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Polyprenylated Phloroglucinols and Xanthenes

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12.1

Introduction

Guttiferae (Clusiaceae) is a family of plants that includes more than 37 genera and 1600 species [1]. Characteristic to this family is its large variation in plant morphology, which makes it an important group of plants for the study of floral diversification and evolutionary plasticity. Although mainly confined to the tropical areas, this family also includes the genus *Hypericum*, a plant that is found widely around the Mediterranean area. Several plants of the Guttiferae family have a rich history in ethnomedicine for their broad-spectrum antibacterial and healing properties. For instance, the antibacterial and antidepressant activities of *Hypericum perforatum* (St. John's wort) have been noted in traditional European medicine. In fact, *Hypericum* extracts have been tested in various clinical trials and are currently used in certain countries for the treatment of depressive, anxiety, and sleep disorders [2–11]. On the other hand, members of the *Garcinia* genus of tropical trees have considerable value as sources of medicines, pigments, foodstuffs, and lumber [12, 13].

Chemically, the Clusiaceae family of plants constitutes a rich source of polyprenylated acylphloroglucinols and xanthenes. Both chemical classes have generated substantial interest due to their fascinating chemical structures and potent bioactivities [10]. This chapter summarizes the chemical classification, biosynthesis, and synthetic approaches toward these compounds.

12.2

Polycyclic Polyprenylated Phloroglucinols

12.2.1

Introduction and Chemical Classification

The chemical structures of all known polycyclic polyprenylated acylphloroglucinols (PPAPs) can be classified into three types that are related to the biosynthesis

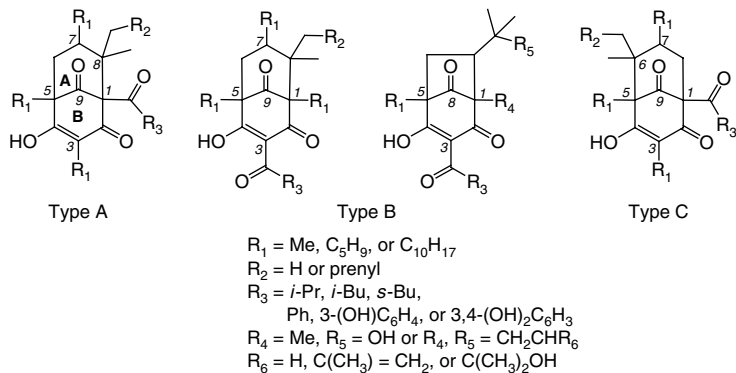


Figure 12.1 Classification of polycyclic polyprenylated acylphloroglucinols (PPAPs).

proposal (Scheme 12.2 below). Types A, B(I), and C PPAPs are distinguished by the presence of a highly oxygenated bicyclo[3.3.1]nonane-2,4,9-trione motif, while type B(II) PPAPs contain a bicyclo[3.2.1]octane-2,4,8-trione carbon framework (Figure 12.1). In all types, the bicyclic motif is further decorated with prenyl, geranyl, and related side chains. Certain family members contain additional rings, formed by cyclizations between the β -diketone and an alkene, leading to adamantanes, pyrano-fused, or other cyclic substructures. Type A PPAPs have an acyl-substituent at C1 adjacent to a quaternary C8 carbon, while the type B compounds have the acyl-substituent at C3. The more rare type C PPAPs have the acyl group at C1 but the quaternary carbon is located at the distant C6 (Figure 12.1) [14]. For the purpose of this chapter, the carbon numbering of these molecules is based on the nemorosone numbering [14].

Figure 12.2 shows representative members of the PPAPs. Hyperforin (**1**), one of the bioactive ingredients of *Hypericum perforatum* [15, 16], belongs to the type A PPAPs and is also known for its antibacterial [17] and anticancer properties [9, 18]. Another type A phloroglucinol is garsubellin A (**2**), a natural product noted for its activities against neurodegenerative diseases. In fact, recent studies have shown that garsubellin A induces biosynthesis of acetylcholine, a neurotransmitter that at low concentrations can lead to Alzheimer's disease [19]. Nemorosone (**3**) exhibits antimicrobial [20, 21], cytotoxic, and antioxidant activities [20], while, clusianone (**4**), a type B(I) PPAP, is known for its anti-HIV activity [22]. The type B(II) enaimeone A (**5**) was isolated from *Hypericum papuanum*, the leaves of which are used in the traditional medicine of Papua New Guinea for treating sores [23]. Garcinielliptone M (**6**), a type C PPAP, isolated from *Garcinia subelliptica*, shows potential anti-inflammatory activity [24].

12.2.2

Biosynthesis of PPAPs

PPAPs derive biosynthetically from the less complex monocyclic polyprenylated acylphloroglucinols (MPAPs), a class of natural products isolated from plants of the

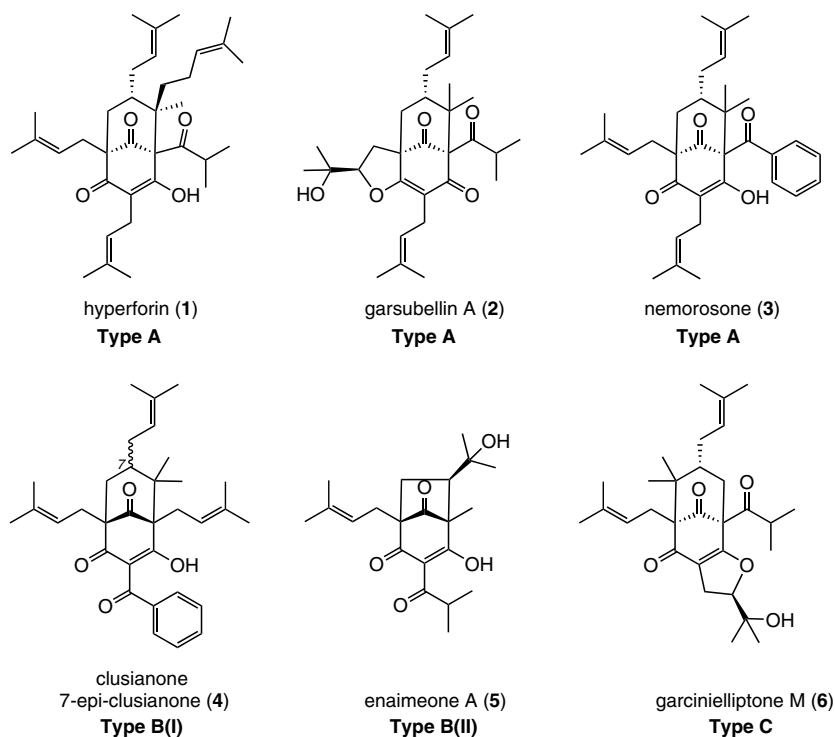


Figure 12.2 Representative members of the PPAP family.

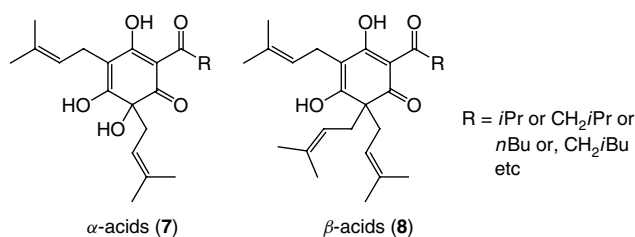
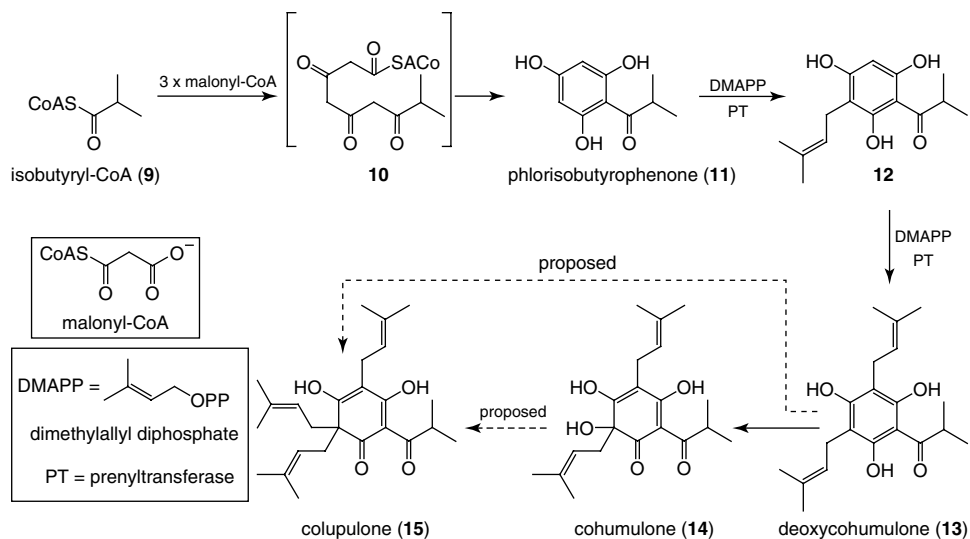


Figure 12.3 Monocyclic polyprenylated acylphloroglucinols (MPAPs) from *Humulus lupulus*.

Myrtaceae and Cannabinaceae families [10]. There are two main classes of MPAPs: the diprenylated α -acids (7) and triprenylated β -acids (8) (Figure 12.3). α -Acids are responsible for the flavor and bitter taste of beer [25] while β -acids show, among other properties, free radical scavenger activity [7, 26].

Labeling and enzymological experiments have provided evidence that bitter acids are biosynthesized via condensation of three malonyl-CoA and one acyl-CoA, such as isobutyryl-CoA (9) (Scheme 12.1) [27–30]. The intermediate polyketide 10 can then cyclize via an intramolecular Dieckmann condensation to produce acylphloroglucinol 11 [31, 32]. Subsequent prenylations (or geranylations) occur via an enzymatic process that involves prenyltransferase-catalyzed reactions



Scheme 12.1 Biosynthesis of acylphloroglucinol 11 and bitter acids 14 and 15.

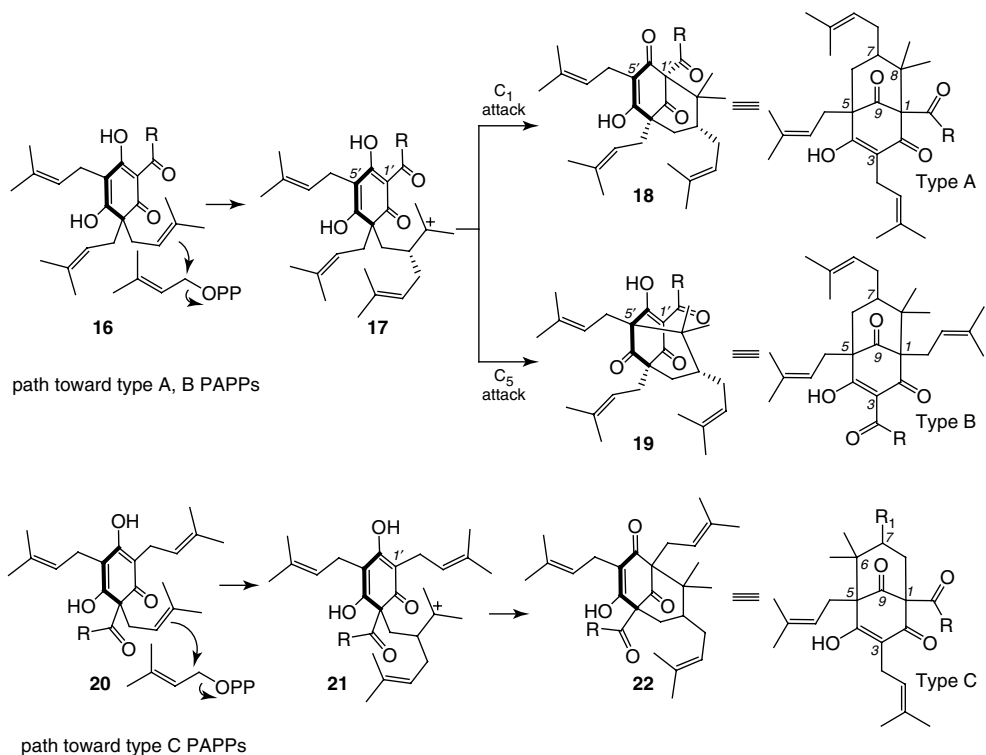
of the appropriate diphosphates with phloroglucinol [25, 33–37]. This stepwise prenylation process is illustrated in Scheme 12.1 for the construction of 12 and 13 (deoxycohumulone) from 11. It has been shown that chemical and/or enzymatic oxidation of 13 can lead to cohumulone (14), a representative α -acid. It has also been proposed that additional prenylation of 13 can form colupulone (15), a typical β -acid [25].

Type A and type B PPAPs are proposed to arise via reaction of acylphloroglucinol 16 with prenyl diphosphate. The resulting carbocation 17 can be attacked by the C1' or C5' enol to produce compounds 18 or 19, respectively, that represent type A and type B PPAPs (Scheme 12.2) [14]. Acylphloroglucinol 20, containing a prenylated C1' center, is the proposed intermediate of type C PPAPs. Specifically, reaction of 20 with prenyl diphosphate can form carbocation 21 and, after cyclization, bicyclic 22, a type C PPAP [10].

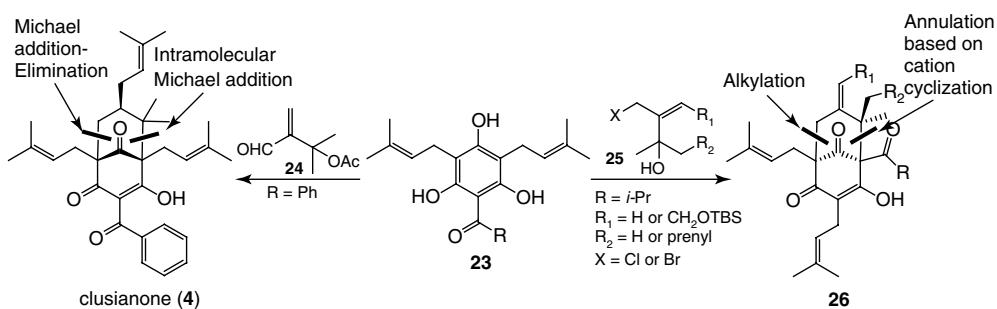
12.2.3

Biomimetic Synthesis of PPAPs

A 2006 review summarizes the synthetic efforts toward PPAPs [10]. These studies set the stage for the first total synthesis of garsubellin A, reported by the Shibasaki group [38], and were followed a few months later by a synthesis from the Danishefsky group [39]. Since then, additional total syntheses have been published of either type A [hyperforin (1), garsubellin A (2), nemorosone (3)] [40–42], or type B [clusianone (4)] [41, 43–45] PPAPs. Among all published approaches there are only two strategies built upon biomimetic considerations that involve: (i) formation of a fully prenylated B ring and (ii) construction of the A ring via a cation-based alkylative dearomatization. Both strategies departed from the



Scheme 12.2 Biosynthesis of type A, type B, and type C PPAPs from MPAPs.

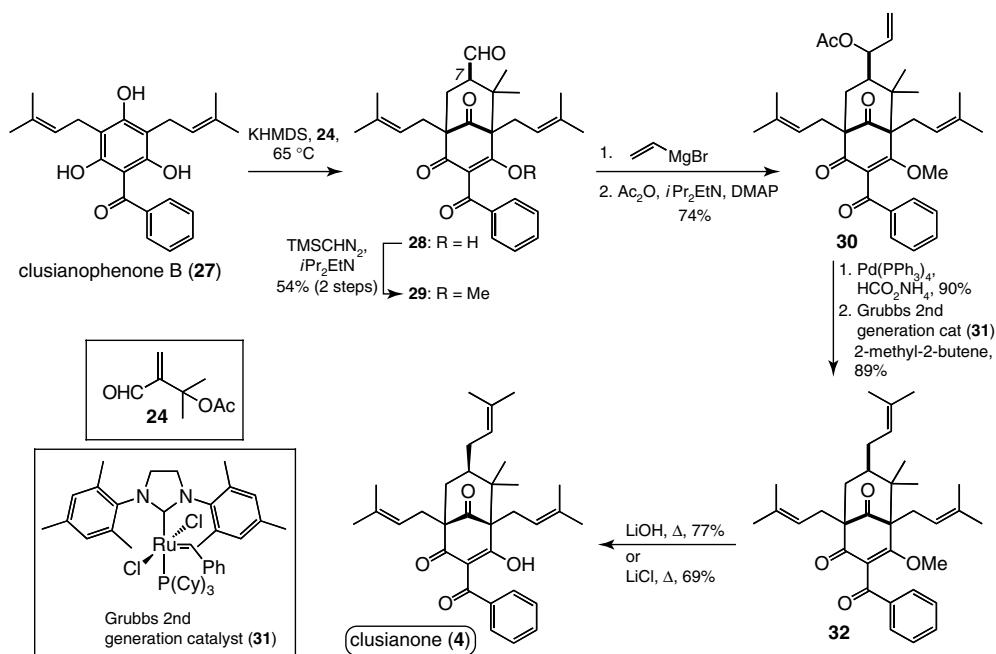


Scheme 12.3 Biomimetic approaches toward type A and type B PPAPs.

bis-prenylated acylphloroglucinol **23**, a key intermediate in the biosynthesis of these natural products (Scheme 12.3). The first one, reported by the Porco group, resulted in the total synthesis of clusianone (type B PPAP) [45] using a double Michael reaction as a key step. More recently, the Couladouros group produced compound **26**, representing the fully functionalized bicyclic core of the type A PPAPs, by a double alkylation of **23** with allyl electrophile **25** [46].

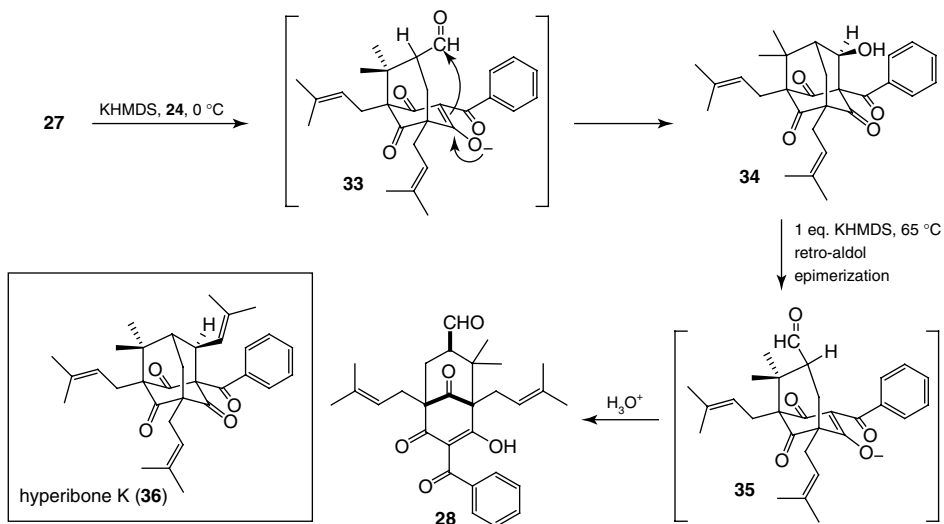
12.2.3.1 Biomimetic Total Synthesis of (\pm)-Clusianone

The Porco synthesis of clusianone (**4**) is summarized in Scheme 12.4 and features a double Michael addition of clusianophenone B (**27**) with α -acetoxy enal **24**. The bicyclic product **28** was methylated to form **29** as a mixture of regioisomers [45]. The employment of enal **24** proved to be a useful handle for the ensuing installation of the prenyl group at C7 (Scheme 12.4). Addition of vinyl magnesium bromide to aldehyde **29** and acetylation of the resulting alcohol gave access to acetate **30**. Palladium-mediated formate reduction followed by cross metathesis using Grubbs second-generation catalyst (**31**) yielded methylated clusianone **32** (81% over two steps). Finally, demethylation of **32** afforded (\pm)-clusianone (**4**) as a mixture of enol tautomers.



Scheme 12.4 Biomimetic synthesis of clusianone by Porco, Jr. *et al.*

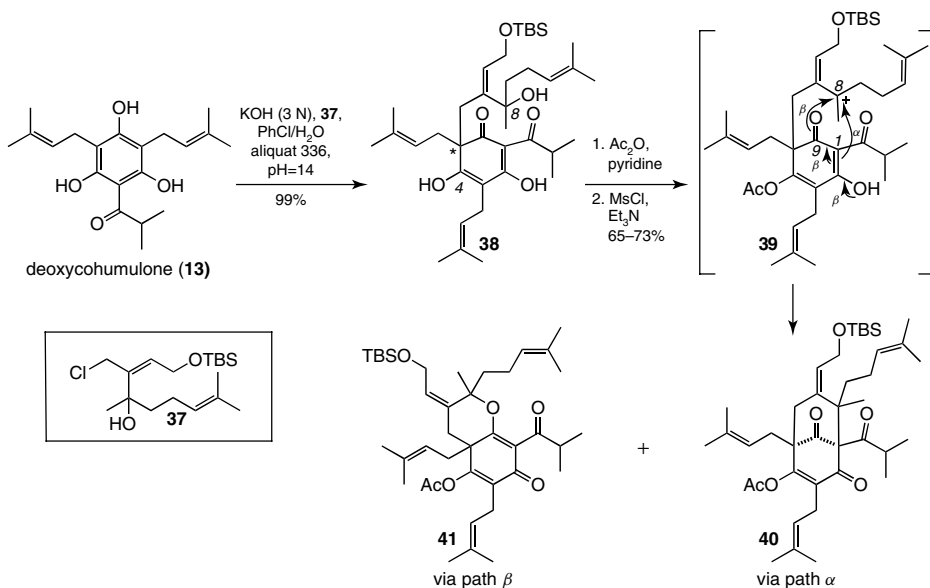
The double Michael reaction, used for the conversion of **27** into **28**, deserves an additional comment. The authors reported that heating of this reaction at 65 °C led to desired compound **28** via epimerization of the C7 aldehyde stereocenter. Interestingly, performing this reaction at 0 °C formed the adamantane-like compound **34** via an intramolecular aldol reaction. When **34** was treated with potassium hexamethyldisilazane (KHMDS) at 65 °C compound **28** was synthesized, presumably via a retro-aldol epimerization process (Scheme 12.5). This observation allows the synthesis of adamantane-like compounds that are structurally related to hyperibone K (**36**).



Scheme 12.5 Observations related to the double Michael reaction 27 \rightarrow 28.

12.2.3.2 Biomimetic Approach to the Bicyclic Framework of Type A PPAPs

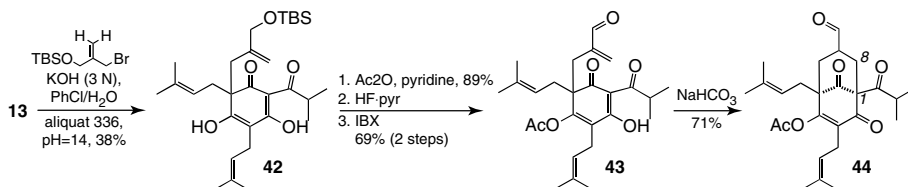
The Couladouros approach towards the bicyclic core of type A PPAPs is highlighted in Scheme 12.6 [46]. C-alkylation of deoxycohumulone (13) with chloride 37, under a two-phase solvent system at pH 14, produced compound 38 as a mixture of two diastereoisomers. Acetylation of the C4 hydroxyl group of 38 followed by mesylation



Scheme 12.6 Biomimetic formation of the type A carbon framework.

of the C8 alcohol produced bicyclic motifs **40** and **41** in 1.5 : 1 ratio, presumably via common intermediate **39**. Compound **41** is generated via O-alkylation of the C9 enol to the intermediate C8 carbocation formed during the reaction (path β). Notably, the presence of the double bond, allylic to the tertiary alcohol, is of importance for the stabilization of the cation **39**.

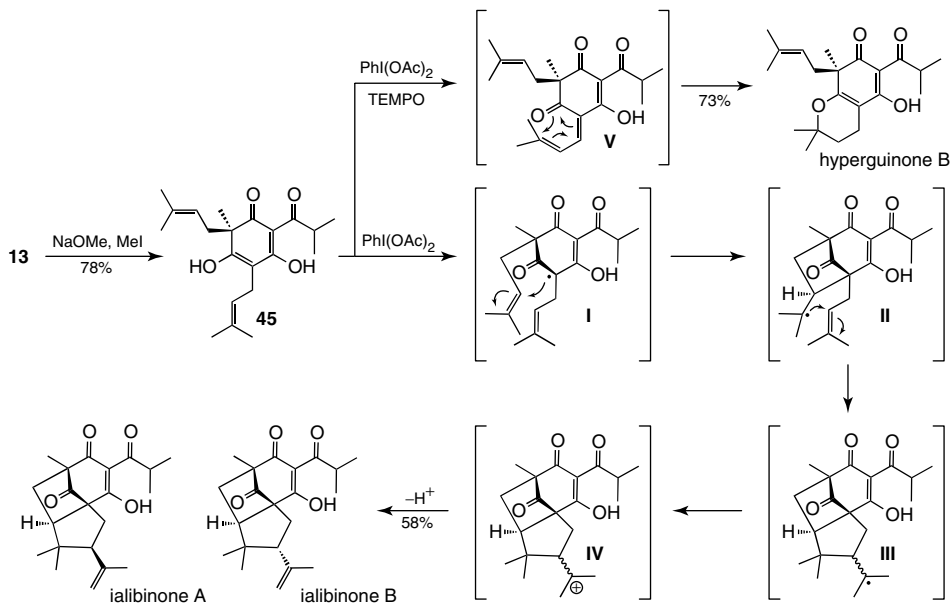
The authors have also evaluated a Michael addition for construction of the type A skeleton, in a similar manner as that presented above, in the synthesis of clusianone [45]. This approach was only successful for the synthesis of compounds non-substituted at C8 (Scheme 12.7). These results illustrate the difficulty in synthesizing the fully functionalized carbon framework of type A PPAPs, where the quaternary bridgehead C1 is located next to the fully substituted C8.



Scheme 12.7 Construction of a type A PPAP motif via an intramolecular Michael addition.

12.2.3.3 Biomimetic Synthesis of (\pm)-Ialibinone A and B and (\pm)-Hyperguinone B

Very recently a biomimetic synthesis of PPAPs isolated from *Hypericum papuanum* was reported. Scheme 12.8 depicts the total synthesis of racemic ialibinones A and



Scheme 12.8 Biomimetic synthesis of PPAPs via oxidative cyclization reactions.

B and hyperguinone B [47]. The synthesis of all three natural products started with compound **13**, which is the same starting material used in Couladouros' approach and similar to that used in Porco's synthesis of clusianone. The C-methylation of **13** was carried out by treatment with NaOMe–MeI to give **45** in very good yield. Reaction of **45** with $\text{PhI}(\text{OAc})_2$ gave a 1 : 1 mixture of (\pm)-ialibinones A and B in 58% combined yield. The reaction most likely proceeds via an initial single-electron oxidation of **45** to give intermediate I. A stereoselective 5-*exo*-trig cyclization of this radical onto the pendant prenyl group would then give tertiary radical II, which can undergo a second cyclization onto the other prenyl group to give the tertiary radical III. Finally, an additional single-electron oxidation of III would lead to the tertiary carbocation IV and then to the final racemic natural products. In contrast, treatment of **45** with $\text{PhI}(\text{OAc})_2$ in the presence of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) gave (\pm)-hyperguinone B in 73% yield. The reaction presumably proceeds via hydride abstraction by the *in situ* generated TEMPO cation to give intermediate V, which undergoes a 6π -electrocyclization leading to the pyran ring of hyperguinone B.

12.2.4

Non-biomimetic Synthesis of PPAPs

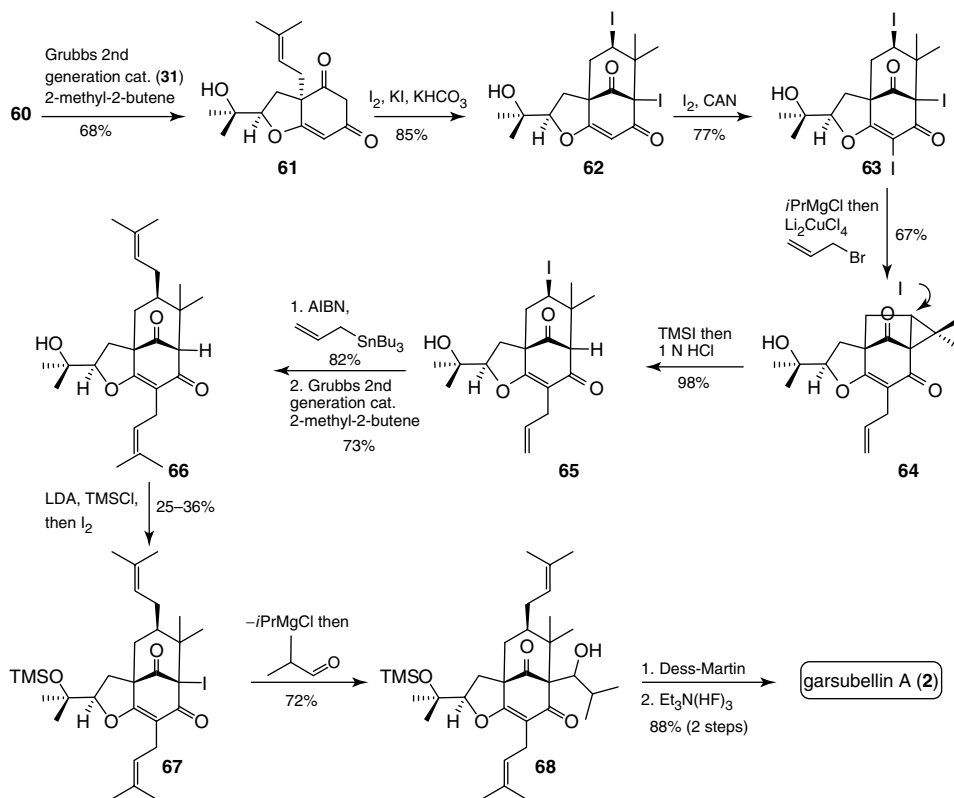
In addition to the biomimetic approaches toward PPAPs, presented above, there are also a few non-biomimetic total syntheses that have been reported in the literature in the past few years. In this section we present briefly the total synthesis of garsubellin A, nemorosone, and hyperforin – representative members of type A PPAPs – and the synthesis of clusianone, a type B PPAP.

12.2.4.1 Total Synthesis of Garsubellin A

The Shibasaki synthesis of garsubellin A (**2**) is summarized in Scheme 12.9 [38]. An interesting structural feature of this natural product is the additional ring (C-ring) that is formed by oxidative cyclization of a prenyl group. Key to the synthesis was the conversion of compound **47** into **51** via two steps: (i) a stereoselective Claisen rearrangement of **47** \rightarrow **49** via intermediate **48**, which installs the alkene substituents at C1 and C5 *syn* to each other, and (ii) a ring-closing metathesis using the Hoveyda–Grubbs catalyst **50**. The fused tetrahydrofuran ring was constructed after allylic oxidation, hydrolysis of the carbonate, and Wacker oxidative cyclization. Finally, Stille coupling of **53** with tributyl(prenyl)tin completed the total synthesis of (\pm)-garsubellin A.

The Danishefsky synthesis of garsubellin A (**2**) is highlighted in Schemes 12.10 and 12.11 [39]. Compound **54**, representing the B ring of the target molecule, was converted into acetonide **55** in five steps in 43% overall yield (Scheme 12.10). Treatment of **55** with HClO_4 at 80°C led to a mixture of bicyclic adducts **57** and **58** that, upon further heating, produced initially **59** and ultimately adduct **60** (71% isolated yield).

Iodocarbocyclization of **61** provided **62** using standard iodolactonization conditions (Scheme 12.11). Conceptually, this reaction is similar to the Se-mediated

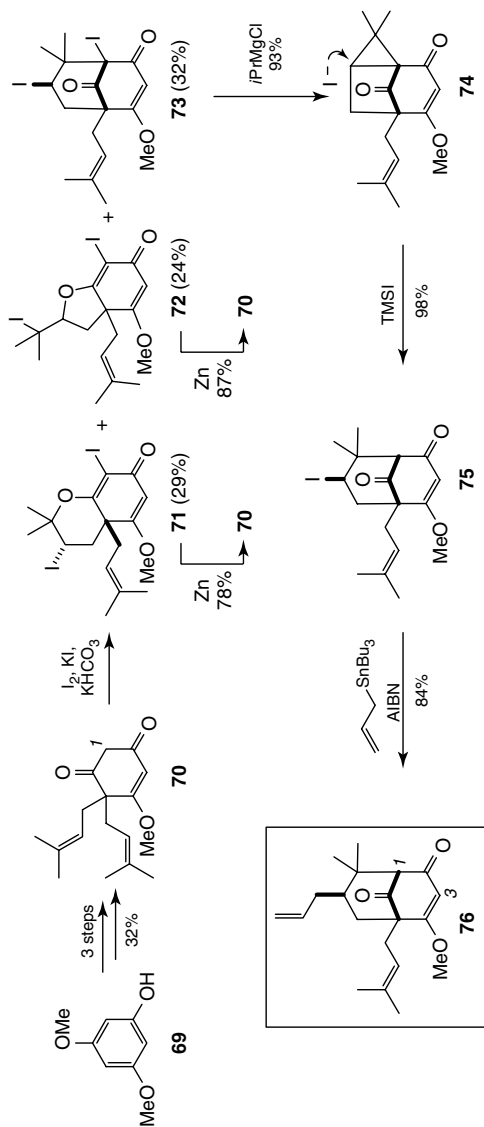


Scheme 12.11 Total synthesis of garsubellin A by the Danishefsky group.

12.2.4.2 Total Synthesis of Nemorosone and Clusianone through Differentiation of “Carbanions”

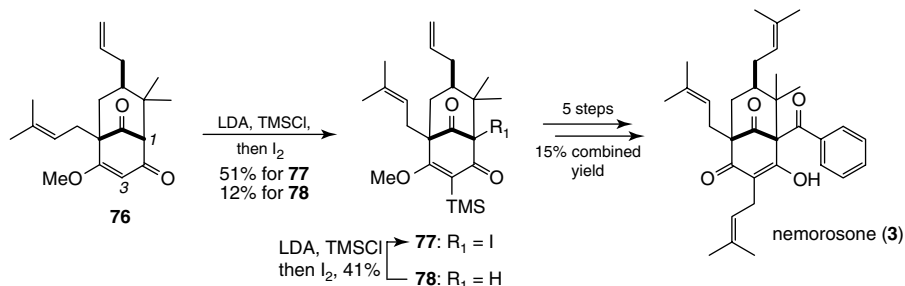
More recently, the Danishefsky group has extended the above strategy to the synthesis of nemorosone (**3**) and clusianone (**4**) [41]. These natural products proved to be more demanding targets than garsubellin A, due to the lack of the furano-fused ring that provides further stability to the molecule. A significant complication arose during the iodonium-induced carbocyclization of compound **70** (Scheme 12.12). In addition to the desired product **73**, the authors obtained substantial quantities of **71** and **72** (53% combined yield). Most likely, these side products were formed via O-alkylation of an iodonium intermediate. Gratifyingly, treatment of **71** and **72** with zinc in aqueous THF could regenerate **70** in high yield, allowing recycling of the starting material. Reaction of **73** with isopropylmagnesium chloride produced cyclopropane adduct **74** that, in turn, upon treatment with TMSI gave rise to bicyclic motif **75**. Radical allylation then produced compound **76**, a common intermediate in the synthesis of nemorosone and clusianone.

Completion of the synthesis of **3** and **4** required differentiation of carbons C1 and C3 of common intermediate **76**. To this end, treatment of **76** with an excess



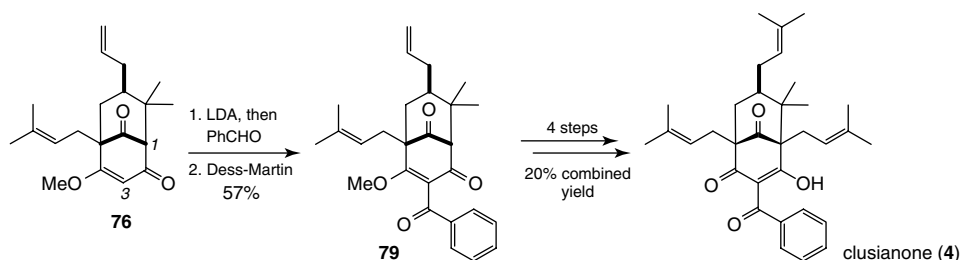
Scheme 12.12 Formation of the common intermediate **70** towards the synthesis of nemorosone and clusianone.

of LDA (lithium diisopropylamide) and TMSCl (trimethylsilyl chloride) followed by oxidative quenching with iodine provided **77** in moderate yield along with **78**, which can in turn be converted into **77** by applying the same reaction conditions (Scheme 12.13). The total synthesis of **3** was completed after, first, acylation of C1 and then lithium-mediated allylation at C3.



Scheme 12.13 Total synthesis of nemorosone.

On the other hand, treatment of **76** with LDA without the presence of TMSCl and quenching with benzaldehyde gave rise to **79**, after acylation at C3 (Scheme 12.14). Conversion of **79** into its C1 iodo derivative and transformation of the iodo group into an allyl functionality concluded the synthesis of clusianone (**4**).

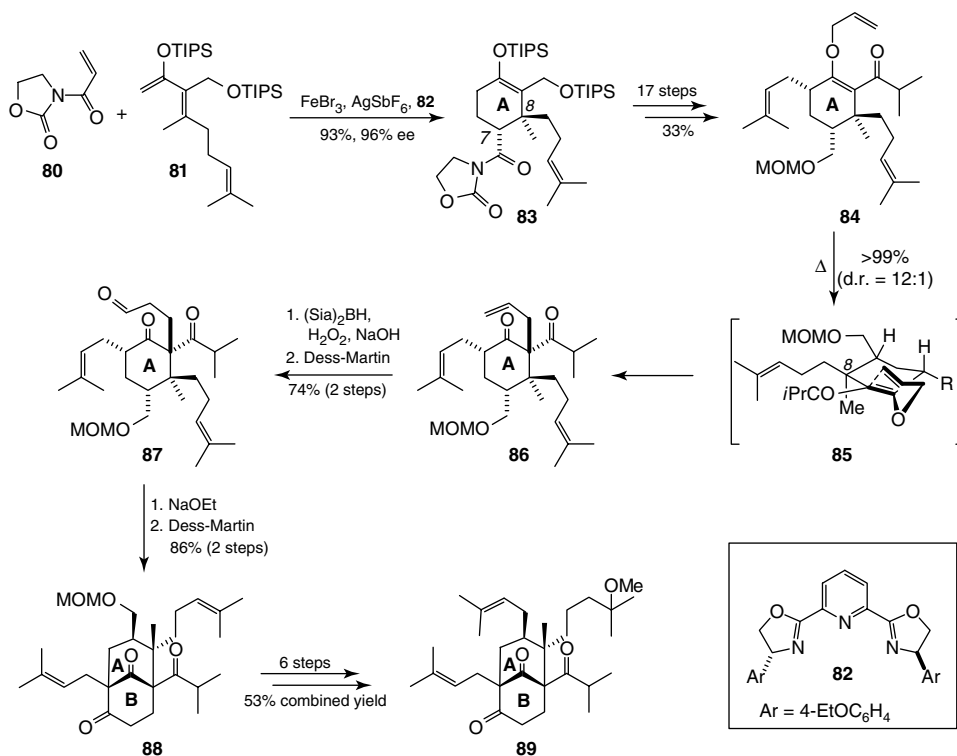


Scheme 12.14 Total synthesis of clusianone by the Danishefsky group.

12.2.4.3 Total Synthesis of (–)-Hyperforin

(+)-Hyperforin (**1**), a type A PPAP, contains an additional chiral quaternary center compared to the other herein mentioned acylphloroglucinols, thus presenting greater difficulties towards its total synthesis. In early 2010 a catalytic asymmetric total synthesis of (–)-hyperforin was published by Shibasaki and coworkers [42]. Notably, this is the first catalytic asymmetric synthesis of any PPAP, since the previously reported asymmetric synthesis of clusianone involved a late-stage kinetic resolution (Section 12.2.4.4) [50].

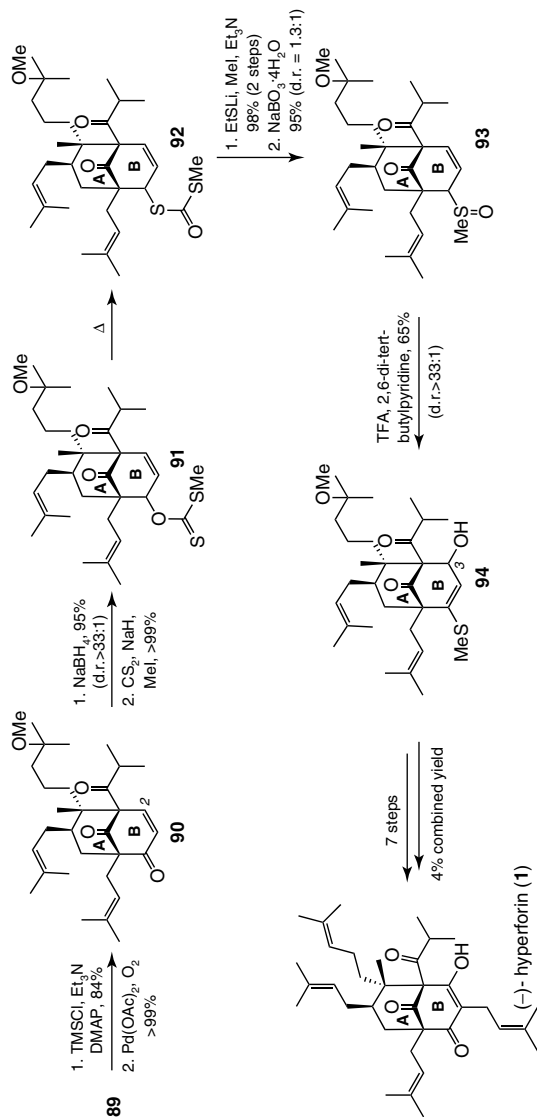
Compound **83**, having the desired stereochemistry at C7 and C8 carbons, was constructed via a catalytic asymmetric Diels–Alder reaction between **80** and **81** (Scheme 12.15). Compound **83** was then converted into allyl ether **84**, which underwent a stereoselective Claisen rearrangement to form ketone **86**. This rearrangement proceeded with high selectivity from the β face, most likely due to the



Scheme 12.15 Catalytic asymmetric synthesis of the bicyclic framework of hyperforin.

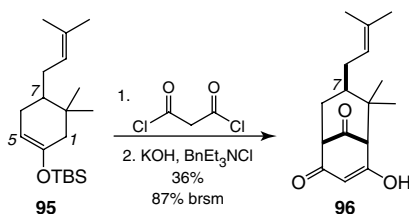
pseudo-axial orientation of the methyl group at C8, which blocks the α face, as shown in intermediate **85**. Initial attempts to form the B ring of hyperforin via an olefin metathesis approach proved unsuccessful, prompting the development of an alternative strategy using an intramolecular aldol reaction [51]. With this in mind, hydroxylation and oxidation of the terminal alkene of **86** produced aldehyde **87** that after intramolecular aldol reaction and oxidation gave rise to bicyclic adduct **88**. Peripheral decoration of **88** afforded ketone **89** in six steps (53% combined yield).

Scheme 12.16 shows the completion of the (–)-hyperforin synthesis from **89**. Oxidation of C2 proved to be more difficult than anticipated since any attempt at nucleophilic addition in **90** failed. Furthermore, efforts to induce a [3.3] sigmatropic rearrangement of xanthate **91** led to dithionate **92** after a [1.3] rearrangement. This finding, however, allowed the use of a vinylogous Pummerer rearrangement for the oxidation of C2. To this end, dithionate **92** was converted into methylsulfoxide **93** and, after Pummerer rearrangement, to the desired allylic alcohol **94** (three steps, 61% combined yield). Finally, the prenyl group at C3 was installed by intramolecular allyl transfer via a π -allyl-palladium intermediate and cross metathesis to give (–)-(1).

Scheme 12.16 Total synthesis of *ent*-hyperforin.

12.2.4.4 Total Synthesis of Clusianone

In 2006 the Simpkins laboratory reported the first total synthesis of (\pm)-clusianone using as a key step a regioselective lithiation of enol ether derivatives [43]. The construction of the bicyclic core was inspired by the approach described by Spessard and Stoltz (Scheme 12.17) [52]. These authors accomplished a diastereoselective conversion of enol ether **95** into bicyclic trione **96**, using dichloromalonate as the electrophile. Notably, construction of the bicyclo[3.3.1]nonane by the use of malonyl dichloride was reported initially by Effenburger [53].

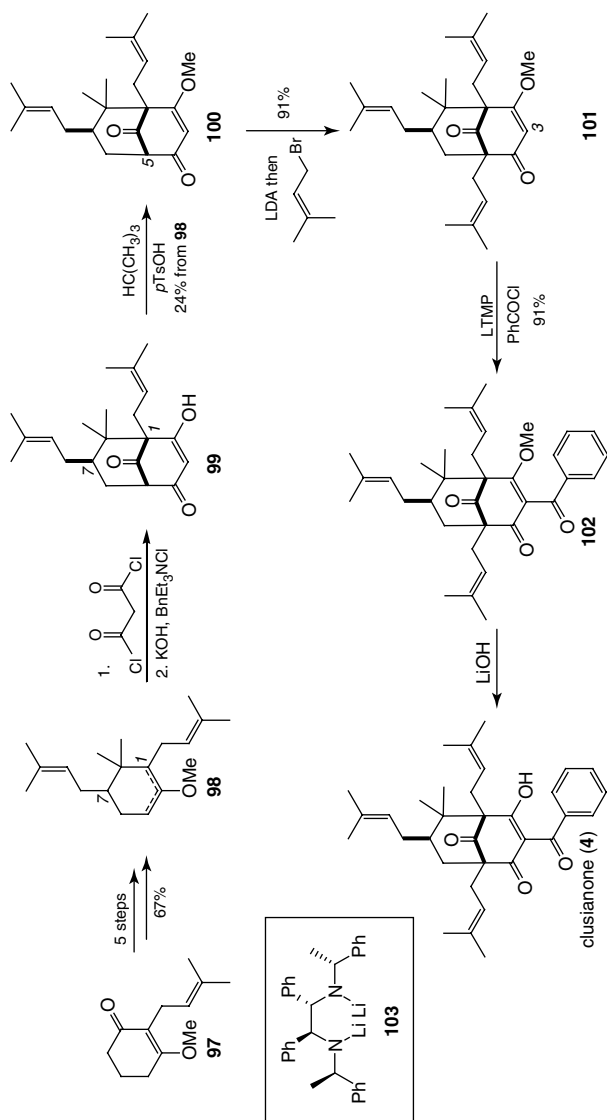


Scheme 12.17 Model studies toward the synthesis of bicyclo[3.3.1]nonane-2,4,9-triones.

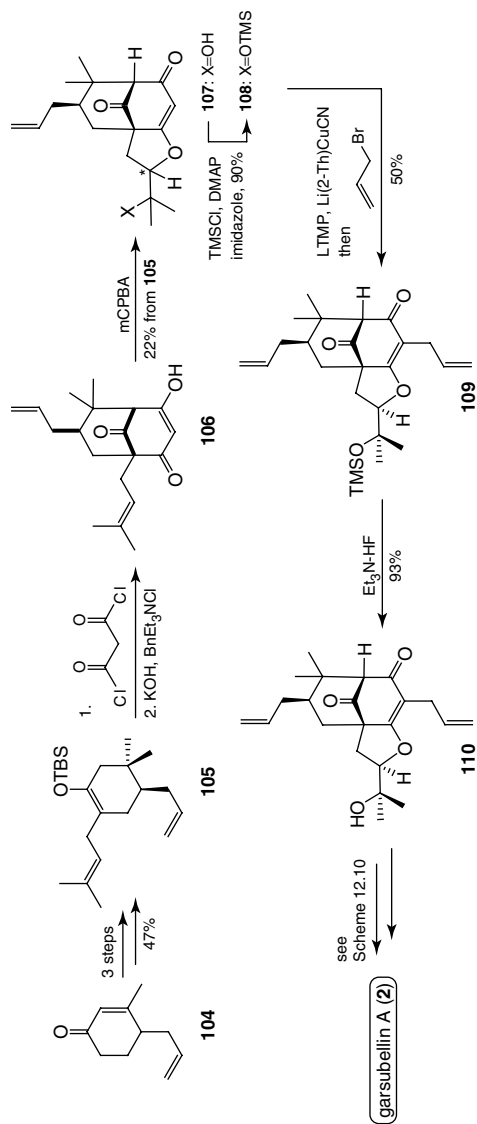
Scheme 12.18 summarizes Simpkins' synthesis of clusianone [43]. Notably, enol ether **98** was pre-functionalized with a prenyl group at the C1 center to overcome problems deriving from the steric hindrance of this center after the formation of the bicycle. In fact, Danishefsky had already reported similar problems during the installation of such a substituent in the synthesis of garsubellin A (Section 12.2.4.1). Interestingly, prenylation of **100** at the bridgehead position afforded compound **101** in high yield. The same efficiency was observed for the acylation of C3 by the action of lithium tetramethyl piperidine (LTMP), leading, after hydrolysis, to racemic clusianone. Importantly, prenylation of racemic **100** using a chiral base, such as **103**, led to selective alkylation of the (–) isomer via a kinetic resolution process. This reaction allowed assignment of the absolute configuration of clusianone, isolated from *Clusia torresii*, as the (+) isomer. Interestingly, the (–) isomer of **4** matches the data of a compound reported by a Brazilian group [54]. Based on this, it is possible that clusianone exists in Nature in either enantiomeric form [50].

The above strategy was then extended to a formal synthesis of garsubellin A [40]. Specifically, application of the Effenburger-type cyclization to **105** afforded **110**, a compound isolated by the Danishefsky group *en route* to the synthesis of garsubellin A (Scheme 12.19) [39].

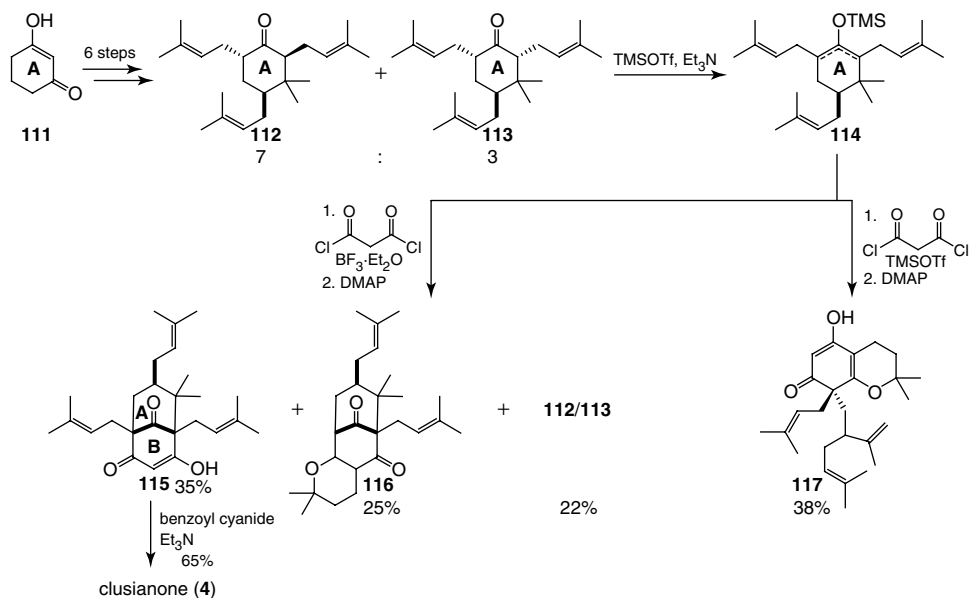
Marazano and coworkers have also published their synthesis of (\pm)-clusianone incorporating a similar approach [44]. In their synthesis the starting enol ether **114** contains all three prenyl groups, yielding, after reaction with dichloromalonate, compound **115**, which has both quaternary bridgehead centers (Scheme 12.20). Notably, formation of the desired product **115** was accompanied with side product **116** and desilylated compounds **112/113**. Under different Lewis acid catalysis, this reaction produced significant amounts of bicyclic adduct **117**. In principle the double alkylation of **114** to **115** has some biosynthetic relevance. However, the sequence of ring construction (formation of the B ring at the end) is not in accordance with the biosynthesis scenario in which the B ring is formed at the



Scheme 12.18 Total synthesis of clusianone by the Simpkins group.



Scheme 12.19 Formal synthesis of garsubellin A by the Simpkins group.



Scheme 12.20 Total synthesis of clusianone by Marazano and coworkers.

beginning. Based on this, such an approach cannot be considered as a biomimetic strategy.

12.2.5

Concluding Remarks

In short, biomimetic approaches toward PPAPs are based on double alkylation on a functionalized B ring with an electrophile. These strategies require fewer steps in a linear sense and can potentially produce the natural product target in higher yield. The total synthesis of racemic clusianone, by the Porco group [45], was completed in seven synthetic steps, starting from the biosynthetic intermediate **27**, with a total yield of 25%. The approach is based on biosynthetic hypotheses that involve alkylative dearomatization of phloroglucinols and carbocation-mediated cyclization. This method can be applied with minor changes for the synthesis of other type B PPAPs and can also be implemented to the synthesis of adamantane-like PPAPs. The strategy presented by Couladouros *et al.* [46] can give access in few steps and satisfactory yields to several compounds possessing the bicyclic framework of natural products for SAR (structure–activity relationship) studies. In contrast to other reported methods, the two quaternary centers (C1 and C8) are connected during the cyclization step, thereby eliminating steric hindrance problems encountered in other reported approaches. A similar approach, and the most recently published biomimetic synthesis of PPAPs [47], starts with alkylation of a functionalized B ring, yet formation of the second ring occurs after oxidative cyclization. On the other hand, the non-biomimetic strategies require many steps,

as shown by the Danishefsky group syntheses of garsubellin A, nemorosone, and clusianone that were completed in 17, 14, and 12 steps respectively, or by the synthesis of (–)-hyperforin by the Shibasaki group, which required 44 steps. The advantage of the non-biomimetic approaches is that they are more flexible in terms of the synthetic route followed to the target and can lead to asymmetric final products. In such a way the asymmetric total synthesis of (–)-hyperforin was achieved.

In addition to the synthetic strategies described herein, there is still ongoing interest towards the synthesis of PPAPs and their analogs. New approaches have appeared in the literature, aimed at a facile method for the construction of the bicyclic core of PPAPs that will allow easier access to those compounds for their biological evaluation and SAR studies [55–61].

12.3

Polyprenylated Xanthones

12.3.1

Introduction and Chemical Classification

Polyprenylated xanthones constitute a subclass of a larger class of compounds known as xanthones, all bearing a dibenzo- γ -pyrone scaffold [62]. Polyprenylated xanthones can further be divided, according to their oxidation degree, into mono-, di-, tri-, and so on, oxygenated compounds. Recently, the classification, synthesis, and biological evaluation of simple xanthones have been reviewed extensively [62–71]. In this chapter we focus on the so-called caged *Garcinia* xanthones (CGXs), owing to their similarities (isolation, biosynthesis) to the aforementioned polyprenylated phloroglucinols.

Caged xanthones are natural products isolated from plants of the genus *Garcinia* (Guttiferae family) that are found in lowland rainforests of India, Indochina, Indonesia, West and Central Africa, and Brazil [1, 72]. The most studied member of this family is gambogic acid (**118**), a compound isolated from gamboge, the resin of *Garcinia hanburyi* (Figure 12.4). Common to the chemical structure of all CGXs is a xanthone backbone in which the C ring has been converted into an unusual 4-oxa-tricyclo[4.3.1.0^{3,7}]dec-8-en-2-one ring (caged) scaffold (see structure **120**) [73, 74]. This general motif can be further decorated with different substituents on the aromatic ring A and/or can be oxidized to yield a wide range of compounds, representative members of which are shown in Figure 12.4. This concept is exemplified by the structure of forbesione (**125**), a natural product isolated from *Garcinia forbesii* [75] and *Garcinia hanburyi* [76]. Specifically, prenylation at the C5 center of forbesione (gambogic acid numbering) gives access to the gaudichaudione scaffold [77], represented here by deoxygaudichaudione A (**126**) [78]. Alternatively, prenylation of **125** at C5 followed by cyclization with the pendant phenol gives access to the morellin scaffold, represented here by desoxymorellin (**123**) [79]. Progressive oxidations at the C29 center of **123** produce morellinol (**122**), morellin

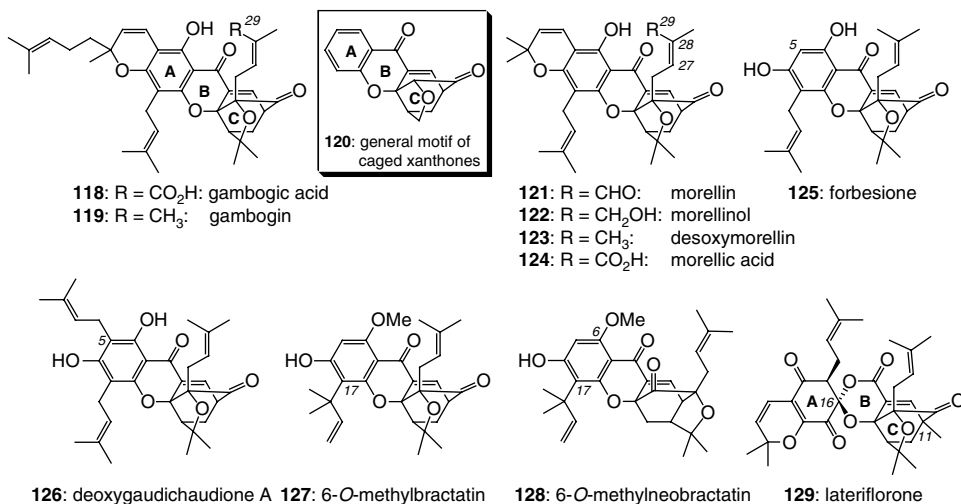


Figure 12.4 Representative members of the caged *Garcinia* xanthere family.

(121), and morellic acid (124) [80]. Geranylation at the C5 center of forbesione affords, after formation of the pyran ring, gambogin (119) [81]. Further oxidation at C29 leads to the structure of gambogic acid (118) [76]. Compounds arising from isomerization around the C27=C28 double bond have also been isolated. Thus, morellin (121), having the *cis* configuration about the C27=C28 double bond, is known to isomerize to the *trans* isomer, isomorellin [82]. Similar observations have been reported for gambogic acid [83]. In contrast, the bractatin subfamily (127, 128) [84, 85] provides examples of forbesione-type natural products that contain a reverse prenyl group at the C17 center.

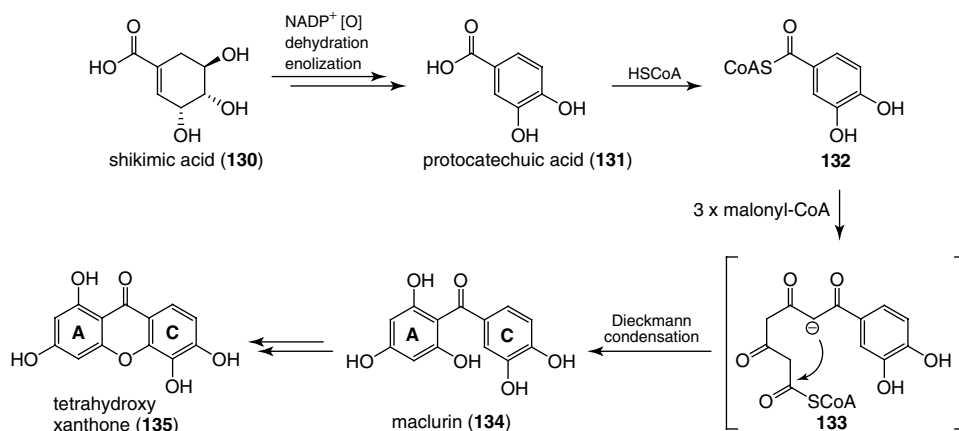
Although the vast majority of the CGXs contain the general motif 120, there are a few examples of natural products with alternative cage structures or with additional oxidations of the xanthere motif. For instance, 6-O-methylneobractatin (128) is the only natural product known to contain a modified caged scaffold, referred to as the *neo-motif* [84, 85]. In addition, in the structure of lateriflorone (129) [86], the caged motif is attached to a spiroxalactone core, which is likely a product of oxidation of the xanthere B ring.

Biologically, CGXs are known for their antimicrobial and anticancer activities and are widely used as herbal medicines in traditional Eastern medicine [83, 87–89]. Initial biological studies with semi-purified gamboge extracts documented its antiprotozoal activities, thus lending support for its indigenous use in the treatment of enteric diseases [90–94]. It has also been shown that morellin (121) and gambogic acid (118) exhibit a high specific growth inhibitory effect on Gram-positive bacteria *in vitro* and a protective action against experimental staphylococcal infections in mice [95–98]. In addition to their antimicrobial activity, most CGXs have received a great deal of attention for their anticancer activity [99, 100]. An ever increasing body of evidence indicates that these compounds are cytotoxic against various cancer cell lines at low micromolar concentrations [79].

12.3.2

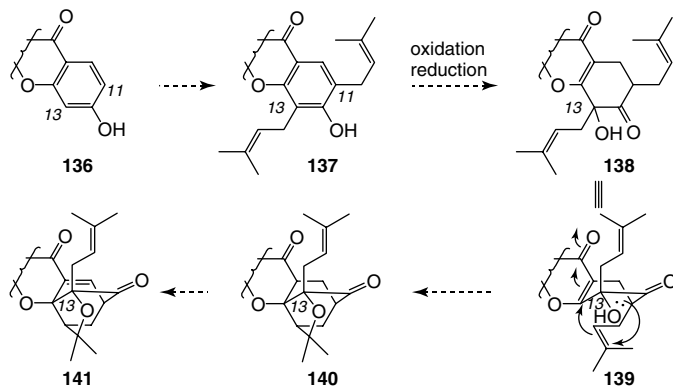
Biosynthesis of Polyprenylated Xanthenes

Biosynthetically, the xanthone backbone of the caged compounds is assumed to derive from common benzophenone intermediates that are synthesized in a similar manner to that described for PPAPs. Their oxygenation patterns indicate a mixed shikimate (formation of C ring)–acetate (formation of A ring) pathway [101–106]. The proposed biosynthesis is exemplified with the synthesis of maclurin (134) and 1,3,5,6-tetrahydroxyxanthone (135) in Scheme 12.21 [107–110]. Shikimic acid, derived from the shikimic pathway, can be converted into protocatechuic acid (131) after oxidation, dehydration, and enolization. Reaction of 131 with coenzyme A (HSCoA) can produce activated ester 132 that can further react with three units of malonyl-coenzyme A to yield intermediate 133. A Dieckmann condensation gives rise to benzophenones, such as maclurin (134). Depending upon the benzophenone produced, this is a branch point in the biogenesis of other benzophenone-type natural products. It is generally accepted that xanthenes such as 1,3,5,6-tetrahydroxyxanthone (135) are formed by means of phenolic coupling of the benzophenone precursors [109, 110].



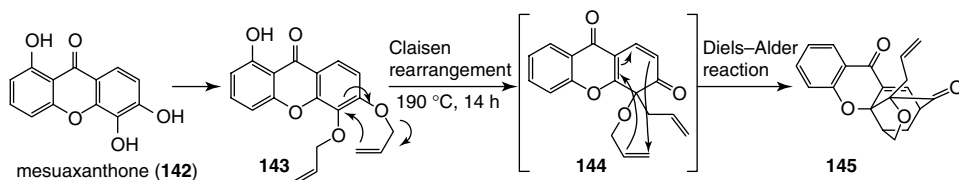
Scheme 12.21 Biosynthesis of the backbone of xanthenes in higher plants.

Different hypotheses have been proposed for the biosynthetic conversion of simpler xanthenes such as 135 into the more complex caged structures. The first proposal, illustrated in Scheme 12.22, requires at an early stage the prenylation of a xanthone, as 136, at C11 and C13 positions to produce 137 [111]. An oxidation–reduction–oxidation sequence of reactions is then required to form the final caged structure 141. Essential to this hypothesis is a presumed nucleophilic attack by the C13 tertiary alcohol of 138 on the pendant prenyl group that could initiate a cyclization cascade leading to the caged structure 140. Nonetheless, as shown with structure 139, neither the molecular geometry nor the reactivity required for this cascade is optimal, making this proposal unlikely.



Scheme 12.22 Proposed biosynthesis of the CGX motif via a cascade of nucleophilic attacks.

A more plausible biosynthetic scenario stems from the pioneering work of Quillinan and Scheinmann [112]. In their work, they proposed that the caged motif can be formed via a Claisen rearrangement followed by a Diels–Alder reaction on the intermediate dienone (Scheme 12.23). The authors also provided experimental evidence in support of the Claisen/Diels–Alder reaction cascade: upon heating of compound **143**, prepared by allylation of mesuaxanthone B (**142**), at 190 °C for 14 h they observed products showing NMR signals characteristic of cage structure **145**. At present, there have been no labeling experiments testing the biosynthetic feasibility of the Claisen/Diels–Alder reaction cascade. Nonetheless, additional support for the validity of this proposal was obtained by recent studies in which retro-Diels–Alder fragments have been detected in mass spectroscopy studies of several CGXs [113, 114].



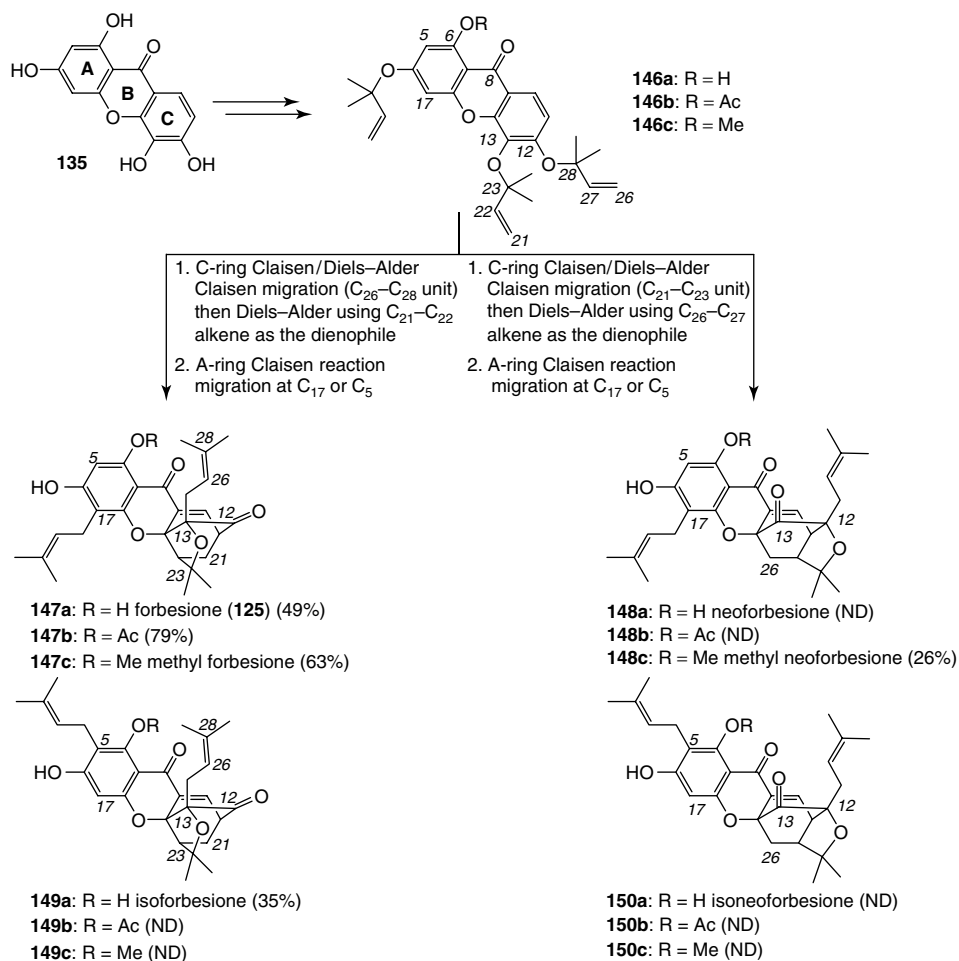
Scheme 12.23 Proposed biosynthesis of the CGX motif via a Claisen/Diels–Alder reaction cascade.

12.3.3

Biomimetic Synthesis of Caged *Garcinia* Xanthenes

Inspired by Quillinan and Scheinmann's proposed biosynthesis, both the Nicolaou [115] and Theodorakis [116] groups evaluated the tandem Claisen/Diels–Alder sequence for the synthesis of representative members of the CGX family. Their work provided further support for the proposed biosynthetic hypothesis.

Starting from the tris-allylated xanthone **146** both groups investigated the possibility of synthesizing forbesione (**125**) in one pot. In principle, exposure of such motif to heat could produce four products arising from a combination of two competing C-ring Claisen/Diels–Alder reactions, leading to regular and neo-caged motifs, and two A-ring Claisen migrations, producing C17 and C5 prenylations. Working with methoxy xanthone **146c**, the Nicolaou group was the first to describe its conversion into methyl forbesione **147c** and methyl neoforbesione (**148c**) in a 2.4 : 1 ratio and 89% combined yield (Scheme 12.24) [115]. On the other hand, studies by the Theodorakis group showed that heating of xanthone **146a** led only to the isolation of forbesione **147a** and isoforbesione (**149a**). The neo-C-ring isomers



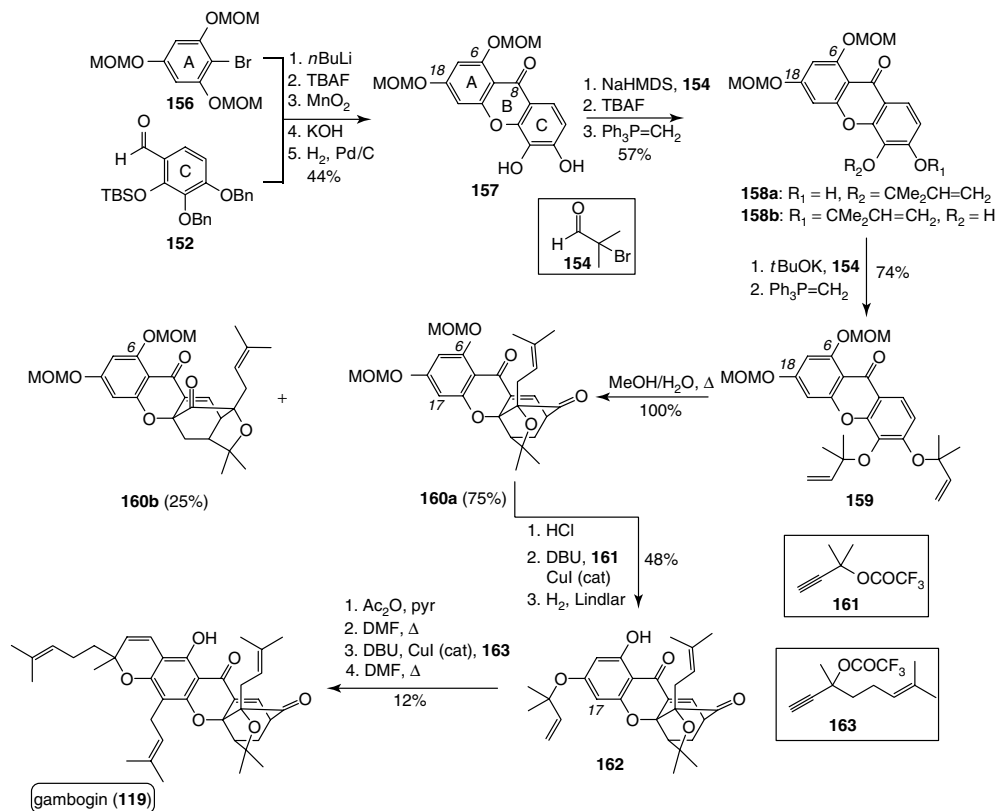
Scheme 12.24 Biomimetic synthesis of forbesione (**125**) and related structures via a Claisen/Diels–Alder/Claisen reaction cascade.

148a and **150a** were not detected in this case. More impressively, the O6-acetylated xanthone **146b** afforded, upon heating, solely acetyl forbesione (**147b**) [116]. Similar observations have been reported more recently by other groups [117]. The above-described results towards the synthesis of forbesione along with the results from several model studies [118] can be summarized as follows:

- The C-ring Claisen/Diels–Alder rearrangement proceeds first and is followed by an A-ring Claisen reaction.
- The site-selectivity of the A-ring Claisen rearrangement (C17 versus C5 prenylation) is controlled by the steric and electronic effects of the C6 phenolic substituent.
- The site-selectivity of the C-ring Claisen/Diels–Alder reaction is attributed to and governed by the electronic density of the C8 carbonyl-group. Being para to the C12 allyloxy unit, the electron-deficient C8 carbonyl carbon polarizes selectively the O–C28 bond and facilitates its rupture. In turn, this leads to a site-selective Claisen rearrangement of the C12 allyloxy unit onto the C13 center, thereby producing exclusively the regular caged motif found in the structure of forbesione (**147a**).
- Substitution of the C6 phenol can regulate the electronic density of the C8 carbonyl group, thus affecting the site selectivity of the C-ring Claisen/Diels–Alder reaction.

The experimental findings on the tandem Claisen/Diels–Alder/Claisen reaction cascade provide useful insights regarding the biosynthesis of all known CGXs [118]. All these natural products (representative examples shown in Figure 12.4) share a common caged motif, exemplified by structure **120**, except for 6-*O*-methylneobractatin (**128**), which contains the neo-caged motif. The remote electronic effects of the seemingly innocuous 6-*O*-methyl group may explain the concomitant biosynthesis of both 6-*O*-methylbractatin (**127**) and 6-*O*-methylneobractatin (**128**).

Studies by the Nicolaou group have shown that the Claisen/Diels–Alder reaction can be accelerated in the presence of polar solvents [119]. For instance, as depicted for the synthesis of gambogin (Scheme 12.25), the conversion of allyl ether **159** into caged structure **160a** and the neo-isomer **160b** was dramatically accelerated upon changing the solvent from benzene to DMF to a MeOH–water (1:2) mixture. It has been proposed that polar aprotic solvents, such as DMF, and more impressively protic solvents, such as water, can accelerate the Claisen rearrangement by stabilizing its polar transition state [120–124]. The concurrent acceleration of the Diels–Alder component of this cascade may be due to the hydrophobic effect of water [125] rather than to a polarity or hydrogen-bonding phenomena [126–128]. Computational studies on the above-mentioned reaction have also concluded that the Claisen rearrangement is reversible and the energetics of the irreversible Diels–Alder cyclization can determine the product formation [129].

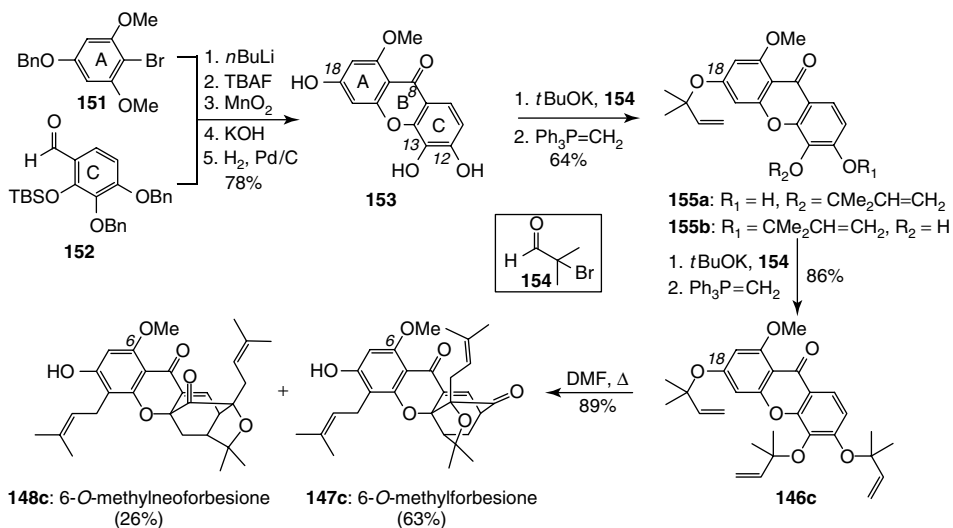


Scheme 12.25 Biomimetic synthesis of gambogin by the Nicolaou group.

12.3.3.1 Nicolaou Approach to Forbesione and Gambogin

Scheme 12.26 depicts the synthetic strategy developed by Nicolaou and Li [115] for the synthesis of 6-O-methylforbesione (**147c**). Xanthone **153** was generated in five steps and in 78% combined yield starting from the aryl bromide **151** and the benzaldehyde **152**. Treatment of **153** with α -bromoisobutyraldehyde (**154**) under basic conditions followed by Wittig olefination produced a mixture of the diallylated compounds **155a** and **155b** that, after reiteration of the alkylation/olefination reactions, yielded the triallylated xanthone **146c**. Heating of **146c** in DMF at 120 °C induced the Claisen/Diels–Alder/Claisen reaction cascade to produce compound **147c** along with its neo-isomer **148c** in 89% combined yield.

In a similar manner, the total synthesis of gambogin was achieved starting from the partially protected xanthone **157** (Scheme 12.25) [119]. This time the Claisen/Diels–Alder reaction proceeded quantitatively in refluxing MeOH–H₂O (1 : 2) to produce the regular caged motif **160a** along with its neo-isomer **160b** in a 3 : 1 ratio. Methoxymethyl (MOM) deprotection of **160a** followed by propargylation with alkyne **161** at C18 and partial reduction with Lindlar catalyst gave rise to compound **162**. Gambogin was then synthesized after a sequence of four reactions



Scheme 12.26 Biomimetic synthesis of 6-O-methylforbesione (**147c**).

that included: (i) acetylation of C6 phenol; (ii) Claisen rearrangement to install the prenyl group at C17; (iii) propargylation of the resulting phenol with alkyne **163**; and (iv) Claisen rearrangement to form the dihydropyran ring of the natural product.

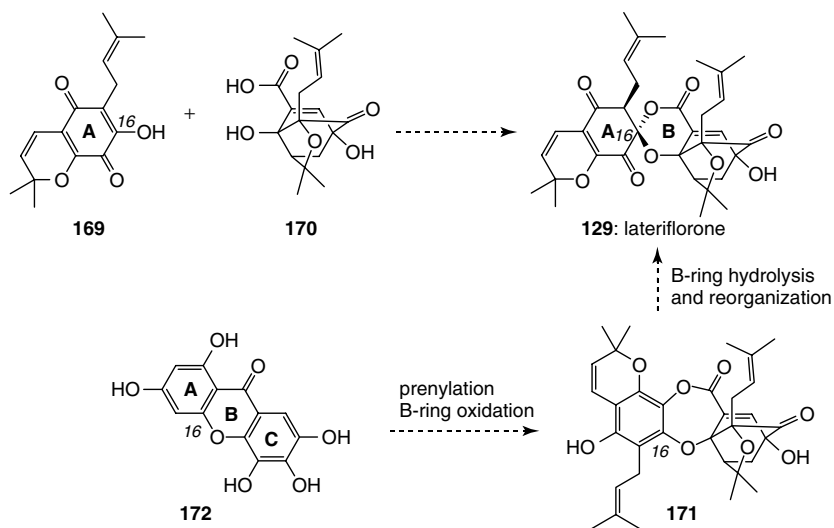
12.3.3.2 Theodorakis' Unified Approach to Caged *Garcinia* Xanthenes

The common structural motif of most CGXs suggests that they can be synthesized by functionalizing the A ring of forbesione. Along these lines, the Theodorakis group developed a strategy that uses forbesione (**125**) to gain access to representative members of the gaudichaudiones, morellins, and gambogins [118].

As illustrated in Scheme 12.27, ZnCl₂-mediated condensation of phloroglucinol (**164**) with benzoic acid **165** produced xanthone **135**. Propargylation of **135** with the propargyl chloride **166** followed by partial reduction using Lindlar catalyst and acetylation of phenol at C6 gave rise to compound **146b**. Heating of **146b** (DMF, 1 h, 120 °C) set the stage for a site-selective Claisen/Diels–Alder/Claisen reaction cascade that produced, after deprotection of the C6 acetate, forbesione (**125**) in 72% combined yield. Further decoration of the A ring of forbesione gave access to more functionalized CGX family members. Specifically, propargylation of the C18 phenol of forbesione with chloride **166** afforded, after Lindlar reduction and Claisen rearrangement, deoxygaudichaudione A (**126**). On the other hand, propargylation of **125** and immediate Claisen rearrangement formed desoxymorellin (**123**). Finally, condensation of forbesione (**125**) with citral (**168**) in Et₃N produced gambogin (**119**).

12.3.3.3 Synthesis of Methyllateriflorone

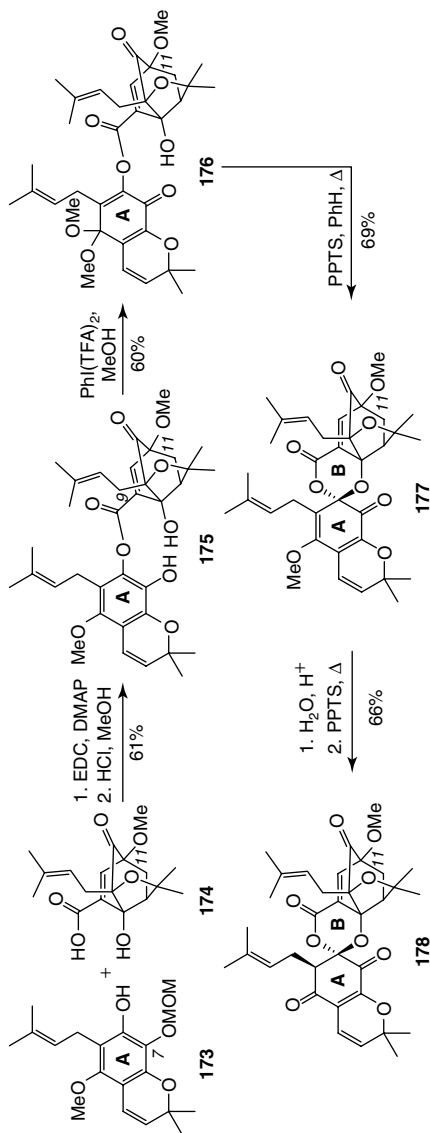
It has been proposed that the unprecedented spiroxalactone motif of lateriflorone (**129**) could be formed by condensation of two fully functionalized fragments, **169** and **170** (Scheme 12.28) [86]. An alternative and likely more biosynthetically



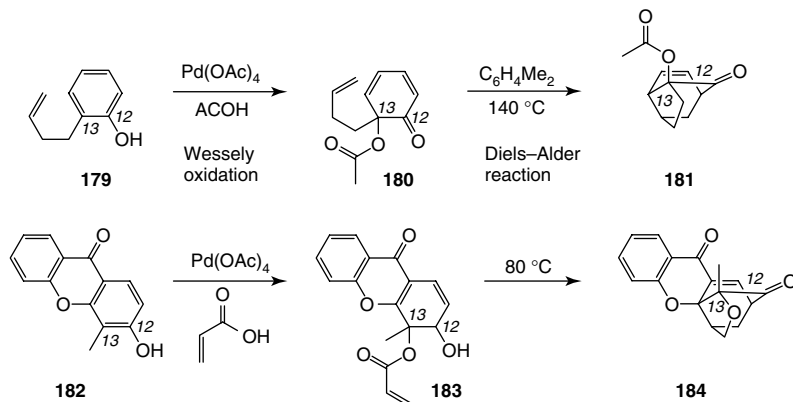
Scheme 12.28 Proposed biosynthesis of lateriflorone (**129**).

of phenol **179** with $\text{Pb}(\text{OAc})_4$ in acetic acid produced 2,4-cyclohexadienone **180** that, upon heating at 140°C , formed compound **181** (gambogic acid numbering) (Scheme 12.30) [131]. In a previous study, xanthene **182** was treated with lead tetraacrylate [formed *in situ* by $\text{Pb}(\text{OAc})_4$ and acrylic acid] to produce dienone **183** and, after an intramolecular Diels–Alder reaction, caged compound **184** [132].

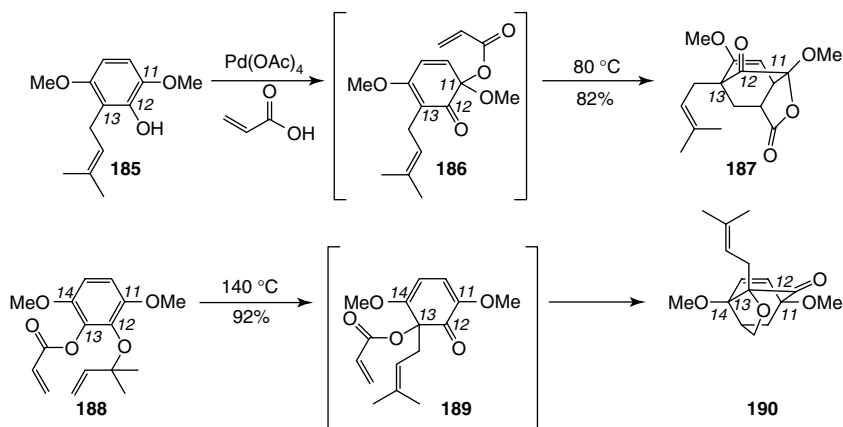
Theodorakis and coworkers [133] investigated the application of the Wessely/Diels–Alder strategy for the synthesis of a more hydroxylated caged motif related to the structure of lateriflorone (**129**) (Figure 12.4). Treatment of **185** with $\text{Pb}(\text{OAc})_4$ in acrylic acid–dichloromethane produced, after heating in refluxing benzene (80°C), tricyclic lactone **187** in 82% combined yield (Scheme 12.31). Crystallographic studies established that **187** is a constitutional isomer of the desired structure **190** and is reminiscent of the so-called neo-caged structure. The connectivity of compound **187** suggested that during the Wessely oxidation the acrylate unit was attached exclusively at the more electronically rich C11 center of **185**, instead of the desired C13 carbon. In turn, this produced dienone **186** that subsequently underwent an efficient Diels–Alder cycloaddition with the pendant acrylate dienophile. To alter the connectivity of the caged structure, one could have the acetoxy group preinstalled at the C13 center and promote the migration of the prenyl group. Along these lines, heating of allyl ether **188** in *m*-xylene (140°C) gave rise exclusively to caged motif **190** via a Claisen rearrangement and Diels–Alder cycloaddition. The selectivity of the Claisen rearrangement at the C13 center can be explained by considering that intermediate **189** has the necessary geometry that allows it to be trapped as the Diels–Alder adduct.



Scheme 12.29 Total synthesis of C11-methylateriflorone (178).



Scheme 12.30 Representative examples of caged structures, **181** and **184**, formed via a Wessely oxidation/Diels-Alder reaction cascade.



Scheme 12.31 Synthesis of caged structures **187** and **190**.

12.3.3.5 Concluding Remarks

CGXs are a family of polyprenylated xanthenes that have a remarkable chemical structure, inspiring biosynthesis, and significant medicinal potential. Their chemical structure is represented by an unusual xanthone backbone in which the C ring has been converted into a 4-oxa-tricyclo[4.3.1.0^{3,7}]dec-8-en-2-one (caged) scaffold. Their biosynthesis is proposed to involve a cascade of Claisen and Diels-Alder reactions and has provided the inspiration for the development of efficient laboratory syntheses of the parent molecules and designed analogs. Their medicinal value stems from their use in ethnomedicine and remains still largely unexplored [134]. The recent advances in the synthesis of these compounds have paved the way for the generation of analogs with the desired pharmacological and biological profile. In particular, the biosynthetically inspired Claisen/Diels-Alder reaction

cascade can reliably produce the caged motif of CGXs in excellent yields. On the other hand, the non-biomimetic Wessely/Diels–Alder strategy can form analogs of the caged motif that cannot be made by fragmentation of the natural products. It is very likely that these strategies will be used for the development of more potent CGX analogs. One limitation of both strategies is that, at present, they both deliver racemic mixtures of the caged structures. Thus, the development of an enantioselective variant of the Claisen/Diels–Alder and Wessely/Diels–Alder reaction cascades still needs to be addressed.

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