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Pseudoguaianolides: Recent Advances in Synthesis and Applications

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Pseudoguaianolides belong to the class of sesquiterpene lactones and are characterized by the lactone ring *cis* or *trans*-anellated (in 6,7- or 7,8- position) to fused seven- and five-membered rings; they differ from guaianolides for the position of the methyl group in 5. The unusual tricyclic fused core 5/7/5 was a challenge and inspired new synthetic methodologies to install substituents with proper stereochemistry. Despite their potential of application in different fields, their exploitation is so far very limited. Because of this, with this review we wanted to give perspectives in terms of availability and resupply of the most active compounds of the class.

Keywords: Sesquiterpene lactones, Pseudoguaianolides, Exo-methylene, Michael addition.

Pseudoguaianolides belong to the class of sesquiterpene lactones, one of the most abundant class of natural products [1]. More than 8000 structures have been reported, and they have broad structural and functional diversity[2]. All natural sesquiterpene lactones show a 15-carbon core structure (hence the prefix sesqui-) which is derived from the assembling of three isoprene units and a γ-lactone ring. They are characterized by a rather scattered botanical distribution, but they occur chiefly in the Asteraceae [3, 4]. The lactone component is characterized by an exo-methylene fragment thought to be responsible for the majority of biological activities induced by sesquiterpene lactones when administered to organisms or cells. Sesquiterpene lactones are primarily classified on the basis of their carbocyclic skeletons into germacranolides, which represent the largest subgroup and contain a 10-membered ring, eudesmanolides which are bicyclic 6/6 compounds, guaianolides (including *seco*-guaianolides and featuring a 5/7 bicyclic core), and pseudoguaianolides (Figure 1).

The exocyclic α,β-unsaturated carbonyl structures react by a Michael-type addition with nucleophiles in biological systems, such as the sulfhydryl group of the amino acid cysteine. By testing sesquiterpene lactones in cell-based assays, however, it has been found that some have very specific effects, and possibly specific targets. With their 5/7/5 skeleton, guaianolides and pseudoguaianolides represent the most common structure. Whilst guaianolides have been excellently recently reviewed by Macias and al. [5, 6], in this paper we intend to give an overview on the most updated synthetic methodologies in the synthesis of pseudoguaianolides, whilst their natural occurrence, possible ecological role and biological activities have been already reviewed [7, 8].

PSEUDOGUAIANOLIDES

Pseudoguaianolides are characterized by the lactone ring *cis* or *trans*-anellated (in 6,7- or 7,8- positions, Figure 1) to fused seven- and five-membered rings; they differ from guaianolides for the position of the methyl group in 5. Pseudoguaianolides include the less abundant helenanolides group in which the methyl in C-10 is α- on the *trans*-hydroazulene nucleus (Table 1, i.e. helenalin, mexicanin, aromatin) and the more abundant ambrosanolides group (with 10β-methyl configuration; i.e. confertin, parthenin, damsin, ambrosin); in both the methyl configuration in C-7 is β. Pseudoguaianolides show several strong biological activities; in this paper, we reviewed the syntheses of compounds with known cytotoxic or antitumor activity, as listed in Table 1.

The basic synthetic strategies of guaianolides differ in the construction of the hydroazulene skeleton. The most used approach consisted in the addition of a cycloheptene ring to an oxidated cyclopentane. Other strategies utilized the transannular cyclizations of a proper cyclodecane or the rearrangement of a hydronaphthalene precursor. Final stages of the syntheses are the careful construction of the γ-butyrolactone and its α-methylenation.

Helenalin (1). Total syntheses of the racemic linear pseudoguaianolide **helenalin (1)** have been reported by Grieco[9, 10] and Schlessinger [11]. In the former approach, Grieco demonstrated that the intermediate **11**, already used for the synthesis of ambrosanolides damsin and ambrosin (6,7-annulated pseudoguaianolides), could be as much usefully employed in the synthesis of helenanolides, which differ for the α or β configuration of the methyl in C10. The norbornadiene derived cyclopentenol **11**

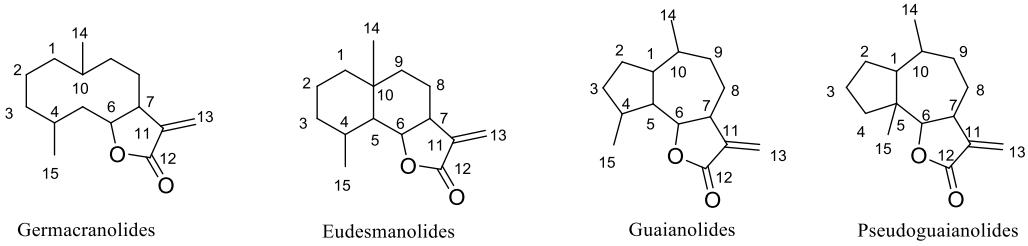
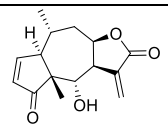
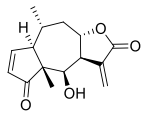
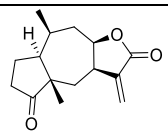
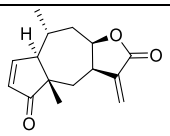
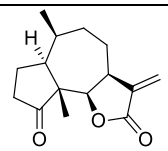
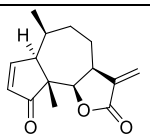
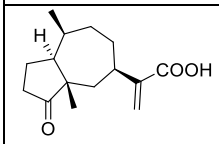
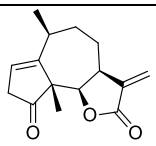
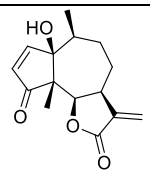
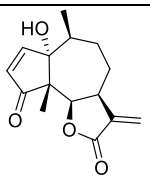
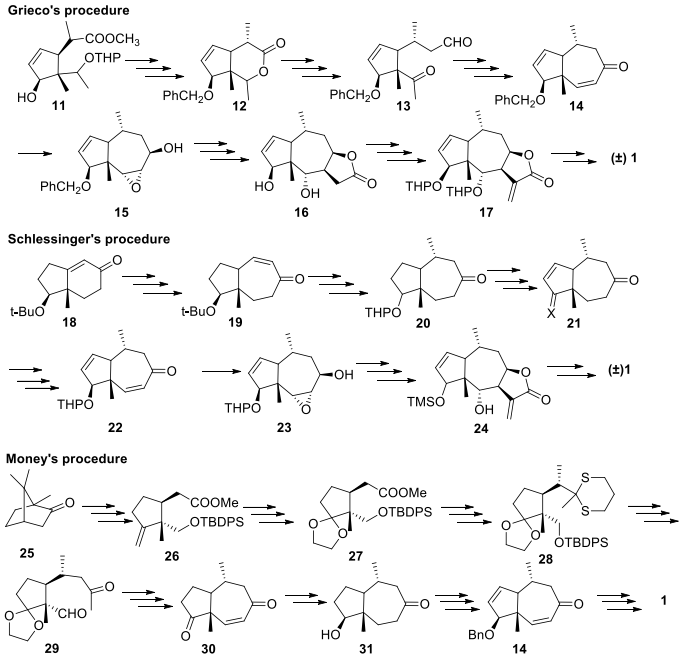


Figure 1: Structure and numbering of the main classes of sesquiterpene lactones.

Table 1: List of pseudoguaianolides, their first isolation and biological activity.

Compound / First isolation / Cytotoxicity		Compound / First isolation / Cytotoxicity	
 **Helenalin (1)**	*Helenium microcephalum* [12] Alkylating bifunctional agent which induces: 1.direct modification of the p65 subunit of NF-κB, leading to molecule inactivation. 2.thiol depletion 3.induction of apoptosis [2, 13-15] Genotoxic [14]	 **Mexicanin I (2)**	*Helenium mexicanum* [16] Cytotoxic towards the human KB cervix carcinoma cell line; it inhibits c-Myb target genes expression in human leukemia cell line and human leukemia cells proliferation [17].
 **Confertin (3)**	*Ambrosia confertiflora* [18] Significant cytotoxic activity against a panel of six human tumor cell lines [19]	 **Aromatin (4)**	*Helenium aromaticum* [20] Aromatase inhibitor. Cytotoxic against KB cell line [21]
 **Damsin (5)**	*Ambrosia maritima* [22] Significant cytotoxic activity against a panel of human tumor cell lines [19, 23] Candidate to treat refractory tumors [24]	 **Ambrosin (6)**	*Ambrosia maritima* [22] Cytotoxic inducing apoptosis in Jurkat leukemia T cells and against a panel of human tumor cell line [23, 25]
 **Damsinic acid (7)**	*Ambrosia ambrosioides* [26] Cytotoxic [27]	 **Neoambrosin (8)**	*Hymenoclea salsola* [28] Cytotoxic and candidate to treat refractory tumors [24]
 **Hymenin (9)**	*Hymenoclea salsola* [29] Cytotoxic inducing apoptosis in Jurkat leukemia T cells [30]	 **Parthenin (10)**	*Parthenium hysterophorus* [31] Cytoxic against several human cancer cell lines [32-34]



Scheme 1: Syntheses of helenalin (**1**).

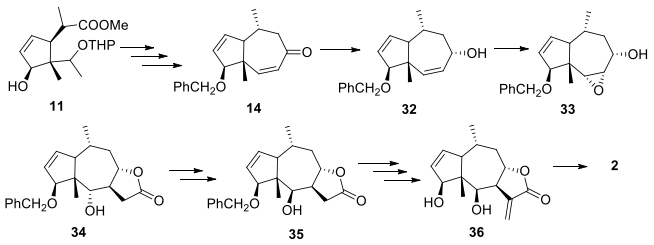
was converted into the hydroazulenone **14** through several steps of protection and deprotection, lactonization with complete isomerization of the C10 methyl group (**12**), reduction to the corresponding lactol converted into the ketoaldehyde **13**, intramolecular aldol condensation, final multi-step conversion of the protected aldol (Scheme 1). Diastereoselective epoxidation (with hindered *t*-butylhydroperoxide) and quantitative and exclusive stereospecific reduction gave the epoxyalcohol **15**, which was treated with excess dilithioacetate in order to introduce the necessary two carbon chain in C7 along with epoxide opening. The following step of debenzylation however would require the noxious protection step of the lactone ring. This was avoided by directly adding the intermediate trianion to a solution of lithium in liquid ammonia, followed by acidic aqueous workup; this procedure enabled the direct conversion of **15** into the tricyclic debenzylated lactone **16**. α-Methylenation was performed on the lactone bis(tetrahydropyrany1) ether via hydroxymethylation, mesylation, and elimination to give intermediate **17**; deprotection and final oxidation gave (±)-helenalin [9].

In the latter synthetic approach, Schlessinger proposed the same precursor hydroazulenone **19** for the synthesis of (±)-helenalin as for confertin and damsin [11]. The intermediate **19**, prepared from the readily available enone **18**, was converted into the 10-methyl analogue **20** by using methylmagnesium bromide, that underwent ketal protection and oxidation. The cyclopentenone ring in **21** (X=O) was obtained by alkylation with a disulfide, followed by oxidation and sulfoxide elimination; it was then converted into **21** (X=OTHP, H) through intermediate steps of reduction and alcohol protection. The cycloheptenone ring in **22** (THP analogue of **14**)

was obtained via deprotonation and treatment of the intermediate silylenol ether with palladium acetate. Then diastereoselective epoxidation and ketone reduction gave α-epoxy alcohol **23**. Subsequent epoxide ring opening using excess dilithioacetate, acid-catalysed lactonization, and eventually methylenation afforded protected dihydrohelenalin **24**; deprotection and oxidation gave pure racemic helenalin in 6.6% yield from enone **18**.

Formal racemic and enantioselective syntheses of helenalin have been described later [35-37]. In the Money's enantioselective version [37], key intermediate was the ketal ester **27** derived from camphor (**25**), which showed to be useful in the synthesis of both helenanolides and ambrosanolides. Steps of the synthesis were the stereoselective methylation of the above ketal ester, reduction to alcohol, conversion into iodide and then to ketal dithiane **28**. After ketal hydrolysis, TBDPS deprotection and Swern oxidation gave keto aldehyde **29**, which upon intramolecular aldol condensation was converted into enedione **30**. Regio- and stereoselective reduction and catalytic hydrogenation gave hydroxy ketone **31** which was finally converted in enantiomerically pure enone **14** previously used in helenalin synthesis (Scheme 1, Grieco' s synthesis) [10].

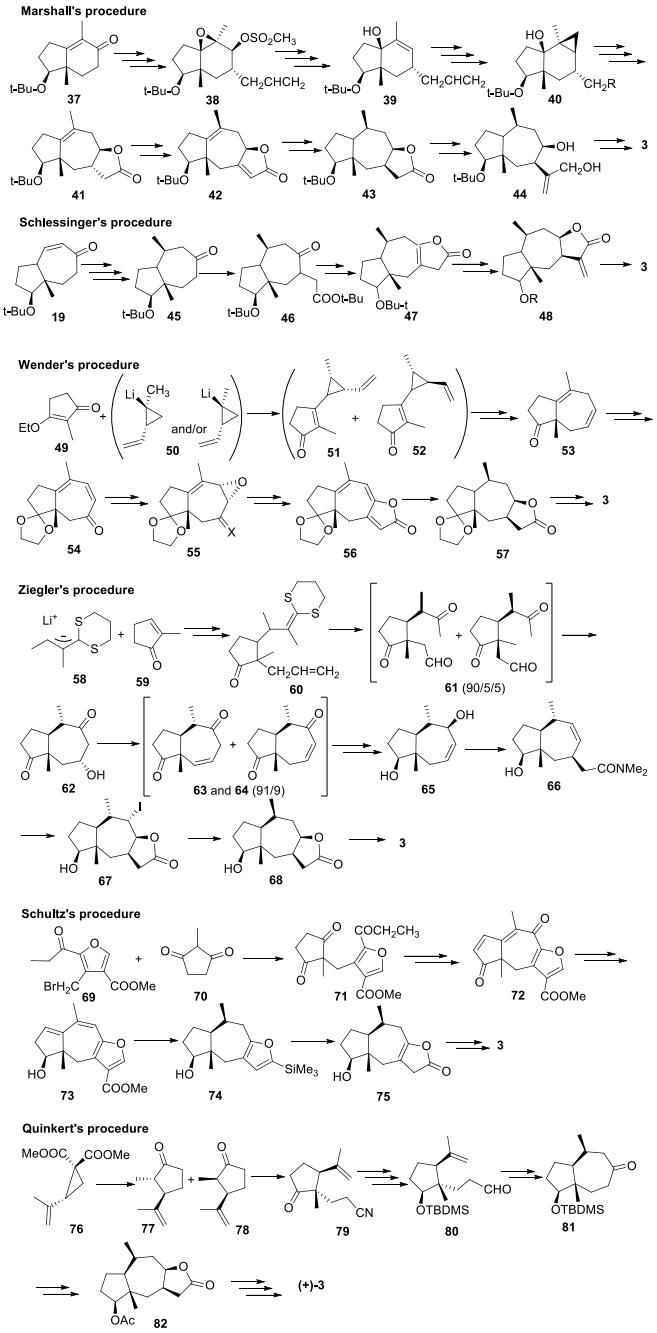
Mexicanin I (2). Structurally related to helenalin, **mexicanin I** features opposite configuration in C6 and C8, therefore their syntheses were reported at the same time. In 1983 Grieco described stereocontrolled mexicanin I synthesis as described in Scheme 1 for helenalin, by using as starting reagent the same cyclopentenol **11** until hydroazulenone **14** (Scheme 2) [38]. In order to obtain proper configuration, the reaction sequence required a first reduction to alcohol **32** and then diastereoselective epoxidation to epoxyalcohol **33**. Treatment with metalated acetic acid gave the tricyclic lactone **34.** The inversion of configuration at C6 was achieved through consecutive oxidation/ reduction that, in the presence of the bulky angular methyl in C5 occurred at the α face (**35**). The completion of the synthesis required a modified procedure with respect to that of helenalin. In order to maintain the *trans*-fused tricyclic lactone in C7-C8, protection of the C(6) hydroxyl group as tetrahydropyranyl ether was requested. The subsequent three-step sequence of α-methylenation and deprotection led to tricyclic lactone **36**, that underwent final oxidation to (±)-mexicanin I (**2**; Scheme 2).



Scheme 2: Grieco's synthesis of mexicanin I (**2**).

Confertin (3). The previously mentioned Money's enantioselective approach for helenalin was applied also in the formal synthesis of mexicanin I from camphor derived dienone **14** as well as in that of confertin [37]. After the first stereoselective total synthesis of (±)-**confertin** (**3**) reported in 1976 [39], several other procedures were reported [39-50], which often include the synthesis of the C10 epimer (±)-aromatin and of the 6,7-annullated lactone damsin and damsinic acid. Total syntheses of (+)-confertin date from 1987 [51-54].

In 1976 Marshall constructed hydroazulene skeleton starting from the keto ether **37** (Scheme 3) derived from 2-methyl-1,3-cyclopentanedione [39]. Key steps of α-allylation, ketone reduction,



Scheme 3: Syntheses of confertin (**3**).

epoxidation and lithium-ammonia reduction of mesylated derivative **38** gave alcohol **39**, which underwent Simmons-Smith cyclopropanation to cyclopropylcarbinol **40** (R=$CHCH_2$) with well-defined stereochemistry. Ozonolysis and treatment with silver oxide afforded acid **40** (R=COOH) which stereospecifically rearranged to the hydroazulene lactone **41** with the uncorrected configurations of the lactone ring. Conversion into the *cis*-lactone **43** was obtained through treatment with diphenyl diselenide and lithium diisopropylamide followed by hydrogen peroxide to **42** and then catalytic hydrogenation to **43**. α-Methylenation required the use of 11-carbomethoxy derivative of lactone **43**, enolate formation and reduction to the diol **44**. Oxidation of the primary alcohol, cyclization into the desired α-methylene-γ-butyrrolactone, *t*-butyl ether cleavage and final oxidation of the resulting alcohol gave (±)-confertin (**3**).

The Schlessinger protocol relies on the hydroazulenone **19**, key intermediate for the synthesis of (±)-helenalin [11, 42]. The first step was the methylation to afford β-methyl derivative **45** which was converted into (±)-confertin and (±)-damsin. In the first case, the enolate of cycloheptanone **45** was reacted with *t*-butyl iodoacetate (**46**), which in turn was converted into its corresponding enol lactone **47** and then reduced. The final α-methylenation of the protected lactone and oxidation of the deprotected secondary alcohol (**48**) gave confertin (30% overall yield from **19** over 12 steps).

In Wender's procedure, (±)-confertin was synthesized along with (±)-damsinic acid from the cycloheptadienone **53** [43], relying on the same methodology previously described for divinylcyclopropane preparation, which effected the requisite pseudoguaiane annulation. The mixture of the two divinylcyclopropanes **51** and **52** was subjected to repeated cycles of photoepimerization and pyrolysis to give exclusively ketone **53**; this was converted into its ketal and then almost chemoselectively oxidized to the common precursor **54**. Further steps involved epoxidation, olefination to *E* and *Z* esters **55** (X=CHCOOEt), whose treatment with acid gave hydroxylactones and, upon base treatment, triene lactones **56**. Catalytic hydrogenation of **56** gave final lactone **57** further converted in (±)-confertin **3**; the overall yield was 5-10% (12 steps).

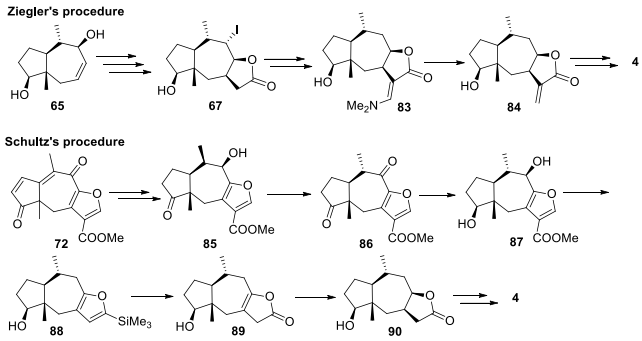
Heathcock reported a new route for pseudoguaianolide synthesis which employed hydronaphthalene compounds as precursor of the hydroazulene skeleton [45]. The complex synthesis furnished (±)-confertin in 2.7% overall yield, and additionally accomolished the formal synthesis of (±)-helenalin. A different approach was proposed by Semmelhack: in this case a low yield of (±)-confertin was obtained by hydrogenation of the pseudoguaiane tricyclic skeleton obtained via a Ni-promoted intramolecular coupling of a sulfonium intermediate giving rise to cyclization-lactonization [41]
In the frame of Michael addition of vinylogous dithiane (dithianylidene) anions investigations, Ziegler and Fang reported a new methodology for the synthesis of (±)-confertin (**3)** and (±)-aromatin (**4**) [44, 47, 55, 56]. The lithium anion **58**, easily available from 2-ethylidene-1,3-dithiane, was reacted with 2-methylcyclopentenone (**59**) and allylated to give a mixture of three diastereomers **6.** These ones when subjected to ozonolysis gave a mixtures of tricarbonyl compounds (**61**). Base treatment afforded the single aldol **62**, whose dehydration with methanesulfonic acid//P_2O_5 gave a mixture of enones **63** and **64**; reduction and chromatographic purification finally gave diol **65** which bears the required stereochemistry at C1, C5 and C10. The introduction of acetic acid chain in C7 was achieved using the Eschenmoser variant of Claisen rearrangement furnishing amide alcohol **66**; subsequent steps were the formation of iodide *cis*-lactone **67**, dehydroalogenation and diastereoselective catalytic hydrogenation (**68**); final oxidation and α-methylenation gave confertin **3**.

A new strategy to pseudoguaianolides was proposed by Schultz for total syntheses of (±)-confertin and (±)-aromatin on a multigram scale [46, 48]. This synthetic approach was based on an annulation strategy that attempted to incorporate the α-methylene-γ-butyrolactone feature within the annulation reagent and allowed a formal total synthesis of confertin in a 22% overall yield from the annulation product **72**, this one prepared as reported in Scheme 3. The annulation reagent was prepared starting from the readily available furan ester **69** and 2-methylcyclopentane-1,3-dione (**70**); dehydrogenation and cyclodehydration gave enetrione **72**, which was converted, through several steps, into the final lactone **75** (intermediate also in both the Schlessinger and Heathcok syntheses of confertin).

Total synthesis of pure (+)-confertin has been reported by Quinkert [51, 53]. The enantiomerically pure dicarboxylate **76**, accessible via diastereoselective Linstead cyclopropanation, was converted by stereospecific ring expansion into cyclopentanones **77** and **78**, which trough intermolecular Michael addition to acrylonitrile gave the *trans* adduct **79** as the only product. Following steps of synthesis were intramolecular hetero-ene reaction, oxidation and hydrogenation to give ketone **81**. Regioselective alkylation in C-7 and successive steps following Schlessinger procedure to **82** [42] gave pure (+)-confertin.

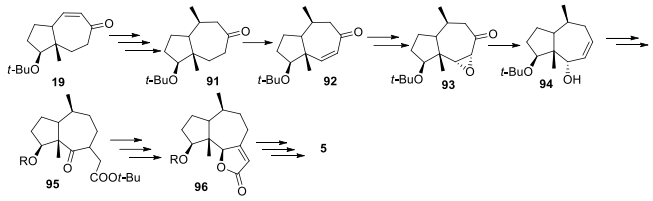
In 1992 Quinkert published an improvement in the enantioselectivity of this synthesis; the starting cyclopentanones **77** and **78** were prepared via enantioselective conjugate addition of a chirally modified organocuprate to 2-methylcyclopent-2-enone [54]. Finally, a formal enantioselective synthesis of (+)-confertin was reported by Shishido in 1998 in which the key step was a highly diastereoselective acyl radical-mediated cyclization [57].

Aromatin (4). Ziegler's procedure for confertin was applied also for (±)-**aromatin** (**4**) synthesis (Scheme 4) [44]. As previously described, the key intermediate *cis*-diol **65** was converted into the *cis*-iodolactone **67**; deiodination, methylenation with Bredereck's reagent to **83** and then reduction gave α-methylene-γ-butyrolactone **84**. Alcohol oxidation afforded dihydroaromatin, which was converted in aromatin via selenylation and selenoxide elimination.
The seven-membered ring annulation strategy of Schultz was successfully applied in the synthesis of (±)-aromatin (**4**) [48]. The hydroxylactone **90**, was prepared from the annulation product **72** through several steps of reduction and oxidation (leading to ketoalcohol **85**, diketone **86** and diol species **87**), where epimerization occurred at C10 into the more stable α-configuration of the methyl group. Then hydrogenolysis, saponification, decarboxylation and reaction with *n*-butyllithium gave the TMS-derivative **88**. peroxyacid oxidation of **88** and catalytic hydrogenation gave intermediate **89.**



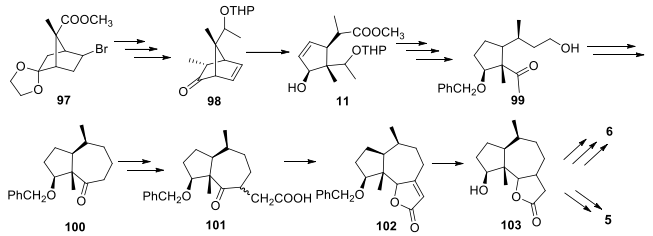
Scheme 4: Syntheses of aromatin (**4**).

Damsin (5), Ambrosin (6). The Schlessinger synthesis of (±)-**damsin** (**5**) was based on the hydroazulenone **19** (Scheme 5), the same key intermediate for the synthesis of (±)-helenalin and (±)-confertin, where transposition of the carbonyl residue from C8 to C6 is needed [11, 42]. After methylation to the β-methyl derivative **91**, the subsequent reaction steps included dehydrogenation on an intermediate enolsilane to give cycloheptenone **92**, stereoselective epoxidation to **93** and conversion into the allylic alcohol **94**, catalytic hydrogenation, alcohol oxidation and alkylation with *t*-butyl iodoacetate to give keto ester **95**. Formation of the enol lactone **96**, catalytic reduction, alcohol deprotection and final oxidation furnished damsin in an overall yield of 20% in 15 steps.



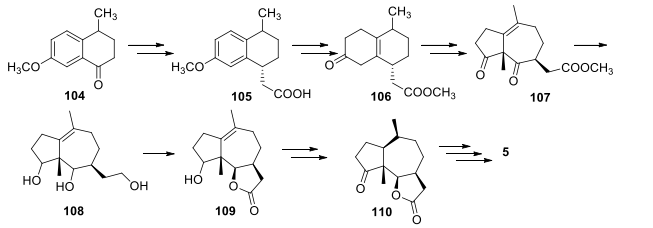
Scheme 5: Schlessinger's synthesis of damsin (**5**)

(±)-Damsin (**5**) and (±)-ambrosin (**6**) have been synthesized by Grieco [58]. The cyclopentenol derivative **11** (common reagent in Grieco helenalin synthesis, which bears correct configurations at Cl, C5, and C10) was prepared from the norbornadiene derived ketal ester **97** through several synthetic steps. The perhydroazulenone scaffold **100** was then constructed via reduction, benzylation, chain elongation, iodide conversion, intramolecular alkylation. Then it was converted first into ketoacid **101** through three steps (alkylation, ozonolysis, Jones oxidation), then butenolide **102**, and finally 4-hydroxyl γ-lactone **103** (after debenzylation and reduction), which bears the correct five chiral centers of damsin. Damsin synthesis was completed by α-methylenation of the y-butyrolactone ring and oxidation at C4. Ambrosin synthesis required introduction of an α-phenylselenenyl group in C-3 of damsin followed by its oxidative removal.



Scheme 6: Grieco's synthesis of damsin (5) and ambrosin (**6**)

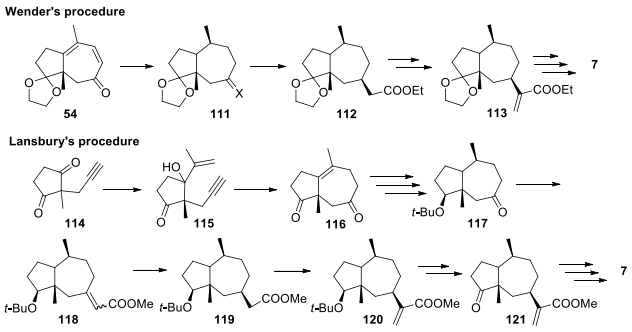
We have already abovementioned damsin syntheses described by Schlessinger [42], Grieco [58] and Money [37]. In a different approach Kretchmer started from the tetralone derivative **104**; reaction sequence afforded unsaturated ketone **106**, ozonolysis followed by a reductive work-up and methylation gave azulenedione **107** (via chromatography separation from its diastereomer) [59]. Ketone and acid reductions gave the triol intermediate **108**, which underwent oxidation to hydroxylactone **109**, catalytic hydrogenation and Jones oxidation to **110**, and final α-methylenation sequence to give damsin (**5**).



Scheme 7: Kretchmer's synthesis of damsin.

Almanza in 2015 described ambrosin semisynthesis from damsin, available in good amounts from *Ambrosia arborescens* [60]. (±)-Ambrosin was obtained by Saegusa-Ito oxidation of a silylenol ether derivative of damsin in better yields than the above Grieco procedure.

Damsinic Acid (7). Following the aforementioned Wender's protocol [43], **damsinic acid (7)** was prepared in a 20% overall yield over 11 steps. Ketal ketone **52** was stereoselectively reduced

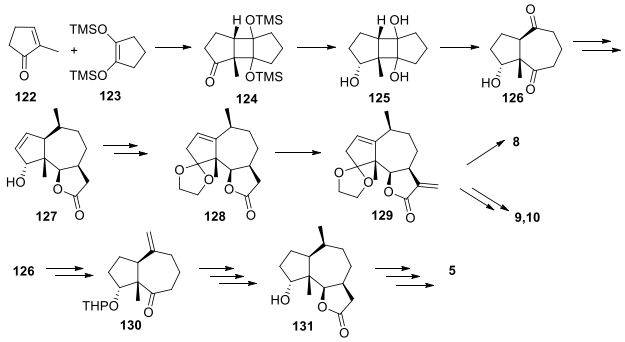


Scheme 8: Synthesis of damsinic acid (**7**).

to ketone **111** (X=O), then converted into ester **111** (X=CHCOOEt) which was hydrogenated to ester **112** with 90% stereoselectivity; final standard methylenation afforded **113** and then (±)-damsinic acid (**7**).

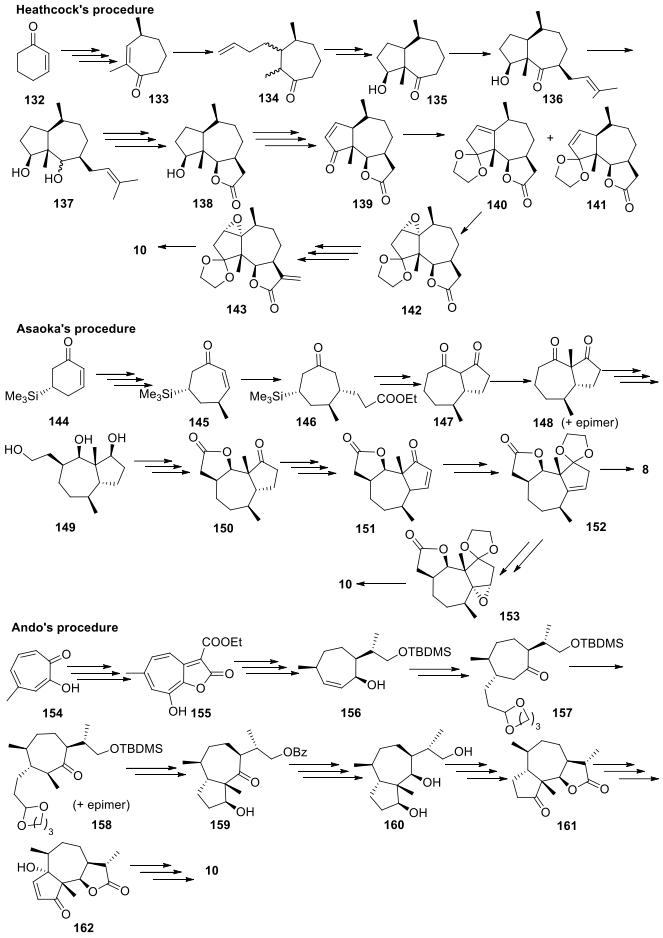
Total synthesis of damsinic acid has been reported by Lansbury [61]. In the Lansbury procedure, hydroazulenedione **116** was prepared from conversion of substituted cyclopentanedione **114** into **115** and then intramolecular cyclization to **116**; reduction (on a 7-thioketal intermediate) and hydrogenation to **117**, side chain introduction (**118**), hydrogenation again (**119**), α-methylenation (**120**),oxidation (**121**) and finally hydrolysis furnished damsinic acid. A formal synthesis of damsinic acid was also reported by Kawahara [62].

Neoambrosin (8), hymenin (9), parthenin (10). Vandewalle reported the first total synthesis of racemic **damsin (5), neoambrosin (8), hymenin (9)** and **parthenin (10)** [63]. The key intermediate of the synthetic procedure was obtained via intermolecular [2+2] photocycloaddition of 1,2-bis(trimethylsilyl-oxy)cyclopentene (**123**) and 2-methyl-2-cyclopentenone (**122**) gave the photoproduct **124**; reduction and deprotection generated tricyclic triol **125**; cyclobutane ring cleavage furnished hydroxy-ketone **126**. The same intermediate, transformed into the lactone **127**, was used in the synthesis of the three above mentioned pseudo-guaianolides. Selenylation and selenoxide elimination gave the corresponding cyclopentenone derivative; migration of the double bond was achieved by acidic treatment on the ketal derivative (**128**), α-methylenation to **129** and finally ketal hydrolysis gave neoambrosin **8**. Epoxidation furnished two isomers; chromato-graphic separation afforded epoxide ring opening and β-elimination yielding directly racemic hymenin (**9**) and parthenin (**10**).



Scheme 9: Vandewalle's synthesis of neoambrosin, parthenin, hymenin and damsin.

After the first synthesis reported by Vandewalle (Scheme 9), few years later Heathcock reported a new multi-step procedure for (±)-parthenin [64]. The synthetic approach entailed first the synthesis of



Scheme 10: Syntheses of parthenin

the cycloheptane ring and then the fusion of the-five membered ring following a method developed by the same authors. As reported in Scheme 10, cycloheptanone **133** (easily obtained from cyclohexenone **132**) was converted into diastereomeric mixture of adduct **134** by using Yamamoto's reagent; annulation product **135** was then obtained via ozonolysis and acidic treatment of the aldehyde intermediate. A subsequent five-step procedure enabled an efficient and enantioselective construction of the γ-butyrolactone ring of **138** on a gram-scale by choosing proper alkylating and protecting groups. After alcohol oxidation, silyl enol ether formation and direct oxidation to enone **139**, enone ketalization afforded a diastereomeric mixture of **140** and **141**. Single epoxidation of **140** afforded **142** with the desired configurations at C1 and C2; α-methylenation of the lactone ring (as Schlessinger's work, Scheme 1) and final acidic treatment of **143** gave racemic parthenin (22 steps from **134**, 0.25% overall yield).

An enantioselective synthesis of parthenin and neoambrosin from optically pure **144** was described by Asaoka [65]. The stereocontrol strategy took advantage from the presence of the trimethylsilyl group on the unsaturated seven membered ring. Adduct **145** was obtained by stereoselective introduction of methyl group to give a silyl enol ether intermediate, cyclopropanation and dehydrochlorination. 1,4-Addition gave a diastereomeric mixture of **146**; by reacting pure (−)-**146**, pure desilylated lactone **147** was obtained. Methylation gave **148** in epimeric mixture; pure (−)-**148** was converted in a multi-step reaction into the triol **149**, which was oxidized first to lactone and then to ketolactone **150**. Silylation and oxidation gave **151**, followed by protection and migration of the double bond to **152**. α–Methylenation and deacetalization of **152** gave neoambrosin (**8**), whilst Heathcock's procedure through epoxide **153** afforded parthenin (**10**).

Few years later, total synthesis of (±)-**10** was described by Ando [66]. The key intermediate **156**, prepared from 4-methyltropolone (**154**) through intermediacy of **155**. Upon oxidation and Grignard reagent addition from the α-facethe resulting enone**157** was obtained**,** whose methylation gave **158**. The benzoate ester of **158** was then subjected to acid-catalyzed intramolecular aldol condensation (**159**). Reduction afforded triol **160**; air oxidation of the primary alcohol, lactonization and oxidation of the secondary alcohol furnished ketolactone **161**. Several steps were required in order to stereoselectively introduce the γ-hydroxy-α,β-unsatureted ketone, involving protection/deprotection steps, dehydrogenation, epoxidation and hydrolysis; the final intermediate α-methyl-γ-lactone hymenolin **162** was converted into the α-methylene-γ-lactone parthenin through α-bromination and then dehydrobromination.

Conclusions

Sesquiterpene lactones represent a large and vastly important group of compounds. A number of compounds belonging to this class have been shown to be active in terms of bioactive agents combating human disease, the most known are for example parthenolide and helenalin. It seems almost certain that, even though the reasons of efficacy cannot be generalized too broadly, the effects can often be ascribed to the presence of functional groups specific to the class, typically the characterizing α-methyl-γ-lactone group, or extra-ring unsaturated carbonyl moiety. Among the sesquiterpene lactones, pseudoguaianolides represent an interesting class of targets. In this review, we collected the most recent syntheses of the pseudoguaianolide core. The unusual tricyclic fused core 5/7/5 was a challenge and inspired new synthetic methodologies to install substituents with proper stereochemistry. The most of the references relied on synthesis rather than semi-syntheses, implying that the stereochemistry is installed correctly by the exploitation of mainly diastereoselective reactions. Pseudoguaianolides, guaianolides and more in general sesquiterpene lactones as a whole represent a large and vastly important group of compounds, with high potentiality for biomedical applications. Despite this, their exploitation is so far very limited. Because of this, with this review we wanted to give perspectives in terms of availability and resupply of the most active compounds of the class.

References

[1] Adekenov SM. (**2013**) Natural sesquiterpene lactones as renewable chemical materials for new medicinal products. *Eurasian Chem.-Technol. J.*, **15**, 163-174.
[2] Chadwick M, Trewin H, Gawthrop F and Wagstaff C. (**2013**) Sesquiterpenoids lactones: benefits to plants and people. *International Journal of Molecular Sciences*, ***14***, 12780-12805, 12726 pp.
[3] Herz W. (**1974**) Pseudoguaianolides in Compositae. *Nobel Symposium*, ***25***, 153-172.
[4] Seaman FC. (**1982**) Sesquiterpene lactones as taxonomic characters in the Asteraceae. *The Botanical Review*, ***48***, 121-595.

[5] Santana A, Molinillo JMG and Macias FA. (**2015**) Trends in the Synthesis and Functionalization of Guaianolides. *European Journal of Organic Chemistry*, **2015**, 2093-2110.

[6] Macias FA, Santana A, Duran AG, Cala A, Galindo JCG, Galindo JLG and Molinillo JMG. (**2013**) Guaianolides for multipurpose molecular design. *ACS Symposium Series*, **1141**, 167-188.

[7] Fischer NH. (**1991**) Sesquiterpenoid lactones. *Methods in Plant Biochemistry*, ***7***, 187-211.

[8] Lampretsa E. (**1991**) Sesquiterpene lactones, a short review. *Pharmakeutike*, ***4***, 55-64.

[9] Ohfune Y, Grieco PA, Wang CLJ and Majetich G. (**1978**) Stereospecific total synthesis of DL-helenalin: a general route to helenanolides and ambrosanolides. *Journal of the American Chemical Society*, ***100***, 5946-5948.

[10] Grieco PA, Ohfune Y, Majetich GF and Wang CLJ. (**1982**) Pseudoguaianolides. 2. Stereocontrolled total synthesis of the helenanolide dl-helenalin. *Journal of American Chemical Society*, ***104***, 4233-4240.

[11] Roberts MR and Schlessinger RH. (**1979**) Total synthesis of dl-helenalin. *Journal of the American Chemical Society*, ***101***, 7626-7627.

[12] Adams R and Herz W. (**1949**) Helenalin. I. Isolation and properties. *Journal of the American Chemical Society*, ***71***, 2546-2551.

[13] Chaturvedi D. (**2011**) Sesquiterpene lactones: structural diversity and their biological activities. Research Signpost, 313-334.

[14] Amorim MHR, Gil da Costa RM, Lopes C and Bastos MMSM. (**2013**) Sesquiterpene lactones: Adverse health effects and toxicity mechanisms. *Critical Reviews in Toxicology*, ***43***, 559-579.

[15] Bosco A and Golsteyn RM. (**2017**) Emerging anti-mitotic activities and other bioactivities of sesquiterpene compounds upon human cells. *Molecules*, ***22***, 459/451-459/425.

[16] Dominguez E and Romo J. (**1963**) Mexicanin. I. A new sesquiterpene lactone related to tenulin. *Tetrahedron*, ***19***, 1415-1421.

[17] Bujnicki T, Wilczek C, Schomburg C, Feldmann F, Schlenke P, Mueller-Tidow C, Schmidt TJ and Klempnauer KH. (**2012**) Inhibition of Myb-dependent gene expression by the sesquiterpene lactone mexicanin-I. *Leukemia*, ***26***, 615-622.

[18] Romo J, Romo-de-Vivar A, Velez A and Urbina E. (**1968**) Franserin and confertin: new pseudoguaianolides isolated from *Franseria* and *Ambrosia* species. *Canadian Journal of Chemistry*, ***46***, 1535-1538.

[19] Aponte JC, Yang H, Vaisberg AJ, Castillo D, Malaga E, Verastegui M, Casson LK, Stivers N, Bates PJ, Rojas R, Fernandez I, Lewis WH, Sarasara C, Sauvain M, Gilman RH and Hammond GB. (**2010**) Cytotoxic and anti-infective sesquiterpenes present in *Plagiochila disticha* (plagiochilaceae) and *Ambrosia peruviana* (asteraceae). *Planta Medica*, ***76***, 705-707.

[20] Romo J, Joseph-Nathan P and A FD. (**1963**) Aromatin and aromaticin, new sesquiterpene lactones isolated from *Helenium aromaticum*. *Chemistry and Industry (London, U. K.)*, 1839.

[21] Harimaya K and Inayama S. (**1990**) Structure-activity relationships of pseudoguaianolides isolated from *Gaillardia pulchella* and their derivatives. *Heterocycles*, ***30***, 993-1008.

[22] Abu-Shady HA and Soine TO. (**1953**) The chemistry of *Ambrosia maritima*. I. The isolation and preliminary characterization of ambrosin and damsin. *Journal of the American Pharmaceutical Association (1912-1977)*, ***42***, 387-395.

[23] Villagomez R, Collado JA, Munoz E, Almanza G and Sterner O. (**2014**) Natural and semi-synthetic pseudoguaianolides as inhibitors of NF-κB. *Journal of Biomedical Science and Engineering*, ***7***, 833-847, 816 pp.

[24] Saeed M, Jacob S, Sandjo LP, Sugimoto Y, Khalid HE, Opatz T, Thines E and Efferth T. (**2015**) Cytotoxicity of the sesquiterpene lactones neoambrosin and damsin from Ambrosia maritima against multidrug-resistant cancer cells. *Frontiers in Pharmacology*, ***6***, 267/261-267/212.

[25] Dirsch VM, Stuppner H and Vollmar AM. (**2001**) Cytotoxic sesquiterpene lactones mediate their death-inducing effect in leukemia T cells by triggering apoptosis. *Planta Medica*, ***67***, 557-559.

[26] Doskotch RW and Hufford CD. (**1969**) Damsin, the cytotoxic principle of *Ambrosia ambrosioides*. *Journal of Pharmaceutical Science*, ***58***, 186-188.

[27] Nagaya H, Nagae T, Usami A, Itokawa H, Takeya K and Omar AA. (**1994**) Cytotoxic chemical constituents from Egyptian medicinal plant, *Ambrosia maritima* L. *Nature Medicine*, ***48***, 223-226.

[28] Geissman TA and Toribio FP. (**1967**) Sesquiterpene lactones. Constituents of *Hymenoclea salsola*. *Phytochemistry*, ***6***, 1563-1567.

[29] Toribio FP and Geissman TA. (**1968**) Sesquiterpene lactones. New lactones from *Hymenoclea salsola*. *Phytochemistry*, ***7***, 1623-1630.

[30] Saad MMG, Abdelgaleil SAM and Suganuma T. (**2012**) Herbicidal potential of pseudoguaninolide sesquiterpenes on wild oat, *Avena fatua* L. *Biochemical Systematics and Ecology*, ***44***, 333-337.

[31] Herz W and Watanabe H. (**1959**) Parthenin, a new guaianolide. *Journal of the American Chemical Society*, ***81***, 6088-6089.

[32] Ren Y, Yu J and Kinghorn AD. (**2016**) Development of Anticancer Agents from Plant-Derived Sesquiterpene Lactones. *Current Medicinal Chemistry*, ***23***, 2397-2420.

[33] Mew D, Balza F, Towers GHN and Levy JG. (**1982**) Antitumor effects of the sesquiterpene lactone parthenin. *Planta Medica*, ***45***, 23-27.

[34] Picman AK. (**1986**) Biological activities of sesquiterpene lactones. *Biochemical Systematics and Ecology*, ***14***, 255-281.

[35] Welch MC and Bryson TA. (**1988**) Boron annulation in organic synthesis. 2. Confertin and helenalin. *Tetrahedron Letters*, ***29***, 521-524.

[36] Welch MC and Bryson TA. (**1989**) Boron annulation in organic synthesis. 3. Stereoselectivity and the formal synthesis of (±)-helenalin. *Tetrahedron Letters*, ***30***, 523-526.

[37] Money T and Wong MKC. (**1996**) A formal, enantiospecific synthesis of pseudoguaianolides. *Tetrahedron*, ***52***, 6307-6324.

[38] Grieco PA, Ohfune Y and Majetich GF. (**1983**) Helenanolides: stereocontrolled total synthesis of dl-bigelovin, dl-mexicanin I, and dl-linifolin A. *Journal of Organic Chemistry*, ***48***, 360-366.

[39] Marshall JA and Ellison RH. (**1976**) The stereoselective total synthesis of pseudoguaianolides: confertin. *Journal of the American Chemical Society*, ***98***, 4312-4313.

[40] Anon. (**1978**) Synthesis of (±)-confertin. *Nachrichten aus Chemie, Technik und Laboratorium.*, ***26***, 729-730.

[41] Semmelhack MF, Yamashita A, Tomesch JC and Hirotsu K. (**1978**) Total synthesis of confertin via metal-promoted cyclization-lactonization. *Journal of the American Chemical Society*, ***100***, 5565-5567.
[42] Quallich GJ and Schlessinger RH. (**1979**) Total syntheses of dl-confertin and dl-damsin. *Journal of the American Chemical Society*, ***101***, 7627-7629.
[43] Wender PA, Eissenstat MA and Filosa MP. (**1979**) A general methodology for pseudoguaiane synthesis: total synthesis of (±)-damsinic acid and (±)-confertin. *Journal of the American Chemical Society*, ***101***, 2196-2198.
[44] Ziegler FE and Fang J-M. (**1981**) Regiochemical control in the conjugate addition of dithianylidene anions: total syntheses of ±-aromatin and ±-confertin. *Journal of Organcic Chemistry*, ***46***, 825-827.
[45] Heathcock CH, DelMar EG and Graham SL. (**1982**) Synthesis of sesquiterpene antitumor lactones. 9. The hydronaphthalene route to pseudoguaianes. Total synthesis of (±)-confertin. *Journal of the American Chemical Society*, ***104***, 1907-1917.
[46] Schultz AG and Motyka LA. (**1982**) New approach to pseudoguaianolide sesquiterpene lactone construction. Total synthesis of dl-confertin. *Journal of the American Chemical Society*, ***104***, 5800-5801.
[47] Ziegler FE, Fang JM and Tam CC. (**1982**) Conjugate addition of dithianylidene anions to α,β-unsaturated ketones. An application to the total synthesis of (±)-aromatin and (±)-confertin. *Journal of the American Chemical Society*, ***104***, 7174-7181.
[48] Schultz AG, Motyka LA and Plummer M. (**1986**) An annulation approach to the synthesis of pseudoguaianolide sesquiterpene lactones. Total syntheses of dl-confertin and dl-aromatin. *Journal of the American Chemical Society*, ***108***, 1056-1064.
[49] Kennedy M and McKervey MA. (**1988**) A new route to functionalized hydroazulenes. Synthesis of (±)-confertin. *Journal of the Chemical Society, Chemical Communications*, 1028-1030.
[50] Kennedy M and McKervey MA. (**1991**) Pseudoguaianolides from intramolecular cycloadditions of aryl diazoketones: synthesis of (±)-confertin and an approach to the synthesis of (±)-damsin. *Journal of the Chemical Society, Perkin Transactions 1*, 2565-2574.
[51] Quinkert G, Schmalz HG, Walzer E, Kowalczyk-Przewloka T, Duerner G and Bats JW. (**1987**) Total synthesis of the pseudoguaianolide (+)-confertin. *Angewandte Chemie*, ***99***, 82-84.
[52] Bolm C and Sharpless KB. (**1988**) Total synthesis of pseudoguaianolides (+)-confertin. *Chemtracts: Organic Chemistry*, ***1***, 403-405.
[53] Quinkert G, Schmalz HG, Walzer E, Gross S, Kowalczyk-Przewloka T, Schierloh C, Duerner G, Bats JW and Kessler H. (**1988**) Total synthesis of the pseudoguaianolide (+)-confertin. *Liebigs Annalen der Chemie*, 283-315.
[54] Quinkert G, Mueller T, Koeniger A, Schultheis O, Sickenberger B and Duerner G. (**1992**) Enantioselective conjugate addition greatly improves the synthesis of (+)-confertin. *Tetrahedron Letters*, ***33***, 3469-3472.
[55] Fang JM. (**1981**) Sulfur stabilized carbanions: the total synthesis of (±)-aromatin and (±)-confertin. 201 pp.
[56] Fang JM. (**1982**) Michael reactions in aprotic media. An effective method for construction of α,α,β-trisubstituted ketones and application to natural product synthesis. *Journal of Organic Chemistry*, ***47***, 3464-3470.
[57] Ohtsuka M, Takekawa Y and Shishido K. (**1998**) Novel and general entry into pseudoguaianolides. Formal and enantioselective synthesis of (+)-confertin. *Tetrahedron Letters*, ***39***, 5803-5806.
[58] Grieco PA, Majetich GF and Ohfune Y. (**1982**) Pseudoguaianolides. 1. Stereospecific total synthesis of the ambrosanolides dl-ambrosin and dl-damsin. *Journal of the American Chemical Society*, ***104***, 4226-4233.
[59] Kretchmer RA and Thompson WJ. (**1976**) The total synthesis of (±)-damsin. *Journal of the American Chemical Society*, ***98***, 3379-3380.
[60] Villagomez R, Quiroz M, Tito A, Sterner O and Almanza GR. (**2015**) Natural Pseudoguaianolides Prepared from Damsin. *Chemistry of Natural Compdounds*, ***51***, 675-680.
[61] Lansbury PT and Serelis AK. (**1978**) A facile entry to pseudoguaianes. Total synthesis of damsinic acid. *Tetrahedron Letters*, 1909-1912.
[62] Nishida A, Miyoshi I, Ogasawara Y, Nagumo S, Kawahara N, Nishida M and Takayanagi H. (**2000**) The Novel Skeletal Rearrangement of Cyclopentanones into Hydroazulenones via a Radical Process and its Application to the Formal Synthesis of Damsinic Acid. *Tetrahedron*, ***56***, 9241-9257.
[63] Kok P, De Clercq P and Vandewalle M. (**1978**) Pseudoguaianolides. The total synthesis of (±)-neoambrosin, (±)-parthenin and (±)-hymenin. *Bulletin des Sociétés Chimiques Belges*, ***87***, 615-619.
[64] Heathcock CH, Tice CM and Germroth TC. (**1982**) Synthesis of sesquiterpene antitumor lactones. 10. Total synthesis of (±)-parthenin. *Journal of the American Chemical Society*, ***104***, 6081-6091.
[65] Asaoka M, Ohkubo T, Itahana H, Kosaka T and Takei H. (**1995**) Enantioselective synthesis of neoambrosin, parthenin, and dihydroisoparthenin. *Tetrahedron*, ***51***, 3115-3128.
[66] Shimoma F, Kusaka H, Azami H, Wada K, Suzuki T, Hagiwara H and Ando M. (**1998**) Total Syntheses of (±)-Hymenolin and (±)-Parthenin. *Journal of Organic Chemistry*, ***63***, 3758-3763.