Chapter 5
Chemistry of Sesquiterpene Lactones

Francis J. Barrios

Abstract Sesquiterpene lactones are a class of bioactive plant products that display an array of biological and pharmacological activities such as antimicrobial, cytotoxic, anti-inflammatory, antiviral, antibacterial, and antifungal. A vast amount of sesquiterpene molecular structures has been reported, and the largest numbers of these types of compounds can be isolated from the Asteraceae (formerly known as Compositae) family. An important feature of these sesquiterpene lactones is the presence of an α-methylene-γ-lactone moiety which can react with nucleophilic sulfhydryl groups present in enzymes, proteins, and glutathione. The differences in the activities found among sesquiterpene lactones are due to the number of alkylating elements, lipophilicity, and chemical environment. This chapter discusses some of the synthetic pathways and summarizes the chemical transformation and biological activities of these sesquiterpene lactones.

Keywords Sesquiterpene lactones · Synthesis · Chemical transformation · α-Methylene-γ-lactone · Germacranolides · Guaianolides

5.1 Synthesis of Sesquiterpene Lactones

The assembly of the core skeleton and the formation of the α-methylene-γ-lactone moiety are two essential steps for the synthesis of sesquiterpene lactones exhibiting a variety of skeleton structures. In the following sections, the different routes for the generation of the ten-membered germacrene carbocycle and the hydroazulene skeleton that is characteristic of the guaiane sesquiterpenoid will be presented. Methodologies for the formation of the α-methylene-γ-lactone and strategies for the synthesis and semi-synthesis of germacranolide and guaianolide derivatives will be considered.

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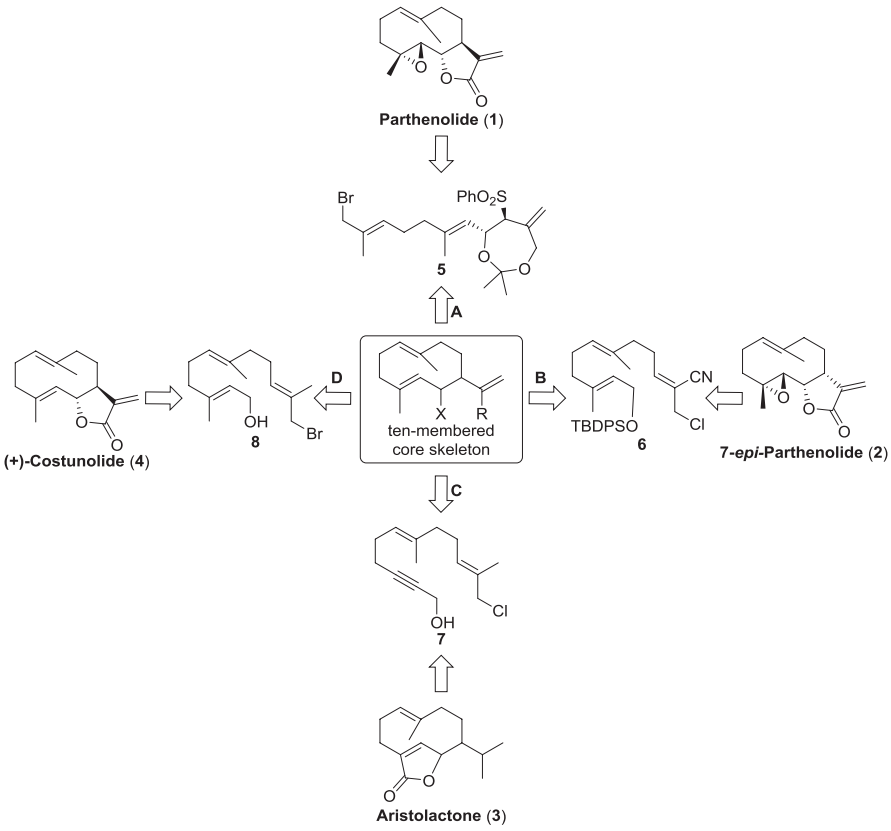
5.1.1 General Strategies for the Synthesis of the Germacranolide Skeleton

Germacranolides are a type of germacrene sesquiterpene lactones that contain a unique ten-membered carbocyclic skeleton that is fused with a γ-lactone. Many classes of cyclic terpenes are made from germacrene intermediates, and it has been demonstrated that these terpenes exhibit a broad range of biological activities. This important intermediate can be converted into other sesquiterpene subclasses such as eudemanes and guaianes, because of the accessibility of germacrene precursors in great quantity (Adio 2009; Bulow and Konig 2000). Although the total synthesis of germacranolides has been a field of intense research for decades, the synthesis of the ten-membered carbocyclic core has remained a challenge. The cyclodecadiene core is broken down to render cyclized and rearranged fragmented products upon subjection to acidic, basic, and high temperature conditions. Moreover, at room temperature, germacranolides exist as conformer isomers, a phenomenon that creates a challenge for the purification and analysis of the product (Azarken et al. 2008; Minnaard et al. 1999). The general synthetic method for germacrene lactones comprises four basic steps: (a) the synthesis of medium size rings by a direct method, (b) the regio- and stereoselective installation of the (E) and (Z) bonds on the ten-membered ring system, c) the highly selective introduction of functional groups, and d) the efficient synthesis of the α-methylene-γ-lactone group. A wide range of methodologies for the synthesis of the ten-membered core skeleton of germacranolides have been reported and are shown in Scheme 5.1. Based on the biosynthetic route of sesquiterpene lactones, the synthesis of parthenolide **1** was accomplished by strategy **A**, in which the synthesis of the ten-membered ring core skeleton starts by the intramolecular α-alkylation of a sulfone derivative **5** (Yang et al. 2015). The synthesis of 7-*epi*-parthenolide **2** was obtained by strategy **B**, in which the synthesis of the α-methylene-γ-hydroxyl nitrile germacrene system begins with an intramolecular Barbier-type reaction involving compound **6** (Long et al. 2014). In the synthesis of aristolactone **3**, the generation of the germacrene skeleton was performed by method **C**, in which the cyclization of the chloro alcohol **7** precursor is carried out (Marshall et al. 1987). Finally, in strategy **D**, used for the synthesis of costunolide **4**, the bromo alcohol cyclization precursor **8** was used for the generation of the key ten-membered ring skeleton (Shibuya et al. 1986). Baran et al. have achieved the assembly of the carbocyclic terpene backbone, epoxy-germacrenol, by means of a low oxidation state (cyclase phase) followed by oxidative modifications (oxidase phase). This key intermediate allows the access to a wide variety of family members, such as selinanes, guaianes, and elements in a different manner (Foo et al. 2012).

5.1.2 Synthesis of the α-Methylene-γ-Lactone Moiety

The α-methylene-γ-lactone moiety is an important substructural unit found in a vast array of biologically active natural products, such as sesquiterpenoids. They exhibit a variety of biological properties, including antibacterial, cytotoxic,



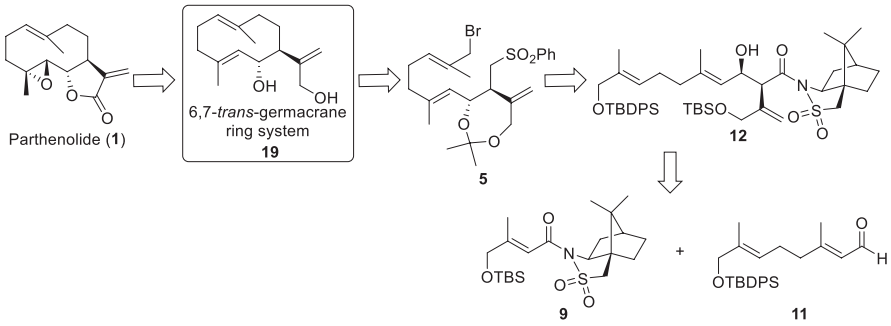
Scheme 5.1 Selected strategies for the generation of germacranolide ten-membered skeleton

anti-inflammatory, antioxidant, and antimicrobial (Chen et al. 2008; Mang et al. 2006; Reynolds et al. 2003; Siedle et al. 2004; Kummer et al. 2005). Taking into account the significance of this functional group, several strategies have been developed to synthesize α-methylene-γ-lactones; and these methodologies have been applied to the synthesis of natural products, such as sesquiterpene lactones. The preparation of α-methylene-γ-butyrolactones involving the reaction of the γ-butyrolactone enolate with formaldehyde, followed by base-mediated elimination is a commonly used process. Metz et al. have employed this method for the synthesis of the antileukemia agents (−)-eriolanin and (−)-eriolangin (Merten et al. 2004, 2006). A similar approach using lithium diisopropylamine (LDA) and gaseous formaldehyde has been described by Mukai for the total synthesis of (+)-achalensolide (Hirose et al. 2008). Instead of formaldehyde, the Eschenmoser's salt was employed in the total synthesis of the guaianolide arglabin (Kalidindi et al. 2007). During the latter process, a tertiary amine is formed, which traps the lactone enolate derivative with the Eschenmoser's salt. The subsequent methylation reaction followed by the Hofmann elimination provided the desired product. The deprotonation/Eschenmoser's salt

methylation pathway has been used by Kobayashi et al. in the total synthesis of (−) diversifolin, an inhibitor of the NF-κβ transcription factor (Nakamura et al. 2009). The ten-membered ring of (−)-diversifolin has been generated through the Grubbs ring-closing metathesis. Then, deprotonation with LDA and subsequent treatment with Eschenmoser's salt afforded the spontaneous generation of the corresponding α-methylene-γ-butyrolactone without the addition of methyl iodide to promote the Hofmann elimination (Mihelcic and Moeller 2003). Another widely employed strategy involves the oxidation of an α-phenylselenide intermediate followed by β-elimination to introduce unsaturation (Justicia et al. 2008; Fuchs et al. 2007; Arantes et al. 2009). This approach has been employed by Shishido et al. in the synthesis of the antibacterial terpenoid (−)-xanthanin (Yokoe et al. 2008). The treatment of α-methyl-γ-butyrolactone with LDA followed by diphenyl diselenide forms the α-phenylselenide intermediate. Oxidation and then elimination provided the anticipated methylene lactone. An efficient palladium-catalyzed carbonylation/lactonization sequence was used by Martin et al. to achieve the total synthesis of (+)-8-epixanthatin, a sesquiterpene lactone known to exhibit antimalarial and antitumor activities (Kummer et al. 2005). In the preparation of 6-epicostunolide, Massanet et al. have efficiently applied manganese dioxide to oxidize an allylic alcohol to render the corresponding lactone (Azarken et al. 2008). A one-pot methodology was developed in the early 1970's by Dreiding and Schmidt to synthesize an α-methylene-γ-butyrolactone moiety. They have demonstrated that a functionalized organometallic reagent could be generated by treating 2-bromomethyacrylic esters with zinc. The addition of an aldehyde followed by spontaneous cyclization renders α-methylene-γ-butyrolactone. This widely used methodology is one of the simplest and most direct methods for the synthesis of α-methylene-γ-butyrolactone (Kitson et al. 2009). Novel methods for the efficient preparation of α-methylene-γ-butyrolactones have been devised by chemists working in organic synthesis. These methodologies have been applied to develop new compounds for biological screening and to design synthesis routes for the generation of complex natural products.

5.1.3 Strategy to the Total Synthesis of Parthenolide

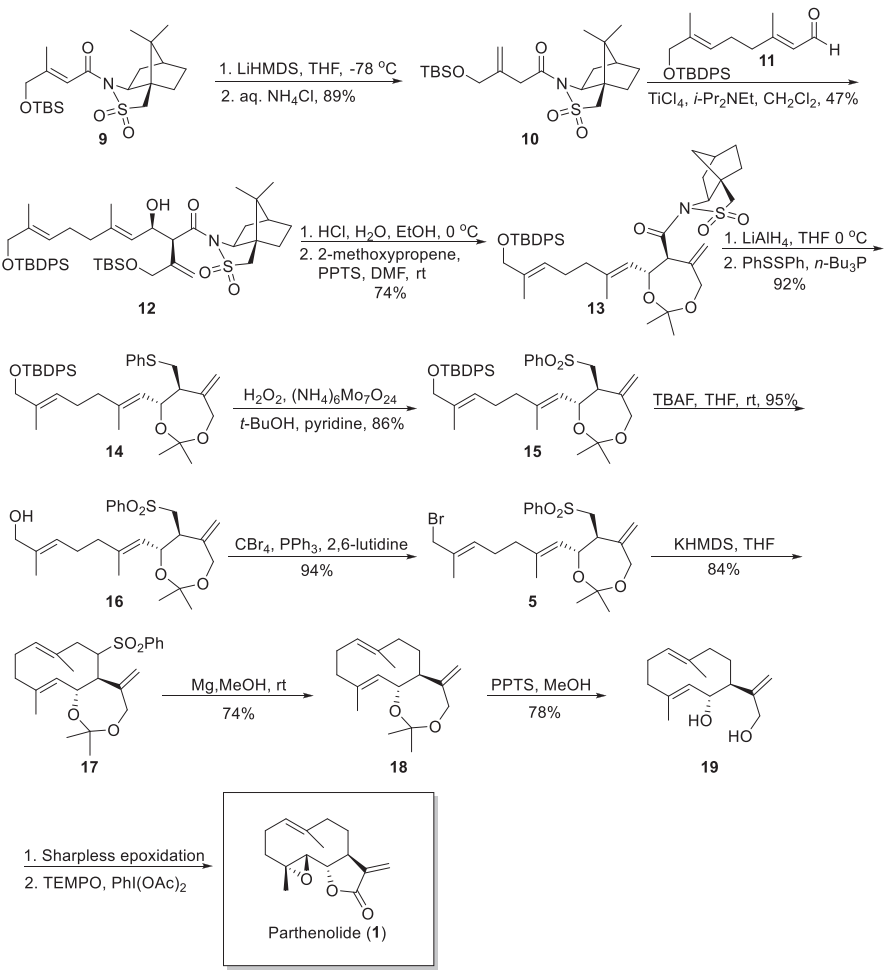
Parthenolide belongs to the sesquiterpene lactone class of natural products and is the active principle isolated from feverfew, a the traditional herbal remedy (Neukirch et al. 2003). It has been demonstrated that parthenolide targets leukemia stem cells with high selectivity in the presence of normal hematopoietic stem cells (Guzman et al. 2005). The asymmetric total synthesis of parthenolide **1** developed by Chen et al. (Yang et al. 2015) has been based on the biosynthetic route of sesquiterpene lactones. This synthetic route involves an aldehyde and a β, γ-unsaturated chiral sulfonylamide as starting materials from which, after a series of chemical transformations, the synthesis of the desired product is achieved. The strategy **A**, shown in Scheme 5.1, has been used for the generation of the ten-membered carbocyclic ring intermediate of parthenolide **1**. Analyzing the retrosynthetic pathway of Scheme 5.2, compound **1** was



Scheme 5.2 Retroanalysis to the synthesis of parthenolide (**1**)

planned to be synthesized from the 6,7-*trans*-germacrane ring system **19** that could be generated from the sulfone **5** through an intermolecular α-alkylation. Sulfone **5** has been obtained from compound **12** which could be manipulated by the aldol reaction between β, γ-unsaturated sulfonyl amide **9** and aldehyde **11**.

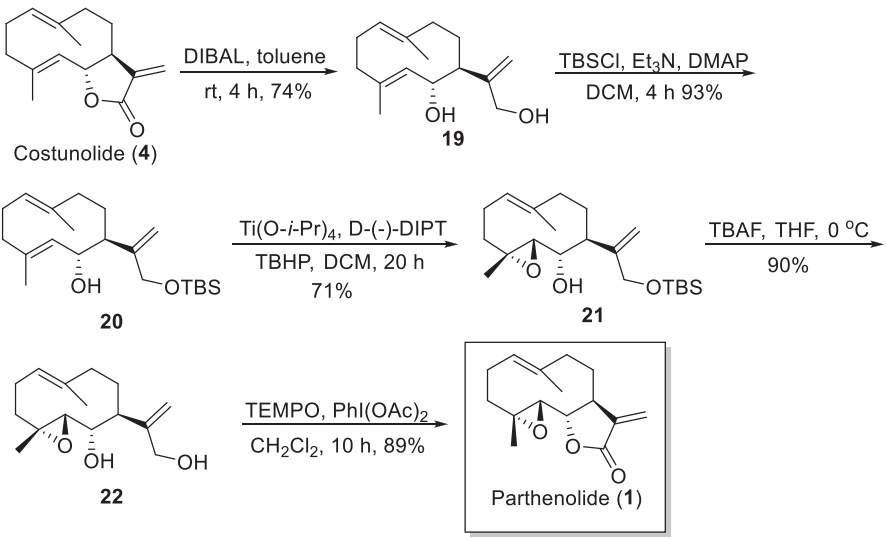
The steps employed to obtain parthenolide **1** are depicted in Scheme 5.3. The first step was the synthesis of the unsaturated sulfonyl amide **9**, and this was accomplished by a Horner–Wadsworth–Emmons reaction between a ketone and diethylphosphonoacetic acid in two stages, with an overall yield of 59%. The aldol reaction between compound **10** and aldehyde **11** in the presence of titanium tetrachloride ($TiCl_4$) and di-isopropylethyl amine (i-Pr_2NEt) in dichloromethane (CH_2Cl_2) afforded compound **12** with the desired 6,7-stereochemistry as the major product and with 47% yield. The selective cleavage of the *tert*-butyldimethylsylyl ether (TBS) protecting group of compound **12** with HCl in ethanol at 0 °C followed by the treatment with 2-methoxypropene furnished acetonide **13**. The thioether product **14** was then obtained by a reduction reaction followed by the treatment of the crude product with diphenyl disulfide/tri-*n*-butylphosphine. The oxidation of compound **14** with hydrogen peroxide/ammonium heptamolybdate (H_2O_2/$(NH_4)_6Mo_7O_{24}$) in *tert*-butanol (*t*-BuOH) and pyridine provided product **15** in with 86% yield. Removal of the *tert*-butyldiphenylsilyl ether (TBDPS) group of compound **15** with tetrabutylammonium fluoride afforded alcohol **16** with 95% yield. Alcohol **16** was then converted to its corresponding brominated compound **5** with tetrabromomethane (CBr_4), triphenylphosphine (PPh_3), and 2,6-lutidine as a base at 0 °C with 94% yield. The treatment of this compound with four equivalents of potassium bis-(trimethylsilyl)amide (KHMDS) rendered the desired cyclized product **17** with 84% yield. The sulfone moiety on the cyclized product **17** was then removed by adding magnesium/methanol (Mg/MeOH) furnishing product **18** with 74% yield. The solution of pyridinium *p*-toluenesulfonate in methanol has proved to be a good reagent to remove the acetonide group of **18** to generate the desired ten-membered carbocyclic germacrene ring intermediate **19**. The Sharpless epoxidation of diol **19** followed by oxidation with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and (diacetoxyiodo)benzene ($PhI(OAc)_2$) afforded parthenolide **1** with 62% yield.



Scheme 5.3 Synthesis of parthenolide **1**

5.1.4 Semi-synthesis of Parthenolide

The semi-synthesis strategy is one that often involves large and complex molecules isolated from natural sources as starting materials. This methodology becomes useful when the precursor molecule contains a structurally complex moiety that is either too costly or too challenging to be generated by total synthesis. The simplest strategy for the synthesis of a complex natural product is to start with molecules that



Scheme 5.4 Semi-synthesis of parthenolide

already contain the desired germacranolide skeleton and, through a series of chemical transformations, the synthesis of the target molecule is achieved. The stereoselective synthesis of parthenolide **1** involves a protection-free strategy employing the natural product costunolide **4** as starting material (Scheme 5.4) (Long et al. 2013). Costunolide has been found to be a good substrate for the synthesis of parthenolide because this germacranolide is readily isolated from the roots of *Saussurea lappa* (Zhang et al. 2011). Costunolide **4** is treated with diisobutylaluminum hydride (DIBAL) in toluene at room temperature to obtain the key germacrane intermediate **19** with 79% yield. The treatment of **19** with *tert*-butyldimethylsilyl chloride (TBSCl) furnished the protected primary alcohol **20** with a good yield. The selective epoxidation of the C4–C5 bond of compound **20** with titanium isopropoxide (Ti(O-*i*-Pr)$_4$), (−)-diisopropyl D-tartrate (D-(−)-DIPT), and *tert*-butyl hydroperoxide (TBHP) in CH_2Cl_2 at room temperature afforded compound **21** with 71% yield. The deprotection of compound **21** followed by oxidation with TEMPO and PhI(OAc)$_2$ rendered parthenolide **1** with an 80% yield over two steps.

5.1.5 General Strategies for the Synthesis of Guaianolides

Guaianolides are an important and diverse group of biologically active sesquiterpenes. They are often used as scaffolds for the design of new active molecules. The guaianolides central skeletal backbone consists of a 5,7,5-ring system that exists in

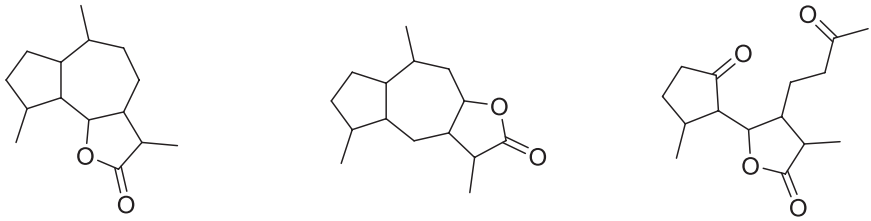
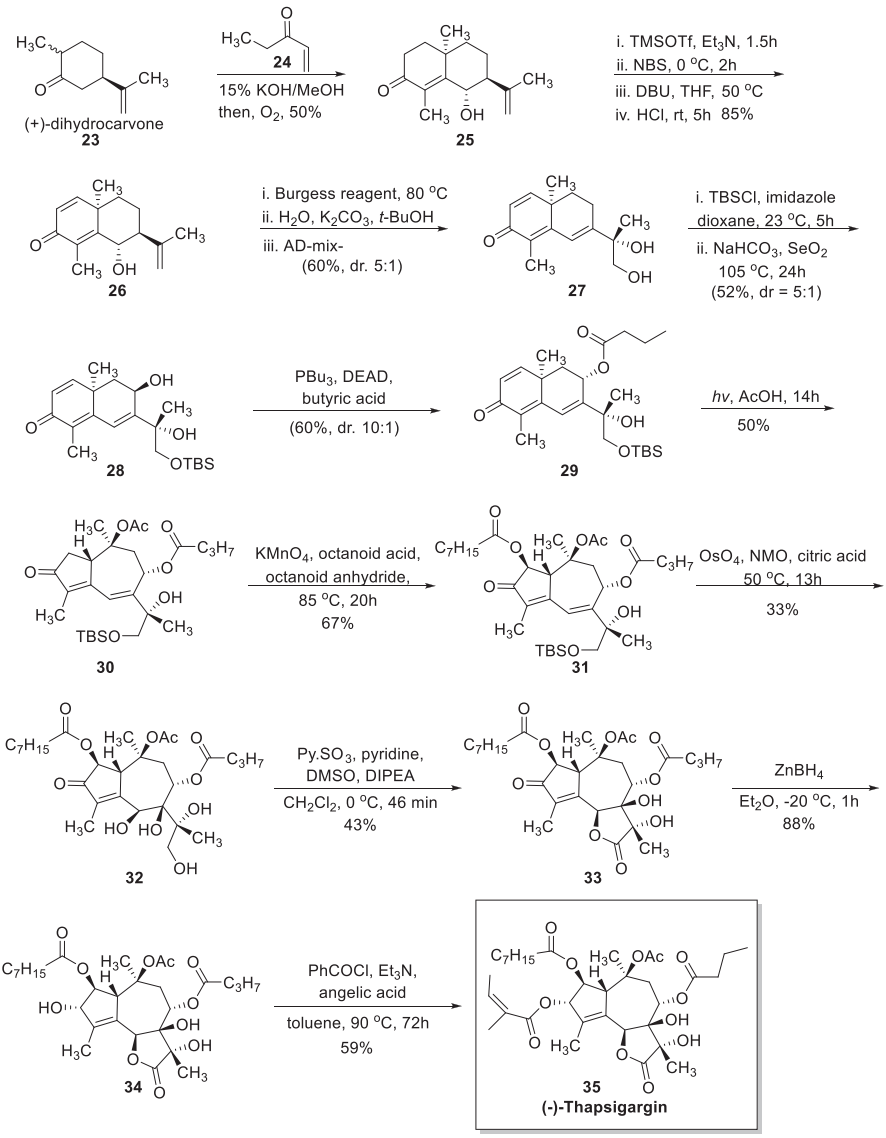


Fig. 5.1 Guaianolides central skeleton backbone

the forms of the guaian-6,12-olide and the guaian-8,12-olide structures. The least common skeleton is that corresponding to the *seco*-guaianolides, in which a C–C single bond is broken in one of the rings (Fig. 5.1). Several synthetic methodologies for the generation of the hydroazulene skeleton have been developed, including ring rearrangement or enlargement and intra- and intermolecular cycloaddition. The aim of this section is to provide a summary of the relevant and updated synthetic approaches for the synthesis of this important class of natural products.

The use of rearrangement reactions is one of the most common synthetic strategies implemented in the generation of the hydroazulene skeleton of guaianolides. An interesting and convenient methodology developed by Baran et al. includes two key steps: (1) the application of the classic photosantonin rearrangement and (2) the installation of multiple oxygen atoms in the guaianolide skeleton to achieve the scalable total synthesis of (−)-thapsigargin **35** (Scheme 5.5) (Chu et al. 2017). Thapsigargin is known to be a potent inhibitor of the sarco-endoplasmic reticulum Ca^{+2} ATP-dependent (SERCA) pump protein, and it has proved to be a good candidate in many medical areas (Andrews et al. 2007). The main challenge in the synthesis of **35** has been to efficiently install six additional oxygen atoms with the correct stereochemical configuration to obtain a guaiane with a high oxidation level. The generation of the skeletal carbons of the target molecule starts with the Robinson annulation and further γ-hydroxylation between (+)-dihydrocarvone **23** and ethyl vinyl ketone **24** affording decalin **25** with 50% yield. The one-pot gram scale bromination/elimination sequence of **25** furnished the dienone **26** with 85% yield. The treatment of compound **26** with the Burgess reagent followed by the chemo- and diastereoselective dihydroxylation of the terminal olefin with AD-mix-α rendered diol **27** with a good yield. The diastereoselective synthesis of the allylic alcohol **28** has been accomplished by first, the selective protection of the primary alcohol and then the in situ allylic C–H oxidation with selenium dioxide (SeO_2). The butyrate was then installed with the required stereochemical configuration at C–8 by the Mitsunobu inversion with butyric acid. The ring enlargement was achieved by the irradiation of a 0.01 M solution of **29** in glacial acetic acid with an Hg lamp. This gram-scale process provided the key guaianolide skeleton intermediate **30** with good stereoselectivity and with 50% yield. The treatment of **30** with potassium per-



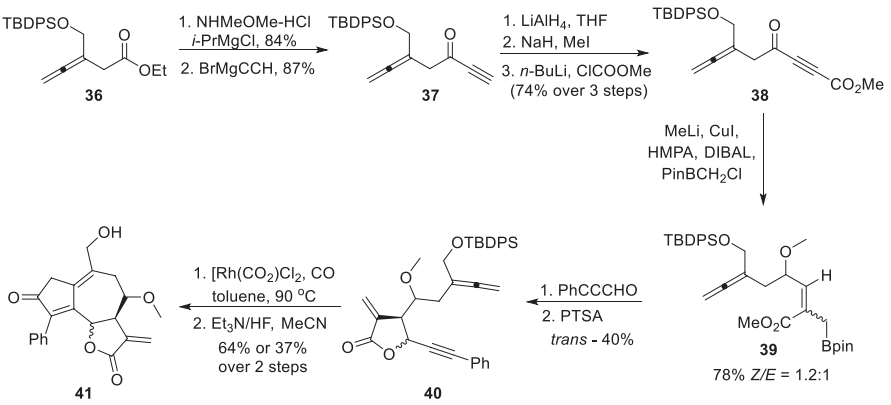
Scheme 5.5 Concise synthesis of (−)-thapsigargin

manganate ($KMnO_4$) in the presence of octanoic acid and octanoic anhydride under reflux conditions in toluene exerted the desired oxidation to provide the α-octanoylated enone **31** with 67% yield. Upjohn's modified procedure, which employs citric acid at 50 °C, subsequently provided the tetra-ol **32**. The lactonization of **32** then took place under Parikh–Doering conditions to afford **33**. The final step of their total synthesis consisted of the reduction of **33** with zinc borohydride

followed by acylation with angelic anhydride and benzoyl chloride. The final product was (−)-thapsigargin **35**, which was obtained with 59% yield in 11 steps.

Related strategies have been developed where the hydroazulene backbone is obtained by an intramolecular cycloaddition reaction after the formation of the lactone ring. Recently, Brummond et al. have reported an innovative methodology for the synthesis of highly oxygenated 6,12-guaianolide derivatives (Grillet et al. 2011; Wen et al. 2013). It has been demonstrated that functionalized allene-yne-containing α-methylene butyrolactones could undergo a cyclocarbonylation reaction in the presence of Rh^{I} as a catalyst to afford the 5,7,5-ring system. The synthesis starts with a Johnson–Claisen rearrangement of the monoprotected butynediol to afford the allenyl ester **36**. Ester **36** is then treated with methoxyethyl amine hydrochloride and *i*-PrMgCl to afford the corresponding Weinreb amide, which is converted into the alkynone **37** by treatment with ethyl magnesium bromide. Next, reduction of the carbonyl group of alkylynone with lithium aluminum hydride, followed by the formation of the corresponding methyl ether, deprotonation of the terminal alkyne with *n*-butyl lithium, and then the addition of chloromethyl ester gives the alkynoate **38** with 84% yield. The reaction of **38** with diisopropylaluminum hydride (DIBAL), copper (I) iodide (CuI), methyl lithium, and $ClCH_2BP$ provided alkyl boronates in a *Z/E* ratio of 1.2:1. A complex mixture was obtained after subjecting the alkyl boronate mixture to an allylboration/lactonization step by heating with 3-phenylpropiolaldehyde. The lactone *trans*-**40** was then generated in a 2:1 mixture of diastereomers after treatment with *p*-toluenesulfonic acid (PTSA). The subsequent treatment with rhodium biscarbonyl chloride dimer and the removal of the *tert*-butyldiphenylsilyl ether (TBDPS) yielded the cyclocarbonylation product as a mixture of diastereomers (Scheme 5.6).

Another prominent member of one of the largest groups of naturally occurring sesquiterpene lactones is arglabin **42** (Fig. 5.2). This natural product can be isolated from *Artemisia glabella*, and it has proved to be a potent farnesyl transferase inhibi-



Scheme 5.6 Synthesis of 6,12-guaianolide derivatives

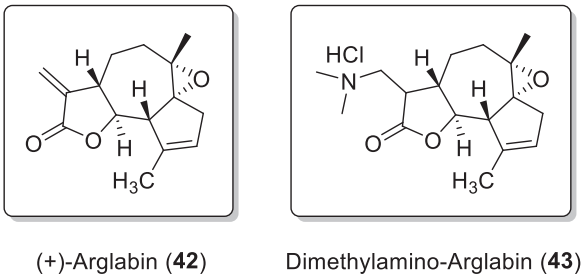
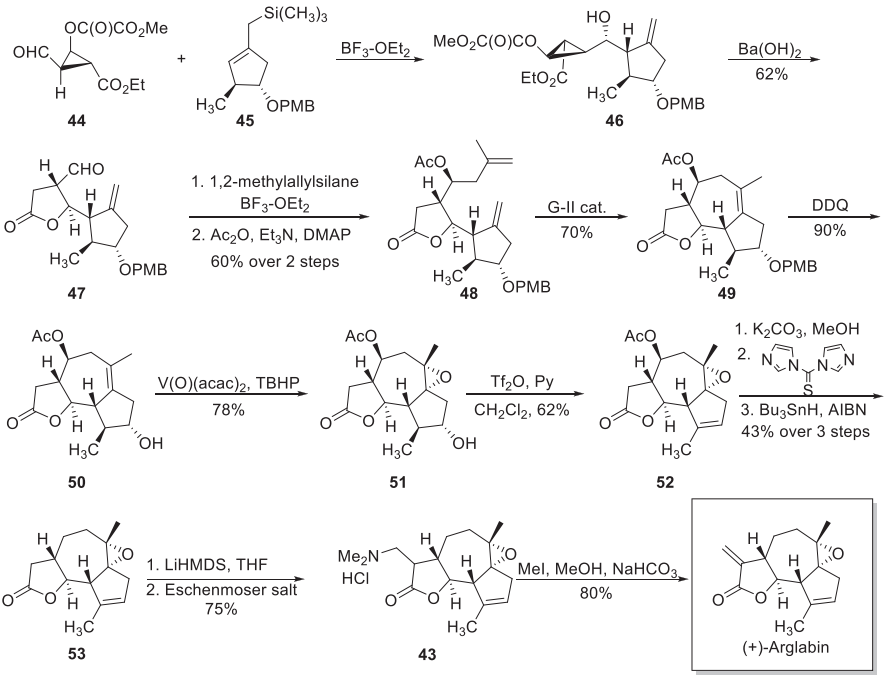


Fig. 5.2 Structures of sesquiterpene lactones arglabin and dimethylamino arglabin



Scheme 5.7 Total synthesis of (+)-arglabin

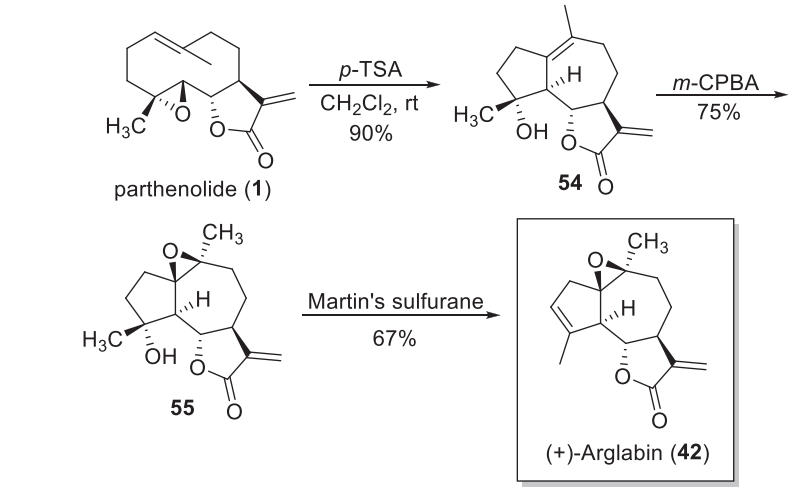
tor with promising antitumor activity and cytotoxicity against human tumor cell lines. To increase bioavailability, arglabin has been converted into its dimethylamine hydrochloride adduct and has been successfully used in Kazakhstan for the treatment of colon, breast, ovarian, and lung cancers (Shaikenov et al. 2001).

The first enantioselective synthesis of arglabin has been accomplished by Reiser et al. using furan derivatives as starting materials (Scheme 5.7) (Kalidindi et al. 2007). A two-step process starting with methyl-2-furoate and involving Cu^{I}-catalyzed asymmetric cyclopropanation followed by ozonolysis afforded

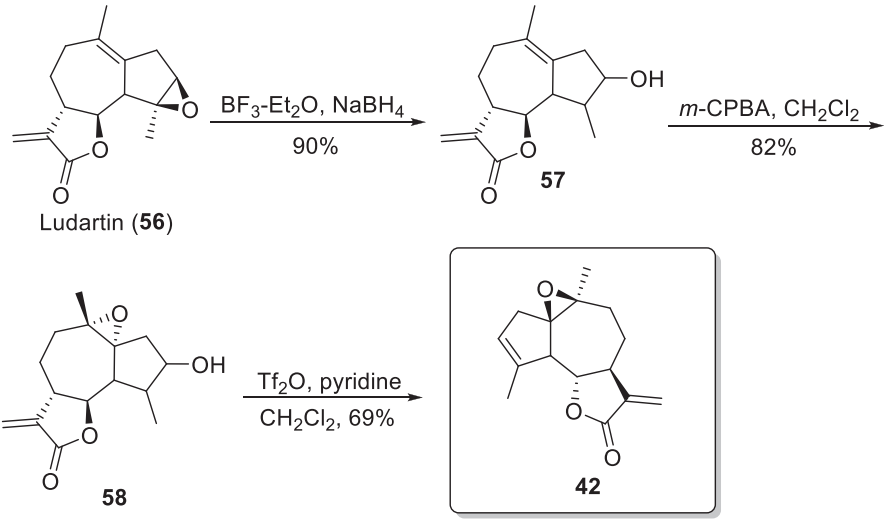
cyclopropanecarbaldehyde **44** in its diastereo- and enantiomerically pure form. The chiral *trans*-substituted allylsilane **45** has been synthesized from furfuryl alcohol by a selective methyl cuprate addition and Ni(II)-catalyzed cross coupling with trimethylsilylmethylenemagnesium chloride. When these two compounds were combined, the formation of **46** proceeded with high stereocontrol where the carbonyl group of **44** is attacked by allylsilane **45** from the face opposite of its methyl group in accordance with the Felkin-Anh paradigm. The saponification of the labile oxalic ester in **46** was induced by the addition of a base, and subsequent lactonization provided the lactone-aldehyde **47**. The synthesis of diene **48** in a 4:1 mixture of diastereomers was accomplished by subjecting compound **47** to a Hosomi–Sakurai allylation with 2-methylallylsilane followed by acylation. The desired guaianolide skeleton **49** was completed by a ring-closing metathesis in the presence of a Grubbs second-generation catalyst. The homoallyl alcohol **50** was generated by PMB deprotection. The desired α-epoxide **51** was afforded by employing catalytic amounts of vanadyl acetylacetonate ($VO(acac)_2$) and *t*-butyl hydroperoxide (TBHP) as the stoichiometric oxidant and with the free hydroxyl group serving as a directing group. Exposure of epoxide **51** to trifluoromethanesulfonic anhydride (Tf_2O) in the presence of pyridine generated alkene **52** as a single regioisomer. The acetate deprotection followed by the Barton–McCombie protocol provided the deoxygenated product **53**. The final step of this synthesis is to introduce the *exo*-methylene group responsible for the biological activity of sesquiterpene lactones. The alkylation of **53** with the Eschenmoser's salt gave rise to a dimethylamino arglabin derivative **43**. Subsequent quaternization with methyl iodide followed by elimination of trimethylamine afforded the target molecule (+)-arglabin **42** with 80% yield.

5.1.6 Semi-synthesis of Guaianolides

In drug discovery, natural products have been the most successful sources. However, these compounds are often generated in small quantities. However, another natural product can serve as starting material for the semi-synthesis of the target drug. The biomimetic semi-synthesis of arglabin **42** has recently been developed from the abundant natural product parthenolide **1** (Scheme 5.8). Parthenolide is readily available from the root bark of *Magnolia delavayi*. It has been demonstrated that parthenolide displays a variety of biological activities and its dimethylamine derivative is being evaluated in a clinical trial (Zhai et al. 2012; Roboz and Guzman 2009; Peese 2010). Parthenolide has been found to be suitable as the staring material for the synthesis of arglabin because it bears a *trans*-6,12 moiety which is key for the synthesis of guaianolides. The treatment of parthenolide **1** with *p*-toluenesulfonic acid (*p*-TSA) afforded micheliolide **54** with excellent yields. The epoxidation of the double bond on the seven-member ring of compound **54** with *m*-chloroperbenzoic acid (*m*-CPBA) furnished the desired β-epoxide **55** as a single stereoisomer. The high stereoselectivity of this process is possible because epoxidation from the top face has to overcome the steric effects from the upward methyl group. It is also



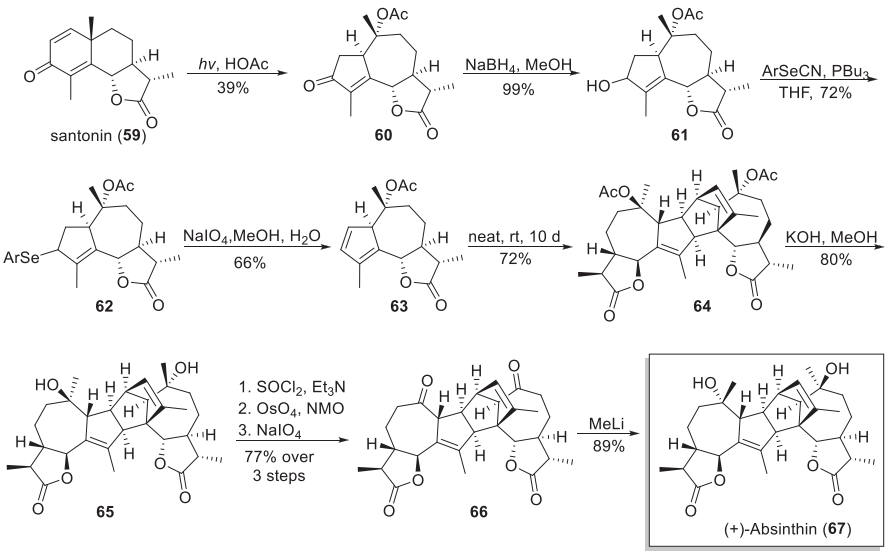
Scheme 5.8 Transformation of parthenolide into arglabin



Scheme 5.9 Semi-synthesis of arglabin from ludartin

known that the hydroxyl substituent can serve as a directing group in the epoxidation of homoallylic alcohols. In the following step, the dehydration of **55** with Martin's sulfurane in CH_2Cl_2 afforded arglabin with good yields. This methodology constitutes a convenient and efficient three-step semi-synthesis of arglabin from parthenolide.

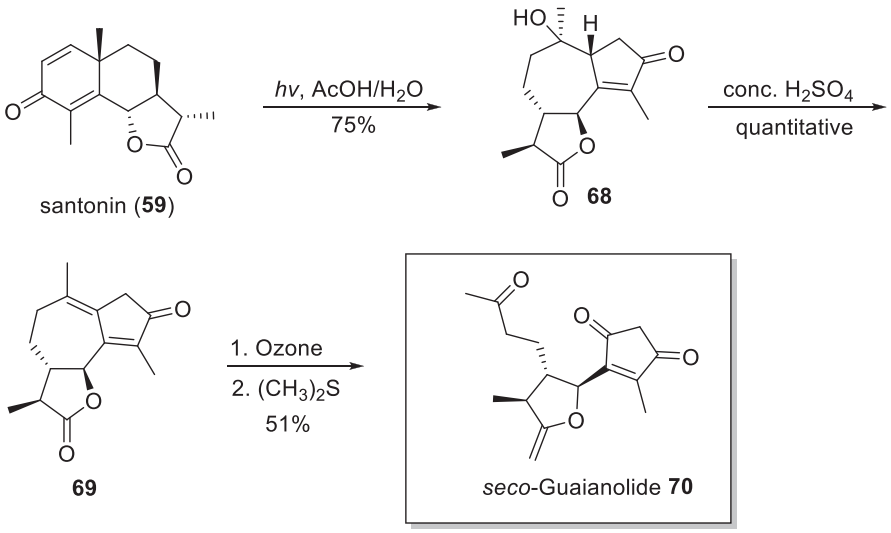
The semi-synthesis of arglabin has also been carried out using ludartin **56** as the starting point of the synthesis (Scheme 5.9) (Lone and Bhat 2015). The synthesis



Scheme 5.10 Synthesis of (+)-absinthin

started with the stereoselective ring opening of the epoxide in ludartin using BF_3•Et_2O in a 1:1 mixture of dioxane-water affording compound **57** with good stereoselectivity. The epoxidation of its C(1)10 double bond with *m*-CPBA yielded a mixture of diastereomers which were separated by column chromatography to obtain compound **58**. Finally, dehydration using Tf_2O and pyridine furnished the desired trisubstituted alkene product in arglabin. A concise three-step route for the semi-synthesis of antitumor arglabin from ludartin has been demonstrated. This process had an overall yield of 51%.

In 1953, Herout et al. isolated (+)-absinthin **67** from *Arthemisia absinthium* as a dimeric guaianolide. The structural complexity along with its biological activity as a promising anti-inflammatory agent led Zhang et al. to develop the synthesis of this natural product (Scheme 5.10) (Zhang et al. 2005). Using santonin **59** in acetic acid as starting material, the photolysis with an Hg lamp rendered the *O*-acetylisophotosantonic lactone **60**. The reduction of the enone carbonyl with $NaBH_4$ provided a mixture of the diastereomeric alcohol **61**. The Mitsunobu aryl selenylation of **61** allowed obtaining selenides **62** and the subsequent treatment with $NaIO_4$ led to the formation of the substituted cyclopentadiene **63**. A [4 + 2] Diels-Alder cycloaddition of **63** gave rise to compound **64** with not only high regioselectivity but also with high stereoselectivity. During this process, the steric interactions were minimized because the two Diels-Alder moieties approached each other through the less hindered faces, adopting a head-to-head orientation with respect to the lactone carbonyl groups. The saponification of **64** with a methanolic potassium hydroxide solution followed by acidification with HCl afforded



Scheme 5.11 Synthesis of *seco*-guaianolide from α-santonin

epi-absinthin **65**. Since the two alcohols had the wrong configuration, diol **65** was converted to diketone **66** by an oxidative degradation. The chemo- and stereoselective installation of the methyl groups completed the synthesis of (+)-absinthin **67** with an overall yield of 18.6%.

Over the last years, and in order to find new bioactive compounds that can act as leads for drug discovery, researchers have focused on *seco*-guaianolides. Recently, Westwood et al. have reported the synthesis and biological evaluation of two iso-*seco*-tanapartholides (Makiyi et al. 2009). Their study has demonstrated that a late-stage oxidative cleavage reaction in the absence of protecting groups was necessary for the direct synthesis of the natural products and that the *seco*-guaianolides derivatives were inhibitors of the NF-κB signaling pathway. In a different study conducted by Macías et al., the easy preparation of *seco*-guaianolides has been demonstrated (Macias et al. 2012). In their work, the sesquiterpene lactone derivatives were synthesized from commercially available santonin, involving a high-yield photochemical transformation. Specifically, α-santonin **59** was transformed into the guaianolide isophotosantonin **68** at low temperatures, in the presence of filter solutions, Ni(II) and Co(II), and with a mixture of 16/65 ratio of acetic acid (AcOH) and water. The acid-catalyzed dehydration of the alcohol on molecule **68** provided the diene **69**. Subsequent oxidation of **69** with ozone and dimethyl sulfide provided *seco*-guaianolide **70** (Scheme 5.11).

5.2 Chemical Transformation of Sesquiterpene Lactones

The sesquiterpene lactone class of natural products is a large and diverse group of biologically active compounds found in several plant families such as Acanthaceae, Anacardiaceae, Apiaceae, Euphorbiaceae, Lauraceae, Magnoliaceae, Menispermaceae, Rutaceae, Winteraceae, and Hepatideae (Modzelewska et al. 2005; Nam 2006). One important feature of this group of secondary metabolites is the existence of the α-methylene-γ-lactone moiety which is responsible for the biological effects and cytotoxicity. Structure–activity relationship (SAR) investigations have demonstrated that the mechanism of action of these compounds involves the nucleophilic addition of thiols, such as cysteine, to the α-methylene-γ-lactone moiety. However, many of these compounds are poorly soluble in water, and, frequently, the α-methylene-γ-lactone displays a nonselective binding to undesired targets as a Michael acceptor (Ghantous et al. 2010). Furthermore, over the last decade, researchers have been interested in developing new compounds to improve the cytotoxic effects as well as to establish structure–activity relationship.

5.2.1 Costunolide and Its Derivatives

Costunolide (**4**, Scheme 5.1), which can be readily extracted from the dried roots of *Saussurea lappa*, has been considered a potential candidate for cancer treatment. It has been reported that costunolide can induce apoptosis in cancer cells and that it suppresses the nuclear transcription factor-κB (NF-κB) activation. It is known that the *exo*-methylene group of the α-methylene-γ-lactone of costunolide is required to elicit cytotoxicity and that its reduction renders an inactive derivative(s) (Sun et al. 2003). A variety of amino adducts of costunolide **4** involving Michael-type addition has been synthetized, and these derivatives have been tested in eight different cell lines (Srivastava et al. 2006). As a rule, several amino derivatives of costunolide have shown higher cytotoxicity and selectivity, with an improved safety index. Overall, all the amino adducts synthesized from dimethyl pyrrolidines, or from piperidines, have exhibited significant antiproliferative activity similar to costunolide **4**. Furthermore, all of the compounds prepared from piperazines proved to be inactive. The structures of the active amino derivatives are illustrated in Fig. 5.3.

Suresh et al. have reported the application of the Heck arylation reaction in the synthesis of costunolide derivatives (Vadaparthi et al. 2015). Under standard Heck reaction conditions, 12 costunolide analogues (**76–85**, Fig. 5.4) have been synthesized after arylation of the α-methylene-γ-lactone and subjected to evaluation for their cytotoxic activities against cervical cancer (HeLa), breast cancer (MCF-7), lung cancer (A549), mouse melanoma (B-16), and prostate cancer (DU-145) cell lines. A broad range of potencies was observed, but when compared to the parent compound costunolide, most of the analogues displayed higher cytotoxicity against the tested cell lines. Compounds **77** and **83** proved to be the most potent compounds

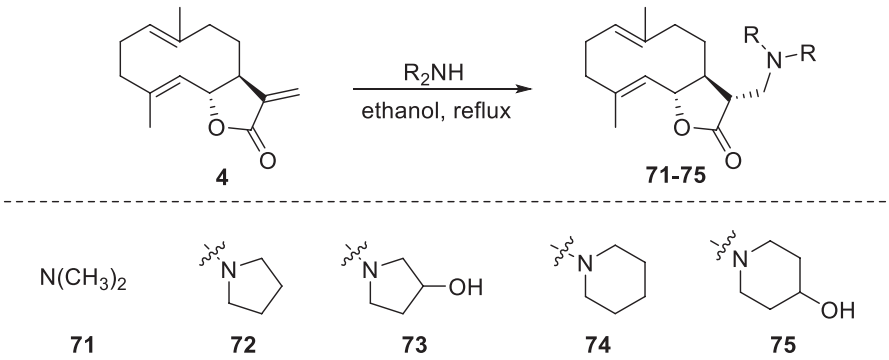


Fig. 5.3 Amino derivatives of costunolide (**4**)

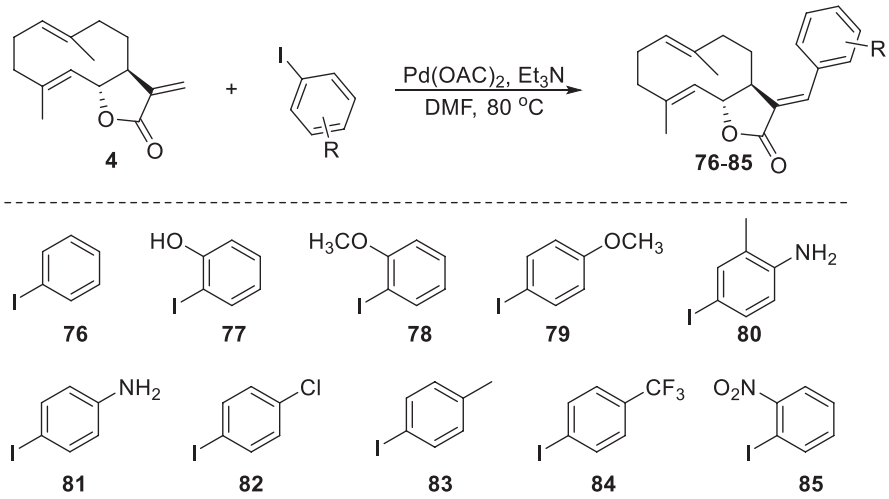


Fig. 5.4 Heck strategy for the synthesis of costunolide analogues **76–85**

against HeLa cells, while compound **82** containing the *p*-chloro substituent showed good activity in all tested cell lines.

5.2.2 Parthenolide and Analogues

Parthenolide **1**, is the main active constituent isolated from feverfew (*Tanacetum parthenium*), which is a traditional herbal remedy. This compound belongs to the sesquiterpene lactone class of natural products. Parthenolide **1** is known to have a strong inhibitory effect on NF-κB activation, a process responsible for the strong

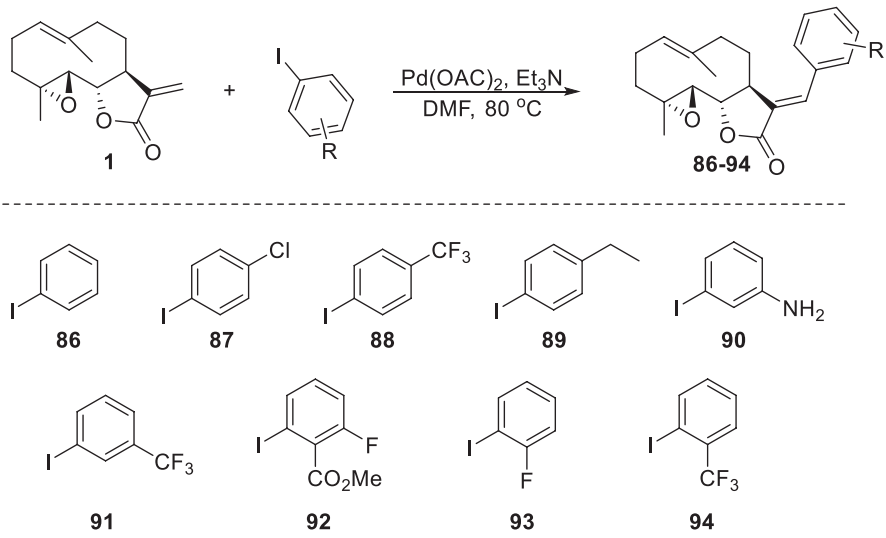


Fig. 5.5 Heck strategy for the synthesis of parthenolide analogues **86–94**

anti-inflammatory activity (Kwok et al. 2001a, b). This natural product was demonstrated to selectively target leukemia stem cells while leaving normal hematopoietic cells unaffected. Clinical trials have demonstrated its inadequacy to be used directly, due to the low potency and poor water solubility. As a consequence, researchers have designed new parthenolide derivatives with higher solubility and potency. Colby et al. have successfully applied the palladium-catalyzed arylation reaction of parthenolide with aryl iodide derivatives (Han et al. 2009). To determine the antiproliferative effect, growth inhibition assays with HeLa cells have been conducted. Typically, the authors found that sesquiterpene lactone derivatives bearing electron-withdrawing groups at the *meta*- and *para*-positions retain their activity when compared to the parent compound (Fig. 5.5).

The first amino derivatives of parthenolide have been tested for hepatitis C virus (HCV) infection (Hwang et al. 2006). In that study, it was demonstrated that the seven parthenolide derivatives synthesized from secondary amines (Fig. 5.6) had similar anti-HCV effects to parthenolide. Based on a report demonstrating that parthenolide initiates apoptosis in leukemia stem cells, Crooks et al. have prepared a series of amino adducts of parthenolide from primary and secondary amines (Nasim and Crooks 2008; Neelakantan et al. 2009). It has been demonstrated that dimethylaminoparthenolide (DMAPT) has excellent oral bioavailability, greater aqueous solubility and the outstanding antileukemic activity of parthenolide (Guzman et al. 2007; Hassane et al. 2010). The design, synthesis, and biological evaluation of fluorinated parthenolide amino derivatives have been described by Colby et al. (Fig. 5.6) (Woods et al. 2011). These authors have employed fluorinated aminoparthenolides derived from pyrrolidines and piperidines for mechanistic analysis by ^{19}F NMR.

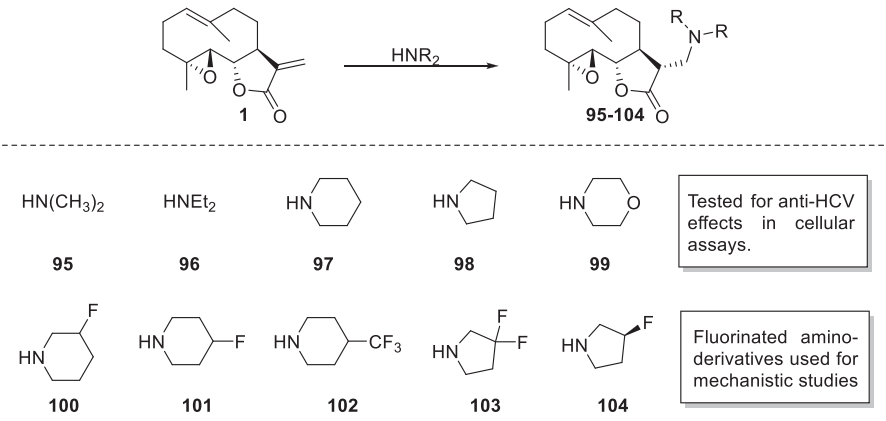


Fig. 5.6 Synthesis of amino derivatives of parthenolide

Studies of their lead compound have demonstrated that the dissociation of the fluorinated amine from the aminoparthenolide prodrug was higher in the presence of glutathione.

5.2.3 Artemisinin and Its Derivatives

Artemisinin **105** (ART) is a sesquiterpene lactone containing a peroxide bridge. This compound is obtained from plant *Artemisia annua*. The increase in resistance levels against most of the drugs currently used to treat malaria has led the World Health Organization to use the artemisinin class of compounds as the preferred basis for treatment of infections with *Plasmodium falciparum* strains, cerebral malaria, and malaria in children (Yeung et al. 2004). Artemisinin is an emerging lead compound for malaria treatment that shows a broad range of effectiveness. However, this compound has poor water and oil solubility. In an effort to improve ART bioavailability and efficacy, several artemisinin-like derivatives (ADs) have been synthesized, such as artesunate (ARS), which proved to be more active and less toxic than its parent drug; artemotil, only used in severe cases of malaria; and dihydroartemisinin (DHA), which was found to be more active that ART but thermally less stable (Ploypradith 2004; Krishna et al. 2004; Duthaler et al. 2012). It has been found that polyamines have a significant number of implications of various processes in the malaria parasite. Several amino derivatives of artemisinin have been synthesized, and their mechanism of action has been proposed (Chadwick et al. 2010; Calas et al. 1997; Calas et al. 2000). A new class of amino derivatives of ART with different lipophilic moieties and substituents has been synthesized. The synthesis includes compounds where aliphatic, alicyclic, and aromatic amine groups were introduced through an ethyl ether linker at the C-10 of artemisinin (Fig. 5.7a).

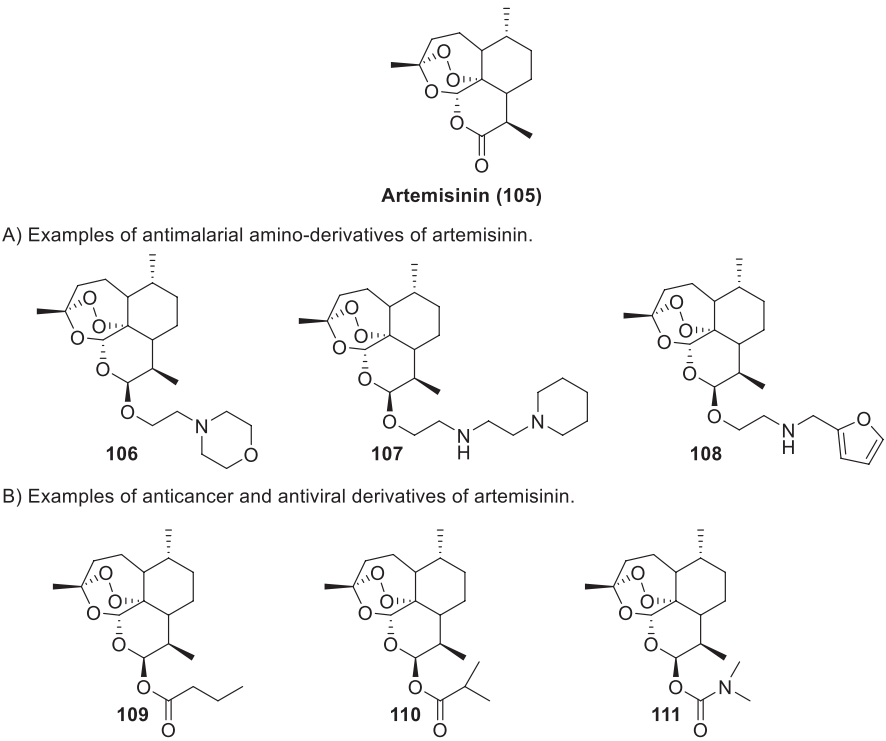
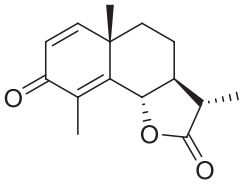


Fig. 5.7 Chemical structure of artemisinin and its derivatives

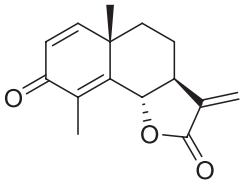
Their antimalarial activity against chloroquine-sensitive (D10) and chloroquine-resistant (Dd2) strains of *Plasmodium falciparum* has been reported. As a rule, all compounds were found to be more potent than chloroquine (CQ) against both strains, and none of the compounds exhibited higher activity against the D10 strain when compared to DHA (Cloete et al. 2012). Several semisynthetic artemisinin derivatives have been evaluated as anticancer and antiviral drugs, and they have shown promising results (Efferth et al. 2008a, b). With the aim of increasing ART solubility and its circulating half-life, Marin et al.. have developed the synthesis of artemisinin analogues with bulky groups linked to the C-10 position of DHA (Fig. 5.7b), and their biological activity against liver/colon cancer and viral hepatitis has been tested (Blazquez et al. 2013).

5.2.4 Santonin and Its Analogues

Alpha-santonin **59**, a sesquiterpene lactone containing a eudesmane skeleton, has been isolated from *Artemisia santonica*. Over the past decades, researchers have studied its chemical and biochemical transformation along with its pharmacological

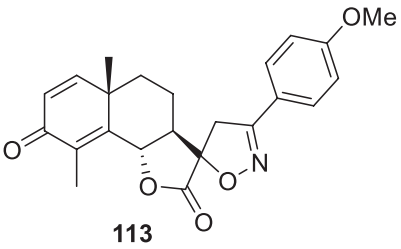


Santonin **59**



11,13-dehydrosantonin **112**

A) Spiro-isoxazoline and spiro-isoxazolidine derivatives of santonin.



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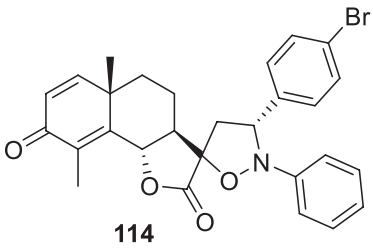
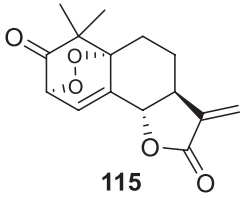


114

B) Sesquiterpene lactone with an endo-peroxide functionality.



115

Fig. 5.8 Chemical structure of α-santonin and its derivatives

properties. In the past, α-santonin has been used as anthelminthic, and studies have demonstrated that α-santonin exhibits important biological properties such as antipyretic, anti-inflammatory, and fungicidal (Singh et al. 2001). Additionally, the sesquiterpene lactone α-santonin has been modified to install the required α-methylene-γ-lactone, and these derivatives exhibited relatively high cytotoxic activity against cancer cells (Arantes et al. 2009). Based on the continuous interest in the design and synthesis of sesquiterpene lactones with anticancer properties, researchers have developed several analogues of α-santonin. Novel spiro derivatives have been synthesized and tested for their anticancer activity against six human cancer cell lines. Specifically, spiro-isoxazoline and spiro-isoxazolidine derivatives have been prepared by a 1,3-dipolar cycloaddition of 11,13-dehydrosantonin **112** with nitrile oxides and nitrones (Fig. 5.8a). Among the spiro-isoxazoline series, compound **113** has displayed significant activity with IC_{50} values of 0.02 and 0.2 μM in MCF-7 (breast) and A549 (lung) cell lines, respectively. The spiro-isoxazolidine derivative **114** has been evaluated and has shown inhibitory activity against the

central regulator of cancer cell growth and survival NF-κB (Khazir et al. 2013). Santonin derivatives containing the α-methylene-γ-lactone and an endo-peroxide moiety have been synthesized and tested against cancer cell lines (Fig. 5.8b). These compounds have shown high cytotoxicity; however, they were less potent than the control reference compound (Arantes et al. 2010).

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