Sesterterpenoids

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Contents

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1 Introduction

Sesterterpenoids are a relatively small group of natural products. Even though they belong to one of the largest families of natural products, the "terpenoids," only around 1000 natural sesterterpenoids have been reported [1–5]. Considering that over 80,000 terpenoids have already been isolated [6–8], the number of known sesterterpenoids is quite small. Moreover, in almost all cases, their biological role is unknown. However, sesterterpenoids have been isolated from many kinds of organisms (e.g., plants, bacteria, fungi, lichens, insects, marine sponges, and other marine organisms) [1–5]. This fact implies that various organisms have the potential to produce sesterterpenoids.

In this contribution, we will introduce the chemical structures of sesterterpenoids. Although the number of sesterterpenoids is not very large, they have a large variety of simple to complicated chemical structures. Herein, we have classified the sesterterpenoids based on the number of carbocyclic moieties in their chemical structures. In addition, we will also explain how the structure of each sesterterpenoid is formed in Nature.

2 What Are the Sesterterpenoids?

2.1 "Sesterterpenoids" Are Members of the "Terpenoids"

As mentioned above, the sesterterpenoids are a subgroup of the terpenoids. Therefore, we will start by briefly describing the terpenoids. Terpenoids are defined as a group of natural products composed of simple "C_5" units, called isoprene units (Fig. 1). Thus, terpenoids are also called "isoprenoids." In this definition, "C_5" means that a compound contains five carbon atoms. This notation will be frequently used in this chapter, and thus "C_{25}" refers to a compound containing 25 carbon atoms.

For example, the chemical structure of sesterbrasiliatriene (**1**), a type of terpenoid, contains five isoprene units (Fig. 2b) [9]. In another example, four isoprene units (b) constitute the chemical structure (a) of **2** (Fig. 3) [10].

The origins of the isoprene units are dimethylallyl pyrophosphate (DMAPP) (**3**) and isopentenyl pyrophosphate (IPP) (**4**) (Fig. 4) [6–8]. Both are widely distributed in Nature, and generated via two kinds of metabolic pathways, known as the MVA (mevalonate) and MEP (methylerythritol phosphate) pathways [11, 12].

The biosynthesis of all terpenoids starts from condensation reactions of **3** and **4** to yield polyprenyl diphosphates, which are important intermediates of terpenoids.

Fig. 1 Isoprene unit

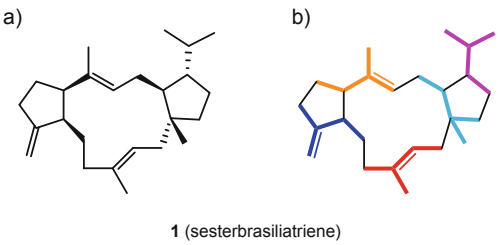


Fig. 2 Structure of **1**. The structure of **1** contains five isoprene units. Each isoprene unit is shown by bold lines with different colors

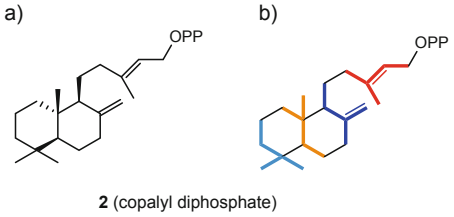


Fig. 3 Structure of **2**. The structure of **2** contains four isoprene units. Each isoprene unit is shown by bold lines with different colors

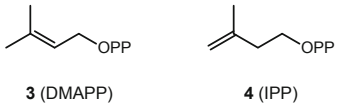


Fig. 4 Structures of dimethylallyl pyrophosphate (DMAPP) (**3**) and isopentenyl pyrophosphate (IPP) (**4**)

Each polyprenyl diphosphate is designated as follows: (C_{10}) geranyl diphosphate (GPP) (**5**), (C_{15}) farnesyl diphosphate (FPP) (**6**), (C_{20}) geranylgeranyl diphosphate (GGPP) (**7**), and (C_{25}) geranylfarnesyl diphosphate (GFPP) (**8**). These condensation reactions are catalyzed by enzymes called "prenyltransferases" (Fig. 5) [6–8].

In many cases, the polyprenyl diphosphates are subjected to cyclization reactions to form a carbocyclic moiety. These cyclization reactions are catalyzed by "terpene cyclases." Generally, the terpene cyclases are divided into two classes, "type 1" and "type 2," based on their catalytic mechanisms.

The type 1 terpene cyclases initiate the cyclization by heterolytic cleavage of the diphosphate moiety of the polyprenyl diphosphates. The heterolytic cleavage leads to the generation of cation intermediates, and the high energy of the cation intermediate is the driving force of the cyclization reaction. The cyclization reaction is finalized by either deprotonation or an attack by H_2O. For example, **1** is formed by a type 1 terpene cyclase (Fig. 6).

The other class of terpene cyclases is known as the "type 2" terpene cyclases. The type 2 terpene cyclases also generate cation intermediates to initiate the cyclization reaction. However, the strategy to generate the cation intermediate is different from that of the type 1 terpene cyclases. The type 2 terpene cyclases generate the cation intermediate via the protonation of a double bond of the polyprenyl diphosphates. For example, **2** is formed by a type 2 terpene cyclase (Fig. 7).

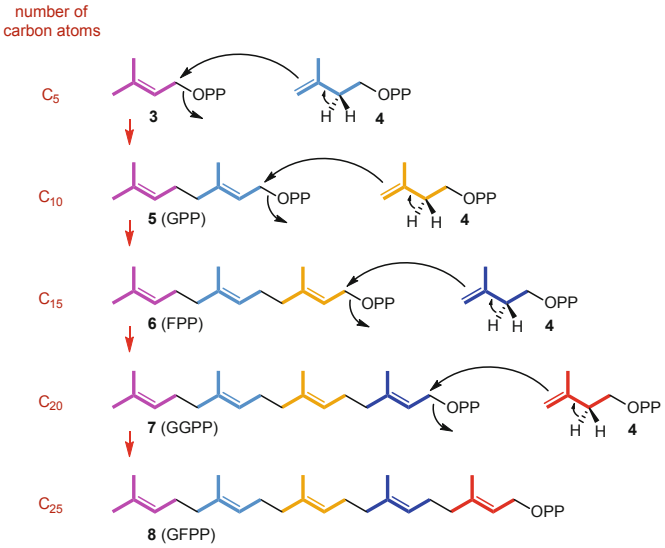


Fig. 5 Condensation reaction catalyzed by prenyltransferases to form polyprenyl diphosphates, and structures of **5**–**8**

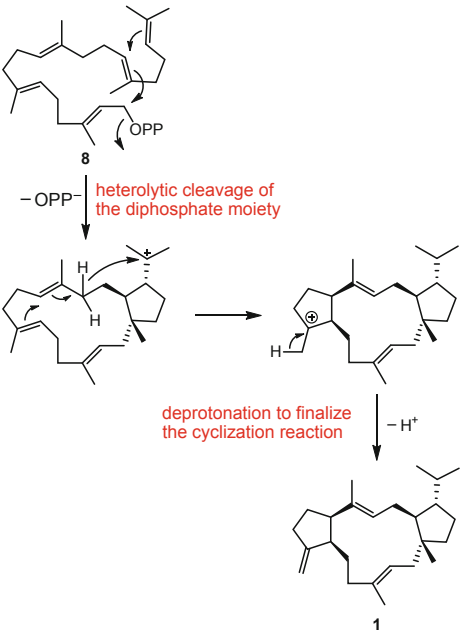


Fig. 6 Cyclization reaction to form sesterbrasiliatriene (**1**). This reaction is catalyzed by the type 1 terpene cyclase

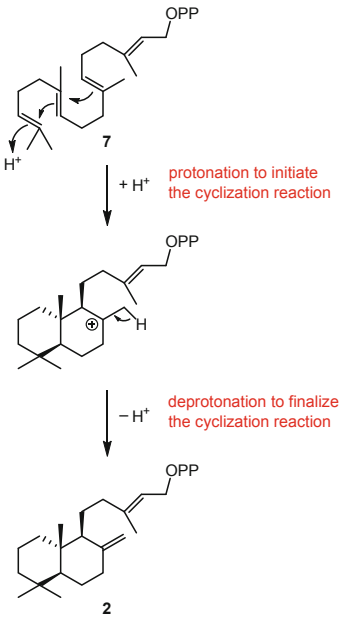


Fig. 7 Cyclization reaction to form **2**. This reaction is catalyzed by the type 2 terpene cyclase

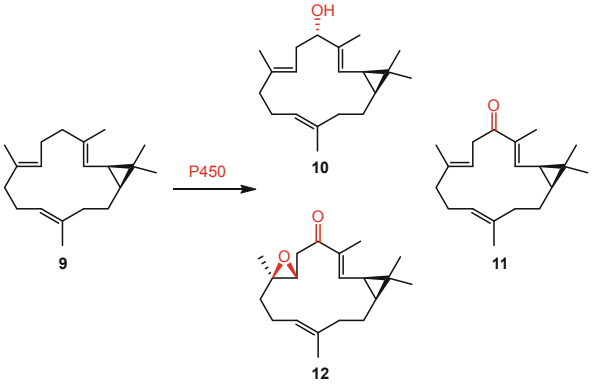


Fig. 8 Compound **9** could be oxidized by a cytochrome P450, forming **10**–**12**

After the fundamental carbon skeleton of the terpenoids is formed by the prenyltransferases and terpene cyclases, the intermediates of the terpenoids are converted into the final products by tailoring enzymes. A typical tailoring enzyme is cytochrome P450, which catalyzes an oxidation reaction. For instance, casbene (**9**) is converted to the oxidized products **10**–**12** by means of cytochrome P450 (Fig. 8) [13]. However, in addition to cytochrome P450, various other enzymes are also involved in the biosynthesis of terpenoids and expand their structural diversity.

For example, many kinds of tailoring enzymes (prenyltransferase, oxidase, aminotransferase, methyltransferase, sugar transferase, and ligase) are involved in the biosynthesis of brasilicardin A (**13**), a terpenoid with potent immunosuppressive

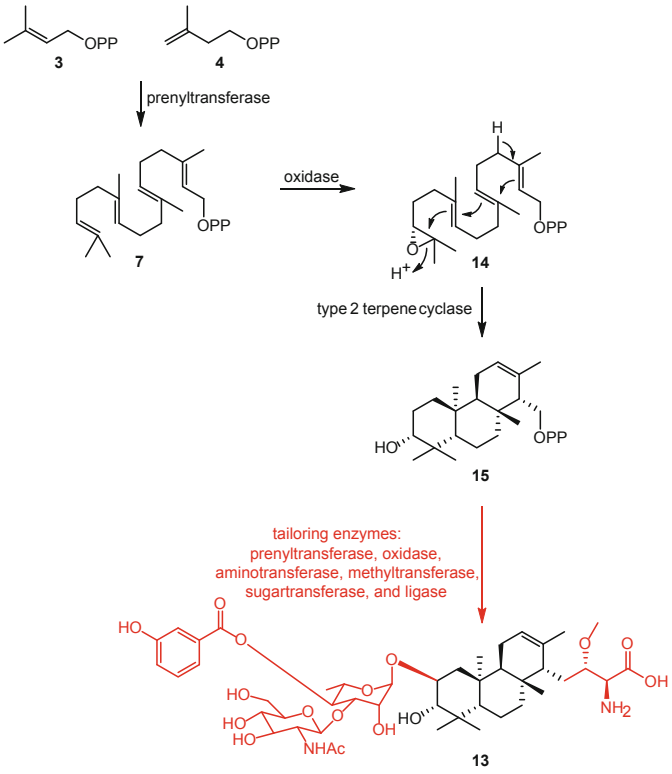


Fig. 9 Putative biosynthesis pathway of brasilicardin A (**13**). The functional groups of **13**, which might be generated by the tailoring enzymes, are shown in red

activity (Fig. 9). After the formation of **15** via **7** and **14**, these tailoring enzymes apparently convert **15** to **13** [14].

2.2 *Definition of "Sesterterpenoids"*

The terpenoids are classified by the chain lengths of the polyprenyl diphosphates used in their biosynthesis. In the case of the sesterterpenoids, they are defined as compounds that are biosynthesized via geranylfarnesyl diphosphate (GFPP) (**8**) (Fig. 10).

For example, preasperterpenoid A (**16**) is biosynthesized via **8** (Fig. 11) [9]. Thus, **16** is a sesterterpenoid. Actually, **1** is also a sesterterpenoid, while **2** is not, by considering their biosynthesis pathways (Figs. 6 and 7). Compounds **9**–**15** are also not sesterterpenoids (Figs. 8 and 9).

The other classes of terpenoids biosynthesized via different polyprenyl diphosphates are defined as follows: "hemiterpenoids" are from (C_5) **3** or **4**, "monoterpenoids" are from (C_{10}) **5**, "sesquiterpenoids" are from (C_{15}) **6**,

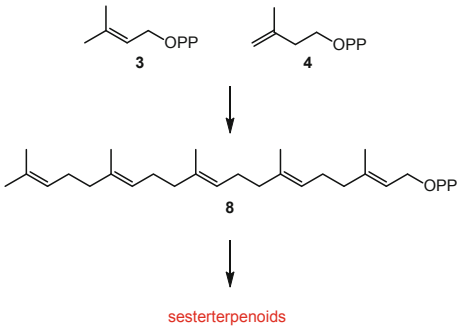


Fig. 10 Definition of sesterterpenoids. The genuine sesterterpenoids should be biosynthesized via **8**

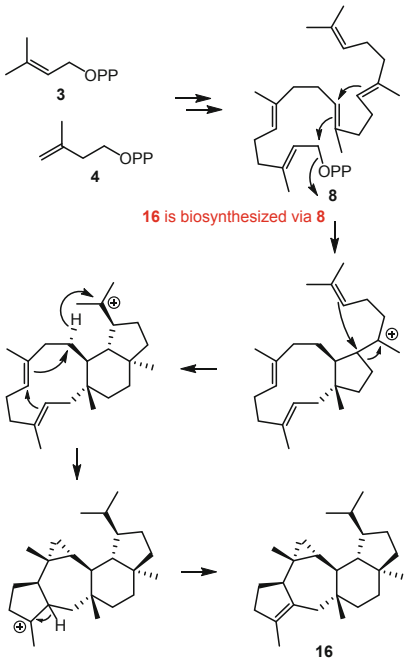


Fig. 11 Biosynthesis of preasperterpenoid A (**16**). Compound **16** is a sesterterpenoid, since **16** is biosynthesized via **8**

"diterpenoids" are from (C_{20}) **7**, and "triterpenoids" are from (C_{30}) squalene (**17**) (Fig. 12).

In contrast to **5**–**8**, **17** is generated by the condensation of two (C_{15}) **6** units. This condensation pattern is known as a tail-to-tail (Fig. 13b) linkage. The other polyprenyl diphosphates **5**–**8** exhibit only head-to-tail linkages (Fig. 13b).

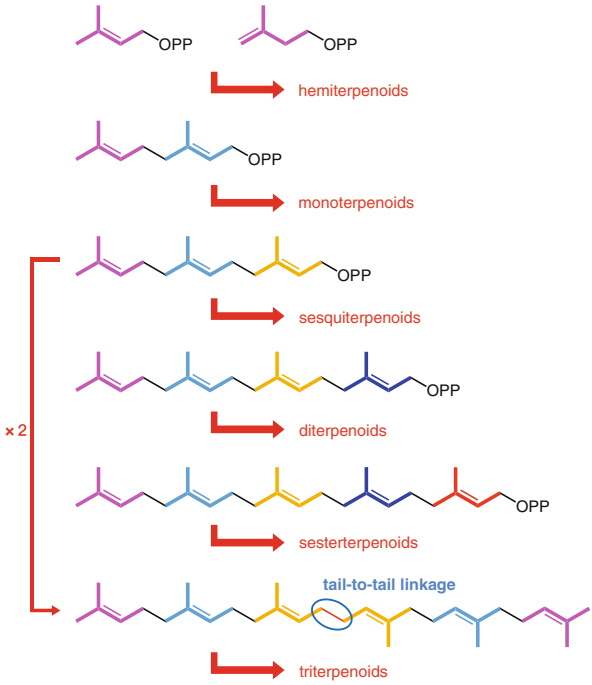


Fig. 12 Classification of the terpenoids

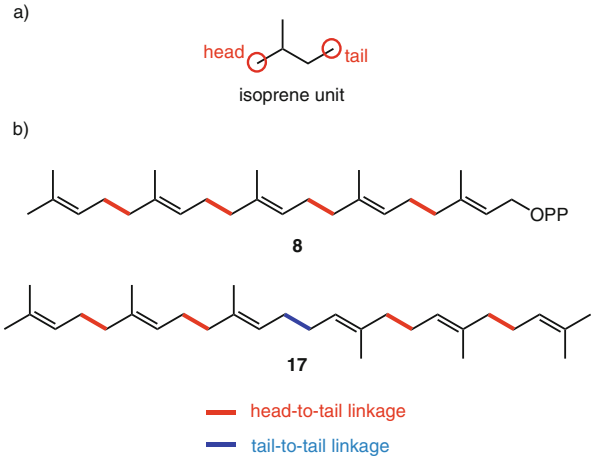


Fig. 13 (**a**) The "head" and "tail" positions in the isoprene unit. (**b**) Compound **8** is formed only by the "head-to-tail" condensation of isoprene units, while **17** is formed not only by the "head-to-tail" linkage but also by the "tail-to-tail" linkage

2.3 Natural Products Confused with Sesterterpenoids

Since all genuine sesterterpenoids should be derived from GFPP (**8**), the basic carbon skeletons of many sesterterpenoids are composed of 25 carbon atoms. However, it should be noted that not all compounds with basic carbon skeletons consisting of 25 carbon atoms are sesterterpenoids. Herein, we introduce examples of natural products that could be confused with sesterterpenoids. When determining whether a compound is a sesterterpenoid, it is essential to consider its biosynthetic origin.

2.3.1 Meroterpenoids

One example of natural products that could be confused with the sesterterpenoids is a group of meroterpenoids containing a C_{10} polyketide moiety (e.g., preterretonin A (**18**), protoaustinoid A (**19**), and andrastin E (**20**)) (Fig. 14) [15]. There are 25 carbon atoms in the basic carbon skeletons of these compounds. However, they are not biosynthesized via **8**, but are generated from a C_{15} terpenoid moiety and a C_{10} polyketide moiety. These C_{15} and C_{10} moieties are combined in their biosynthesis to form the C_{25} basic carbon skeleton.

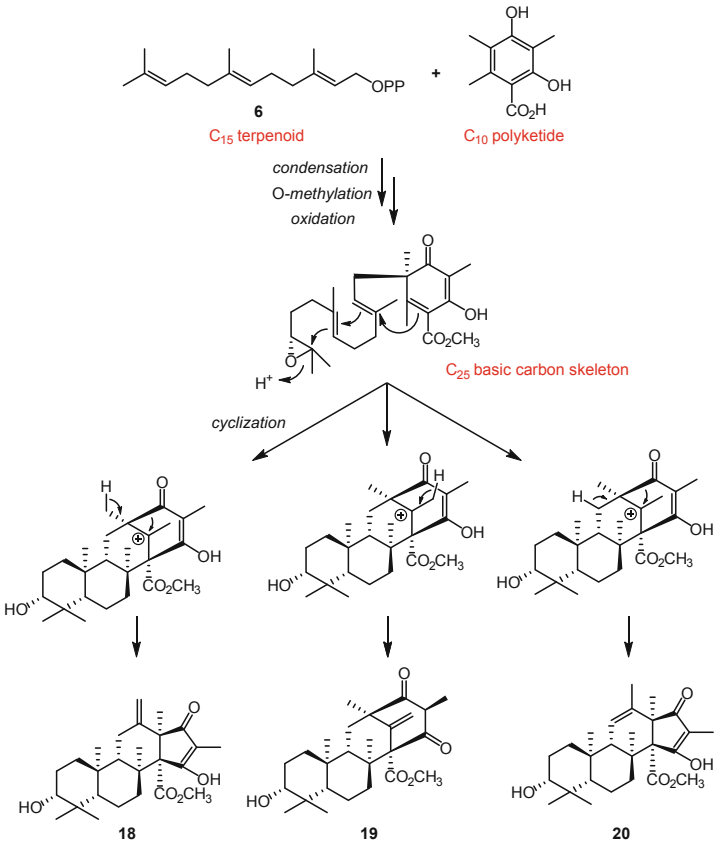


Fig. 14 Biosynthesis of **18**–**20**. In their basic carbon skeletons, there are 25 carbons. However, they are not sesterterpenoids

2.3.2 Highly Branched Isoprenoids

Compound **21** is a highly branched isoprenoid produced by the diatom *Rhizosolenia setigera* [16]. Five isoprene units are found readily in its structure (Fig. 15). Thus, **21** is a member of the terpenoids, and 25 carbon atoms exist in its basic carbon skeleton. However, **21** is not a sesterterpenoid, since **21** is not derived from the C_{25} polyprenyl diphosphate **8**, but from (C_{10}) **5** and (C_{15}) **6** (Fig. 16).

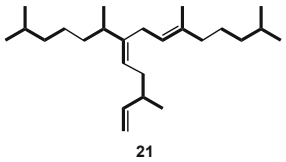


Fig. 15 Structure of **21**. The structure of **21** has five isoprene units, but **21** is not a sesterterpenoid. The isoprene units are shown by bold lines

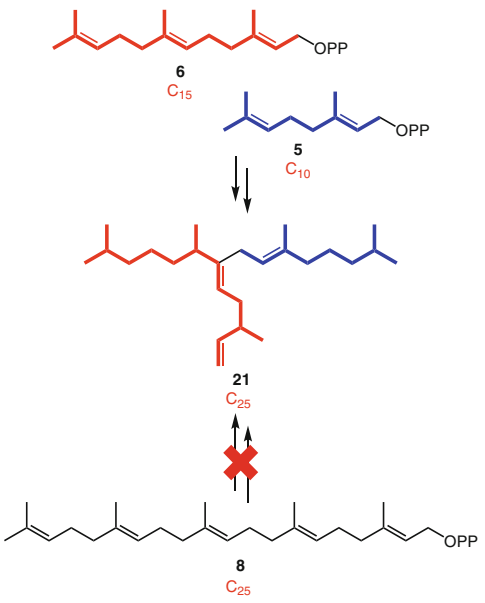


Fig. 16 Putative biosynthesis pathway of **21**. Compound **21** is biosynthesized from **5** and **6**, but not from **8**

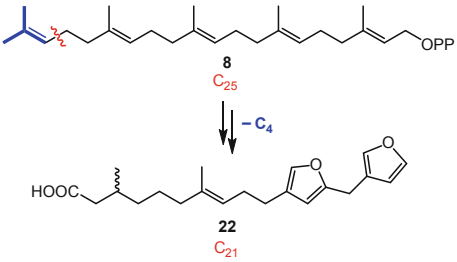


Fig. 17 Compound **22** is considered to be generated from **8**. The C_4 partial structure, which is shown by bold blue lines in **8**, is removed by the degradation reaction during the biosynthesis of **22**

2.3.3 Other Notable Points

The examples shown in Sects. 2.3.1 and 2.3.2 suggest that not all compounds with 25 carbon atoms are sesterterpenoids. However, it should also be noted that the basic carbon skeletons of some sesterterpenoids are composed of fewer than 25 carbons, due to a degradation reaction during their biosynthesis. For example, even though ircinin-3 (**22**) from the sponge *Ircinia oros* possesses only 21 carbon atoms, **22** is a sesterterpenoid (Fig. 17) [17].

3 Linear Sesterterpenoids

The linear sesterterpenoids do not possess a carbocyclic moiety. Thus, the terpene cyclases are not involved in their biosynthesis. The C_{25} polyprenyl chain of GFPP (**8**) is directly modified by tailoring enzymes to form a variety of linear sesterterpenoids.

One of the simplest linear sesterterpenoids is geranylfarnesol (**23**), discovered from the wax of the scale insect *Ceroplastes albolineatus* [18]. Another example of a simple linear sesterterpenoid is geranylnerolidol (**24**) from the fungus *Cochliobolus heterostrophus* [19]. The putative biosynthesis pathways of **23** and **24** should not be complicated, since the elimination of the diphosphate moiety and the attack of H_2O should be sufficient to form **23** and **24** from **8** (Fig. 18).

Actually, **23** and **24** are the simplest examples, and in many cases, further tailoring reactions occur to generate more functionalized linear sesterterpenoids. In spite of their simple basic carbon skeletons, many kinds of linear sesterterpenoids, especially from marine organisms, have been reported.

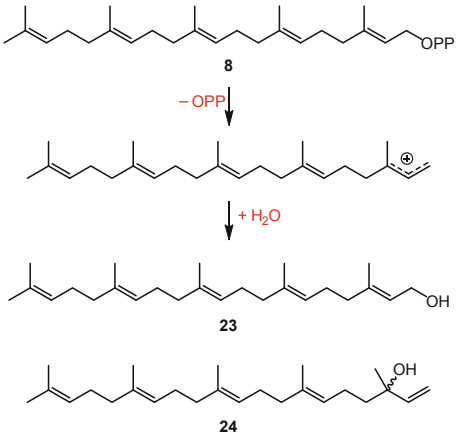


Fig. 18 Putative biosynthesis pathway of geranylfarnesol (**23**) and geranylnerolidol (**24**)

3.1 Linear Sesterterpenoids with a Furan Ring Moiety

A furan ring moiety is observed frequently in the structures of the linear sesterterpenoids. However, in almost all cases, the enzymes responsible for the formation of the furan moiety of the linear sesterterpenoids have not been identified. One example of a possible pathway for the biosynthesis of the furan skeleton is shown in Fig. 19. Other pathways for the formation of the furan ring could also be proposed as shown in Fig. 20.

As examples of linear sesterterpenoids with a furan ring moiety, furospongin-3 (**25**) and furospongin-4 (**26**) were isolated from the marine sponge *Spongia officinalis* (Plate 1) (Fig. 21) [17]. Another example is idiadione (**27**), which was discovered in a different sponge, *Spongia idia* (Fig. 21) [20]. An epoxyfuranosesterterpene carboxylic acid (**28**) was isolated from a Western Australian sponge *Spongia* sp. [21]. These linear sesterterpenoids possess one furan ring moiety in their structures. In addition, other tailoring reactions (e.g., oxidation, reduction, methyl ester formation) also seem to occur in their biosynthesis.

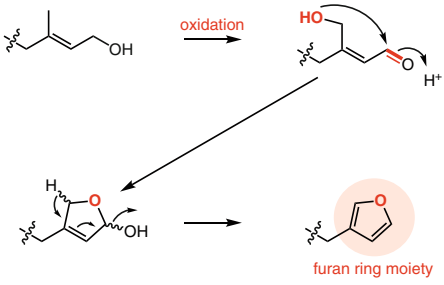


Fig. 19 One example of the proposed pathways for the formation of the furan moiety

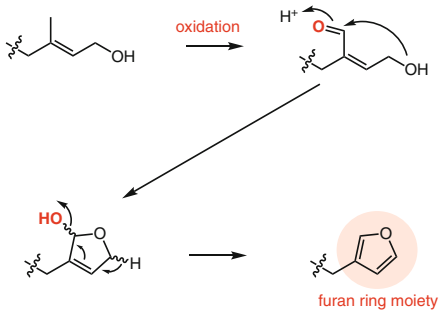


Fig. 20 Another pathway for the formation of the furan moiety

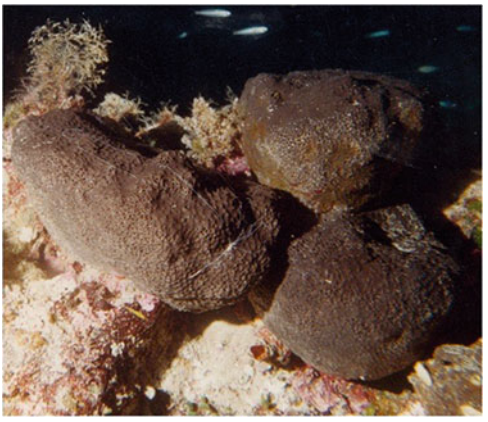


Plate 1 *Spongia officinalis*, Greece. Photograph courtesy E. Voultsiadou et al., Creative Commons 2.5

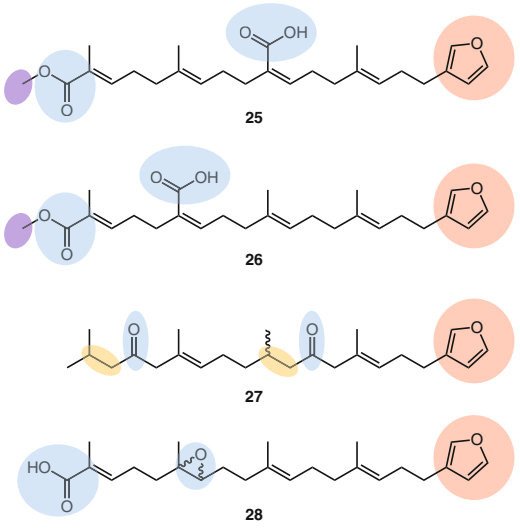


Fig. 21 Structures of **25**–**28**. The furan ring moieties are shown in red circles. The other functional groups, generated by oxidation, reduction, and methyl ester formation, are shown in blue, orange, and purple, respectively

3.2 *Linear Sesterterpenoids with a 2-Furanone Moiety*

Linear sesterterpenoids with a 2-furanone moiety also exist. The formation of the 2-furanone moiety should be similar to that of the furan ring moiety. Two possible pathways are shown in Figs. 22 and 23.

Two linear sesterterpenoids with a 2-furanone moiety, **29** and **30,** were isolated from the Caribbean sponge *Thorecta horridus* (Fig. 24) [22]. In particular, **29** possesses potent inflammatory activity, inducing histamine release (in vitro), and causes edema in rat paws (in vivo).

Compound **29** has also been reported from the Australian sponge *Luffariella geometrica*, and designated as luffarin Q [23]. Luffarin R (**31**) was also isolated from the same sponge (Fig. 25) [23]. Compound **31** possesses a γ-butyrolactone moiety in addition to the 2-furanone moiety.

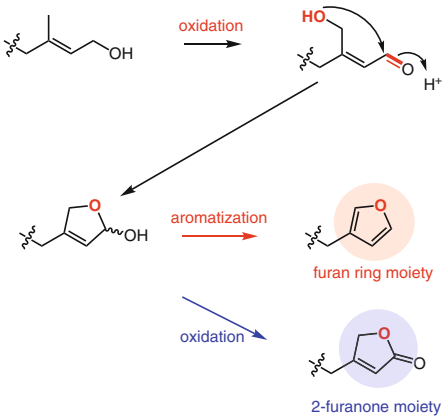


Fig. 22 Formation of the 2-furanone moiety

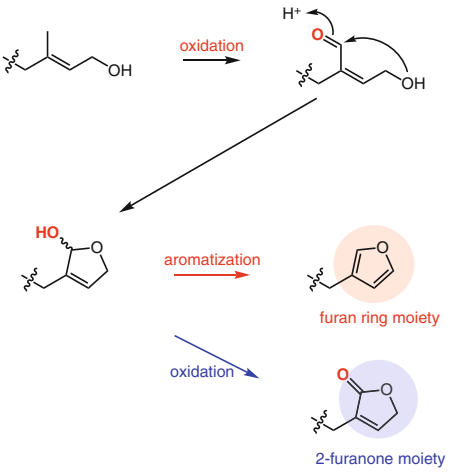


Fig. 23 An alternative pathway for the formation of the 2-furanone moiety

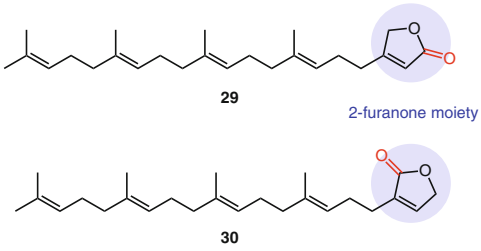


Fig. 24 Structures of **29** and **30**. The 2-furanone moieties are highlighted by blue circles

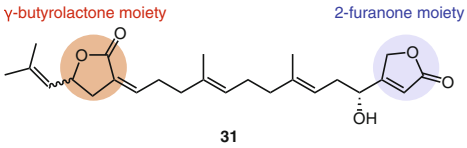


Fig. 25 Structure of luffarin R (**31**), which possesses not only the 2-furanone moiety but also a γ-butyrolactone moiety

3.3 Linear Sesterterpenoids with a Tetronic Acid Moiety

The tetronic acid moiety is present in numerous linear sesterterpenoids, and many of them exhibit bioactivities. The tetronic acid moiety seems to be generated by an oxidation of the 2-furanone moiety (Fig. 26).

For example, **32** was isolated from the Australian sponge *Psammocinia* sp. (Fig. 27) [24] and has antimicrobial activity. A similar compound, isopalinurin (**33**), was reported from the South Australian sponge, *Dysidea* sp. (Fig. 27) [25]. Compound **33** is known as a moderate protein phosphatase inhibitor. In addition to the tetronic acid moiety, **32** and **33** also possess a furan ring moiety.

Variabilin (**34**), an antimicrobial linear sesterterpene with a tetronic acid moiety (Fig. 28) [26], was isolated from the Okinawan sponge, *Amphidmedon* sp. Compound **34** possesses a stereocenter at the C-18 position, and the absolute configuration of this position was determined as (*S*) by the synthesis of the degradation product of **34** [26].

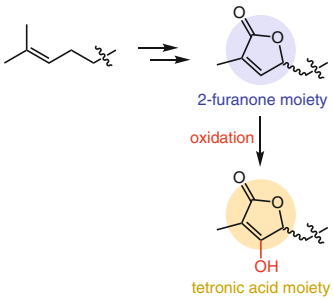


Fig. 26 Proposed pathway for the formation of the tetronic acid moiety

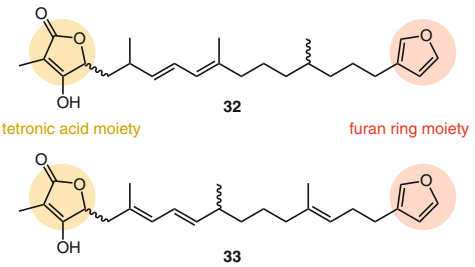


Fig. 27 Structures of **32** and **33**. The tetronic acid and furan ring moieties are highlighted by orange and red circles, respectively

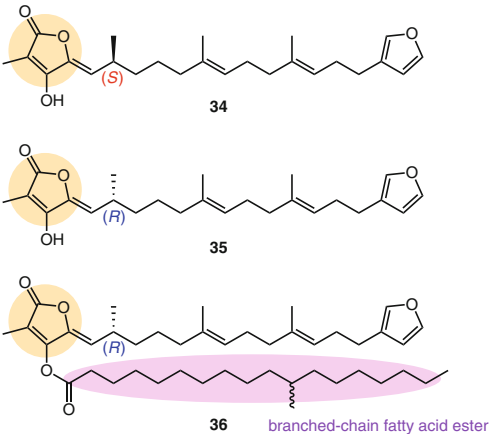


Fig. 28 Structures of **34**–**36**. The tetronic acid and branched-chain fatty acid ester are highlighted by orange and purple circles, respectively

An enantiomer of **34**, (18*R*)-variabilin (**35**), was isolated from the Caribbean sponge *Ircinia felix* (Fig. 28) [27]. Together with **35**, variabilin 11-methyloctadecanoate (**36**), a branched-chain fatty acid ester of **35**, was also isolated [28].

Compounds **32**–**36** possess not only a tetronic acid moiety but also a furan ring moiety. Actually, many linear sesterterpenoids with a tetronic acid moiety have a furan ring moiety, and some of them possess more than one furan ring moiety in their chemical structures. For example, spongionellin (**37**) [29], dehydrospongionellin (**38**) [29], ircinin-1 (**39**) [30, 31], and ircinin-2 (**40**) [30, 31] have two furan ring moieties, in addition to a tetronic acid moiety (Fig. 29). Compounds **37** and **38** are from a Japanese sponge, *Spongionella* sp., and both inhibit the cell division of fertilized starfish (*Asterina pectinifera*) eggs. Compounds **39** and **40** were isolated from the sponge *Ircinia oros*, collected in the Bay of Naples along the south-western coast of Italy [30], and another sponge *Ircinia* sp., collected from the Island of Bora Bora in French Polynesia [31].

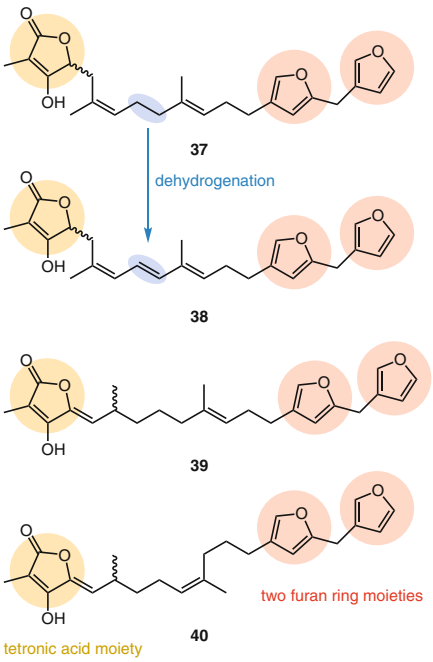


Fig. 29 Structures of **37**–**40**. The tetronic acid and furan ring moieties are highlighted by orange and red circles, respectively. Compounds **37**–**40** possess two furan ring moieties and one tetronic acid moiety

3.4 Degraded Linear Sesterterpenoids

As mentioned in Sect. 2.3.3, the numbers of carbon atoms in some sesterterpenoids are less than 25, because of degradation reactions in their biosynthesis. Herein, we introduce the "C_{21}" and "C_{24}" linear sesterterpenoids.

3.4.1 "C_{21}" Linear Sesterterpenoids

The C_{21} linear sesterterpenoids are one of the largest groups among the degraded linear sesterterpenoids. The C_{21} linear sesterterpenoids are considered to arise from the cleavage of the tetronic acid moiety, which was introduced in Sect. 3.3. This hypothesis is supported by the co-occurrence of the C_{21} linear sesterterpenoids (e.g. **22**, ircinin-4 (**41**)) and the corresponding linear sesterterpenoids with a tetronic acid moiety (e.g., **39** and **40**) (Figs. 17 and 30) [17]. A proposed mechanism of the degradation reaction is shown in Fig. 31 [1, 17]. Some sesterterpenoids with a tetronic acid moiety (e.g., **39** and **40**) possess a double bond, which is attached to the tetronic acid moiety (Figs. 30 and 31). Thus, when this tetronic acid moiety becomes an opened form, a reactive α-dicarbonyl moiety is generated, and the α-dicarbonyl moiety is cleaved. For example, a hydroperoxide compound, which could be formed by autoxidation, is capable of cleaving an α-dicarbonyl compound [32]. However, this is just one possible way, and further studies are required to reveal the mechanism leading to the formation of the C_{21} linear sesterterpenoids.

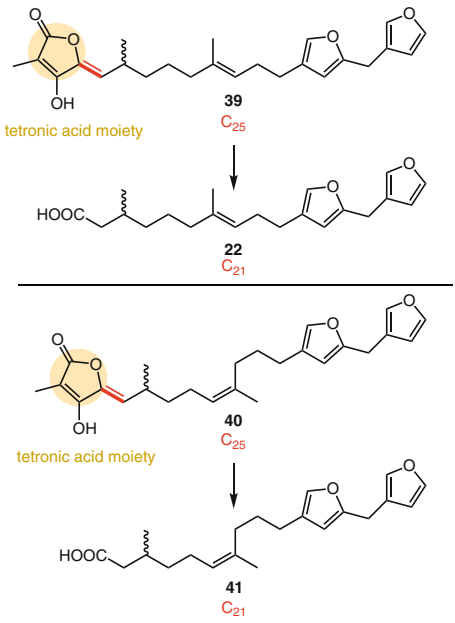


Fig. 30 Comparison of the structures of **22**, **41**, **39**, and **40**, which were all isolated from the same marine sponge, *Ircinia oros*. The double bonds attached to the tetronic acid moiety are highlighted by the bold red line. Compounds **22** and **41** are considered to be generated by the cleavage of **39** and **40**, respectively. The structure of **22** is also shown in Fig. 17, and the structures of **39** and **40** are also shown in Fig. 29

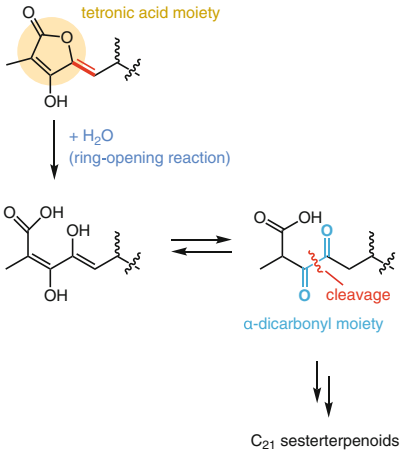


Fig. 31 Proposed mechanism leading to the formation of the C_{21} linear sesterterpenoids. Double bonds attached to the tetronic acid moiety are emphasized by bold red lines

Interestingly, many of the C_{21} linear sesterterpenoids possess furan ring moieties at both ends of their structures. For example, untenospongin C (**42**), obtained from an Okinawan sponge *Hippospongia* sp. (Fig. 32) [33], exhibited cytotoxicity against murine lymphoma L1210 cells (in vitro experiment). Another example is isonitenin (**43**) from the sponge *Spongia officinalis* collected at O Grove, Pontevedra, Spain (Fig. 32) [34]. Anhydrofurospongin-1 (**44**) [35] and furospongin-1 (**45**) [36] have been found in both the *Spongia officinalis* and *Hippospongia communis* sponges,

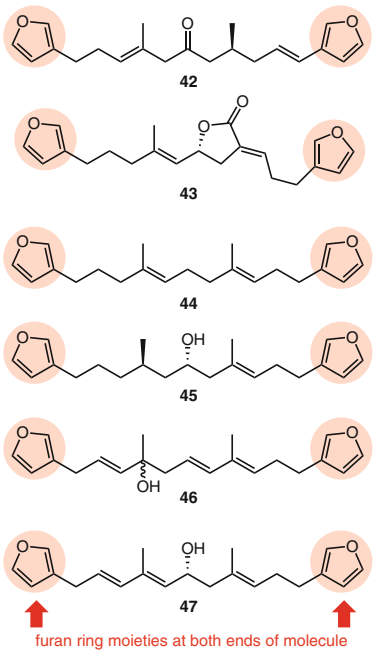


Fig. 32 Structures of **42**–**47**. These are C_{21} linear sesterterpenoids, with the furan ring moiety at both ends of their structures

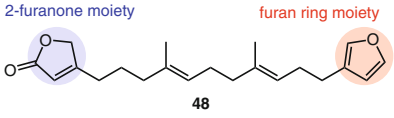


Fig. 33 Structure of furospongolide (**48**), which possesses one furan ring moiety and one 2-furanone moiety at the ends of the molecule

which were collected in the Bay of Naples, Italy (Fig. 32). In addition, **46** has been reported from a sponge *Spongia* sp. collected in Western Australia [37], and tetradehydrofurospongin-1 (**47**) has been found in both the *Leiosella* sp. and *Spongia* sp. sponges (Fig. 32) [37, 38].

On the other hand, furospongolide (**48**), from the sponge *Dysidea herbacea* (Fig. 33) [39], possesses one furan ring moiety and one 2-furanone moiety at the ends of the molecule.

3.4.2 "C_{24}" Linear Sesterterpenoids

The C_{24} linear sesterterpenoids are also considered to be formed from the linear sesterterpenoids with a tetronic acid moiety. In the case of the C_{24} linear

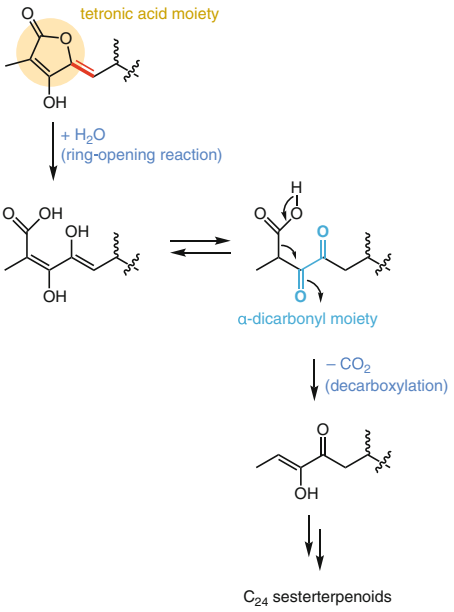


Fig. 34 Proposed mechanism leading to the formation of the C_{24} linear sesterterpenoids

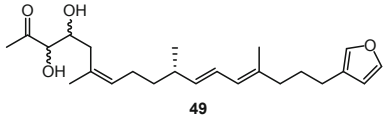


Fig. 35 Structure of sarcotin P (**49**)

sesterterpenoids, decarboxylation occurs to remove one carbon atom from the molecule (Fig. 34).

The C_{24} linear sesterterpenoids are exemplified by sarcotin P (**49**), from a sponge *Sarcotragus* sp. collected off Cheju Island, Korea (Fig. 35) [40]. Compound **49** might show toxicity to brine shrimp larvae, since this compound was isolated by a bioactivity-guided fractionation procedure that evaluated toxicity to brine shrimp larvae, although this was not confirmed.

Halogenated C_{24} linear sesterterpenoids also exist, and are exemplified by konakhin (**50**) [41], **51** [42], and **52** [42] (Fig. 36). Compound **50** was isolated from an unidentified sponge collected off the coast of Konakhè, near Dakar, Senegal, while **51** and **52** were obtained from a North Adriatic Sea collection of *Ircinia oros*.

A proposed mechanism leading to the formation of the halogenated C_{24} linear sesterterpenoids is shown in Fig. 37. In this pathway, after decarboxylation to form the C_{24} fundamental carbon skeleton, a halogenation reaction occurs.

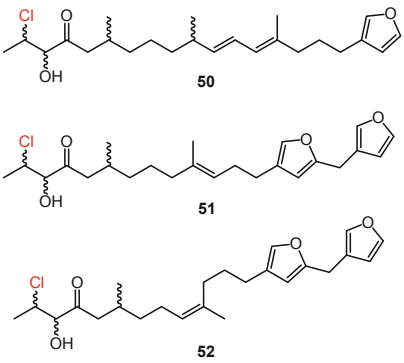


Fig. 36 Structures of **50**–**52**. Halogen atoms are shown in red

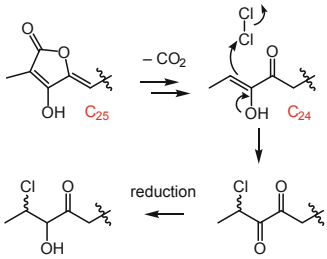


Fig. 37 Proposed mechanism leading to the formation of the halogenated C_{24} linear sesterterpenoids

3.5 Linear Sesterterpenoids Containing a Nitrogen Atom

All linear sesterterpenoids shown above (**22**–**52**) are composed of only carbon, hydrogen, and oxygen atoms. However, some linear sesterterpenoids contain a nitrogen atom, as exemplified by the ircinialactams (**53**–**55**) (Fig. 38) [43], purified

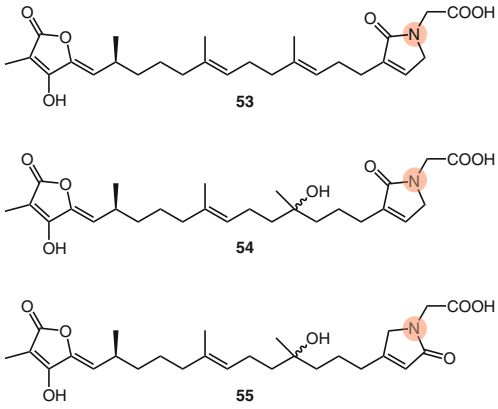


Fig. 38 Structures of the ircinialactams **53**–**55**, which contain a nitrogen atom in their structures

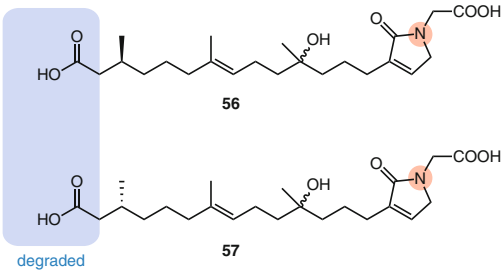


Fig. 39 Structures of **56** and **57**, which contain a nitrogen atom in their structures, and are members of the C_{21} linear sesterterpenoids

from Australian sponges of the family Irciniidae. From these sponges, the C_{21} degraded compounds, **56** and **57**, have also been isolated (Fig. 39) [43]. The proposed degradation mechanism is shown in Fig. 31. Compounds (**53**–**57**) are all modulators of glycine receptor chloride channels.

4 Monocarbocyclic Sesterterpenoids

In the biosynthesis of the monocarbocyclic sesterterpenoids, terpene cyclases are responsible for the formation of the carbocyclic moiety (Figs. 6 and 7). As mentioned above, there are two kinds of terpene cyclases, types 1 and 2. Each cyclase can generate a variety of characteristic basic carbon skeletons of sesterterpenoids.

4.1 Monocarbocyclic Sesterterpenoids Constructed by the Type 1 Terpene Cyclases

4.1.1 14-Membered Ring

Monocarbocyclic sesterterpenoids constructed by the type 1 terpene cyclases are relatively rare. They are exemplified by ceriferol (**58**), ceriferic acid (**59**), ceriferol-I (**60**), 13-methoxycericerene (**61**), and ceriferol-II (**62**), which possess 14-membered ring systems (Fig. 40) [44–49]. They were isolated from the wax of the scale insect *Ceroplastes ceriferus*. In fact, scale insects are known as good sources of sesterterpenoids.

The mechanism of the 14-membered ring formation by the type 1 terpene cyclases is shown in Fig. 41. The cyclization reaction is initiated by the heterolytic cleavage of the diphosphate moiety of **8**, and then the cyclization is finalized by the deprotonation or the attack of H_2O.

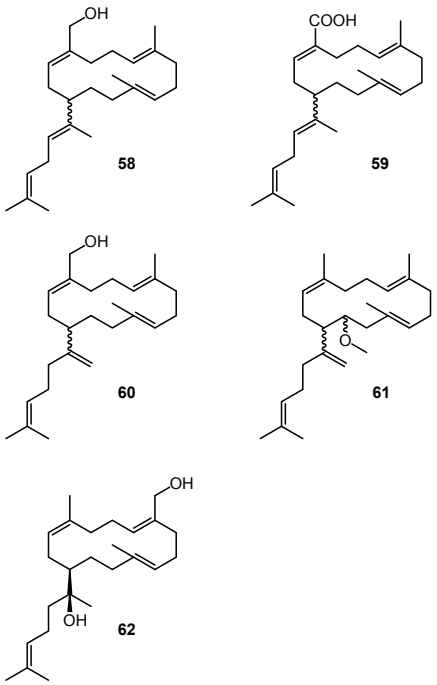


Fig. 40 Structures of **58**–**62**

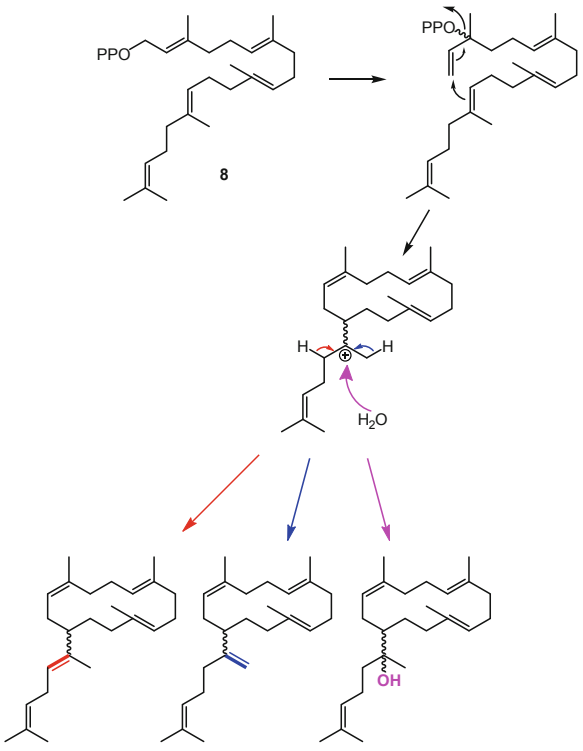


Fig. 41 The mechanism of 14-membered ring formation by the type 1 terpene cyclases

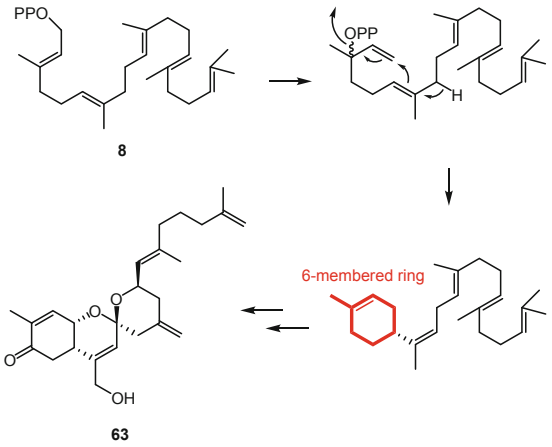


Fig. 42 Structure and formation of (–)-alotaketal A (**63**)

4.1.2 6-Membered Ring

The compound (−)-alotaketal A (**63**), which possesses a 6-membered ring system, was reported from a marine sponge, *Hamigera* sp., collected in Papua New Guinea (Fig. 42) [50], and is known to activate the cAMP cell signaling pathway. Its biosynthesis originates from geranylfarnesyl diphosphate (GFPP) (**8**).

4.2 Monocarbocyclic Sesterterpenoids Constructed by the Type 2 Terpene Cyclases

4.2.1 6-Membered Ring

The type 2 terpene cyclases also generate 6-membered ring systems. Moreover, most of the monocarbocyclic sesterterpenoids constructed by the type 2 terpene cyclases possess a 6-membered ring. For example, **64** [51], **65** [51], luffariolide H (**66**) [52], and luffariolide J (**67**) [52] have been reported (Fig. 43). Compounds **64** and **65** were isolated from the sponge *Hyrtios* cf. *erecta*, collected at Nananu-I-Ra, Fiji. Compounds **66** and **67** were reported from an Okinawan marine sponge, *Luffariella* sp., and exhibit antimicrobial activities against *Staphylococcus aureus*, *Bacillus subtilis*, and *Micrococcus luteus*.

Acantholide A (**68**) [53] and acantholide B (**69**) [53] also possess 6-membered rings (Fig. 44). They were isolated from an Indonesian sponge, *Acanthodendrilla* sp., and **69** has antimicrobial activities against *Staphylococcus aureus* and *Bacillus subtilis*.

A cyclization mechanism for the formation of the 6-membered rings of **64**–**69** is shown in Fig. 45. Since their basic carbon skeletons are formed by the type 2 terpene cyclases, the cyclization reaction is initiated by the protonation of the double bond of geranylfarnesyl diphosphate (GFPP) (**8**).

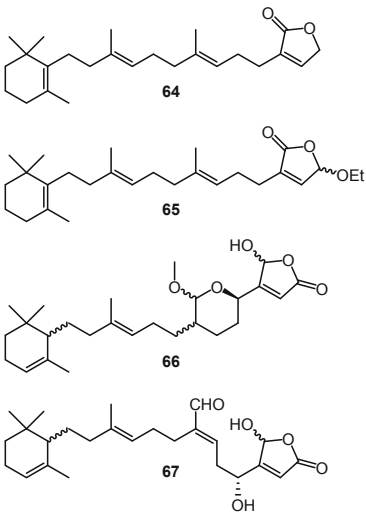


Fig. 43 Structures of **64**–**67**

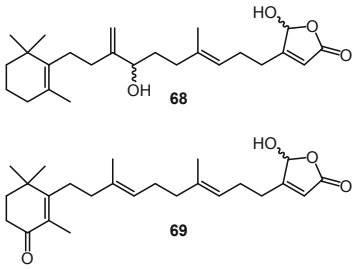


Fig. 44 Structures of acantholide A (**68**) and acantholide B (**69**)

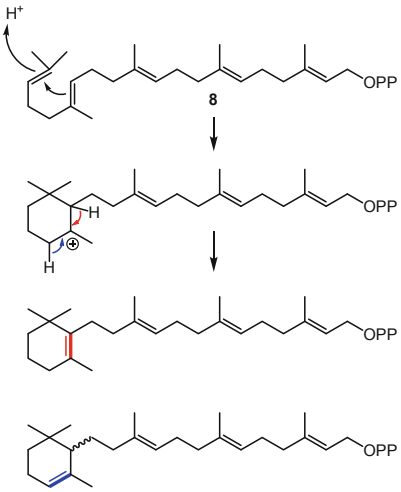


Fig. 45 Cyclization mechanism for the formation of the 6-membered rings of **64**–**69**

Another monocarbocyclic sesterterpenoid with a 6-membered ring is cyclolinteinone (**70**), isolated from the Caribbean sponge *Cacospongia linteiformis* (Fig. 46) [54]. The positions of the methyl groups on the 6-membered ring differentiate **70** from **64**–**69**. Compound **70** can downregulate the protein expression of an inducible NO synthase and cyclo-oxygenase-2 via the inhibition of NF-κB activation.

A cyclization reaction leading to the formation of the basic carbon skeleton of **70** is shown in Fig. 47. In this proposed mechanism, a 1,2-hydride shift and a 1,2-alkyl shift occur to change the position of the methyl group on the 6-membered ring, and then deprotonation finalizes the reaction.

The structures of cyclolinteinol (**71**) and cyclolinteinol acetate (**72**) are similar to that of **70** (Fig. 48) [55]. They were isolated from the Caribbean sponge *Cacospongia* cf. *linteiformis*.

Fig. 46 Structure of **70**

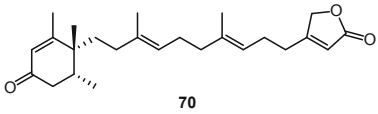


Fig. 47 Cyclization reaction leading to the formation of the basic carbon skeleton of **70**

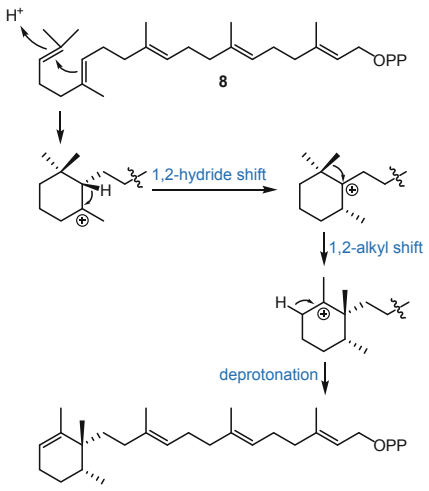
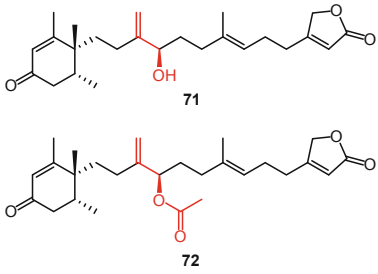


Fig. 48 Structures of cyclolinteinol (**71**) and cyclolinteinol acetate (**72**)



4.2.2 5-Membered Ring

Monocarbocyclic sesterterpenoids with 5-membered ring systems also exist. However, they are rare, as compared with the monocarbocyclic sesterterpenoids with 6-membered ring systems. Such sesterterpenoids are exemplified by 25-acetoxyluffariellins A and B (**73** and **74**) (Fig. 49) [56], isolated from the sponge *Luffariella variabilis* from the Great Barrier Reef, Australia. Notably, they are unstable in the sponge tissue, even though they are stable after isolation. Thus, the sponge apparently has some enzymes that can convert or degrade these compounds.

A proposed mechanism for the formation of the 5-membered ring system is shown in Fig. 50.

A different type of 5-membered ring is seen in the structures of acantholide D (**75**) and acantholide E (**76**) (Fig. 51) [53]. Actually, **75** and **76** were co-isolated with **68** and **69** from the Indonesian sponge, *Acanthodendrilla* sp. [53], and **76** exhibited cytotoxicity against the L5187Y mouse lymphoma cell line. A proposed cyclization mechanism for generating the basic carbon skeleton of **75** and **76** starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 52.

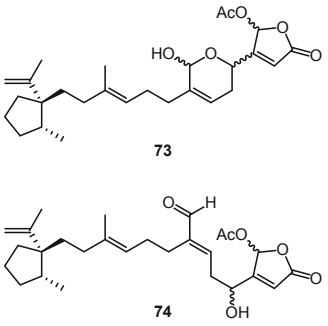


Fig. 49 Structures of 25-acetoxyluffariellins A (**73**) and B (**74**)

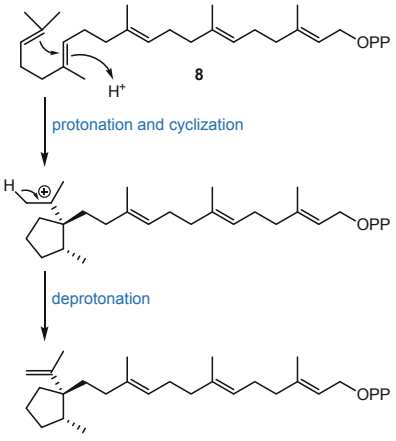


Fig. 50 Proposed mechanism for the formation of the 5-membered rings of **73** and **74**

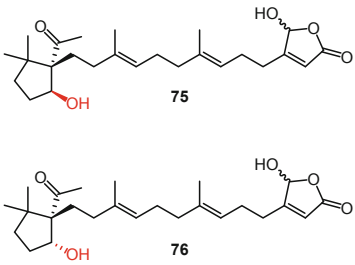


Fig. 51 Structures of acantholide D (**75**) and acantholide E (**76**)

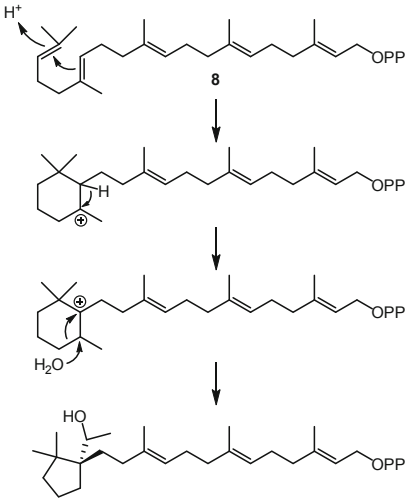


Fig. 52 Proposed cyclization mechanism for generating the basic carbon skeletons of acantholide D (**75**) and acantholide E (**76**)

5 Bicarbocyclic Sesterterpenoids

5.1 Bicarbocyclic Sesterterpenoids Constructed by the Type 1 Terpene Cyclases

5.1.1 15/5-Membered Ring System

Bicarbocyclic sesterterpenoids, constructed by the type 1 terpene cyclases, have been reported from fungi. Terpestacin (**77**), a representative compound with a 15/5-membered ring system (Fig. 53) [57, 58], has been isolated from the fungi *Arthrinium* sp. [57] and *Phomopsis* sp. XZ-26 [58]. Compound **77** reportedly inhibits tumor angiogenesis by binding to the 13.4-kDa subunit of the mitochondrial complex III and suppresses hypoxia-induced reactive oxygen species production and cellular oxygen sensing [59].

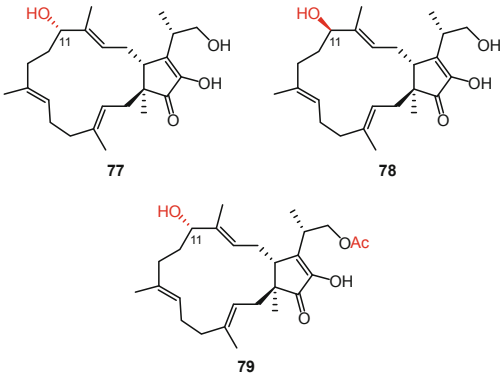


Fig. 53 Structures of **77**–**79**, which possess a 15/5-membered ring system

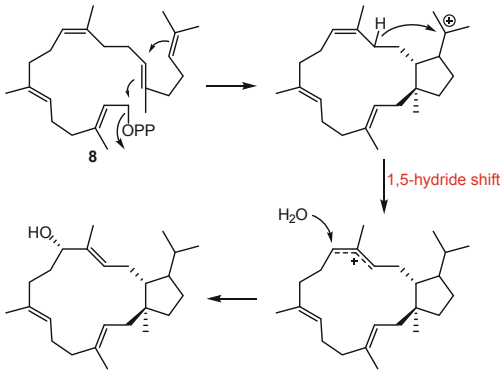


Fig. 54 Proposed cyclization mechanism for the formation of the 15/5-membered ring system

Interestingly, the compound known as "siccanol," isolated from the fungus *Bipolaris sorokiniana* NSDR-011, is also compound **77**. Even though "siccanol" was initially reported as 11-epiterpestacin (**78**), an epimer of **77** (Fig. 53) [60], the total synthesis of **78** revealed that "siccanol" was not **78**, but **77** [61].

Fusaproliferin (**79**), isolated from the fungus *Fusarium proliferatum*, also possesses the 15/5-membered ring system (Fig. 53) [62]. Compound **79** is an acetate ester of **77**, and the stereochemistry of **79** was established by a synthesis approach [63]. A proposed cyclization mechanism for the formation of the 15/5-membered ring system starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 54. This cyclization involves a 1,5-hydride shift, which is seen frequently in the type 1 cyclization reactions of sesterterpenoids.

5.1.2 12/6-Membered Ring System

Emericellene A (**80**) and related compounds have been reported from an endophytic fungus, *Emericella* sp. AST0036, collected from a healthy leaf of the plant

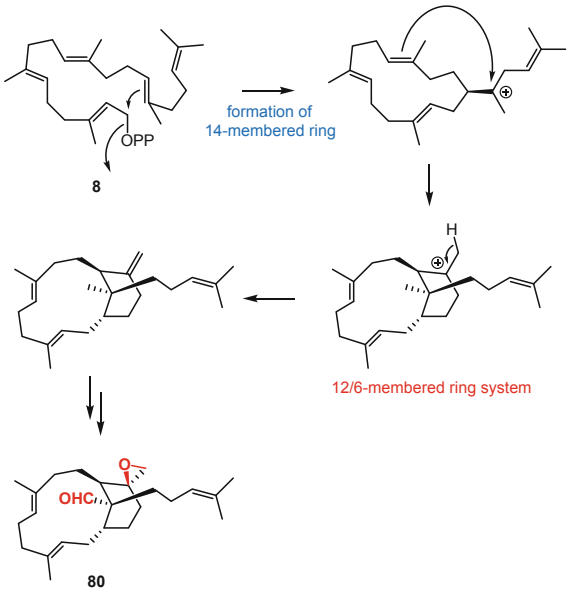


Fig. 55 Structure of mericellene A (**80**), and proposed cyclization mechanism for the formation of the 12/6-membered ring system

Astragalus lentiginosus (Fig. 55) [64]. Compound **80** possesses a 12/6-membered ring system. A proposed cyclization mechanism for generating the 12/6-membered ring system originating in geranylfarnesyl diphosphate (**8**) is shown in Fig. 55, and the formation of a 14-membered ring might be the first step in this reaction.

5.2 *Bicarbocyclic Sesterterpenoids Constructed by the Type 2 Terpene Cyclases*

The majority of bicarbocyclic sesterterpenoids constructed by the type 2 terpene cyclases possess 6/6-membered ring systems. An example of the 6/6-membered ring formation starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 56.

Salvimirzacolide (**81**), with a 6/6-membered ring system, was isolated from the aerial parts of the plant *Salvia mirzayanii* (Fig. 57) [65]. Another example is salvileucolide methyl ester (**82**), which reportedly exists in the aerial parts of two Iranian *Salvia* species plants (Fig. 57) [66]. The structures of both **81** and **82** have been confirmed by X-ray crystallography.

In some cases, an alkyl shift occurs in the middle of the cyclization reaction. For example, the basic carbon skeleton of halisulfate-3 (**83**) is different from those of **81** and **82** (Fig. 58) [67]. Compound **83** is one of the metabolites of a sponge, *Ircinia* sp., which was collected in the Philippines. The cyclization reaction for the formation of the basic carbon skeleton of **83** starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 59.

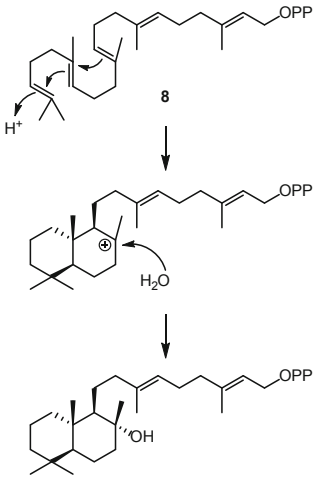


Fig. 56 One example of the 6/6-membered ring formation

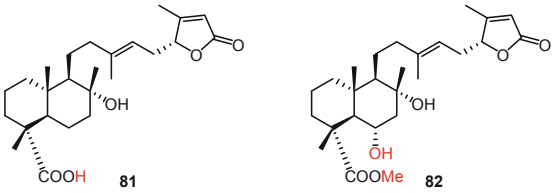


Fig. 57 Structures of salvimirzacolide (**81**) and salvileucolide methyl ester (**82**)

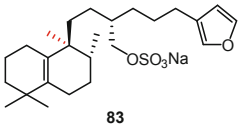


Fig. 58 Structure of halisulfate-3 (**83**)

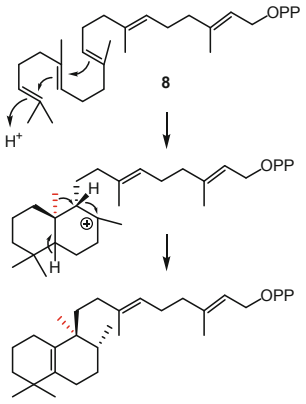


Fig. 59 Proposed cyclization mechanism to generate the basic carbon skeleton of **83**

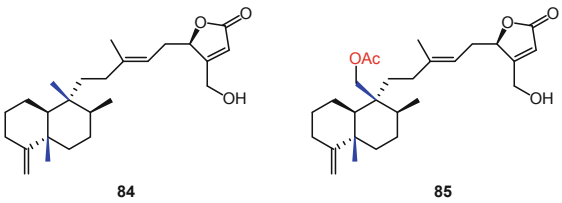


Fig. 60 Structures of thorectandrol A (**84**) and thorectandrol B (**85**)

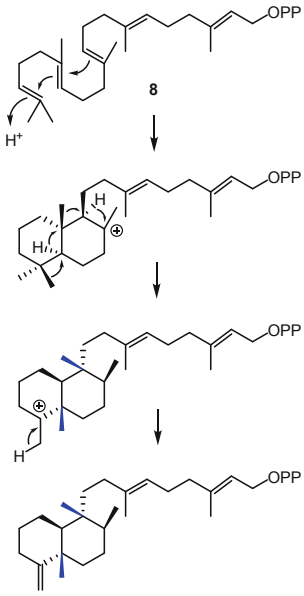


Fig. 61 Proposed cyclization mechanism for generating the basic carbon skeleton of **84** and **85**

Another example of an alkyl shift is found in the formation of thorectandrol A (**84**) and thorectandrol B (**85**) (Fig. 60) [68]. Compounds **84** and **85** were isolated from the sponge *Thorectandra* sp. collected in Palau, and both **84** and **85** inhibited the growth of the MALME-3M and MCF-7 cancer cells. A proposed cyclization mechanism for the formation of the basic carbon skeletons of **84** and **85** starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 61. During this reaction, the alkyl shift occurs twice.

5.3 Other Bicarbocyclic Sesterterpenoids

Even though most of the carbocyclic moieties of sesterterpenoids are formed by the terpene cyclases, some carbocyclic structures are generated in a different manner. For example, the bicarbocyclic ring systems of (+)-wistarin (**86**) [69, 70] and (−)-wistarin (**87**) [71] would not be formed by the typical terpene cyclases (Fig. 62). Compound **87** is an enantiomer of **86**. Compound **86** was found in the sponge *Ircinia*

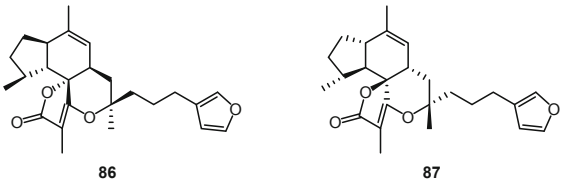


Fig. 62 Structures of (+)-wistarin (**86**) and (−)-wistarin (**87**)

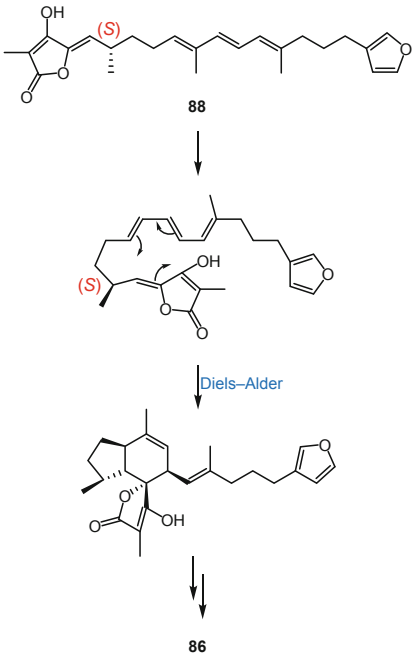


Fig. 63 Proposed mechanism to generate the basic carbon skeleton of **86**

wistarii from the Great Barrier Reef, Australia [69], while **87** was isolated from a sponge, *Ircinia* sp., collected at Hurghada, Red Sea, Egypt [71].

A proposed biosynthesis of **86** is shown in Fig. 63. Actually, **86** seems to be biosynthesized via a linear sesterterpenoid **88**, and the Diels–Alder reaction might occur to form the bicarbocyclic moiety of **86**. In the same manner, **87** should be formed via *ent*-**88**.

The biosynthesis pathway of ircinianin sulfate (**89**) (Fig. 64) [72] should be similar to that of **86**. Compound **89** is an unstable metabolite from the sponge *Ircinia wistarii*, collected from the Great Barrier Reef, Australia.

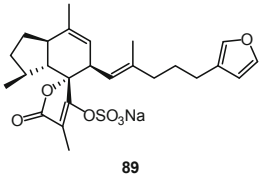


Fig. 64 Structure of ircinianin sulfate (**89**)

6 Tricarbocyclic Sesterterpenoids

A greater number of carbocyclic moieties increases the complexity of the structures of sesterterpenoids. Thus, sesterterpenoids with more than three carbocyclic rings exhibit considerable complexity. Moreover, the diversity of the basic carbon skeleton is also increased. Especially the type 1 terpene cyclases have great potential to generate various kinds of structures with more than three carbocyclic rings.

6.1 Tricarbocyclic Sesterterpenoids Constructed by the Type 1 Terpene Cyclases

6.1.1 5/8/5-Membered Ring System

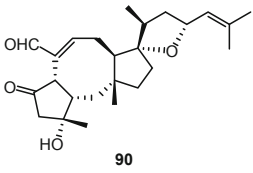
A tricarbocyclic sesterterpenoid with a 5/8/5-membered ring system (**90**), from the fungi *Ophiobolus miyabeanus* and *Helminthosporium oryzae*, was found initially and characterized by Japanese [73] and Italian [74] groups, independently. The Japanese group designated this compound as ophiobolin, while the Italian group named it cochliobolin. In order to avoid confusion, a joint paper from these two groups was published, and this compound was renamed ophiobolin A (**90**) (Fig. 65) [75].

Many derivatives of **90** have been reported, and they are called ophiobolin-type sesterterpenoids. Examples of the ophiobolin-type sesterterpenoids, ophiobolins B-M (**91**–**102**), are shown in Figs. 66 and 67 [19, 76–86]. Notably, the ophiobolin-type sesterterpenoids are known as bioactive compounds. For example, **90**, **91**, **92**, and **100** exhibited activity toward leukemia cells with the induction of apoptosis, at nanomolar concentrations [87].

A proposed cyclization mechanism for the formation of the 5/8/5-membered ring system starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 68. In this reaction, an 11/5-membered ring system first would be generated. Subsequently, a 1,5-hydride shift and the formation of another 5-membered ring would occur.

Epimers of many ophiobolins have also been reported, as exemplified by 6-epiophiobolin A (**103**) [88, 89], 6-epiophiobolin C (**104**) [85], 6-epiophiobolin I (**105**) [82], and 6-epiophiobolin K (**106**) [83] (Fig. 69).

Many ophiobolin-type sesterterpenoids have been described, and even now, the number of ophiobolin-type sesterterpenoids is increasing. For example, the new



90

Fig. 65 Structure of ophiobolin A (**90**)

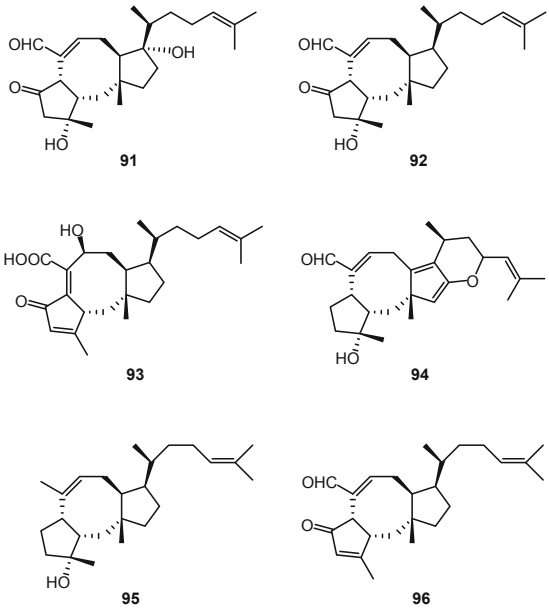


Fig. 66 Structures of **91**–**96**

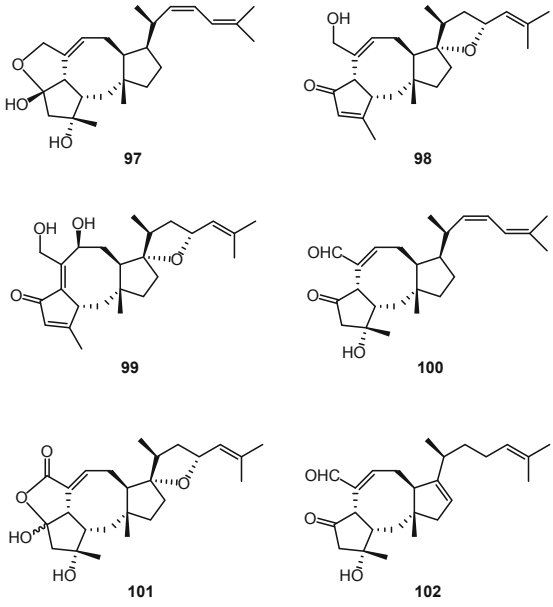


Fig. 67 Structures of **97**–**102**

ophiobolin-type sesterterpenoids, asperophiobolins A (**107**), and ten other related new sesterterpenoids were reported in 2019 (Fig. 70) [90]. They were isolated from cultures of a mangrove endophytic fungus, *Aspergillus* sp. ZJ-68.

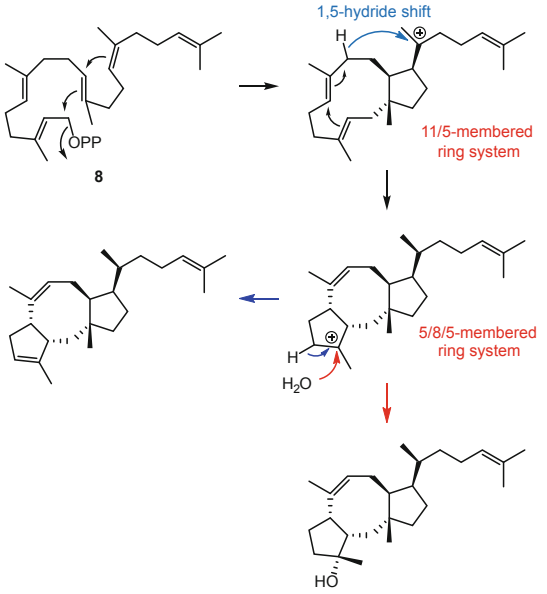


Fig. 68 Proposed cyclization mechanism for the formation of the 5/8/5-membered ring system

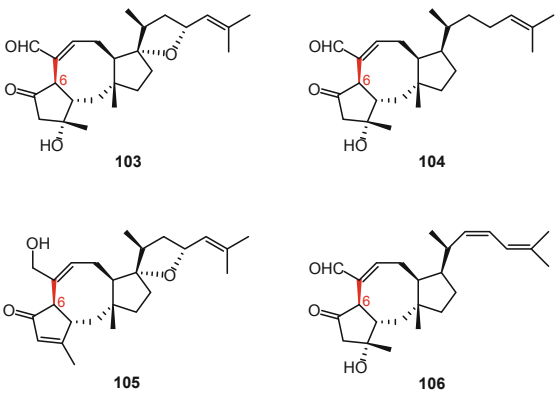


Fig. 69 Structures of **103**–**106**

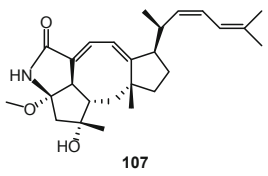


Fig. 70 Structure of asperophiobolin A (**107**)

6.1.2 5/12/5-Membered Ring System

Sesterterpenoids with 5/12/5-membered ring systems have been found in both a fungus and a plant. Variculanol (**108**) was isolated from the fungus *Aspergillus variecolor* [91], while nitinol (**109**) was reported from the plant *Gentianella nitida*, which is used in Peruvian folk medicine (Fig. 71) [92]. Compound **109** exhibits activity to enhance IL-2 gene expression in a human T cell line. A possible cyclization mechanism for the formation of the 5/12/5-membered ring system starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 72.

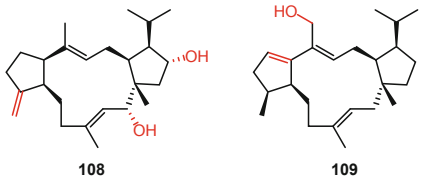


Fig. 71 Structures of variculanol (**108**) and nitinol (**109**)

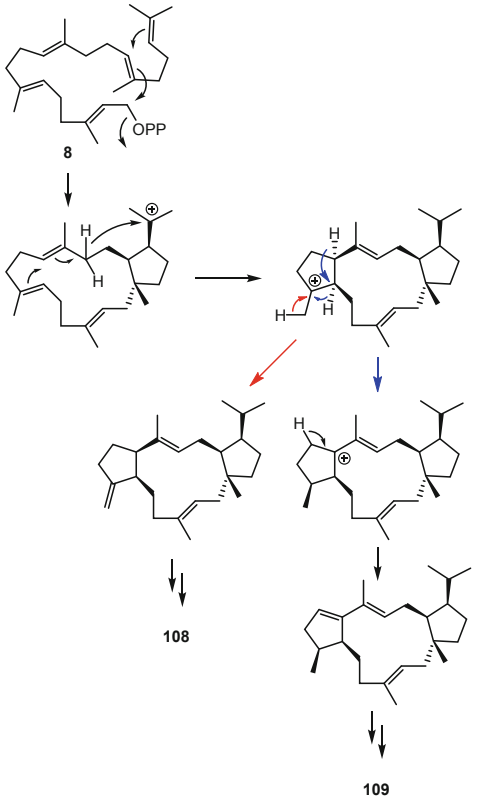


Fig. 72 Proposed cyclization mechanism for the formation of the 5/12/5-membered ring system

6.1.3 11/6/5-Membered Ring System

Two groups of sesterterpenoids possess 11/6/5-membered ring systems. One is exemplified by flocerol (**110**) and floceric acid (**111**) from the secretions of the scale insect *Ceroplastes floridensis*, an orchard pest collected in Osaka, Japan (Fig. 73) [93]. The other is exemplified by stellatic acid (**112**) (Fig. 73) [94], isolated from the metabolites of the fungus *Aspergillus stellatus*.

A proposed cyclization mechanism for the formation of the 11/6/5-membered ring systems of **110** and **111** starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 74. At first, an 11/5-membered ring system is generated. Importantly, the configuration of one of the two double bonds in the 11-membered ring is (*Z*). Next, a ring expansion from a 5-membered ring to a 6-membered ring occurs, and at the

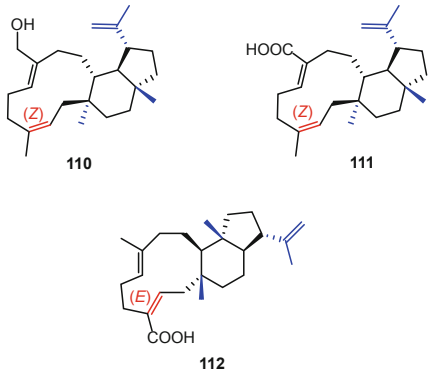


Fig. 73 Structures of **110**–**112**

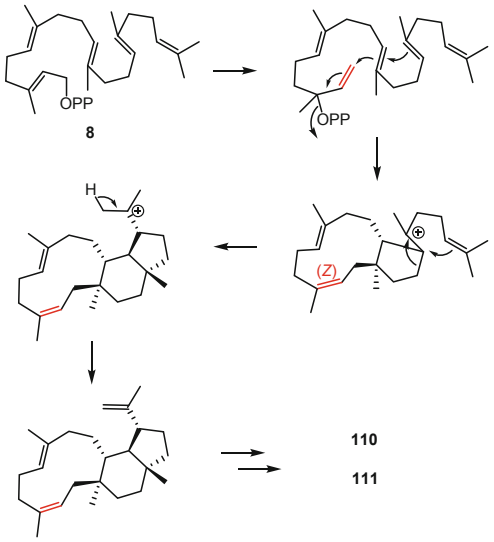


Fig. 74 Proposed cyclization mechanism for the formation of the 11/6/5-membered ring system of **110** and **111**

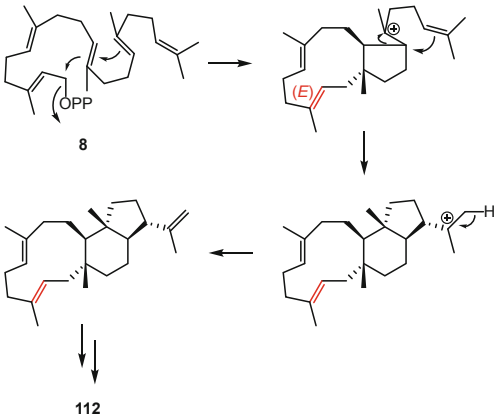


Fig. 75 Proposed cyclization mechanism for the formation of the 11/6/5-membered ring system of **112**

same time, a new 5-membered ring is generated to form the 11/6/5-membered ring system. Subsequently, deprotonation occurs to finalize the cyclization reaction.

A cyclization reaction for generating the basic carbon skeleton of **112** starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 75. There are several differences between the reactions shown in Figs. 74 and 75. First, the configuration of both double bonds in the 11-membered ring is (*E*) in Fig. 75. Second, the ring expansion from the 5-membered ring to the 6-membered ring occurs in a different manner. These two differences result in the generation of two different types of 11/6/5-membered ring systems.

6.1.4 11/6/6-Membered Ring System

Floridenol (**113**) possesses an 11/6/6-membered ring (Fig. 76) [93] and was also isolated from the wax of the scale insect from which **110** and **111** were reported. The formation of the 11/6/6-membered ring system starting from geranylfarnesyl diphosphate (**8**) is illustrated in Fig. 77. The formation of **113** seems to have diverged from those of **110** and **111**.

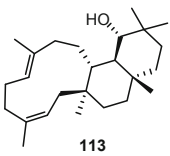


Fig. 76 Structure of floridenol (**113**)

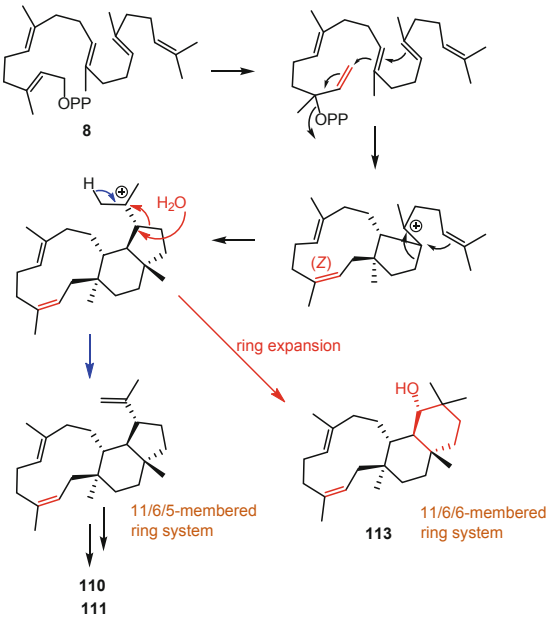


Fig. 77 Proposed cyclization mechanism for the formation of the 11/6/6-membered ring system of **113**

6.2 *Tricarbocyclic Sesterterpenoids Constructed by the Type 2 Terpene Cyclases*

6.2.1 6/6/6-Membered Ring Systems

Many tricarbocyclic sesterterpenoids constructed by the type 2 terpene cyclases exhibit 6/6/6-membered ring systems. For example, suvanine (**114**) [95] and lintenolide F (**115**) [96] possess the 6/6/6-membered ring system (Fig. 78). Compound **114** was isolated from a sponge, *Ircinia* sp., and its chemical structure has been confirmed by the X-ray crystallography of its degradation product [95], while **115** was isolated from a Caribbean sponge, *Cacospongia* cf. *linteiformis* [96].

A proposed cyclization mechanism for the formation of the carbon skeleton of **114** starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 79a, while the cyclization reaction for that of **115** is illustrated in Fig. 79b.

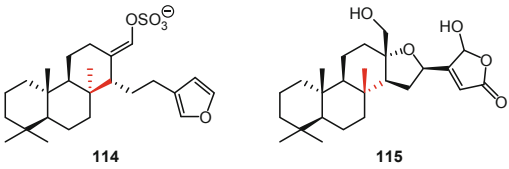


Fig. 78 Structures of suvanine (**114**) and lintenolide F (**115**)

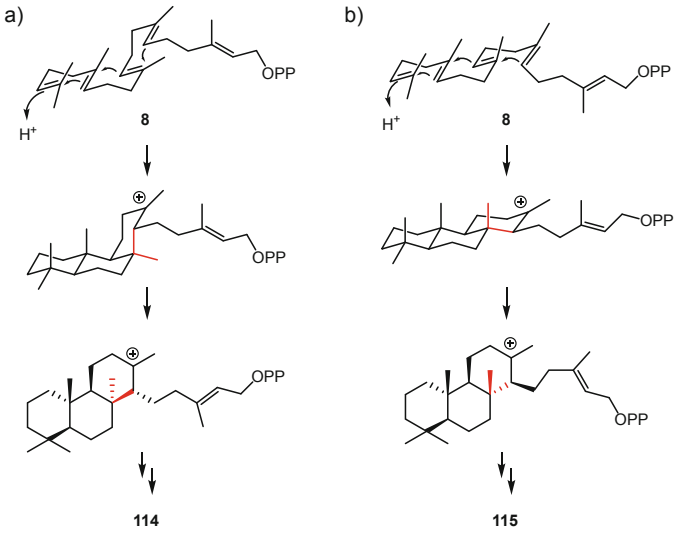


Fig. 79 Proposed cyclization mechanisms for the formation of the 6/6/6-membered ring systems of (**a**) **114** and (**b**) **115**

6.2.2 6/6/5-Membered Ring System

Hyrtiosal (**116**), which possesses a 6/6/5-membered ring system, was isolated from the Okinawan marine sponge *Hyrtios erectus*, collected at a coral reef off Ishigaki Island, Okinawa, Japan (Fig. 80) [97]. Compound **116** has been shown to inhibit the proliferation of KB cells. Its formation starting from geranylfarnesyl diphosphate (**8**) is illustrated in Fig. 80.

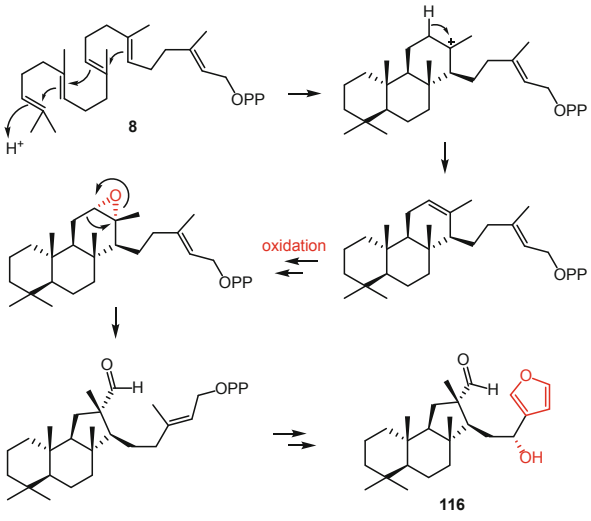


Fig. 80 Structure of hyrtiosal (**116**), and possible cyclization mechanism for the formation of the 6/6/5-membered ring system

6.2.3 3/6/6-Membered Ring System

Cacospongionolide (**117**), with a 3/6/6-membered ring system (Fig. 81) [98, 99], was isolated as a potent antitumor and ichthyotoxic agent from the sponge *Cacospongia mollior*, collected in the Northern Adriatic Sea. The chemical structure of **117** has been confirmed by the X-ray crystallography of its acetyl derivative.

A proposed cyclization mechanism for the formation of the 3/6/6-membered ring system starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 82. One methyl group of **8**, highlighted with a red color in Fig. 82, might be involved in the formation of the cyclopropane ring of **117**.

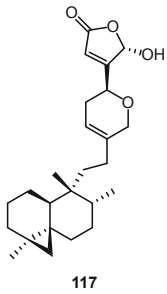


Fig. 81 Structure of cacospongionolide (**117**)

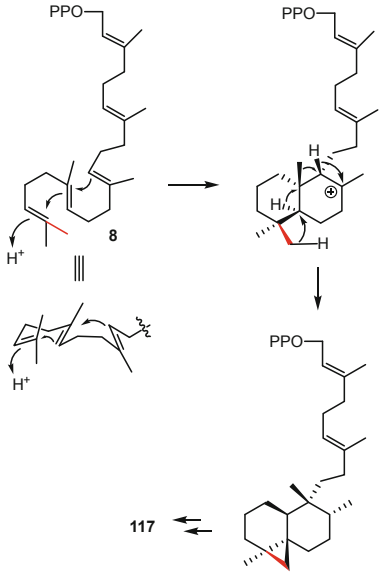


Fig. 82 Proposed cyclization mechanism for the formation of the 3/6/6-membered ring system of **117**

6.2.4 6/5/4-Membered Ring System

Lintenone (**118**) is a representative sesterterpenoid with a 6/5/4-membered ring system (Fig. 83) [100]. Compound **118** was isolated from a Caribbean sponge, *Cacospongia* cf. *linteiformis*, and possesses potent ichthyotoxicity and antifeedant properties.

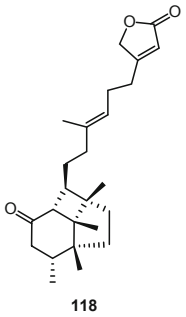


Fig. 83 Structure of lintenone (**118**)

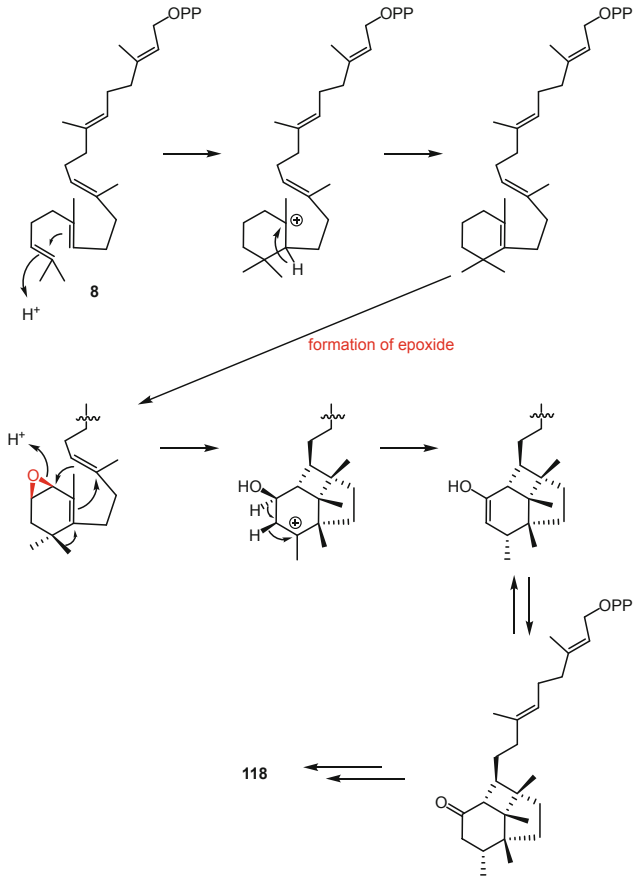


Fig. 84 Proposed cyclization mechanism for the formation of the 6/5/4-membered ring system of **118**

One possible mechanism for the formation of the 6/5/4-membered ring system starting from geranylfarnesyl diphosphate (**8**) is shown in Fig. 84 [3]. In this proposal, the cyclization reactions occur twice to generate the characteristic 6/5/4-

membered ring system. After a 6-membered ring is formed by the first cyclization reaction, an epoxide might be generated by tailoring enzymes. The second cyclization reaction would then be initiated by the protonation of the epoxide.

6.3 *Tricarbocyclic Sesterterpenoids Constructed by Both Type 1 and 2 Terpene Cyclases*

In some sesterterpenoids, the type 1 and 2 terpene cyclases seem to work together to form the complex basic carbon skeleton, and many such sesterterpenoids have been isolated from marine organisms [101].

One example is ansellone A (**119**), isolated from the nudibranch *Cadlina luteromarginata* and a sponge, *Phorbas* sp. (Fig. 85) [102]. Analyses revealed that **119** activates the cAMP signaling pathway. In the proposed biosynthesis pathway, at first the type 1 cyclization starting from geranylfarnesyl diphosphate (**8**) occurs, and then the type 2 cyclization reactions form the basic carbon skeleton of **119** (Fig. 85) [101].

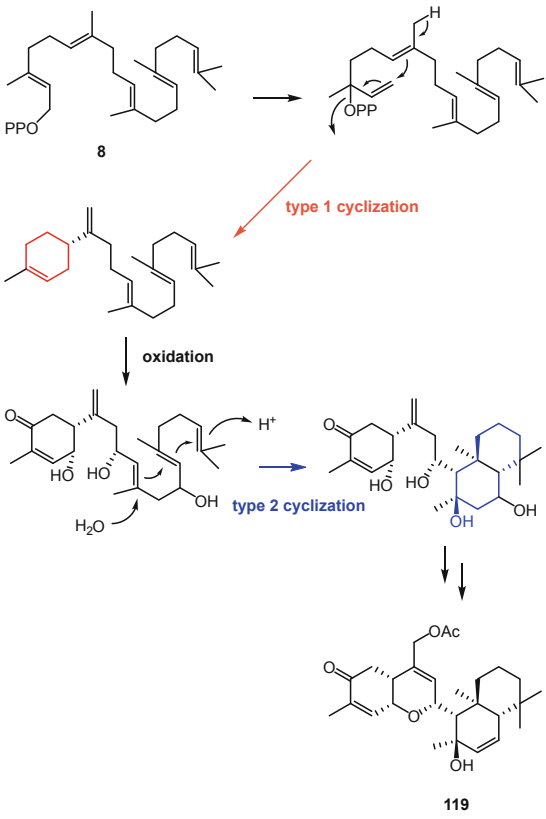


Fig. 85 Proposed biosynthesis pathway of ansellone A (**119**)

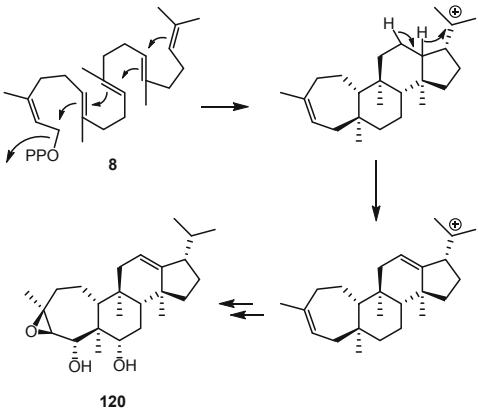


Fig. 86 Structure of aspergilloxide (**120**), and possible cyclization reaction for the formation of the 7/6/6/5-membered ring system

7 Tetracarbocyclic Sesterterpenoids

7.1 Tetracarbocyclic Sesterterpenoids Constructed by the Type 1 Terpene Cyclases

7.1.1 7/6/6/5-Membered Ring System

Aspergilloxide (**120**), isolated from a fungus, *Aspergillus* sp., has a 7/6/6/5-membered ring system (Fig. 86) [103]. A possible cyclization reaction to form the basic carbon skeleton starting from geranylfarnesyl diphosphate (**8**) is also shown in Fig. 86.

7.1.2 5/8/6/6-Membered Ring System

Asperterpenol A (**121**) and a derivative have been reported from a mangrove endophytic fungus, *Aspergillus* sp. 085242 (Fig. 87) [104]. Compound **121** is an acetylcholinesterase inhibitor. Their tetracarbocyclic skeletons would be formed starting from geranylfarnesyl diphosphate (**8**) as shown in Fig. 87.

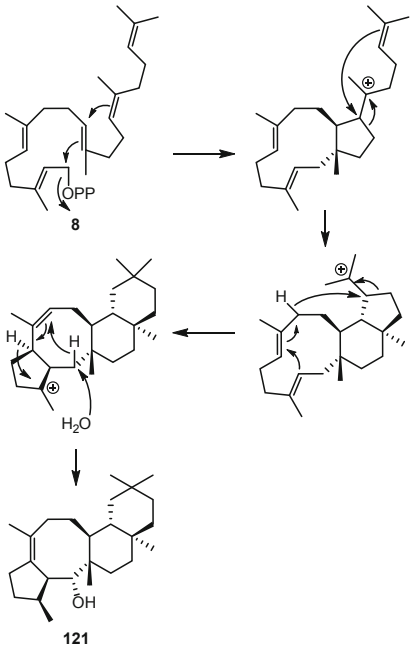


Fig. 87 Structure of asperterpenol A (**121**), and possible cyclization reaction for the formation of the 5/8/6/6-membered ring system

7.1.3 5/8/6/5-Membered Ring System

There are two types of 5/8/6/5-ring systems. One is exemplified by variecolin (**122**), which has been isolated from some fungi, including *Aspergillus variecolor* MF138 [105], *Emericella purpurea* [106], and *Emericella aurantio-brunnea* [107] (Fig. 88). Compound **122** possesses immunosuppressive activity, and the formation of its 5/8/6/5-membered ring system is shown in Fig. 88. In this reaction, an 11/6/5-membered ring system is first formed from geranylfarnesyl diphosphate (**8**), and then protonation occurs to start a second round of cyclization, and the 5/8/6/5-membered ring system is generated.

The other type of 5/8/6/5-membered ring systems is exemplified by aleurodiscal (**123**), from the corticioid fungus *Aleurodiscus mirabilis* [108], and nitidasin (**124**), from the plant *Gentianella nitida* [109, 110] (Fig. 89). The formation of the 5/8/6/5-membered ring systems of **123** and **124** is initiated by generating a 15/5-membered ring system (Fig. 89), while that of **122** starts from the generation of the 11/5-membered ring system (Fig. 88).

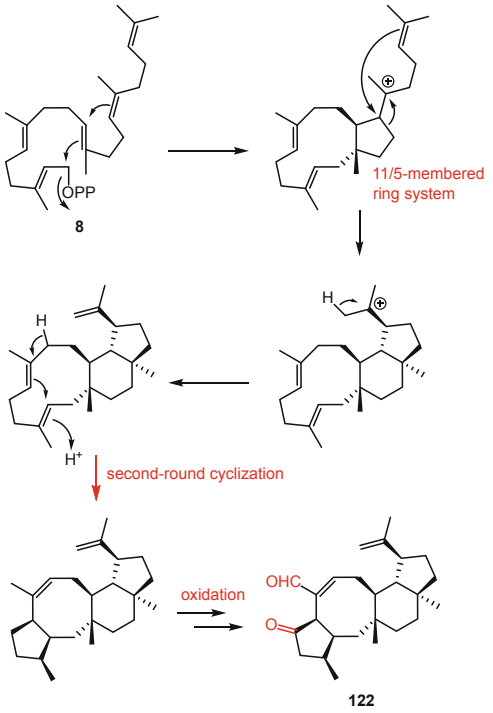


Fig. 88 Structure of variecolin (**122**), and possible cyclization reaction for the formation of the 5/8/6/5-membered ring system of **122**

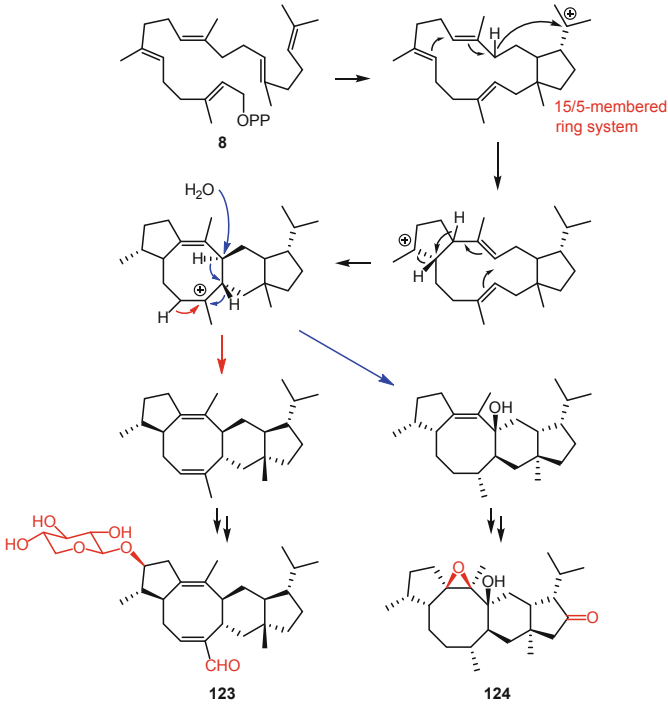


Fig. 89 Structures of aleurodiscal (**123**) and nitidasin (**124**), and possible cyclization reaction for the formation of the 5/8/6/5-membered ring systems of **123** and **124**

7.1.4 5/5/6/5- and 5/6/6/5-Membered Ring Systems

The 5/5/6/5-membered ring system is exemplified by mangicol A (**125**) [111], while the 5/6/6/5-membered ring system is found in the structure of neomangicol A (**126**) (Fig. 90) [112]. A proposed cyclization mechanism for the formation of the 5/5/6/5-membered ring systems is shown in Fig. 91. Since both **125** and **126** were isolated from the same fungus, *Fusarium heterosporum*, it is proposed that the 5/6/6/5-membered ring system of **126** is generated starting from geranylfarnesyl diphosphate (**8**) by the conversion of a precursor possessing the 5/5/6/5-membered ring system [111].

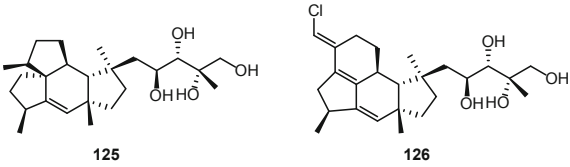


Fig. 90 Structures of mangicol A (**125**) and neomangicol A (**126**)

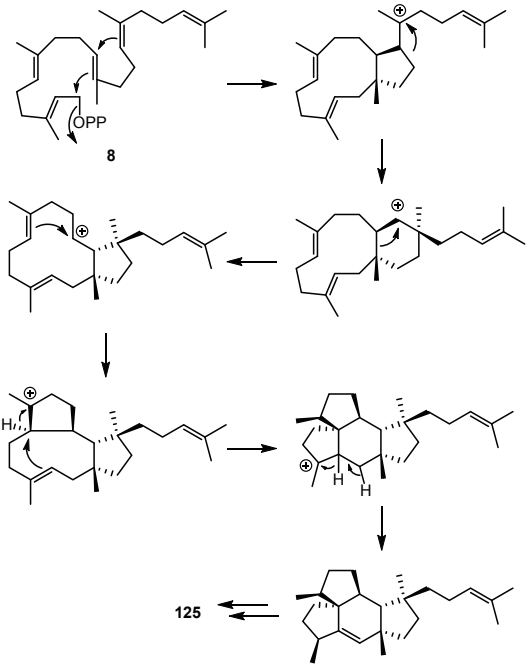


Fig. 91 Possible cyclization reaction for the formation of the 5/5/6/5-membered ring system of mangicol A (**125**)

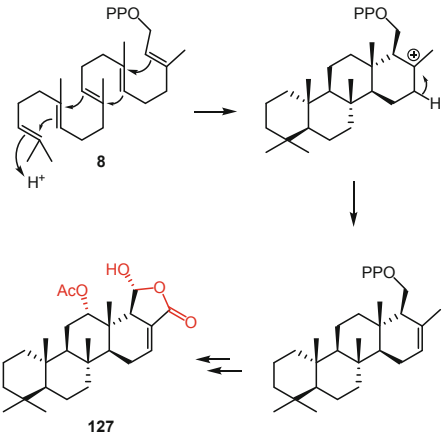


Fig. 92 Structure of scalarin (**127**), and possible cyclization reaction for the formation of the 6/6/6/6-membered ring system of **127**

7.2 *Tetracarbocyclic Sesterterpenoids Constructed by the Type 2 Terpene Cyclases*

7.2.1 6/6/6/6-Membered Ring System

Most tetracarbocyclic sesterterpenoids constructed by the type 2 terpene cyclases exhibit a 6/6/6/6-membered ring system and are among the most common sesterterpenoids. Scalarin (**127**) was the first of this type of compound to be isolated [113, 114]. The chemical structure of **127** and a cyclization mechanism for the formation of the 6/6/6/6-membered ring system starting from geranylfarnesyl diphosphate (**8**) are shown in Fig. 92.

7.2.2 6/6/5/7-Membered Ring System

Salmahyrtisol A (**128**) [115] and hippospongide A (**129**) (Fig. 93) [116] possess a 6/6/5/7-membered ring system. Compounds **128** and **129** were isolated from the sponges *Hyrtios erecta* from the Red Sea and *Hippospongia* sp. from coral reefs off the coast of Tai-tung, Taiwan, respectively. From these two sponges, **116** with a

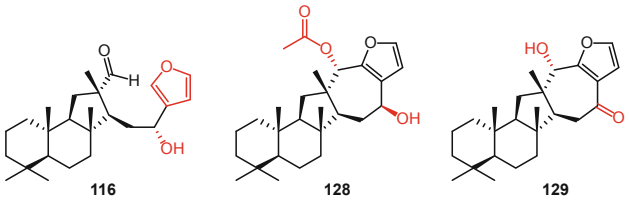


Fig. 93 Structures of **116**, **128**, and **129**. The structure of **116** is also shown in Fig. 80. Compound **116** is a possible intermediate of **128** and **129**

6/6/5-membered ring system has also been isolated. Considering the structural relationship among **128**, **129**, and **116**, **116** might be a biosynthetic intermediate of **128** and **129**.

8 Pentacarbocyclic Sesterterpenoids

Pentacarbocyclic sesterterpenoids are rare, and the complexity of their structures is quite high. In particular, the type 1 terpene cyclases are known to generate fascinating pentacarbocyclic skeletons.

8.1 Pentacarbocyclic Sesterterpenoids Constructed by the Type 1 Terpene Cyclases

8.1.1 5/6/5/6/5-Membered Ring System

Peniroquesine A (**130**) and its derivatives, which possess 5/6/5/6/5-membered ring systems, have been isolated from the fungus *Penicillium roqueforti* YJ-14 (Fig. 94) [117]. Compound **130** is a potent inhibitor of nitric oxide production in

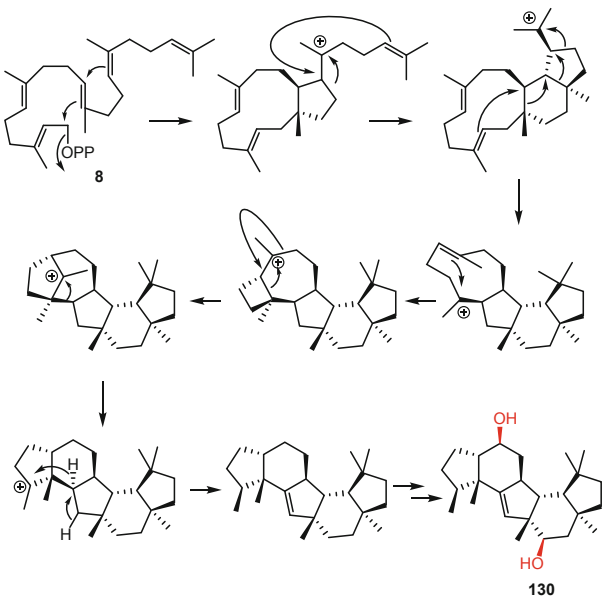


Fig. 94 Structure of peniroquesine A (**130**), and possible cyclization reaction for the formation of the 5/6/5/6/5-membered ring system

LPS-activated RAW264.7 macrophages. During the proposed cyclization reaction for the formation of the 5/6/5/6/5-membered ring system starting from geranylfarnesyl diphosphate (**8**), several complex rearrangements could occur (Fig. 94).

8.1.2 5/7/3/6/5-Membered Ring System

Asperterpenoid A (**131**), with a 5/7/3/6/5-membered ring system, has been isolated from a mangrove endophytic fungus, *Aspergillus* sp. 16-5c (Fig. 95) [118]. Compound **131** is a strong inhibitor of *Mycobacterium tuberculosis* protein tyrosine phosphatase B. Its formation from geranylfarnesyl diphosphate (**8**) is illustrated in Fig. 95.

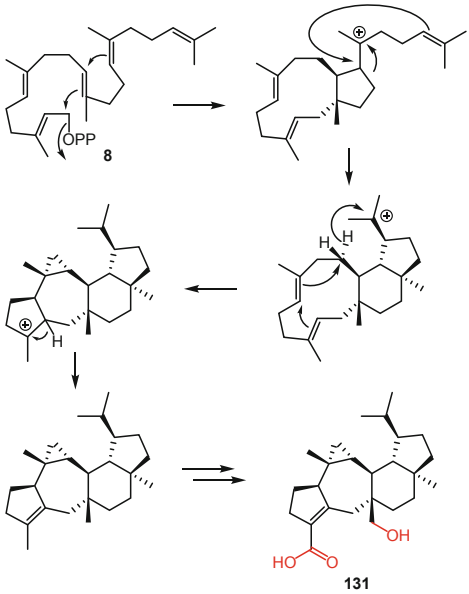


Fig. 95 Structure of asperterpenoid A (**131**), and possible cyclization reaction for the formation of the 5/7/3/6/5-membered ring system of **131**

8.1.3 5/3/7/6/5- and 5/4/7/6/5-Membered Ring Systems

Aspterpenacid A (**132**) [119] has a 5/3/7/6/5-membered ring system, while astellatol (**133**) [120] possesses a 5/4/7/6/5-membered ring system (Fig. 96). Compounds **132** and **133** were isolated from the fungi *Aspergillus terreus* H010 and *Aspergillus variecolor*, respectively. Proposed pathways for the formation of the 5/4/7/6/5- and 5/3/7/6/5-membered ring systems starting from geranylfarnesyl diphosphate (**8**) are also shown in Fig. 96.

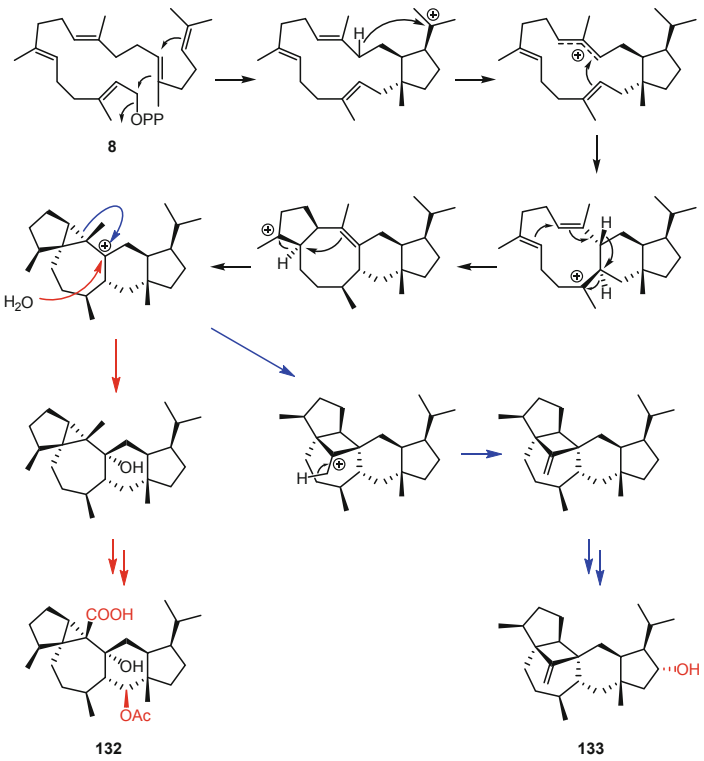


Fig. 96 Structures of **132** and **133**, and possible cyclization reactions for the formation of the basic carbon skeletons of **132** and **133**

8.1.4 5/5/5/6/5-Membered Ring System

Retigeranic acid A (**134**) [121, 122], retigeran-11-ol (**135**) [123], and 4-hydroxyretigeran-11-ol (**136**) [123] possess 5/5/5/6/5-membered ring systems, which originate from geranylfarnesyl diphosphate (**8**) (Fig. 97). Compounds **135** and **136** were isolated from the lichen *Leprocaulon microscopicum*. Compound **134** was isolated from lichens of the *Lobaria retigera* group (Plate 2), and **134** reportedly exists as a mixture with retigeranic acid B (**137**), an epimer of **134**, in Nature (Fig. 98) [124].

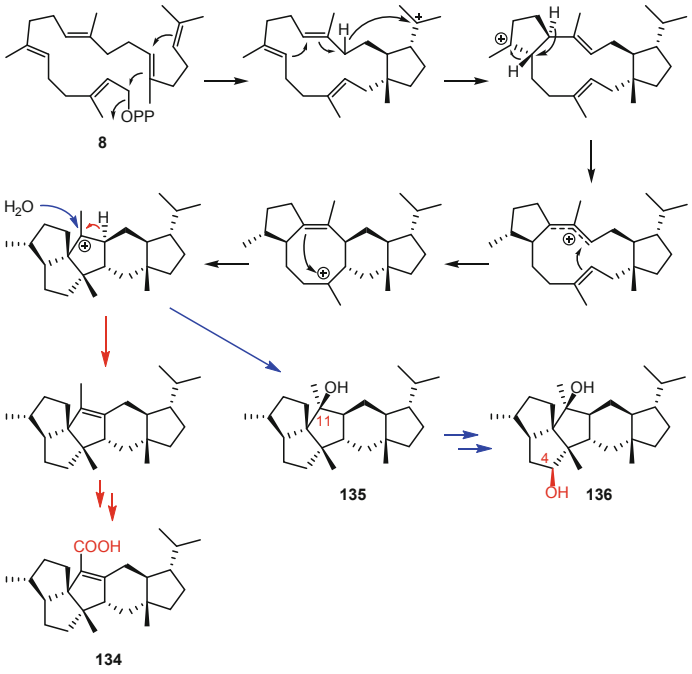


Fig. 97 Structures of **134**–**136**, and possible cyclization reactions for the formation of the basic carbon skeleton of **134**–**136**

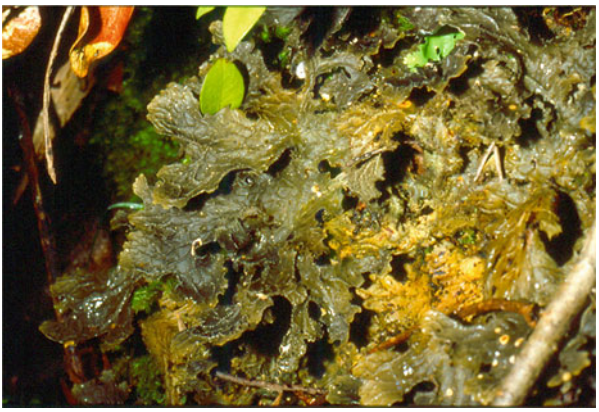
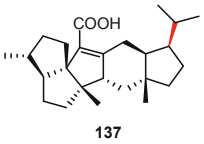


Plate 2 *Lobaria retigera* (Bory) Trevisan, Maungataniwha Ecological District. Photograph courtesy D. J. Galloway, CCBY Auckland Museum, Creative Commons 4.0



137

Fig. 98 Structure of retigeranic acid B (**137**)

9 Hexacarbocyclic Sesterterpenoids

Niduterpenoid A (**138**) and niduterpenoid B (**139**) possess hexacarbocyclic 5/5/5/5/3/5-membered ring systems (Fig. 99) [125]. Both compounds were isolated from *Aspergillus nidulans*. Compound **138** lacks cytotoxicity, but abrogates 17-estradiol-induced cell proliferation. The cyclization reaction for the formation of the hexacarbocyclic system starting from geranylfarnesyl diphosphate (**8**) is quite complicated, as shown in Fig. 100. After the formation of the intermediate **A**, with a 5/5/5/6/5-membered ring system, further rearrangements occur to form the hexacarbocyclic structure. Notably, the 5/5/5/6/5-membered ring system of the intermediate **A** is distinct from those of **134**–**137** (Figs. 97 and 98).

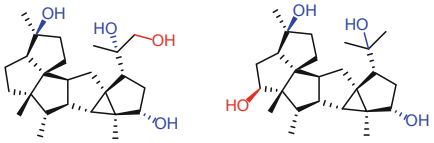


Fig. 99 Structures of niduterpenoid A (**138**) and niduterpenoid B (**139**)

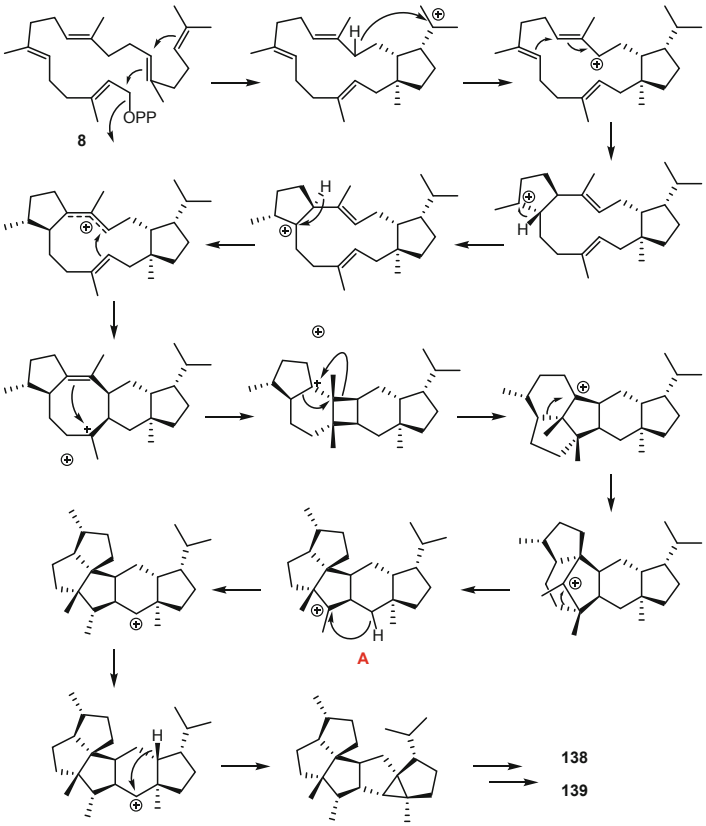


Fig. 100 Possible cyclization reactions for the formation of the hexacarbocyclic skeleton of **138** and **139**. The intermediate **A** possesses a 5/5/5/6/5-membered ring system, which is distinct from that of **134**–**137**

10 Sesterterpenoids Found by a Genome-Based Approach

Recently, a genome-based approach to the search for novel sesterterpenoids has been reported [126, 127]. As in a typical search for new natural products, researchers extract mixtures of compounds from natural sources and search for new compounds in the crude extracts. However, in the genome-based approach, investigators extract the genomic DNA from such natural resources and perform genome sequencing. From the obtained genomic data, a search is made for genes that could be involved in sesterterpenoid biosynthesis. These genes are expressed inducibly utilizing genetic engineering techniques. If the expressed genes are responsible for the formation of unknown sesterterpenoids, then these new sesterterpenoids can be isolated. By utilizing this approach, several new sesterterpenoids have been identified from fungi, plants, and bacteria.

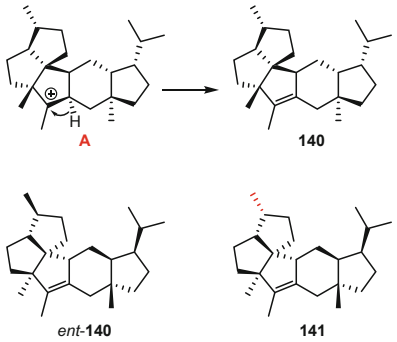


Fig. 101 Structures of quiannulatene (**140**), *ent*-**140**, and boleracene (**141**), and formation of **140**. The formation of intermediate **A** is shown in Fig. 100

10.1 5/5/5/6/5-Membered Ring System

A genome-based approach generated quiannulatene (**140**), with a 5/5/5/6/5-membered ring system (Fig. 101) [128]. The gene responsible for the production of **140** was found from the genomic data of the fungus *Emericella variecolor* NBRC 32302. Notably, the 5/5/5/6/5-membered ring system of **140** is different from those of **134**–**137** (Figs. 97 and 98). It is proposed that **140** is generated by the deprotonation of the intermediate **A** in Fig. 100. The detailed cyclization mechanism leading to the formation of **140** has been investigated by both computational approaches [129, 130] and isotope labeling experiments [128]. From the plant *Arabidopsis thaliana*, a gene for the biosynthesis of *ent*-**140** has also been found [131]. In addition, from the plant *Brassica oleracea*, a gene for the production of boleracene (**141**) has been identified (Fig. 101) [131]. The stereochemistry of **141** is different from those of **140** and *ent*-**140**.

10.2 5/8/6/5-Membered Ring System

Compound Bm2 (**142**) [132] and sesterfisherol (**143**), with a 5/8/6/5-membered ring system, were also discovered by the genome-based approach (Fig. 102) [133, 134]. The genes responsible for the production of **142** and **143** were found in the genomes of the fungi *Bipolaris maydis* ATCC48331 and *Neosartorya fischeri*, respectively. In fact, **123** and **124**, which were mentioned in Sect. 7.1.3, also possess similar 5/8/6/5-membered ring systems (Figs. 89 and 102). However, the stereochemistry and positions of the double bonds of **142**, **143**, **123**, and **124** are different from each other. A possible cyclization reaction starting from geranylfarnesyl diphosphate (**8**) leading to the formation of **142** and **143** is shown in Fig. 103.

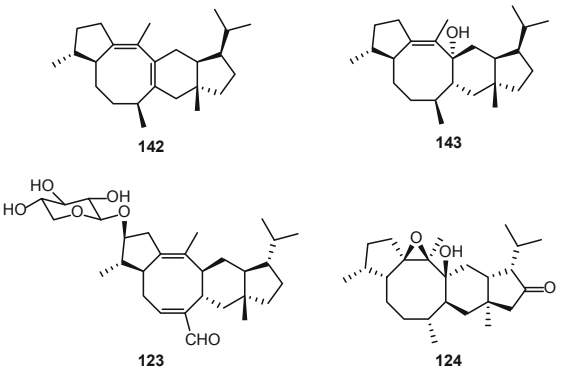


Fig. 102 Structures of **142**, **143**, and **123** and **124**

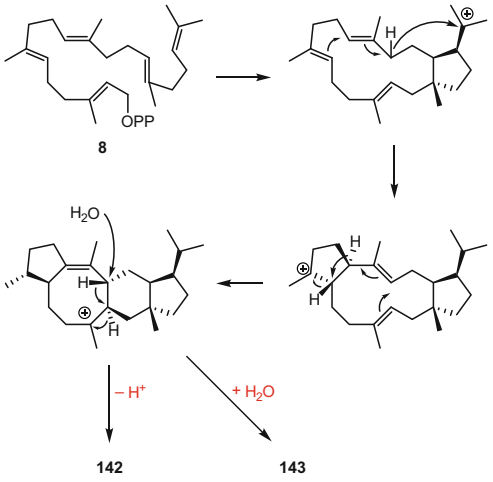


Fig. 103 Formation of **142** and **143**

10.3 11/6/5-Membered Ring Systems

(+)-Thalianatriene (**144**), which is also known as (+)-arathanatriene, possesses an 11/6/5-membered ring system (Fig. 104) [131, 135]. The gene encoding the synthase of **144** has been identified in the *Arabidopsis thaliana* genome. In addition, a gene involved in the production of a related compound, caprutriene (**145**), has been found in the genome of the plant *Capsella rubella* [131].

In Sect. 6.1.3, two kinds of 11/6/5-membered ring systems were introduced. However, the 11/6/5-membered ring systems of **144** and **145** are different from the two known 11/6/5-membered ring systems. The formation of **144** and **145** from geranylfarnesyl diphosphate (**8**) starts from the generation of a 15/5-membered ring system (Fig. 105), while the formation of the other two 11/6/5-membered ring systems is initiated by the formation of the 11/5-membered ring system (Figs. 74 and 75).

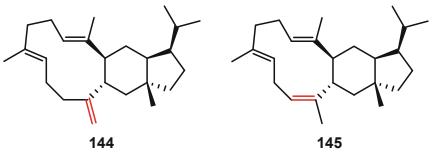


Fig. 104 Structures of (+)-thalianatriene (**144**) and caprutriene (**145**)

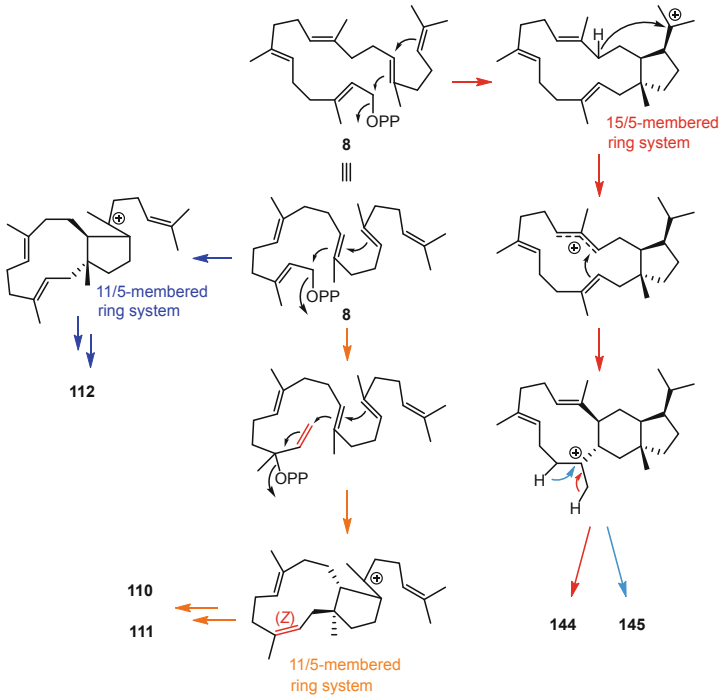


Fig. 105 Formation of **144** and **145**, and comparison with those of **110**–**112**

10.4 6/6/7/5- and 6/11/5-Membered Ring Systems

A sesterterpene synthase, identified from the genetic data of the plant *Capsella rubella*, was found to produce (−)-caprudiene A (**146**), (−)-caprutriene B (**147**), and (+)-caprutriene C (**148**) (Fig. 106) [136]. Compound **146** possesses a 6/6/7/5-membered ring system, while **147** and **148** have 6/11/5-membered ring systems. In addition to **146**–**148**, this enzyme also produces (+)-brassitetraene A (**149**) and (+)-brassitetraene B (**150**) with 15/5-membered ring systems. In fact, **149** and **150** are considered as intermediates of **146**–**148**. Thus, after the formation of **149** and **150** starting from geranylfarnesyl diphosphate (**8**), a second round of cyclization,

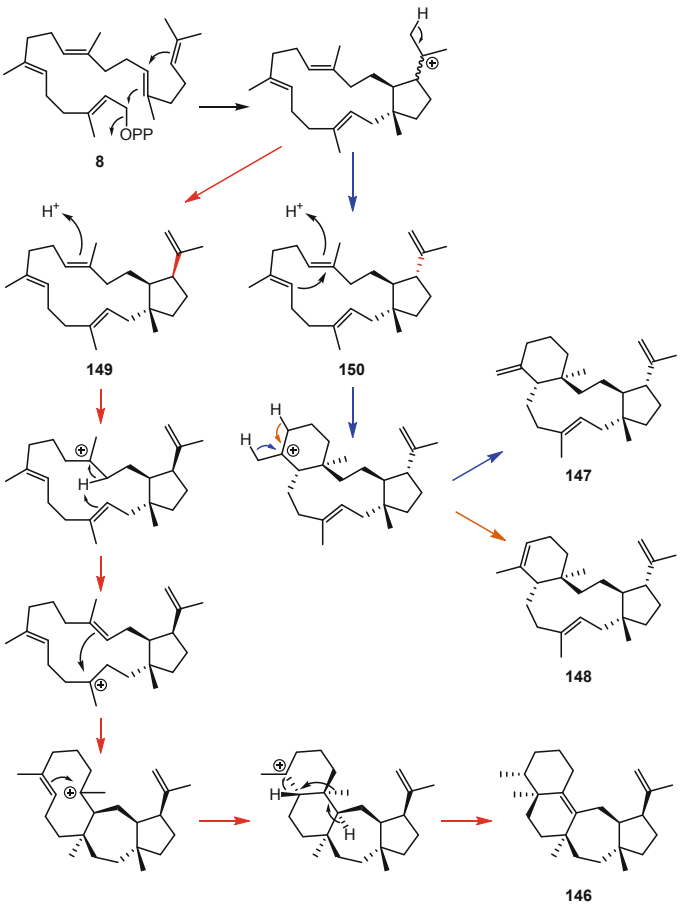


Fig. 106 Structures and formation of **146–150**

initiated by the protonation of **149** and **150**, occurs to form **146–148**. Other genes for the production of related sesterterpenoids with a 6/6/7/5-membered ring system have also been found in the genomes of the plants *Arabidopsis thaliana* and *Brassica rapa* [136].

10.5 5/4/5- and 4/5/5-Membered Ring Systems

A terpene cyclase designated as "spata-13,17-diene synthase" was found in the marine bacterium *Streptomyces xinghaiensis* by the genome-based approach [137]. This enzyme has the potential to produce prenylspata-13,17-diene (**151**), geranylkelsoene (**152**), and other C_{15} sesqui- and C_{20} di-terpenoids. Compound

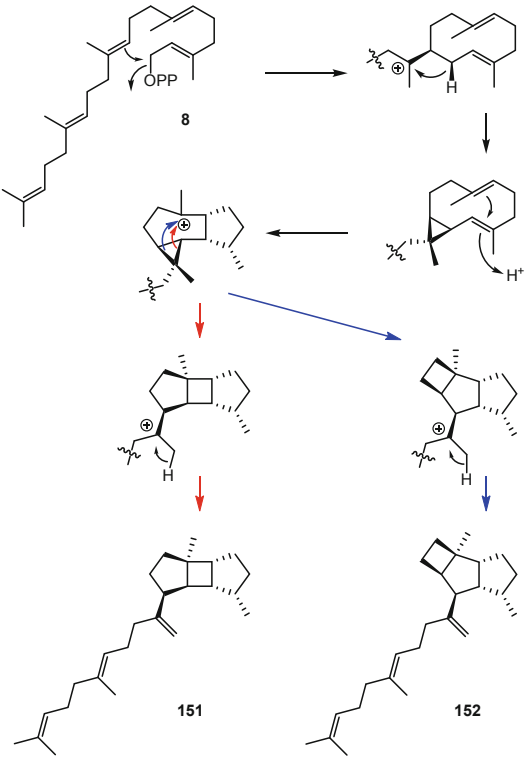


Fig. 107 Structures and formation of prenylspata-13,17-diene (**151**) and geranylkelsoene (**152**)

151 possesses a 5/4/5-membered ring system, while **152** has a 4/5/5-membered ring system (Fig. 107).

10.6 6/8/6/5-Membered Ring System

Astellifadiene (**153**) is a sesterterpenoid with a 6/8/6/5-membered ring system (Fig. 108) [138]. The formation of the 6/8/6/5-membered ring system from geranylfarnesyl diphosphate (**8**) requires two cyclization reactions. In the first cyclization, an 11/6/5-membered ring is generated, and then deprotonation finalizes the reaction. Next, protonation occurs to initiate the second round of cyclization, and the basic carbon skeleton of **153** is formed. The gene for the biosynthesis of **153** has been found in the genome of the fungus *Emericella variecolor* NBRC 32302.

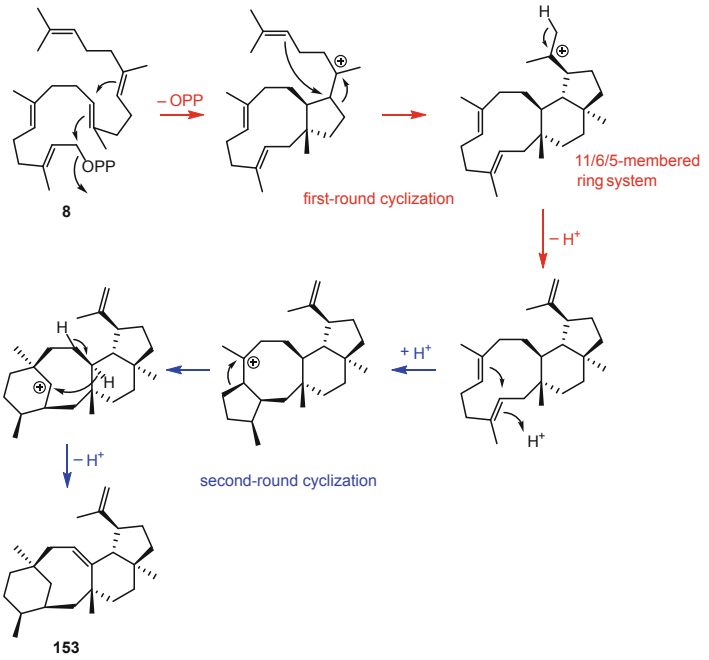


Fig. 108 Structure and formation of astellifadiene (**153**)

10.7 5/12/5-Membered Ring System

Sesterbrasiliatriene (**1**) [9], betaestacin I (**154**) [132], and Bm1 (**155**) [132] have 5/12/5-membered ring systems (Fig. 109) and were found by the genome-based

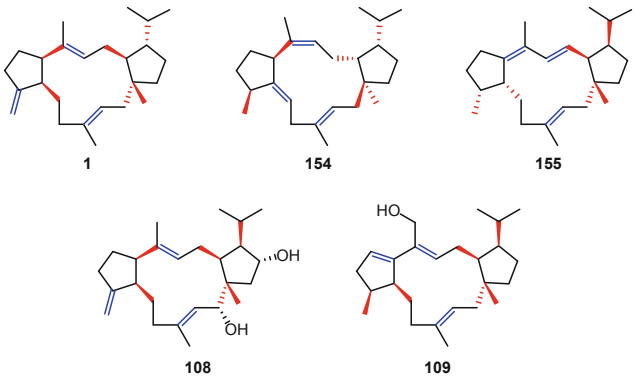


Fig. 109 Structures of **1**, **154**, **155**, **108**, and **109**. Compounds **1**, **154**, and **155** were discovered by a genome-based approach. Structures of **108** and **109** are also shown in Fig. 71

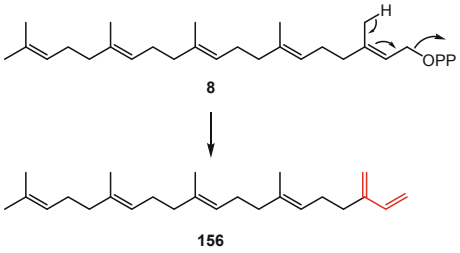


Fig. 110 Structure and formation of β-geranylfarnesene (**156**)

approach. The genes responsible for the production of **1**, **154**, and **155** are from the fungi *Penicillium brasilianum* NBRC 6234, *Phoma betae* PS-13, and *Bipolaris maydis* ATCC48331, respectively. Of these, **108** and **109** with 5/12/5-membered ring systems were isolated from Nature, as mentioned in Sect. 6.1.2. However, the configurations and positions of the double bonds of **1**, **154**, **155**, **108**, and **109** are different from each other.

10.8 Genes for the Formation of a Linear Sesterterpenoid

Genes for the biosynthesis of linear sesterterpenoids have also been found. For example, a gene from the bacterium *Bacillus clausii* encodes an enzyme that can transform geranylfarnesyl diphosphate (**8**) into a linear sesterterpene, hydrocarbon β-geranylfarnesene (**156**) (Fig. 110) [139].

10.9 Genes Encoding a Membrane-Bound Sesterterpene Cyclase

The typical terpene cyclases, which catalyze type 1 terpene cyclization reactions, are soluble proteins. However, there are also membrane-bound terpene cyclases for type 1 cyclization reactions, and they are referred to as UbiA-type terpene cyclases. A gene encoding a UbiA-type terpene cyclase involved in the biosynthesis of sesterterpenoids has been found in the bacterium *Streptomyces somaliensis* [140]. This enzyme can convert geranylfarnesyl diphosphate (**8**) to somaliensenes A (**157**) and B (**158**) (Fig. 111).

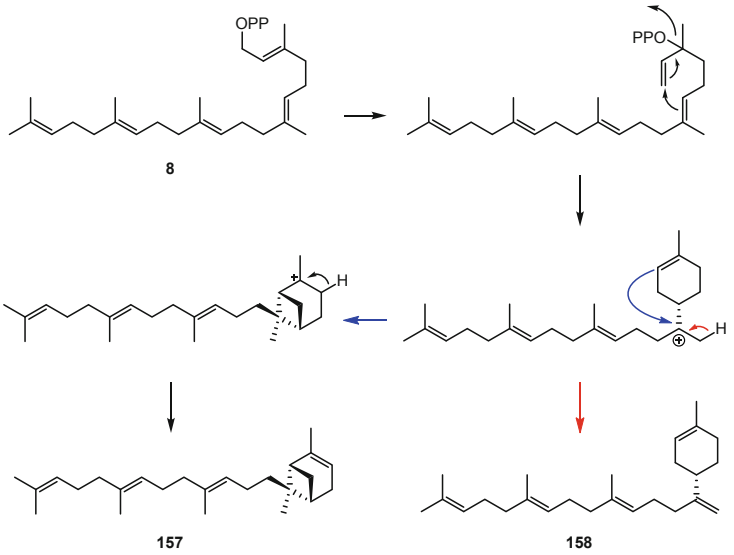


Fig. 111 Structures and formation of somaliensenes A (**157**) and B (**158**)

10.10 A Sesterterpenoid Produced by an Artificially Engineered Enzyme

In many cases, fungal sesterterpene synthases (C_{25}) and diterpene synthases (C_{20}) exist as chimeric enzymes, composed of a terpene cyclase and a prenyltransferase [126, 127]. In other words, the terpene cyclase and the prenyltransferase are linked together (Fig. 112). The reactions catalyzed by these two enzymes are shown in Figs. 5–7. The fusion of these two enzymes is considered to provide a catalytic

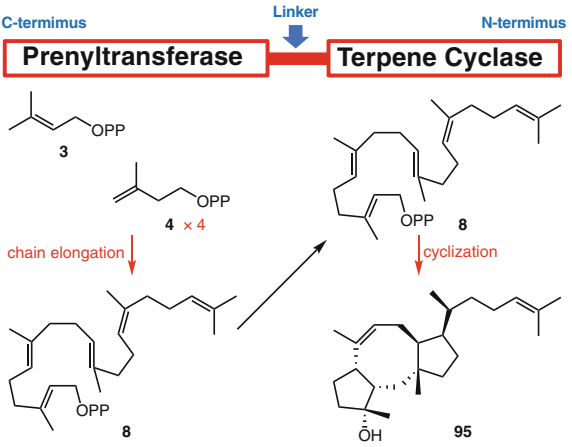


Fig. 112 Constitution of the fungal chimeric diterpene synthase and sesterterpene synthase. The chimeric terpene synthase consists of two domains. The C-terminal domain possesses the prenyltransferase activity, while the N-terminal domain exhibits the terpene cyclase activity

advantage, because the physical proximity of the active sites of the two enzymes can enhance product flux [141, 142]. Polyprenyl diphosphates **7** and **8**, which are produced by the prenyltransferase, could be efficiently moved into the active site of the terpene cyclase if these enzymes are linked together, namely, exist near each other.

The prenyltransferase domain of the fungal diterpene synthase (C_{20}) might produce mainly the (C_{20}) polyprenyl diphosphate **7**, while that of sesterterpene synthase might yield primarily the (C_{25}) version **8**. Therefore, even when the terpene cyclase domain of a fungal diterpene cyclase has the potential to cyclize not only **7** but also **8**, the major products of the enzyme should be diterpenes (C_{20}), because the prenyltransferase domain supplies principally (C_{20}) **7**, not (C_{25}) **8**, to the terpene cyclase domain.

Accordingly, a protein engineering experiment, in which the prenyltransferase domain of a fungal diterpene synthase is exchanged with that of a sesterterpene synthase, could enable the terpene cyclase domain of the diterpene synthase to produce sesterterpenoids, since the prenyltransferase domain of the sesterterpene synthases can supply a sufficient amount of **8**.

A protein engineering experiment based on this hypothesis has been reported [143]. This study utilized a fungal diterpene cyclase, designated as EvVS. The wild-type EvVS produces only C_{20} variediene (**159**). However, after its prenyltransferase domain was exchanged artificially with that of a sesterterpene synthase by genetic engineering, this enzyme produced a sesterterpene, (2*E*)-α-cericerene (**160**) (Figs. 113 and 114). A similar approach using a different fungal diterpene synthase has also been reported [144].

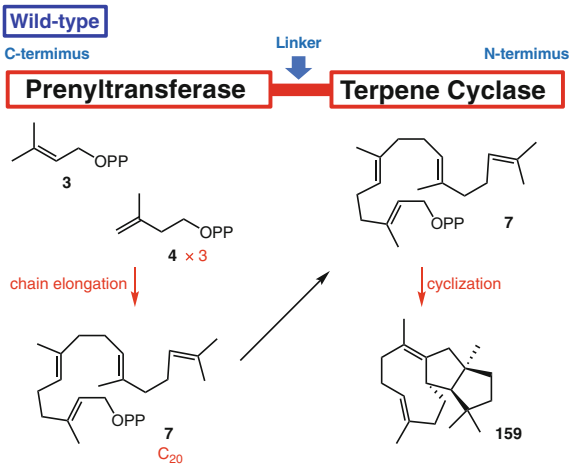


Fig. 113 Reaction catalyzed by the wild-type fungal diterpene synthase (EvVS), which produces **159**. Since the prenyltransferase domain of this enzyme mainly produces **7**, the terpene cyclase domain primarily accepts **7**. Thus, only the cyclized diterpene **159** is produced by the wild-type EvVS

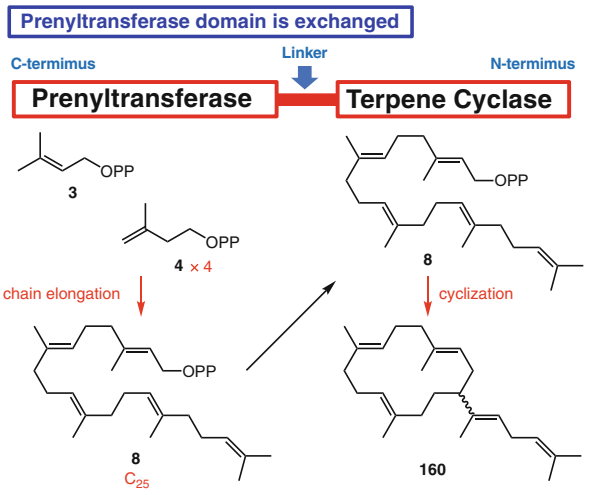


Fig. 114 Reaction catalyzed by the engineered EvVS. The prenyltransferase domain of EvVS was exchanged with that of a sesterterpene synthase. In the case of the engineered EvVS, **8** is primarily supplied to the terpene cyclase domain. Therefore, the terpene cyclase domain starts to accept **8** and produces the cyclized sesterterpene **160**

10.11 Tailoring Enzymes for the Derivatization of Sesterterpenoids

In addition to the enzymes responsible for the formation of the basic carbon skeletons of the sesterterpenoids, modification enzymes, which can attach a functional group to these compounds, have been found by the genome-based approach. For example, from the fungus *Talaromyces wortmannii* ATCC 26942, a cytochrome P450, which can convert **131** to a new sesterterpenoid, asperterpenoid C (**161**), has been identified (Fig. 115) [145]. The cytochrome P450 catalyzes an oxidation reaction and attaches a hydroxy group to **131**.

Another example refers to the tailoring enzymes for the derivatization of **154** [146]. Analyses revealed that three cytochrome P450s, from the fungi *Phoma betae* and *Colletotrichum orbiculare*, are involved in the conversion of **154** into the new sesterterpenoids **162**–**168** (Fig. 116).

In addition, cytochrome P450s for the formation of new sesterterpenoids, quiannulatic acid (**169**) and sesterfisheric acid (**170**), have also been identified (Fig. 117) [128, 133].

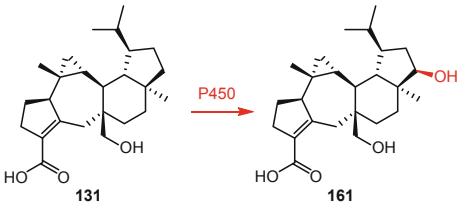


Fig. 115 Structure and formation of asperterpenoid C (**161**). The structure of **131** is also shown in Fig. 95

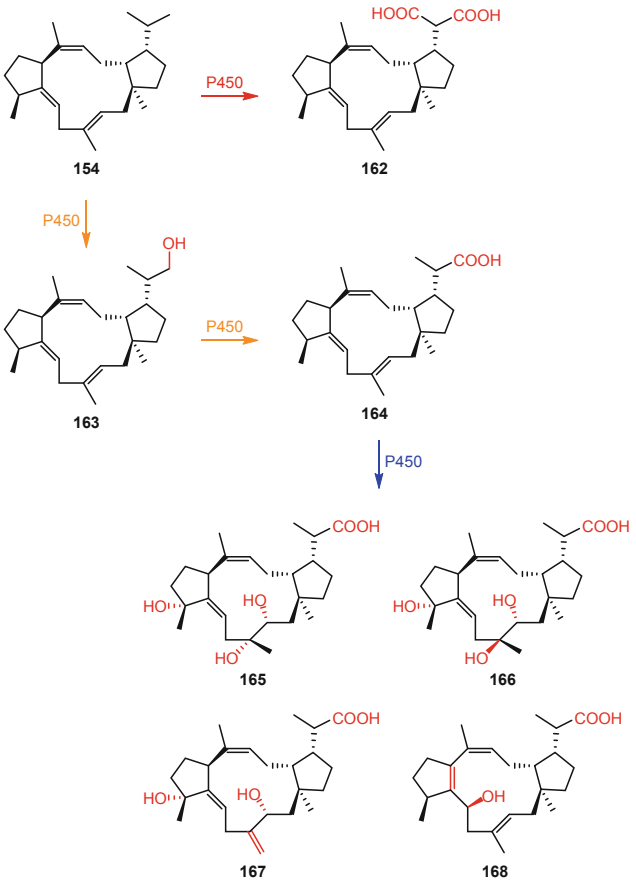


Fig. 116 Structures and formation of **162–168**. Reactions catalyzed by different enzymes are shown by arrows with different colors. The structure of **154** is also shown in Fig. 109

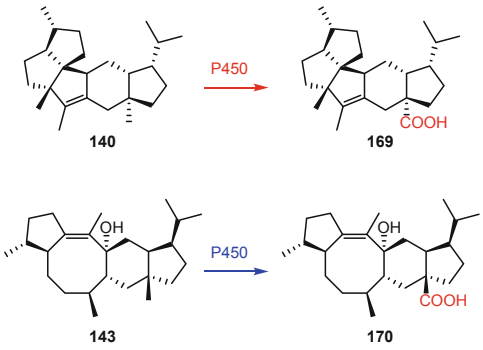


Fig. 117 Structures and formation of **169** and **170**. The structures of **140** and **143** are also shown in Figs. 101 and 102

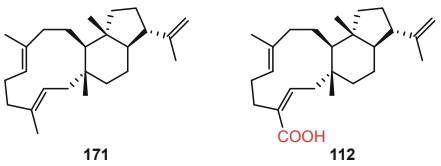


Fig. 118 Structures of **171** and **112**. The structure of **112** is also shown in Fig. 73

10.12 Genes for the Biosynthesis of Known Sesterterpenoids or Their Precursors

The genome-based approach has also identified the genes involved in the biosynthesis of known sesterterpenoids. Herein, such examples are introduced. Importantly, in many cases, the genome-based approach enables the isolation of the biosynthetic precursors of the known sesterterpenoids, which have never been isolated from Nature.

10.12.1 Stellatic Acid

The gene for the production of stellata-2,6,19-triene (**171**) was found in the genome from the fungus *Emericella variecolor* NBRC 32302 (Fig. 118) [147]. In fact, **170** is a biosynthetic precursor of stellatic acid (**112**) and has not been reported from natural sources. Moreover, a cytochrome P450 for the conversion of **170** into **112** has also been identified from the same fungal strain.

10.12.2 Ophiobolin F

A gene encoding a sesterterpene synthase for the production of ophiobolin F (**95**) has been found in the genome from the fungus *Aspergillus clavatus* (Figs. 66 and 112) [148]. Indeed, this enzyme is the first example of a sesterterpene synthase.

The gene for the biosynthesis of **95** has also been found in the genome from the fungus *Aspergillus ustus* 094102, and the genes responsible for the accumulation of **95** in this fungus have been investigated in detail [149, 150]. Based on this information, the production of **95** in *Escherichia coli* has been accomplished [151].

10.12.3 Mangicol A

The gene encoding a sesterterpene synthase for the production of mangicdiene (**172**) has been found in the genome from the fungus *Fusarium graminearum* J1-012 (Fig. 119) [152]. Compound **172** is considered to be a biosynthetic intermediate of mangicol A (**125**).

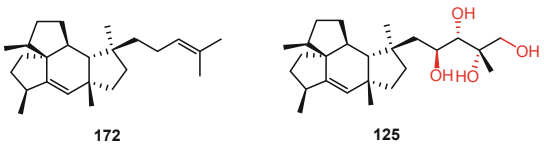


Fig. 119 Structures of **172** and **125**. The structure of **125** is also shown in Fig. 90

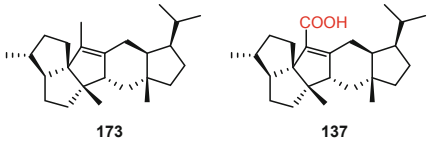


Fig. 120 Structures of **173** and **137**. The structure of **137** is also shown in Fig. 98

10.12.4 Retigeranic Acid B

The gene for the biosynthesis of retigeranin B (**173**) has been found in the genome from the plant *Arabidopsis thaliana* (Fig. 120) [131, 135]. Compound **173** is considered to be a biosynthetic intermediate of retigeranic acid B (**137**).

10.12.5 Astellatol

The gene for the production of astellatene (**174**) has been identified in the genome from the plant *Arabidopsis thaliana* (Fig. 121) [131]. Compound **174** might be a precursor of astellatol (**133**). Incidentally, the genes for the production of **174** (Fig. 121) and *ent*-**140** (Fig. 101) reportedly play an important role in the root microbiota assembly of the plant [153]. This is one of the few examples of an investigation into the biological roles of sesterterpenoids.

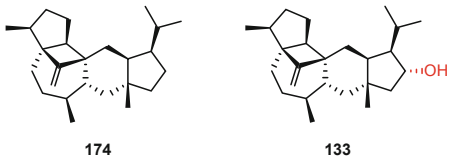


Fig. 121 Structures of **174** and **133**. The structure of **133** is also shown in Fig. 96

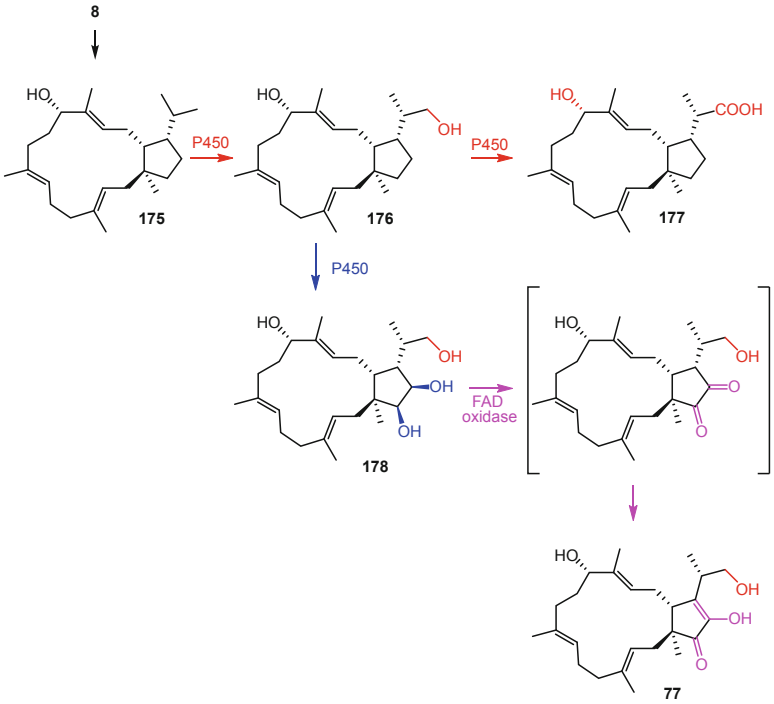


Fig. 122 Structures and formation of **175**–**178**, and **77**. The structure of **77** is also shown in Fig. 53

10.12.6 Terpestacin

Four genes for the biosynthesis of terpestacin (**77**) have been identified in the genome from the fungus *Bipolaris maydis* [132, 154]. One of the four genes encodes a sesterterpene synthase that produces **175**. The other three genes encode oxidases, two cytochrome P450s, and a single flavin-dependent oxidase. These oxidases could convert **175** into **176**, **177**, **178**, and **77** (Fig. 122).

11 Conclusions

This contribution provides an overview of the chemical structures of sesterterpenoids. Even though only relatively few sesterterpenoids are known, their structures are quite fascinating. In particular, the complexity of polycarbocyclic sesterterpenoids is quite high. There are many stereocenters in their structures, and their stereochemistry is well controlled during the cyclization reactions leading to the formation of their basic carbon skeletons. Moreover, many sesterterpenoids are known as bioactive compounds.

Considering that some sesterterpenoids with novel chemical structures have been reported very recently, we can look forward to many exciting discoveries of unknown sesterterpenoids in the near future. Therefore, the present authors believe that it is worthwhile maintaining a sharp focus on sesterterpenoid research.

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