

Progress in the Chemistry of Organic Natural Products

A. Douglas Kinghorn · Heinz Falk
Simon Gibbons · Jun'ichi Kobayashi
Yoshinori Asakawa · Ji-Kai Liu *Editors*

111

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Editors

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Volume 111

With contributions by

Takaaki Mitsuhashi • Ikuro Abe

Zhen Liu • Marian Frank • Xiaoqin Yu • Haiqian Yu •
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Sesterterpenoids



Takaaki Mitsuhashi and Ikuro Abe

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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 “C₅” units, called isoprene units (Fig. 1). Thus, terpenoids are also called “isoprenoids.” In this definition, “C₅” means that a compound contains five carbon atoms. This notation will be frequently used in this chapter, and thus “C₂₅” 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

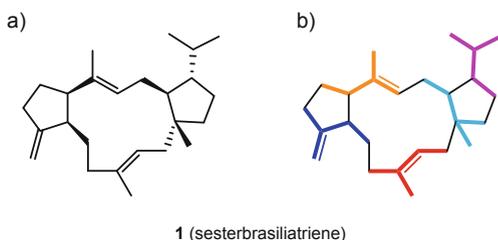


Fig. 3 Structure of **2**. The structure of **2** contains four isoprene units. Each isoprene unit is shown by bold lines with different colors

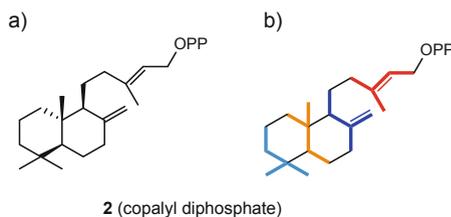
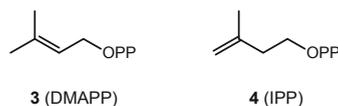


Fig. 4 Structures of dimethylallyl pyrophosphate (DMAPP) (**3**) and isopentenyl pyrophosphate (IPP) (**4**)



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).

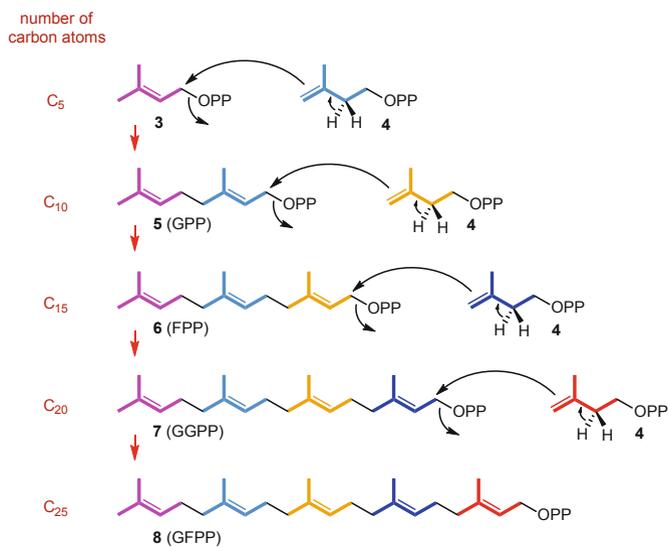


Fig. 5 Condensation reaction catalyzed by prenyltransferases to form polyprenyl diphosphates, and structures of 5–8

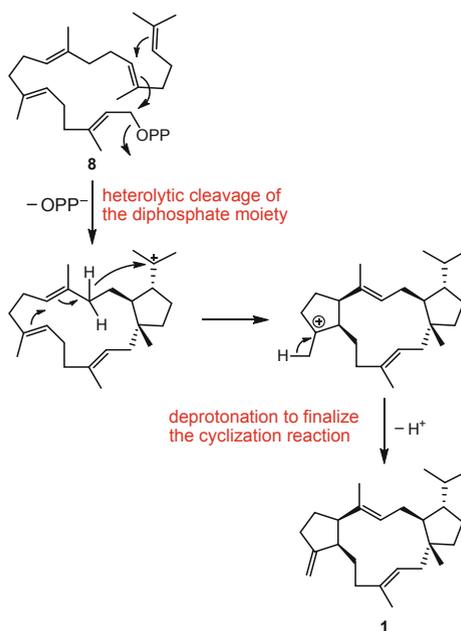


Fig. 6 Cyclization reaction to form sesterbrasiliatriene (**1**). This reaction is catalyzed by the type 1 terpene cyclase

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

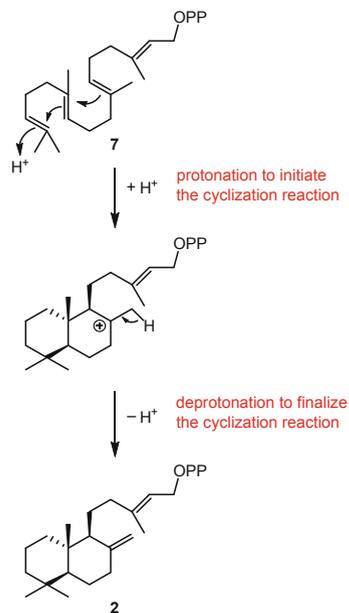
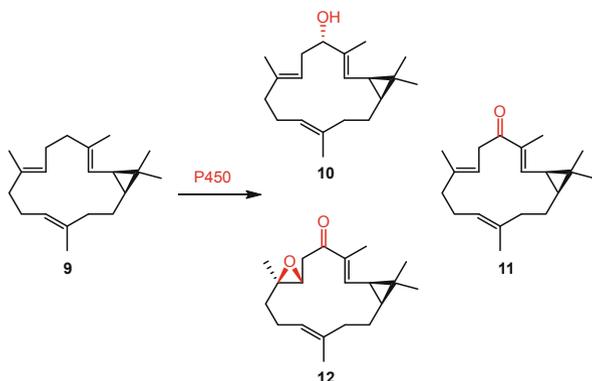


Fig. 8 Compound **9** could be oxidized by a cytochrome P450, forming **10–12**



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

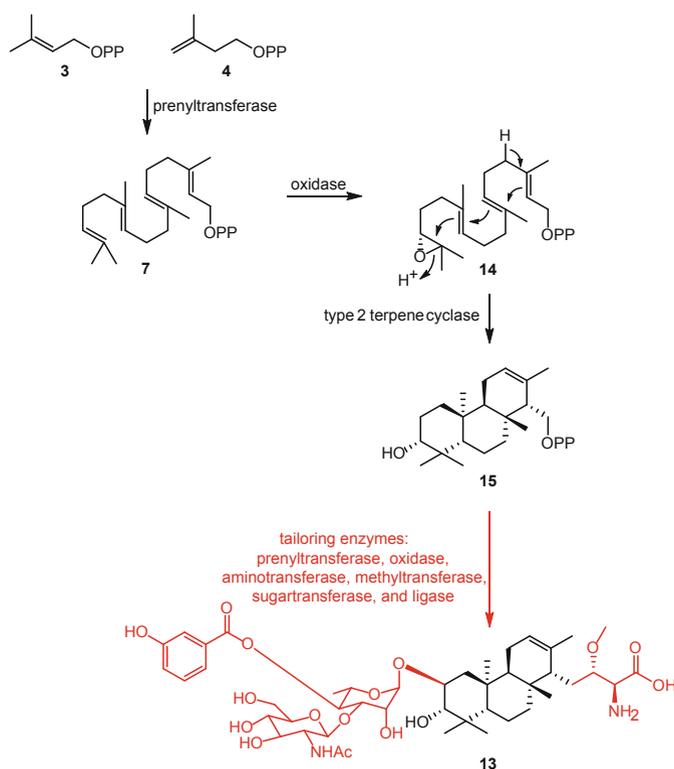


Fig. 9 Putative biosynthesis pathway of brasilicardin A (**13**). The functional groups of **13**, which might be generated by the tailoring enzymes, are shown in red

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 geranylgeranyl diphosphate (GGPP) (**8**) (Fig. 10).

For example, preaspterpenoid 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**,

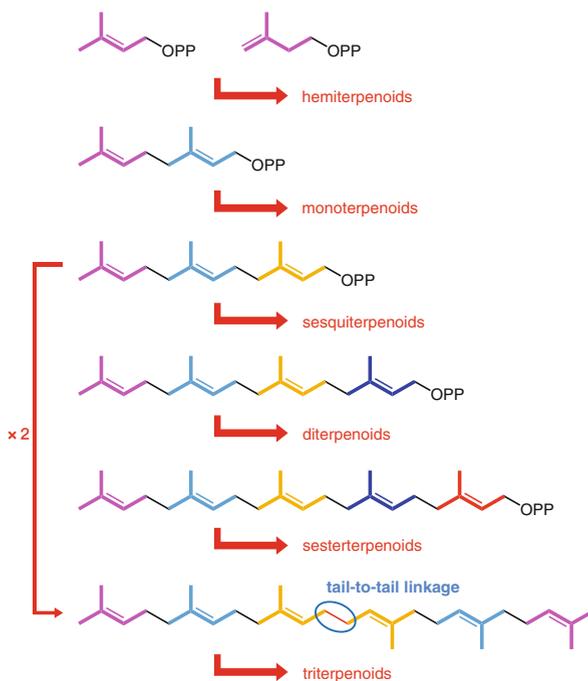
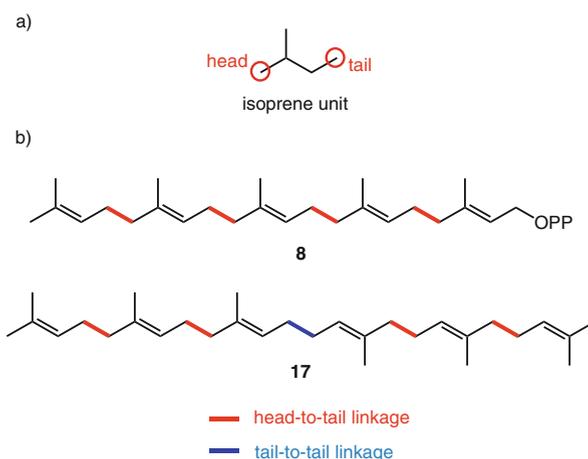
Fig. 12 Classification of the terpenoids

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 C₁₀ 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 C₁₅ terpenoid moiety and a C₁₀ polyketide moiety. These C₁₅ and C₁₀ moieties are combined in their biosynthesis to form the C₂₅ basic carbon skeleton.

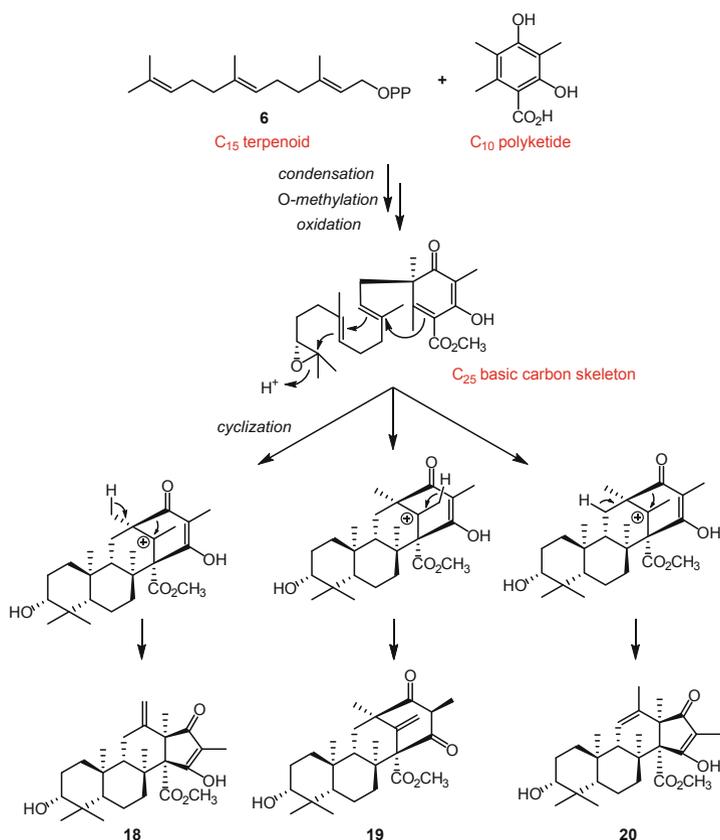


Fig. 14 Biosynthesis of **18**–**20**. In their basic carbon skeletons, there are 25 carbons. However, they are not sesterterpenoids