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Synthesis of Biologically Active Guaianolides with a *trans*-Annulated Lactone Moiety

Andreas Schall[a] and Oliver Reiser*[a]

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The biosynthetic pathways of sesquiterpene lactones are described in conjunction with recent developments in the total syntheses of various biologically active guaianolides. Different strategies towards the 5,7,5-membered ring system are highlighted. Oxidative diol cleavages, aldol reactions, and intramolecular cyclopropanations were used as key reactions to construct the racemic guaianolide core system. Radical cyclizations, as well as ring closing metathesis, were successfully applied in asymmetric approaches. Biomimetic reactions were also applied as versatile tools for the construction of these highly complex natural products.

Introduction

Guaianolides, which consist of a tricyclic 5,7,5-ring system, represent a large subgroup of naturally occurring sesquiterpene lactones exhibiting significant biological activity.[1] Plants containing such compounds as the active principles have been used in traditional medicine throughout history for treating conditions ranging from rheumatic pain and increase of bile production to pulmonary disorders.

As the name indicates, the core structure of guaianolides is derived from guaiane, a natural product with a *cis*-fused 5,7-bicyclic hydroazulene ring system (Figure 1). With only a few exceptions, the hydroazulene core is also *cis* fused in the 5,7,5-tricyclic carbon skeleton, whereas the γ-butyrolactone ring is *trans* annulated in approximately 85% of all known guaianolides.[2]

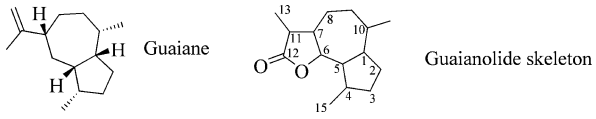
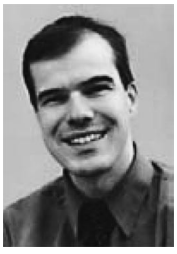


Figure 1. Skeletal relationships.

This interesting class of natural products displays a broad range of biological activity (Figure 2), which has stimulated considerable research activities around them. Although several synthetic strategies, especially towards monocyclic γ-butyrolactone natural products, are reported to

[a] Universität Regensburg, Institut für Organische Chemie, Universitätsstr. 31, 93059 Regensburg
Fax: +49-941-943-4121
E-mail: Oliver.Reiser@chemie.uni-regensburg.de

Andreas Schall was born 1977 in Roding, Germany. He studied chemistry at the Universities of Regensburg and Aberdeen and was awarded with scholarships from the DAAD, Fonds der Chemischen Industrie, and the Erasmus/Sokrates-Programm. He obtained his PhD in 2007 under the supervision of Prof. Dr. Oliver Reiser at the University of Regensburg. His research is dedicated to the total synthesis of biologically active natural products containing a γ-butyrolactone moiety.



Oliver Reiser was born 1962 in Hamburg, Germany. He studied chemistry at the Universities of Hamburg, Jerusalem, and California, Los Angeles (UCLA) and obtained his PhD in 1989 at the University of Hamburg under the supervision of Armin de Meijere. He spent one year as a postdoctoral fellow with Robert Miller at the IBM Research Center, San Jose, CA, and one year with David Evans, Harvard University, Cambridge, MA. In 1992 he joined the University of Göttingen as Assistant Professor, finishing his habilitation in 1995. In 1996, he moved to the University of Stuttgart as Associate Professor, and in 1997 he became Professor of Organic Chemistry at the University of Regensburg. His research group is involved in stereoselective synthesis of natural products, unnatural amino acids, and peptide foldamers, as well as transition-metal and organocatalysis.

date,[3,4] considerably fewer approaches towards the construction of bi- and tricyclic γ-butyrolactone frameworks have been reported.[5]

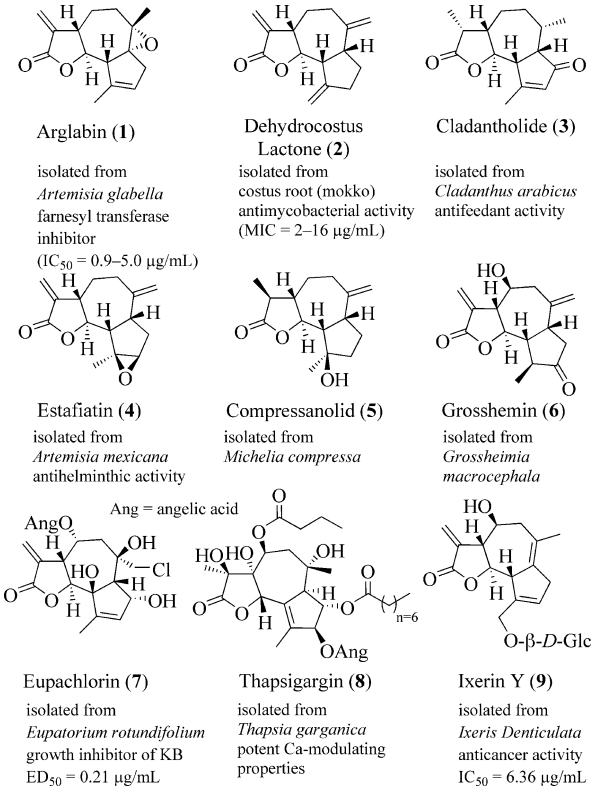
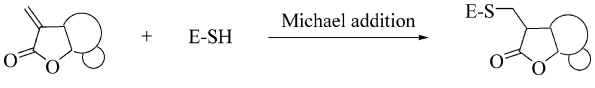


Figure 2. Some representative guaianolides that show the structural diversity of this class of compounds.

The structure–activity relationship (SAR) of tricyclic 5,7,5-γ-butyrolactones is currently still being intensively studied.[6] It was concluded that the hydroxy functionalities at C-5 and C-8 and the methyl group at C-4 are especially important for the biological activity of the compound, as well as the position of the double bond in the cyclopentane ring system and at the C-10 position (Figure 1, right).[7] Furthermore, it was shown that these compounds can readily react with nucleophiles, especially with an *exo* methyleno group in the γ-butyrolactone moiety, which is present in many natural products of this type.

Consequently, α-methylene sesquiterpene lactones undergo additions of biological nucleophiles such as cysteine or thiol-containing enzymes (E-SH, Scheme 1), which results in the manifestation of their biological activity but also their cytotoxicity. Furthermore, there is evidence that compounds of this type inhibit cellular enzyme activity but do not show DNA-alkylating properties.[6b,8] The residual substitution pattern of the guaianolides is assumed to determine the specificity and the resulting biological activity.[5c]



Scheme 1. Michael addition on α-methylene sesquiterpene lactones.

Biosynthesis of Guaianolides

The Mevalonate and Methylerythritol Phosphate (MEP) Pathway

Since ancient times, various oils with intensive and mostly delightful fragrances were extracted from numerous plants. In the beginning direct distillation and later on steam distillation were common techniques to isolate these essential oils, which mainly consisted of terpenes. Until now, more than 30000 terpenes from all sources have been identified, which makes them a large and structurally highly diverse family of natural products. It was early recognized that terpenes are formally derived from C_5 isoprene units **10**, but that isoprene (**11**) itself, a metabolite produced naturally, is not involved in their formation (Figure 3).

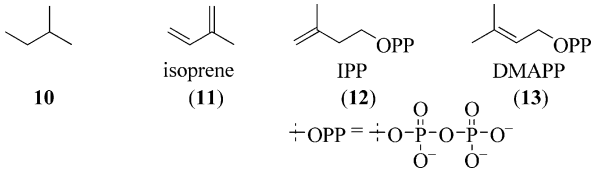
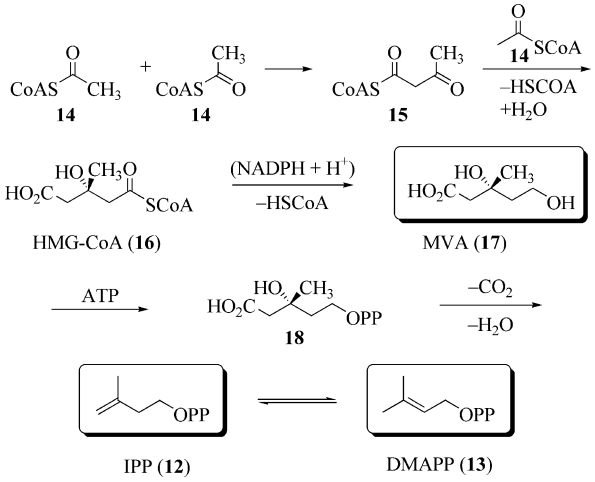


Figure 3. Comparsion of C_5 units.

The biochemically active isoprene units are isopentenyl pyrophosphate (IPP, **12**) and γ,γ-dimethylallyl pyrophosphate (DMAPP, **13**). The formation of these important precursors has been extensively studied over the last 50 years, building up the edifice of the so-called mevalonate biosynthesis pathway of terpenes in organisms.[9]

The biosynthesis of **12** and **13** starts in the cytosol with the assembly of three molecules of activated acetic acid (acetyl-CoA, **14**) by an initial Claisen condensation and a subsequent aldol reaction to give β-hydroxy-β-methylglutaryl-CoA (HMG-CoA, **16**; Scheme 2).

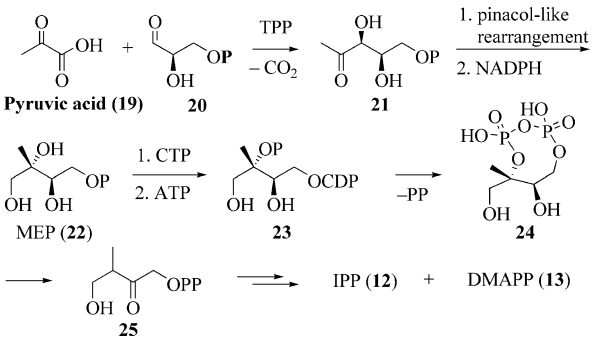


Scheme 2. MVA pathway for the biosynthesis of IPP (**12**) and DMAPP (**13**).

Reduction with NADPH+H$^+$ releases mevalonic acid (MVA, **17**), which is then activated by means of ATP to pyrophosphomevalonic acid (**18**). Decarboxylation and elimination leads to isopentenyl pyrophosphate (IPP, **12**), and further isomerization of the double bond gives rise to dimethylallyl pyrophosphate (DMAPP, **13**).

More recently, a second biosynthetic route was discovered in plants also leading to IPP (**12**) and DMAPP (**13**) as the final products.[9a,10] This so-called mevalonate-independent pathway or methylerythritol phosphate pathway (MEP) is only found in a few plants and microorganisms. It was recognized that the MEP pathway takes place in the plastids (chloroplasts, leukoplasts, etc.) in difference to the MVA pathway, which is manifested in the cytosol. Furthermore, in organisms in which both pathways are operating, a limited exchange of intermediates between MVA and MEP also takes place. This may explain why the MEP pathway was completely overlooked until labeling experiments revealed its existence.[11]

The MEP pathway is initiated by TPP (thiamine diphosphate) mediated decarboxylation of pyruvic acid (**19**) and addition to D-glyceraldehyde 3-phosphate (**20**) to form 1-deoxy-D-xylulose-5-phosphate (**21**, Scheme 3).

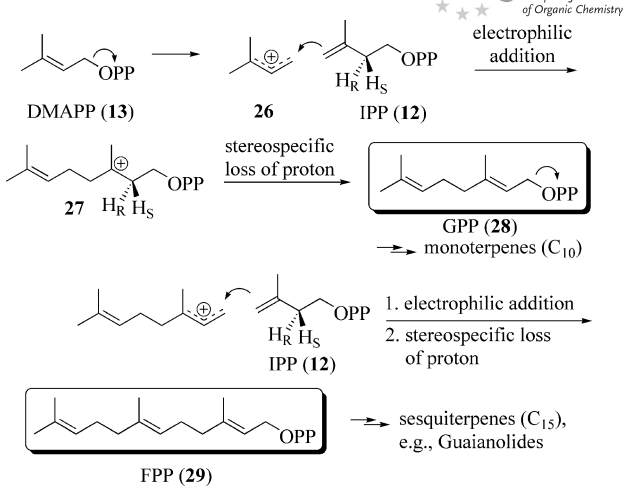


Scheme 3. MEP pathway for the biosynthesis of IPP (**12**) and DMAPP (**13**).

Subsequent pinacol-type rearrangement followed by reduction releases 2-methyl-D-erythritol-4-phosphate (MEP, **22**), which is activated by CTP and ATP to form **23**, which then cyclizes to cyclic phosphoanhydride **24**. Intramolecular elimination and tautomerization releases **25**, which sets the stage for further transformation towards IPP (**12**) and DMAPP (**13**).

To construct the basic backbones of terpenes, prenyltransferases connect IPP (**12**) and its isomer DMAPP (**13**) in a head-to-tail fashion (Scheme 4). In the first step, DMAPP (**13**) is ionized to allylic cation **26**, to which the double bond of IPP (**12**) adds regioselectively to form tertiary cation **27**. Subsequent stereoselective loss of a proton installs a new *trans*-substituted double bond to give rise to geranyl pyrophosphate (GPP, **28**), a fundamental precursor for the biosynthesis of monoterpenes (e.g., menthol).

For the biosynthesis of sesquiterpenes, the C_{10} skeleton of GPP (**28**) has to be extended by the addition of a C_5 IPP (**12**) unit in accordance with the isoprene rule[12] [$(C_5)_n$, n = 3 for sesquiterpenes], which was first discovered by Wallach

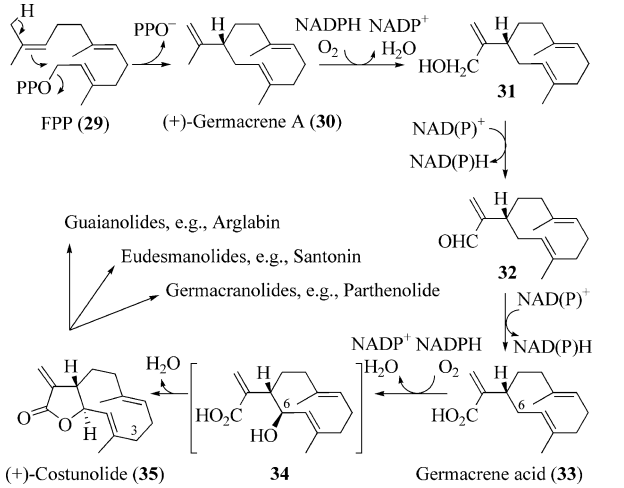


Scheme 4. Biosynthesis of GPP (**28**) and FPP (**29**).

in 1887, but largely ignored until Ruzicka recognized its general significance. Repeating the electrophilic addition of IPP (**12**) and stereospecific elimination of H_R (Scheme 4) gives rise to farnesyl pyrophosphate (FPP) (**29**), which is the precursor for linear and cyclic sesquiterpenes and sesquiterpene lactones.

Biosynthesis of Guaianolides

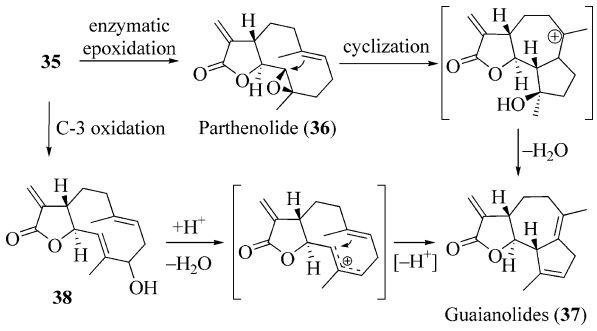
The further assembly of guaianolides used in Nature has been intensively investigated by de Kraker et al. on the basis of the biosynthetic route of sesquiterpene lactones in chicory, which is reasonable to assume to be also valid for other plant species (Scheme 5).[13] According to these studies, cyclization of FPP (**29**) yields (+)-germacrene A (**30**). Because of the double bond configuration in FPP (**29**), two (*E*)-configured double bonds are incorporated within the 10-membered ring system of **30**. Oxidation of the isopropenyl side chain by (+)-germacrene A-hydroxylase to primary alcohol **31** and further oxidation by NAD(P)$^+$-dependent dehydrogenases affords germacrene acid (**33**). It was further demon-



Scheme 5. Biosynthesis of (+)-costunolide (**35**).

strated that hydroxylation at the C-6 position and subsequent lactonization yields (+)-costunolide (**35**).

Compound **35** can be seen as a branching point in the biosynthesis of sesquiterpene lactones, because here the pathways for the formation of guaianolides or the related eudesmanolides [e.g., santonin (**125**); Scheme 24] and germacranolides [e.g., parthenolide (**36**); Scheme 6] are dividing.



Scheme 6. Guaianolides (**37**) by cyclization starting from (+)-costunolide (**35**).

Quite a number of stereospecific biomimetic transformations of germacranolides and their derivatives into eudesmanolides and guaianolides have been reported in the literature.[14] On the basis of these studies, it is postulated that the second cyclization of germacranolides towards the guaianolide skeleton is directed by epoxidations or hydroxylations of the costunolide skeleton **35**. Enzymatic epoxidation at C-4/C-5 directly affords parthenolide (**36**) (Scheme 6). This interesting germacranolide is a highly active antimigraine agent isolated from feverfew and magnolia and also shows antiinflammatory and antitumor activities.[15] *trans*-Annular cyclization of the strained ring system in **36** and subsequent elimination completes the guaianolide skeleton **37**.[16]

In addition to the route described above, an alternative pathway has also been proposed: enzymatic hydroxylation at C-3 in (+)-costunolide (**35**) affords **38**, which upon subsequent dehydration and cyclization would also lead to guaianolide skeleton **37**.[13d]

Further oxidation on the 5,7,5-membered ring system of **37** can introduce a number of different functionalities: Epoxides [e.g., found in arglabin (**1**) or estafiatin (**4**)] or the introduction of hydroxy groups [e.g., eupachlorin (**7**) or thapsigargin (**8**)] on various positions contributes to the diversity and complexity of this biologically important class of natural products. Esterification or glycosylation [e.g., ixerin Y (**9**)][17] of the latter also broadens the structural variety of the guaianolides.

In summary, Nature has proven a tremendous creativity in the construction of the guaianolides with respect to their structures and biological functions. For an organic chemist, the challenge arises to find synthetic entries towards these natural products. Even with modern state-of-the-art techniques in organic synthesis at hand, the complexity of the core structure and the high substitution pattern still makes the class of the guaianolides an exciting target.

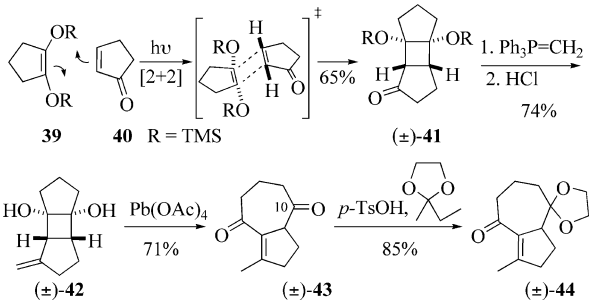
Synthetic Approaches towards Racemic Guaianolides

Total syntheses leading to racemic guaianolides up to the year 1995 have been excellently reviewed in detail within articles on the synthesis of sesquiterpenes by Pirrung[5a] and Adekenov.[5b] Therefore only key strategies are depicted in the following section.

Total Synthesis of (±)-Compressanolide and (±)-Estafiatin

Although there are some reports in the literature dealing with the synthesis of pseudoguaianolides[1] or of guaianolide-related compounds,[18] to the best of our knowledge the first total synthesis of a guaianolide with a *trans*-annulated lactone moiety was reported by Vandewalle et al. in 1982.[19] On the basis of a novel, flexible, and convergent route towards substituted hydroazulenes, the total synthesis of various sesquiterpene lactones was achieved.

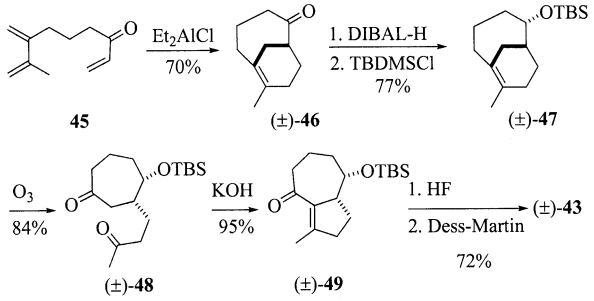
Starting with the photochemical addition of 1,2-bis[trimethylsiloxy]cyclopentene (**39**) to cyclopentenone (**40**), the tricyclic 5,4,5-ring system (±)-**41** can be obtained as a single diastereomer, in which the five-membered rings are *anti* oriented to each other (Scheme 7). Subsequent Wittig reaction and TMS deprotection set the stage for ring expansion by oxidative cleavage of diol (±)-**42**, giving rise to (±)-**43**, in which the *exo* methylene double bond had concurrently migrated into conjugation with the carbonyl group.



Scheme 7. Synthesis of key intermediate (±)-**44**.

At this point, the 5,7-membered ring system of the guaiane system is already complete. The more reactive carbonyl group at C-10 was regioselectively protected by acid-catalyzed acetalization to afford (±)-**44** as a key intermediate, from which a number of different sesquiterpene lactones can be accessed.

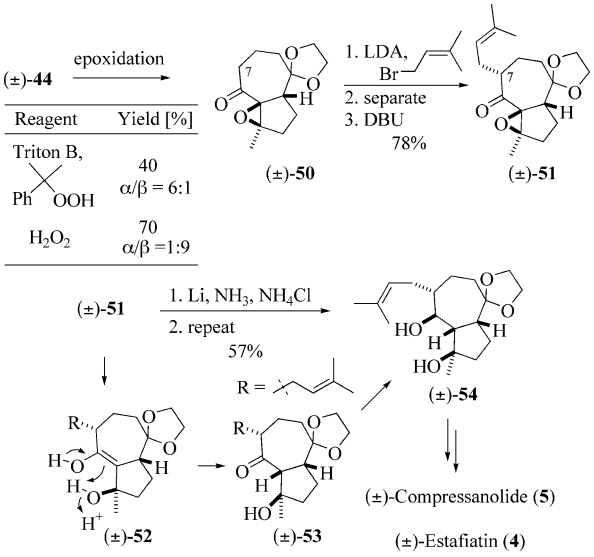
Compound (±)-**43** was also synthesized by Shea and coworkers by a bridged-to-fused-ring-interconversion strategy (Scheme 8).[20] Starting with triene **45**, an intramolecular Diels–Alder reaction gave rise to (±)-**46**, which upon reduction and protection afforded (±)-**47**. Subsequent ozonolysis and intramolecular aldol reaction to afford (±)-**49** was followed by deprotection and oxidation to complete the route to (±)-**43**.



Scheme 8. Bridged-to-fused-ring-interconversion strategy to (±)-**43**.

With substituted hydroazulene (±)-**44** in hand, the group of Vandewalle embarked on the total synthesis of (±)-compressanolide (**5**),[19a] a guaianolide first isolated from *Michelia compressa*.[21] Furthermore, variation of this route allowed the synthesis of (±)-estafiatin (**4**),[19a,19c] a natural product first isolated by Romo and coworkers from *Artemisia mexicana*.[22]

The opening step entails the epoxidation of the double bond in the five-membered ring of (±)-**44**. Controlled by steric hindrance (shielding of the β-face by the encumbering ketal protecting group), the bulkiest reagent gave the best selectivity of 6:1 for α-epoxide (±)-**50** (Scheme 9, top), providing the correct stereochemistry needed for the subsequent transformation into (±)-compressanolide (**5**).



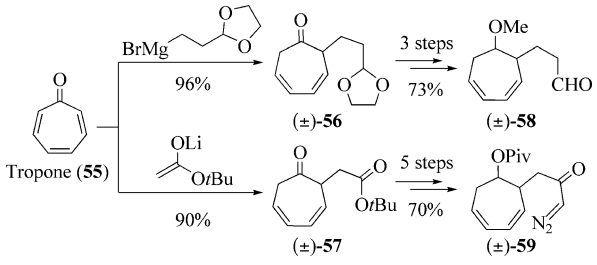
Scheme 9. Synthesis of (±)-estafiatin (**4**) and (±)-compressanolide (**5**).

Surprisingly, the epoxidation of (±)-**44** by using H_2O_2 afforded the epoxide in a 1:9 ratio, this time approaching from the β-face and forming a *trans*-fused 5,7-membered ring system with high preference.

The selective introduction of a prenyl side chain at the C-7 position was accomplished next, which is later on used for the formation of the lactone moiety. Attempts to introduce this moiety by kinetically controlled deprotonation/alkylation failed for intermediate (±)-**44**, but alkylation of epoxide (±)-**50** afforded desired products (±)-**51** along with its 7-epimer. Base-induced equilibration of the latter provided the possibility to epimerize it to the desired isomer. The selective reductive opening of the epoxide with concurrent carbonyl reduction in (±)-**51** was a crucial reaction step, installing three stereocenters present in (±)-compressanolide (**5**) and (±)-estafiatin (**4**) within one step. The complex sequence started with the reductive cleavage of the epoxide present in (±)-**51**, followed by protonation of the resulting enolate (±)-**52** (Scheme 9, bottom). Intramolecular tautomerization to ketone (±)-**53** by intramolecular proton transfer from the nearby hydroxy group led to the less-strained *cis*-annulated hydroazulene ring system. Subsequent in situ reduction gave rise to the more-stable equatorial alcohol (±)-**54**, which is located *trans* to the vicinal prenyl side chain at the C-7 position. The *trans* lactone moiety was finally obtained by ozonolysis and Jones oxidation of the prenyl side chain to complete the guaianolide skeleton. Further functional group manipulation finally led to (±)-compressanolide (**5**) and (±)-estafiatin (**4**).

Total Synthesis of (±)-Dehydrocostus Lactone and (±)-Grosshemin

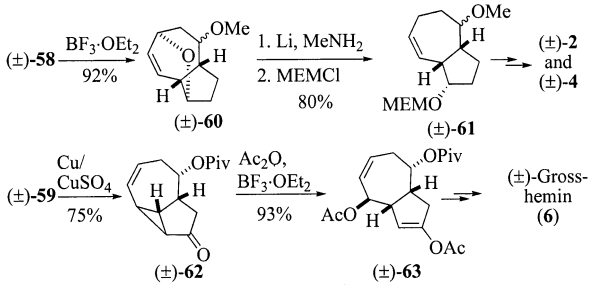
Four years later, Rigby et al.[23] reported the racemic synthesis of three additional guaianolides: (±)-dehydrocostus lactone (**2**) (IC_{50} = 14 μM, CTL cells[24]), (±)-estafiatin (**4**), and (±)-grosshemin (**6**) by starting from commercially available 2,4,6-cycloheptatrienone (tropone, **55**). Similar to the Vandewalle approach described above, the first target was also the construction of the hydroazulene core. By utilizing the seven-membered ring system already present in tropone (**55**), 1,8-addition of the appropriate nucleophiles afforded alkylated products (±)-**56** and (±)-**57**, which were further converted into aldehyde (±)-**58** and diazoketone (±)-**59**, respectively (Scheme 10).



Scheme 10. Functionalization of tropone (**55**) by Rigby et al.

The required *cis*-fused hydroazulene ring system was formed from (±)-**58** through Lewis acid mediated cyclization of the side chain, followed by reductive opening of the oxo bridge in resulting (±)-**60**, which released intermediate (±)-**61** needed for the synthesis of (±)-dehydrocostus lactone (**2**) and (±)-estafiatin (**4**, Scheme 11).

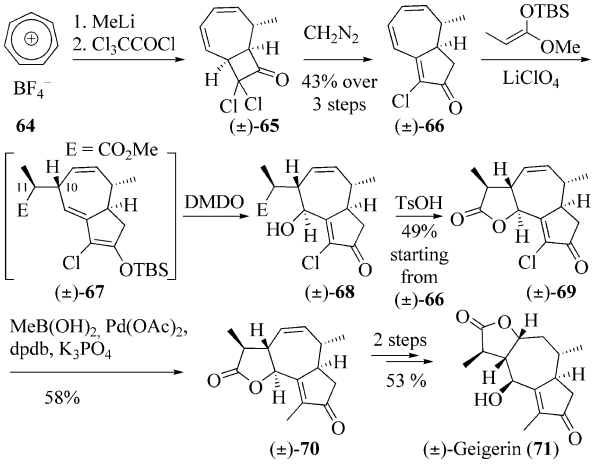
Alternatively, intramolecular cyclopropanation of (±)-**59** gave rise to tricyclic system (±)-**62**, which was then opened by a Lewis acid mediated homoconjugate addition reaction releasing intermediate (±)-**63** needed for the synthesis of



Scheme 11. Formation of *cis*-fused hydroazulene systems.

(±)-grosshemin (**6**), which was first isolated by Rybalko et al. from *Grossheimia macrocephala*.[25]

In a related approach, the group of Deprés was able to construct the guaianolide core by also utilizing the seven-membered ring of readily available tropylium cation **64** (Scheme 12).[26] After methylation and regioselective [2+2] cycloaddition, resulting dichloro compound (±)-**65** was subjected to a ring expansion towards hydroazulene intermediate (±)-**66**.



Scheme 12. Synthesis of (±)-geigerin (**71**).

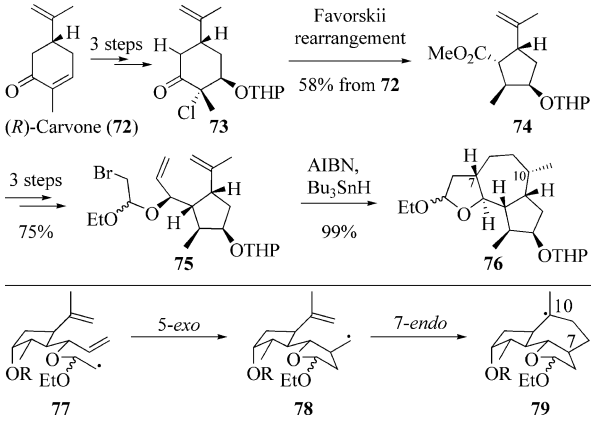
1,6-Conjugate addition of an (*E*)-ketene acetal to (±)-**66** resulted in a 6:1 ratio of epimers at C-10 and a 4:1 ratio at C-11 in (±)-**67**, thus introducing a functionalized sidearm, which is later on used for *trans* lactone formation. By subsequent oxidation, a hydroxy group was installed at C-9 with excellent selectivity, which gave rise to (±)-**68** as a single diastereomer. Acid-catalyzed lactonization completed the tricyclic guaianolide core of (±)-**69**. The incorporated chlorine atom at C-4 was subsequently used in a Suzuki cross-coupling reaction to introduce a methyl group at this position, and in two further steps the first total synthesis of (±)-geigerin [(±)-**71**] was achieved in only eight steps.

Enantioselective Total Synthesis of Guaianolides

Total Synthesis of (+)-Cladantholide and (–)-Estafiatin

A very elegant approach utilizing a radical cyclization cascade was reported by Lee and coworkers,[27] who succeeded in the total synthesis of (+)-cladantholide (**3**) isolated from *Cladanthus arabicus*.[28] and (–)-estafiatin (**4**).

Starting from (*R*)-carvone [(*R*)-**72**], in three steps chlorohydrin derivative **73** could be synthesized, which was subjected to a stereoselective Favorskii rearrangement to afford highly substituted cyclopentanecarboxylate **74** (Scheme 13). Three more steps were necessary to obtain bromoacetal **75**, which was set up for radical cyclization initiated by AIBN/Bu_3SnH under high-dilution conditions. Compound **76** was obtained in quantitative yield and with perfect diastereoselectivity with respect to the newly created stereocenters at the C-7 and C-10 positions.



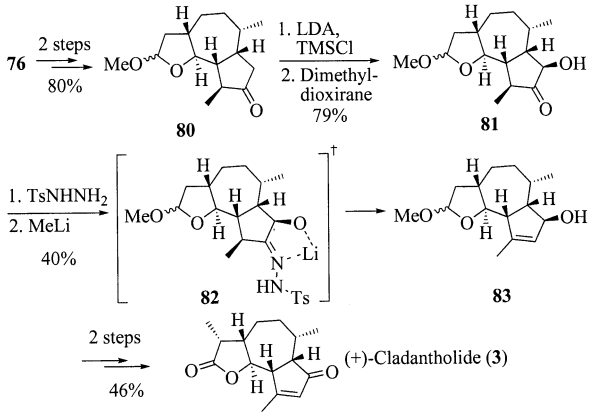
Scheme 13. Favorskii rearrangement and radical cyclization.

The high preference for seven-membered ring formation by radical cyclization was also observed during the investigation on model systems towards the synthesis of bi- and tricyclic sesquiterpene lactones of the xanthanolide and guaianolide family.[29]

The stereochemical outcome of this highly selective and efficient cascade can be explained by conformational analysis of the substrate (Scheme 13, bottom): The most stable conformation of the cyclopentane ring is represented in **77** as having three substituents oriented in equatorial positions and the attached side chains chair-like. Consequently, 5-*exo* cyclization of the primary radical onto the proximal double bond forms primary radical **78**, which thus sets the required stereochemistry at C-7. Subsequent thermodynamically favored 7-*endo* cyclization affords tertiary radical **79**, whereas the alternative kinetically favored 6-*exo* pathway was not observed. Final hydrogen transfer from the tin hydride at C-10 must have occurred from the α-face, which is presumable sterically less hindered.

To finish the synthesis of (+)-clandantholide (**3**), Lee et al. transformed **76** into ketoacetal **80**, in which the introduction of a hydroxy group adjacent to the keto group yielded α-hydroxy ketone **81** (Scheme 14).

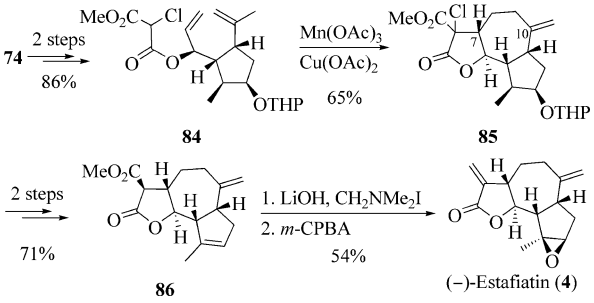
Application of the Shapiro protocol to **81** resulted in the regioselective introduction of a C=C bond to give allyl alcohol **83**. It was argued that the reaction proceeds through intermediate **82**, in which the lithium coordinates with one of the nitrogen atoms of the hydrazone and the adjacent hydroxy group. Consequently, excess base could only deprotonate next to the methyl group to afford the



Scheme 14. Synthesis of (+)-cladantholide (**3**).

trisubstituted double bond in **83**. Finally, oxidation and stereoselective α-methylation completed the synthesis of (+)-cladantholide (**3**).

Compound **74** was also the starting point for the synthesis of (–)-estafiatin (**4**) (Scheme 15), for which again a radical cyclization cascade was the key step. In difference to the reductive conditions employed for the transformation of **75** into **76**, the cyclization of **84** into **85** was carried out under oxidative conditions that were initiated by hydrogen rather than halogen abstraction from the α-halo carbonyl functionality.



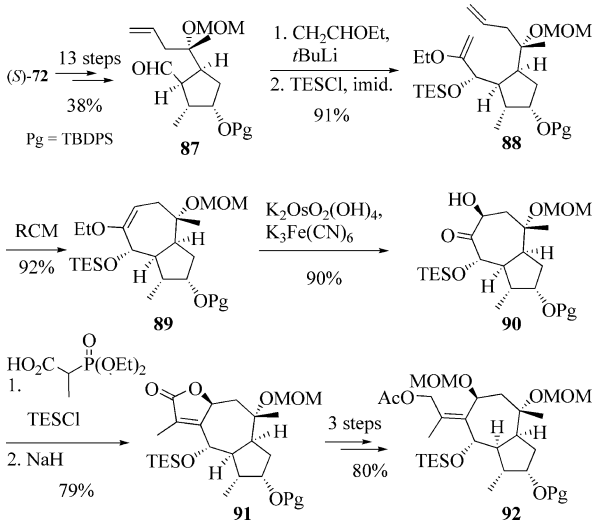
Scheme 15. Synthesis of (–)-estafiatin (**4**).

Reductive dechlorination and dehydration proceeded uneventfully to afford **86** and subsequent α-methylenation by using Eschenmoser's salt and selective epoxidation of the *endo* double bond afforded (–)-estafiatin (**4**).

Synthesis of the Thapsigargins by Ley et al.

A powerful execution of modern organic synthesis was shown by Ley and coworkers with their total syntheses of several members of the thapsigargin family.[30,31] Although extracts from the root of *Thapsia garganica* L. were used for a long time as treatment for rheumatic pain and pulmonary disorders, the identification and characterization of the active principles was not reported until 1980.[32] The potent biological activities reach from histamine liberation[33] to selective Ca^{2+}-modulating properties[34] in subnanomolar concentrations. The outstanding activity and the complex molecular structure consisting of a polyoxygenated 5,7,5-core structure with eight stereogenic centers and up to four different ester groups makes this class of guaianolides an especially challenging target for total synthesis.

The overall strategy towards the thapsigargins was again to construct the hydroazulene core first and subsequently functionalize it towards the target. Consequently, Ley and coworkers also started from (*S*)-carvone [(*S*)-**72**] and followed initially a similar route to that described above by Lee et al.[27] Within 13 steps, aldehyde **87** was assembled with already one allyl side chain and five stereocenters installed (Scheme 16).

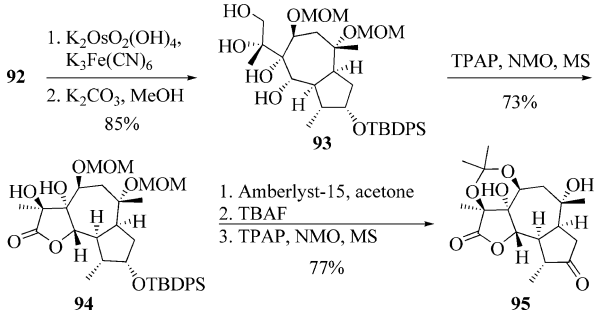


Scheme 16. Synthesis towards thapsigargins.

The second side chain needed for the planned ring closing metathesis was introduced by using the lithium anion of ethyl vinyl ether. Following strictly the Felkin–Anh paradigm,[35] diene **88** was generated as a single diastereomer, which was cyclized into **89** in high yield. The convex face of the bicycle is shielded by the bulky TES protecting group, which explains the good selectivity (16:1) for concave attack in the osmylation reaction of **89**. Esterification of resulting alcohol **90** and subsequent intramolecular Horner–Wadsworth–Emmons reaction provided butenolide **91**, which was within three steps transformed into **92**.

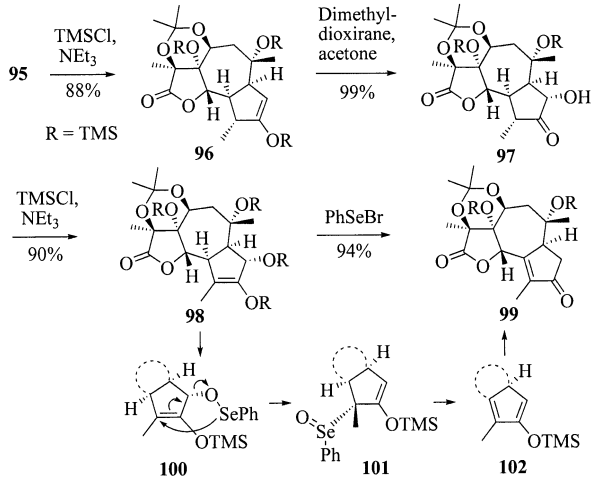
Further functionalization of **92** towards the highly oxygenated core system of the targets was performed by selective dihydroxylation of the side chain to yield **93** (Scheme 17). Desired *trans*-annulated lactone **94** was formed after selective oxidation of the primary alcohol. Up to this point, 23 linear but high yielding steps in the sequence were necessary. Moreover, purification by chromatography was required for only five compounds, which allowed **94** to be acquire in multiple gram quantities in 11% overall yield. After its deprotection, acetonide **95** was formed, which was found to greatly stabilize the already highly functionalized system.

The next aim was the modification of the cyclopentane ring. Kinetically controlled enolization of **95** followed by oxidation from the less-hindered concave face provided α-hydroxy ketone **97** (Scheme 18). Again, enolization, this



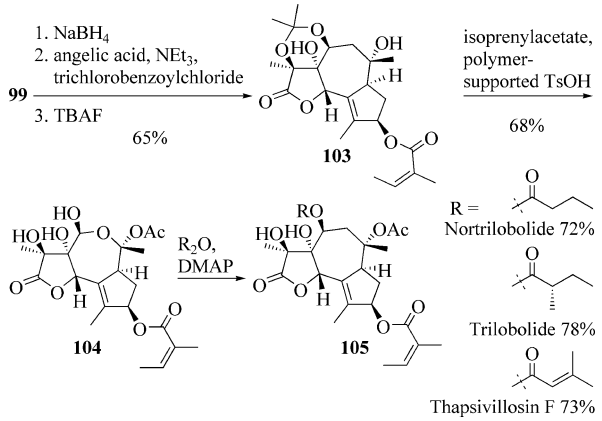
Scheme 17. Synthesis of advanced intermediates towards thapsigargins.

time thermodynamically controlled, afforded highly functionalized **98**, which was the starting point for the conceptually interesting transformation into **99** catalyzed by PhSeBr. To initiate the process, the authors suggested the selenation of the TMS-protected secondary alcohol into **100**; they argued this to be the least hindered position. Subsequent 2,3-sigmatropic rearrangement afforded selenoxide **101**, which rapidly underwent *syn* elimination of phenylselenic acid. Hydrolysis of resulting enol ether **102** released conjugated ketone **99**.



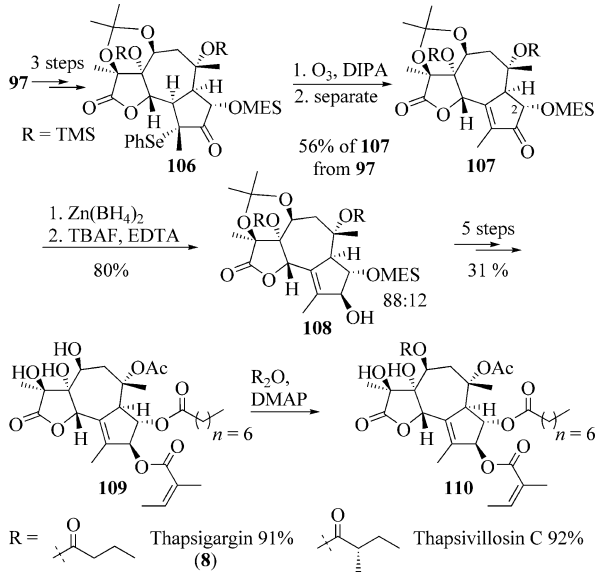
Scheme 18. Synthesis of advanced intermediates towards thapsigargins.

To complete the synthesis, Ley and coworkers were able to introduce the remaining stereogenic hydroxy group by reduction of the cyclopentenone moiety in **99**, which proceeded with 4:1 selectivity for attack from the bottom, that is, the concave face of the molecule. Esterification with angelic acid and removal of the TMS protecting groups afforded diol **103** (Scheme 19), which was selectively acetylated with simultaneous removal of the acetal protecting group. Resulting triol **104** could be transformed into the different natural products **105** by esterification of the more accessible secondary alcohol with the appropriate anhydrides.



Scheme 19. Final synthetic steps towards thapsigargins.

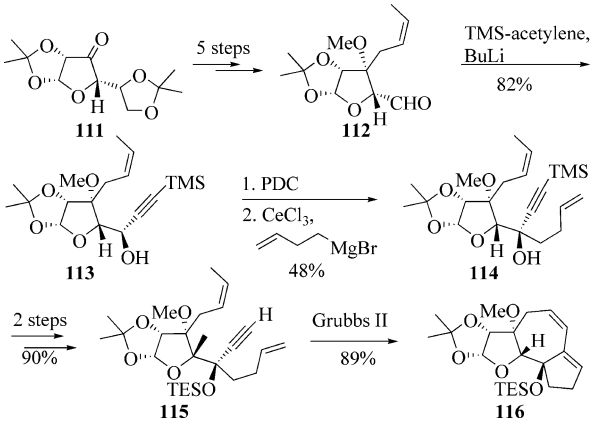
By variation of this route, the synthesis of thapsigargin (**8**) and thapsivillosin C was also accomplished (Scheme 20).[31] Starting from **97**, within three steps selenide **106** could be obtained along with its epimer (4:1), where the former yielded enone **107** upon oxidative elimination, which overall retained the hydroxy functionality at C-2; this is in contrast to that observed for the transformation of **98** into **99** (cf. Scheme 18). The reduction of **107** proved to be more difficult with respect to selectivity and product isolation than the transformation of **99** into **103**, but switching from $NaBH_4$ to $Zn(BH_4)_2$ was found to be suitable to set the last stereocenter at the ring skeleton. Subsequent selective esterification of the hydroxy functionalities afforded thapsigargin (**8**) and thapsivillosin C, and by this overall route further members of the thapsigargin family should become accessible.



Scheme 20. Further thapsigargins by Ley and coworkers.

The thapsigargin skeleton could also be constructed by an elegant domino metathesis reaction, as demonstrated by Kaliappan and coworkers (Scheme 21).[36] Within five steps, aldehyde **112** having already one side chain attached needed

for metathesis, was built up from **111**, which was readily available from D-glucose. Introduction of two more unsaturated side chains by the addition of appropriate metal organyls and an intermittent oxidation gave **114**. After hydroxy group protection, **115** underwent a highly efficient metathesis domino reaction to form simultaneously the five- and seven-membered rings, which thus provided access to guaianolide core **116** in one step.



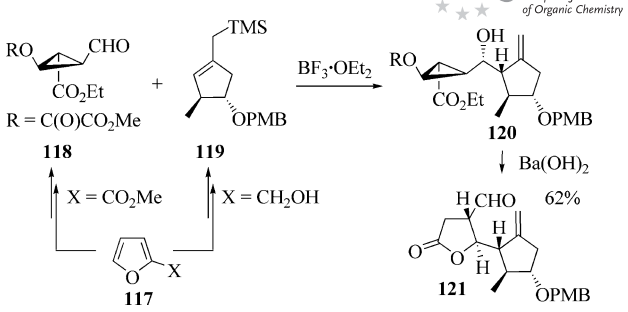
Scheme 21. Domino metathesis route towards the guaianolide skeleton.

Total Synthesis of Arglabin

Another prominent member of the guaianolides is Arglabin (**1**), a potent farnesyl transferase inhibitor with promising antitumor activity and cytotoxicity against human tumor cell lines (IC_{50} = 0.9–5.0 μg/mL).[37] Isolated from *Artemisia glabella*,[38] the dimethylamino hydrochloride salt of **1** was successfully used for cancer treatment and is currently under clinical evaluation.

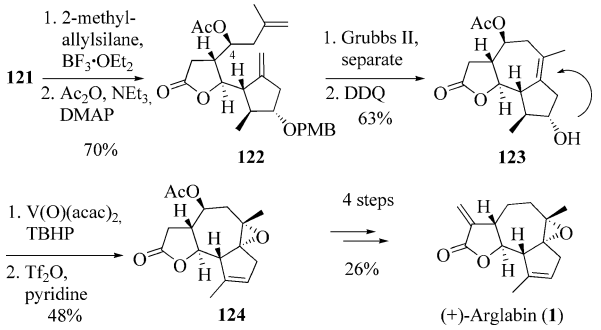
The first synthesis of **1** was recently accomplished[39] by using furan derivatives as a starting point: cyclopropylcarbaldehyde **118** can be prepared by a two-step sequence involving Cu^{I}-catalyzed asymmetric cyclopropanation and subsequent ozonolysis from methyl-2-furoate (**117**, X = CO_2Me; Scheme 22).[3c,29] The chiral *trans*-substituted allylsilane **119** is accessible from furfuryl alcohol (**117**, X = CH_2OH) by enzymatic resolution and functional group transformations. The combination of these two building blocks proceeded with high stereocontrol, that is, the carbonyl group of **118** is attacked in accordance with the Felkin–Anh paradigm[35] by allylsilane **119**, which reacts from the face opposite of its methyl group. Base-induced saponification of the more-labile oxalic ester in **120** and subsequent retroaldol–lactonization afforded lactone aldehyde **121**, which is an advanced intermediate in this synthesis.

Hosomi–Sakurai allylation of **121** and subsequent acetyl protection released diene **122** in a 4:1 ratio at the C-4 position (Scheme 23), which underwent ring-closing metathesis to complete the guaianolide core. PMB deprotection produced homoallyl alcohol **123**, in which the free hydroxy group directs the following epoxidation towards the desired



Scheme 22. Formation of lactone aldehyde **121**.

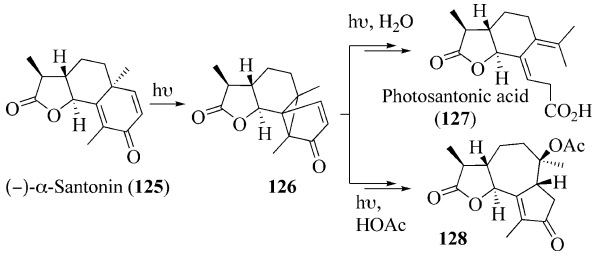
α-face of the molecule to give rise to **124**. In four more steps, including removal of the hydroxy group by the Barton McCombie protocol and α-methylenation, the synthesis of (+)-arglabin (**1**) could be completed.



Scheme 23. Final steps towards (+)-arglabin (**1**).

Hemi-Synthesis Starting from Santonin

First isolated by Kahler et al. in 1830,[40] it was a long and exciting journey to elucidate the full structure of (–)-α-santonin (**125**).[41] Commercially available by extraction,[42] this eudesmanolide provides a perfect starting point for the synthesis of various sesquiterpene lactones. Abe et al.[43] and Marshall et al.[44] also succeeded in its total synthesis starting from a hexahydronaphthalene derivative or 3-methylbenzoic acid, respectively. In the former approach, resolution of an advanced intermediate was possible to give access to enantiopure **125**. Despite its own biological activity, the most important feature of (–)-α-santonin (**125**) is its behavior upon irradiation to form various products, which represents one of the first organic photoreactions known (Scheme 24).[45]

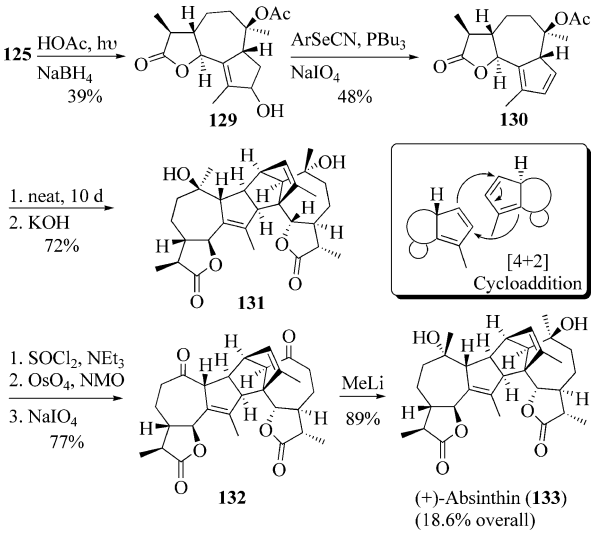


Scheme 24. Structure and rearrangement of (–)-α-santonin (**125**).

Rearrangement of the cross-conjugated dienone present in **125** takes place upon irradiation to form lumisantonin (**126**), which provides the starting point for further transformations, for example, in aqueous solution towards photosantonic acid (**127**)[46] or in acetic acid towards the 5,7,5-membered ring system of guaianolides **128**.[47]

Biomimetic Synthesis of Absinthin

Absinthin (**133**) was isolated in 1953 by Herout et al.[48] as a dimeric guaianolide from *Artemisia absinthium*. Its complex structure, however, could not be determined before the 1980s.[49] The complex architecture of **133** and its biological activity, as a promising antiinflammatory agent,[50] inspired Zhang and coworkers to search for a synthesis of this compound (Scheme 25).[51]

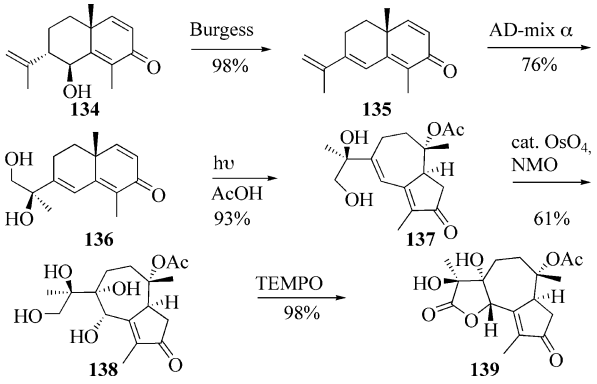


Scheme 25. Biomimetic dimerization by [4+2] cycloaddition.

The recognition that the polycyclic framework of target molecule **133** can be constructed by a Diels–Alder reaction of two identical guainolides was the key for the synthesis. Thus, **130**, being conveniently available from (–)-α-santonin (**125**), could react in a [4+2] cycloaddition in a highly regio- and stereoselective manner to give rise to **131** after basic cleavage of the acetyl groups.

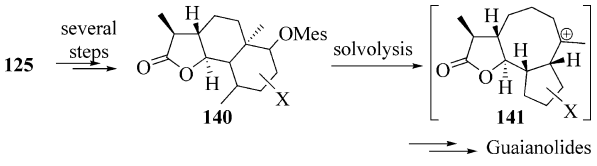
The excellent stereocontrol in the dimerization reaction can be explained by minimizing the interactions during the approach of the reaction partners through the less-hindered faces with respect to the cyclopentadiene moieties and by a head-to-head orientation with respect to the lactone moieties; the latter minimizes the steric interactions between the seven-membered ring systems (cf. inset box in Scheme 24). However, **131** had the wrong absolute configuration on the two tertiary alcohol centers, which made their inversion necessary to arrive at the target molecule. This was accomplished by oxidative degradation of **131** into diketone **132** and reinstallation of the methyl groups, which proceeded with remarkable selectivity to complete the synthesis of (+)-absinthin (**133**).

In a related approach, the group of Massanet used **134**, which is similar to (–)-α-santonin (**125**) because of its dienone system, to access the highly functionalized guaianolide core **139** (Scheme 26).[52] A high-yielding dehydration of **134** afforded the fully conjugated system **135**, which underwent a remarkably chemoselective asymmetric dihydroxylation of the side chain to furnish diol **136**. Upon irradiation in acetic acid, hydroazulene core **137** was formed. Osmylation and regioselective oxidation afforded the highly oxygenated guaianolide ring system **139**.



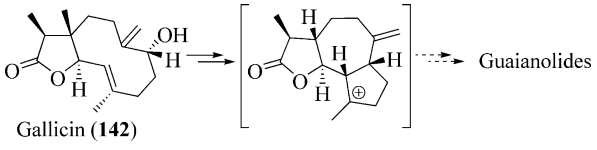
Scheme 26. Photochemical rearrangement and regioselective oxidation.

A further strategy using (–)-α-santonin (**125**) as a starting point was extensively used by the groups of Ando[24,53] and Pedro[54] to access several natural products of the guaianolide family (Scheme 27). The transformation of the 6,6- into the 5,7-ring system is accomplished by a carbocation rearrangement initiated by the solvolysis of **140**.



Scheme 27. Solvolysis towards guaianolides.

Several short biomimetic syntheses of guaianolides starting from suitably modified natural germacranolides have also been reported in the literature.[14e–14h] For example, gallicin (**142**), a germacranolide isolated from *Artemisia maritima gallica*, can be cyclized to afford the guaianolide skeleton to provide the basic guaianolide framework.[14e,55] The main problems with these approaches are the limited availability of the staring materials and the frequently observed complex product mixtures arising during the cyclization reactions in combination with poor yields (Scheme 28).



Scheme 28. Biomimetic cyclization of germacranolides.

Conclusions

The search for synthetic strategies towards guaianolides did not only result in new total syntheses of complex and biologically active natural products, but also contributed to the development of a wide range of new and modern chemistry. The fundamental and methodological aspects of natural product synthesis have always proven to be of great importance, besides the development of straight-forward synthetic pathways towards the target structures. As there are more and more members of the guaianolide family discovered and extracted from different plants with remarkable biological properties, new, efficient, and flexible ways to make these compounds and their derivatives will remain an important task for synthesis.

Acknowledgments

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