring closure. The overall reaction sequence mimics the non-oxidative biosynthesis of terpenes. The radical cation precursor **179** was synthesized from farnesyltri-*n*-butylstannane **176**, 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 λ_{max}=300 nm afforded spongiane **180** in 23% yield after purification. The structure of **180** was unambigously determined by NOE and X-ray analyses.

3.3. Other approaches and total syntheses

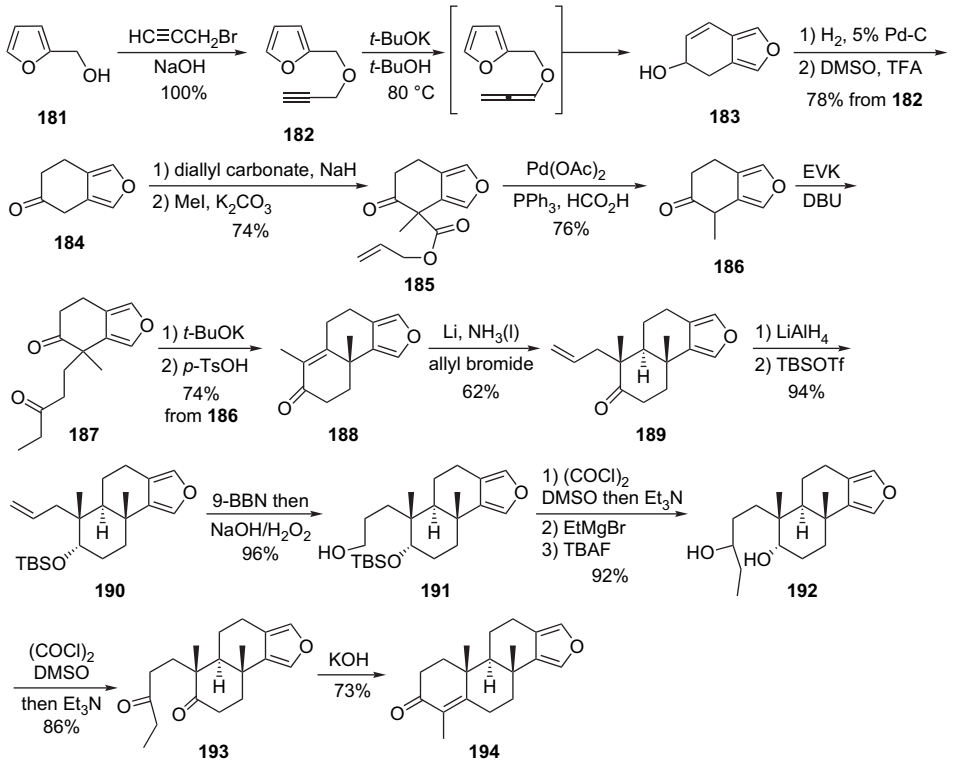
As mentioned previously, the studies toward the synthesis of spongianes are scarce, especially of rearranged metabolites. The synthesis of furanospongiaditerpenoids has been embarked upon starting from natural products and using biomimetic-like reaction sequences, both of which have provided in some cases the synthesis of spongianes 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 (±)-spongiadiosphenol **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 β-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.

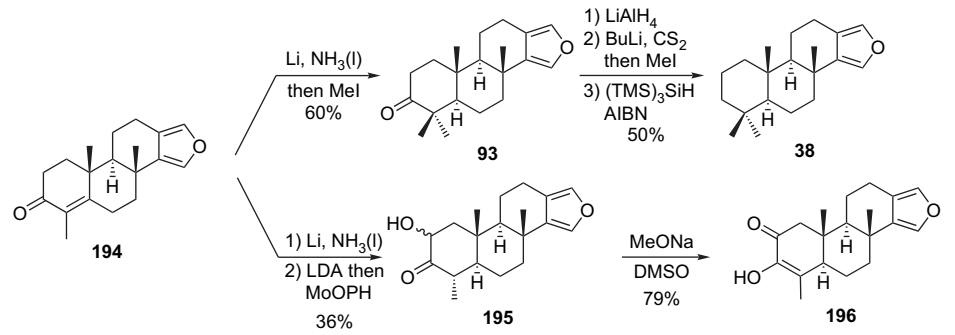
The synthesis of spongiane **38** was successfully completed by forming the *gem*-dimethyl moiety by reductive methylation of **194** to give ketone **93** and removal of the carbonyl group at C3. In parallel studies, compound **194** was reduced,



Scheme 29. Demuth's biomimetic synthesis of (±)-3-hydroxy-spongian-16-one **180**.



Scheme 30. Kanematsu's synthesis of spongian precursor **194**.

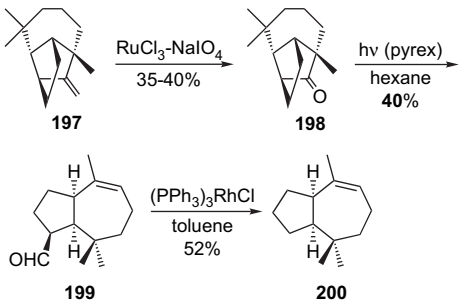


Scheme 31. Kanematsu's synthesis of (±)-spongia-13(16),14-diene **38** and (±)-spongiadiosphenol **196**.

hydroxylated to give ketone **195** and then oxidized to afford the desired (±)-spongiadiosphenol **196**, which represents the first total synthesis of a furanospongiane diterpene with a functionalized A-ring (Scheme 31).

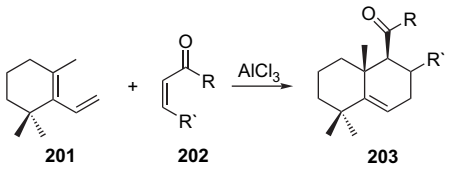
With regard to the synthesis of rearranged spongianes, there are about three reported synthetic approaches to build up the bicyclic systems[82–84] present and, to the best of our knowledge, only two published enantioselective total syntheses.[85,86]

Mehta and Thomas reported in 1992 how the abundant, commercially available (+)-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 35–40% 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 (+)-**200** in 52% yield (Scheme 32).



Scheme 32. Mehta's synthesis of hydroazulene **200**.

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]



Scheme 33. Bhat's synthesis of decalins.

Diene **201** reacts with a series of dienophiles **202**, in the presence of $AlCl_3$, to give a number of decalins **203**, which can be further elaborated to build up the spongiane 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]

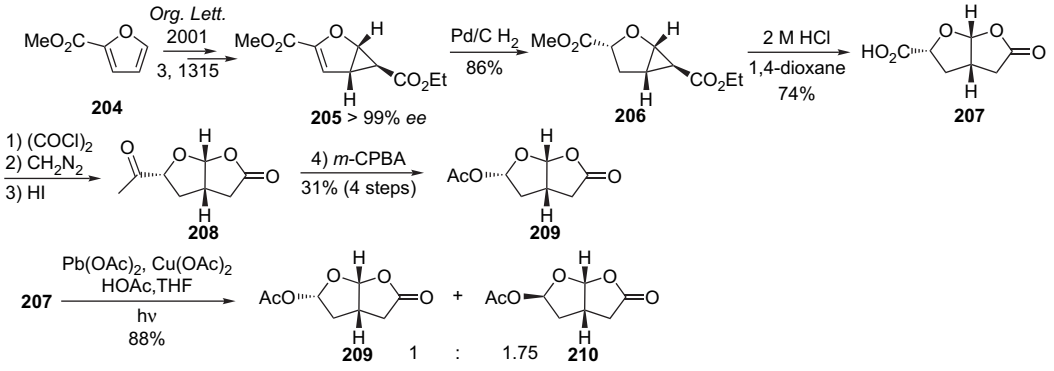
The synthesis starts with a copper-bisoxazoline-catalyzed, enantioselective cyclopropanation of methyl 2-furoate **204** to cyclopropane **205**, a versatile building block toward a broad variety of derivatives, which could be subsequently converted into 5-oxofuro[2,3-*b*]furans. In fact, hydrogenation 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 spongiane 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 decarboxylated 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 easily 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 spongiane skeleton.

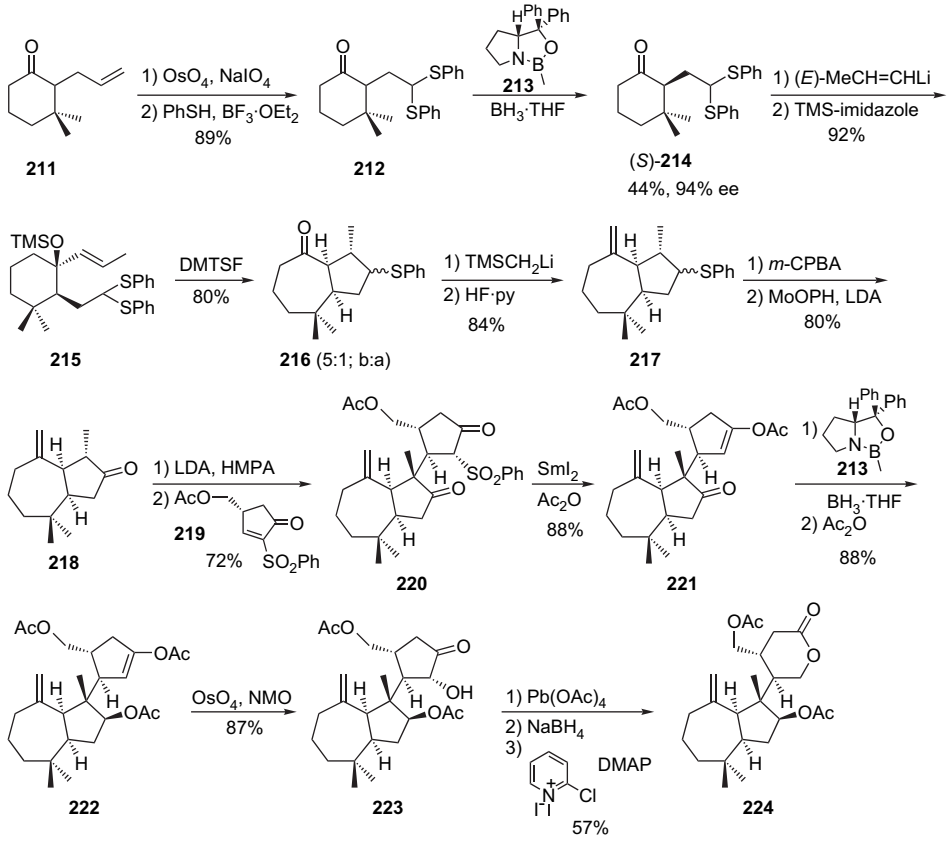
Firstly, in 2001, Overman et al. described the first enantioselective synthesis of a rearranged spongiane, (+)-shahamin K **224** (Scheme 35),[85] a spongian-derived metabolite having a *cis*-hydroazulene unit and an attached highly oxidized six-carbon fragment.

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 enantioenriched ketone (*S*)-**214** in 44% yield. Addition of (*E*)-1-propenyllithium to (*S*)-**214** followed by silylation gave the silyl ether **215** in high yield. Treatment of **215** with dimethyl(methylthio)sulfonium 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 desulfonylation, 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 SmI_2 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 $NaBH_4$ 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 sythesis 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 D-mannose (Scheme 36).



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



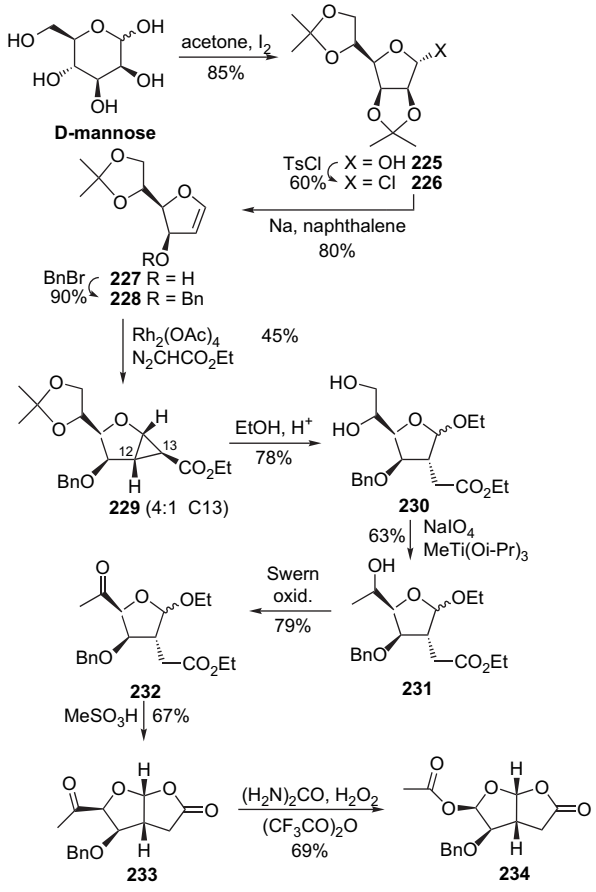
Scheme 35. Overman's synthesis of (+)-shahamin K **224**.

The preparation of the side chain begins with the transformation of D-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 **228** (2 M in DCM) and rhodium(II) acetate at 25 °C gave the cyclopropanation ester **229** with the desired configuration at the C12 center. The only diastereomers acquired during this reaction were produced at the C13 center (4:1 ratio in favor of the *exo* adduct) and both were taken forward.

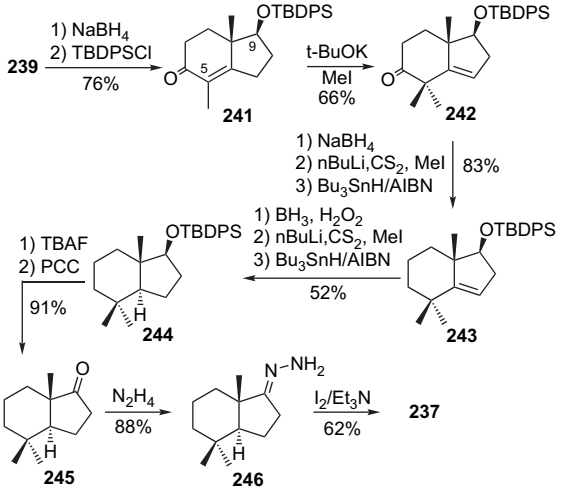
Exposure of **229** to a dilute ethanolic solution of sulfuric acid induced acetonide deprotection and, followed by concomitant opening of the cyclopropane ring, afforded compound **230** in 78% overall yield. After oxidative cleavage of diol **230**, the resulting aldehyde was methylated by treatment with MeTi(O*i*-Pr)$_3$ formed in situ to produce **231** in 63% combined yield. Oxidation of **231** under Swern conditions gave rise to ketone **232** (79%). The best yields for the conversion of **232** in to **233** were obtained using methanesulfonic acid, which at 0 °C produced bicycle **233** 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 **233** in to **234** 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.[86,87] 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 contains 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 (55–65% 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 **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 bicycle **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



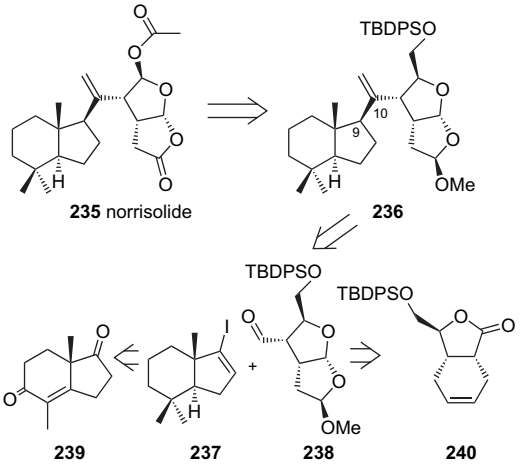
Scheme 36. Theodorakis's synthesis of norrisolide side chain **234**.



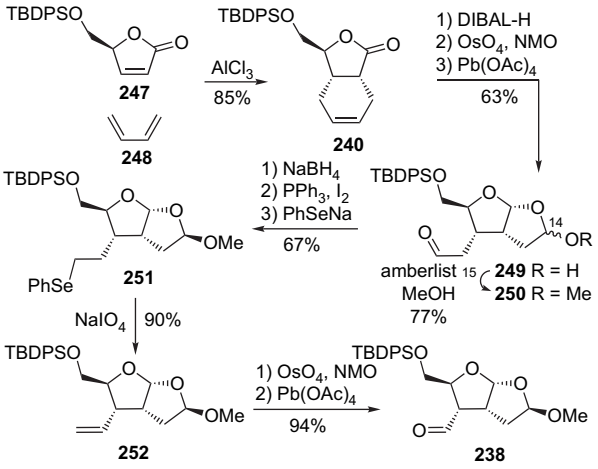
Scheme 38. Theodorakis's synthesis of fragment **237** of norrisolide **235**.

246. Finally, treatment of **246** with I_2/Et_3N 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.



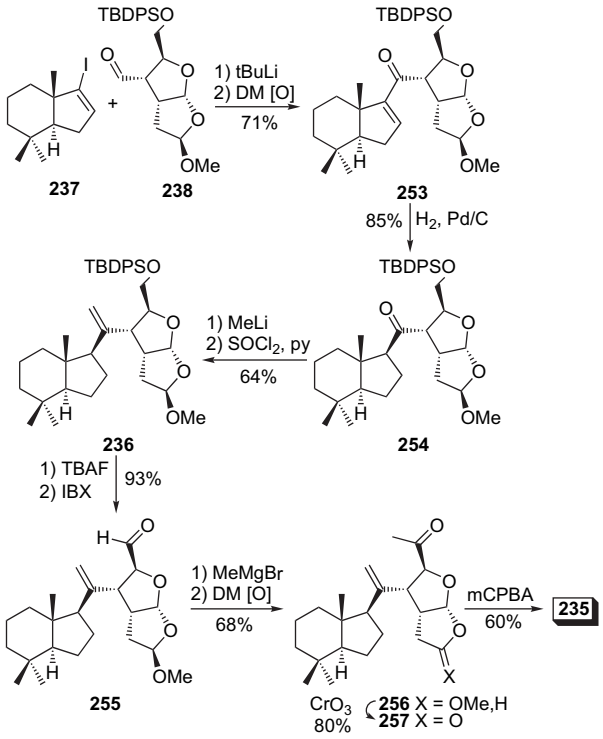
Scheme 37. Theodorakis' retrosynthesis of norrisolide **235**.



Scheme 39. Theodorakis's synthesis of fragment **238** of norrisolide **235**.

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

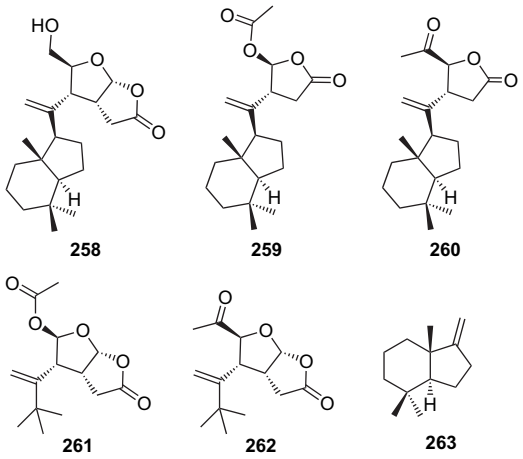
of the resulting alcohol with $SOCl_2$ in the presence of pyridine (two steps, 64% yield). With the alkene **236** in hand, the stage was now set for the final functionalization of the bicycle (Scheme 40). Deprotection of the silyl ether and oxidation of the resulting alcohol gave aldehyde **255**, which was subsequently converted into the ketone **256** via treatment with MeMgBr and Dess–Martin (DM) oxidation (68% yield). Treatment of **256** with 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**.



Scheme 40. Theodorakis's synthesis of norrisolide **235**.

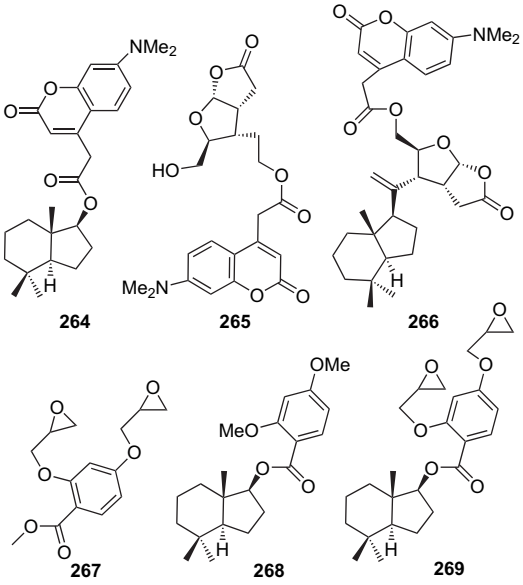
After completion of their total synthesis of norrisolide, this group has also explored the biological activities of some analogs of the parent molecule. Thus, the molecules **233**, **234**, **245**, and **257** from their previous synthetic studies were evaluated together with **258**–**263**, which 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.[88] 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.



Scheme 41. Theodorakis's analogs of norrisolide **235**.

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.



Scheme 42. Theodorakis's norrisolide-based fluorescent probes.

4. Conclusions

The scientific investigations of the spongiane 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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Biographical sketch

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