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# **NPC** Natural Product Communications

## **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  $\gamma$ -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  $\alpha,\beta$ -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 With their 5/7/5 skeleton, guaianolides targets. 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 sevenand 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  $\alpha$ on the *trans*-hydroazulene nucleus (Table 1, i.e. helenalin, mexicanin, aromatin) and the more abundant ambrosanolides group (with 10 $\beta$ -methyl configuration; i.e. confertin, parthenin, damsin, ambrosin); in both the methyl configuration in C-7 is  $\beta$ . 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  $\gamma$ -butyrolactone and its  $\alpha$ -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  $\alpha$  or  $\beta$  configuration of the methyl in C10. The norbornadiene derived cyclopentenol 11



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

Compound / First isolation / Cytotoxicity		Compound / First isolation / Cytotoxicity	
	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]		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].
Helenalin (1)		Mexicanin I (2)	
	Ambrosia confertiflora [18] Significant cytotoxic activity against a panel of six human tumor cell lines [19]		Helenium aromaticum [20] Aromatase inhibitor. Cytotoxic against KB cell line [21]
Confertin (3)		Aromatin (4)	
H. H	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]
Damsin (5)			
н соон	Ambrosta ambrostotdes [26] Cytotoxic [27]		Hymenoclea salsola [28] Cytotoxic and candidate to treat refractory tumors [24]
Damsinic acid (7)		Neoambrosin (8)	
	Hymenoclea salsola [29] Cytotoxic inducing apoptosis in Jurkat leukemia T cells [30]	HO O O O	Parthenium hysterophorus [31] Cytoxic against several human cancer cell lines [32-34]
Hymenin (9)		Parthenin (10)	

Grieco's procedure









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.  $\alpha$ -Methylenation was performed on the lactone bis(tetrahydropyrany1) ether via hydroxymethylation, mesylation, and elimination to give intermediate 17; deprotection and final oxidation gave  $(\pm)$ -helenalin [9].

In the latter synthetic approach, Schlessinger proposed the same precursor hydroazulenone **19** for the synthesis of  $(\pm)$ -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  $\alpha$ -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  $\alpha$  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  $\alpha$ methylenation and deprotection led to tricyclic lactone 36, that underwent final oxidation to  $(\pm)$ -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  $(\pm)$ -**confertin (3)** reported in 1976 [39], several other procedures were reported [39-50], which often include the synthesis of the C10 epimer  $(\pm)$ -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  $\alpha$ -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<sub>2</sub>) with welldefined 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.  $\alpha$ -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  $\alpha$ -methylene- $\gamma$ -butyrrolactone, t-butyl ether cleavage and final oxidation of the resulting alcohol gave  $(\pm)$ confertin (3).

The Schlessinger protocol relies on the hydroazulenone **19**, key intermediate for the synthesis of  $(\pm)$ -helenalin [11, 42]. The first step was the methylation to afford  $\beta$ -methyl derivative **45** which was converted into  $(\pm)$ -confertin and  $(\pm)$ -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  $\alpha$ -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 methodology previously described the same 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  $(\pm)$ -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  $(\pm)$ -confertin (3) and  $(\pm)$ aromatin (4) [44, 47, 55, 56]. The lithium anion 58, easily available from 2-ethylidene-1,3-dithiane, was reacted with 2methylcyclopentenone (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//P2O5 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  $\alpha$ -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  $\alpha$ -methylene- $\gamma$ 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  $(\pm)$ -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  $\alpha$ -methylene- $\gamma$ -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  $(\pm)$ -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  $\alpha$ -configuration of the methyl group. Then hydrogenolysis, saponification, decarboxylation and reaction with *n*-butyllithium gave the TMSderivative 88. peroxyacid oxidation of 88 and catalytic hydrogenation gave intermediate 89.





**Damsin (5), Ambrosin (6).** The Schlessinger synthesis of  $(\pm)$ damsin (5) was based on the hydroazulenone **19** (Scheme 5), the same key intermediate for the synthesis of  $(\pm)$ -helenalin and  $(\pm)$ confertin, where transposition of the carbonyl residue from C8 to C6 is needed [11, 42]. After methylation to the  $\beta$ -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  $\gamma$ -lactone 103 (after debenzylation and reduction), which bears the correct five chiral centers of damsin. Damsin synthesis was completed by  $\alpha$ -methylenation of the y-butyrolactone ring and oxidation at C4. Ambrosin synthesis required introduction of an  $\alpha$ -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  $\alpha$ -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]. ( $\pm$ )-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  $(\pm)$ -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**),  $\alpha$ -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(trimethylsilyloxy)cyclopentene (123) and 2-methyl-2-cyclopentenone (122) gave the photoproduct 124; reduction and deprotection generated tricyclic triol 125; cyclobutane ring cleavage furnished hydroxyketone 126. The same intermediate, transformed into the lactone 127, was used in the synthesis of the three above mentioned pseudoguaianolides. Selenylation and selenoxide elimination gave the corresponding cyclopentenone derivative; migration of the double bond was achieved by acidic treatment on the ketal derivative (128),  $\alpha$ -methylenation to **129** and finally ketal hydrolysis gave neoambrosin 8. Epoxidation furnished two isomers; chromatographic separation afforded epoxide ring opening and  $\beta$ -elimination vielding 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  $(\pm)$ -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 y-butyrolactone ring of 138 on a gram-scale by choosing proper alkylating and protecting groups. After alcohol oxidation, silvl 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 Author A *et al*.

group on the unsaturated seven membered ring. Adduct 145 was obtained by stereoselective introduction of methyl group to give a intermediate, cyclopropanation silyl enol ether and dehydrochlorination. 1,4-Addition gave a diastereomeric mixture of 146; by reacting pure (-)-146, pure desilvlated 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. Silvlation and oxidation gave 151, followed by protection and migration of the double bond to 152.  $\alpha$ -Methylenation and deacetalization of 152 gave neoambrosin (8), whilst Heathcock's procedure through epoxide 153 afforded parthenin (10).

Few years later, total synthesis of  $(\pm)$ -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  $\alpha$ -facethe resulting enone157 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  $\gamma$ -hydroxy- $\alpha$ , $\beta$ -unsatureted ketone, involving protection/deprotection steps, dehydrogenation, epoxidation and hydrolysis; the final intermediate α-methyl-γlactone hymenolin 162 was converted into the  $\alpha$ -methylene- $\gamma$ lactone parthenin through  $\alpha$ -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  $\alpha$ -methyl- $\gamma$ 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.

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