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Germacrenes A–E and related compounds: thermal, photochemical and acid induced transannular cyclizations

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1. Introduction

Germacrenes are an important group of sesquiterpenes widely occurring in nature and are considered as important intermediates in the biosynthesis of other sesquiterpenes. Common to germacranes cyclodecadiene ring system are their ability to undergo conformational changes, their great tendency to undergo Cope rearrangement and transformation to a large variety of products upon acid or irradiation treatment.

Because germacrenes' rearrangement products were eventually found as naturally occurring metabolites, the elucidation of unknown rearrangement products is believed to facilitate the discovery of new natural products.[1,2]

This review will focus on rearrangements and transformations (Cope rearrangements, acid induced cyclizations and photochemical treatments) of germacrenes A–E and related compounds in the last 50 years. The general identification and isolation, stereochemistry and conformational analysis, biosynthesis, biotransformations and bioactivity of selected germacranes are also discussed. Selected germacrane oxidation products that occur in nature, which appeared interesting to the author will also be discussed.

In 1971, Sorm[3] a pioneering member of germacrane chemistry published a review on a survey of structural features of several isolated sesquiterpenes with 10-membered carbon rings. Roberts and Bryson (1984)[4] published a review on isolated sesquiterpenoids including germacranes and beginning from 1985 an annual update of the literature of newly isolated and synthesized sesquiterpenoids including germacranes and related compounds are also being published in the natural products reports by Fraga.[5a–u] Recently, a review on the syntheses of germacrane sesquiterpenes and related compounds was published by Minnaard et al.,[6] and from time to time various topics on germacranes have also been published by various groups and will be cited where appropriate to enable further reading.

The bibliographic search in SciFinder Scholar using the key word germacrene(s) as of June 8th, 2007 gave a total of 4358 journal articles. While in 1962 only one article contained the key word germacrenes, the number has increased to 478 in 2005 and 544 in 2006. These journals range from isolation to synthesis and biosynthesis, synthases, rearrangements reactions and so on. The increase in the number of publications on germacrenes demonstrates how widespread and interesting the compounds are.

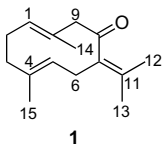

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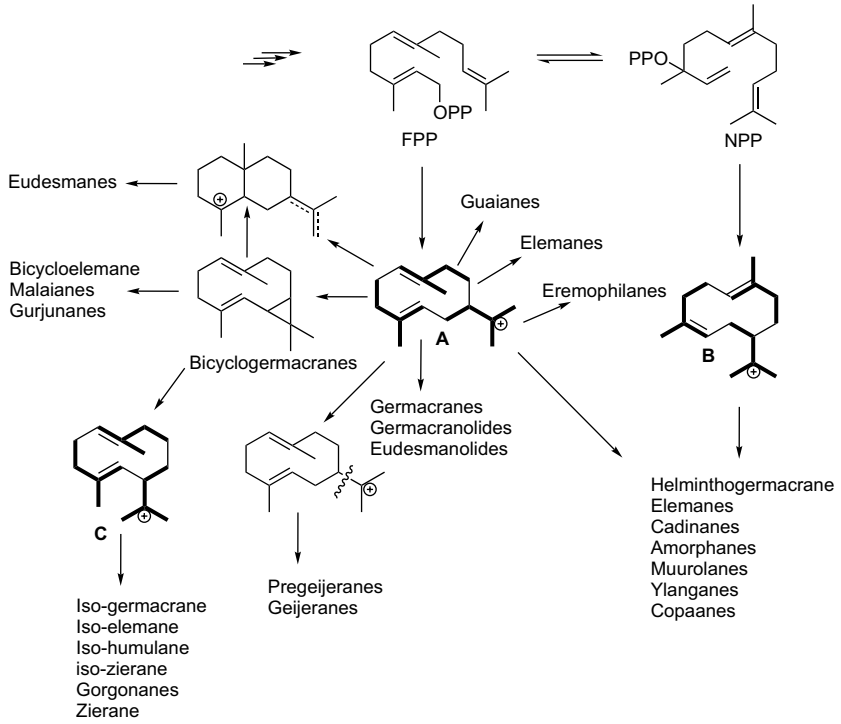
Figure 1. Germacrone (**1**).

The name germacrane-type is derived from the skeleton of germacrone (**1**) the major sesquiterpenoid isolated from the Bulgarian 'Zdravets' oil (*Geranium macrorrhizum*),[7a,b] (Fig. 1). Formerly, structure of **1** had been proposed as an oxide with guaiane skeleton[8] named, germacrol.[9] The structure of germacrol was established in 1957 as a 10-membered ring monocyclic ketone sesquiterpenoid and it was renamed germacrone (**1**).[7a,b]

Germacrane sesquiterpenoids occur widely in nature[10] and they have unique conformational flexibility.[11a–m] They are also an important biogenetic[12a–c] and biosynthetic intermediates[13a,b] between either farnesyl diphosphate (FPP) or nerodily diphosphate (NPP) and several classes of sesquiterpenes such as eudesmanes, guaianes, eremophilanes,[14a–c] germacranolides,[15] spirovetivanes, cadinanes,[16a,b] amorphanes and other types of sesquiterpenes (Scheme 1).

In Scheme 1, germacranyl cations (**A** and **B**) formed from both FPP and NPP could be responsible for the formation of the cadinanes, amorphanes and muurolanes.[14a,16a,b,17]

The biosynthetic pathway for rarely occurring gorgonanes and zieranes has been proposed via formation of isogermacranyl cation (**C**) formed from bicyclogermacrane that had undergone induced enzymatic cyclopropane ring opening followed by deprotonation.[18] In the case of pregeijerene, Cool and Adams[19] suggested the possibility of an enzymatic degradation of a structurally related germacrane.

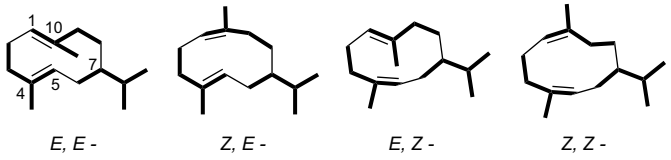


Scheme 1. Proposed biogenetic pathways for other sesquiterpenes from farnesyl diphosphate (FPP) and nerodily diphosphate (NPP) via germacranyl cations.

1.1. Occurrences, structures and selected bioactivities

Germacrane sesquiterpenes are widespread in nature; in higher plants such as Solidago species (*Solidago canadensis*, *Solidago altissima* L.),[2,20a,b] *Ageratum conyzoides* L.,[21] *Chloranthus spicatus* (Thunb.) Makino,[22] caraway herb and root,[23] fresh costus roots (*Saussurea lappa*),[24] *Hedycarya angustifolia* A. Cunn.,[25] *Smyrnium olusatrum*,[26] *Acorus calamus* L.,[27a–c] and *Meum athamanticum*;[28] in liverworts such as *Scapania undulata*,[29] *Lepidozia fauriana*, *Lepidozia vitrea*,[30] and for more liverwort species read the review by Asakawa;[31] in mosses such as *Mnium hornum*, *Mnium marginatum*, *Mnium stellare*, *Plagiothecium undulatum* and *Taxiphyllum wisgrillii*;[32] in arthropods such as termite (*Amitermes wheeleri*,[33a] *Reticulitermes*),[33b] American cockroaches (*Periplaneta Americana*)[34a–c] and aphid (*Therioaphis maculala*);[35a,b] in marine invertebrates such as *Eunicea mimosa*,[36] *Sinularia mayi*,[37] *Sinularia polydactyla*, *Lithophyton arboretum*, *Strereonephthea cundabiluensis*,[38] *Pacifigorgia pulchra exilis*, *Pacifigorgia media* and *Tubipora musica*,[39] and in microorganisms such as *Helminthosporium sativum* fungus[40] and *Streptomyces citreus* bacteria.[41a,b]

Structurally, the cyclodecadiene system of germacranes consists of two endocyclic double bonds at 1(10)- and 4(5)- positions and methyl groups at C_4 and C_{10} with an isopropyl group at C_7. This cyclodecadiene system consists of an isoprene units linked in head-to-tail fashion consistent with the *Isoprene rule*[42a,b] (Scheme 2). With respect to the endocyclic double bonds in the 1(10)- and 4(5)-positions of the cyclodecadiene system, germacranes are classified into four possible geometric isomers namely *E*,*E*-germacranes, (*Z*,*E*)-germacrenes (melampolides), (*E*,*Z*)-germacrenes (heliangolides) and (*Z*,*Z*)-germacrenes,[6,11l,43] (Scheme 2). The trend of natural occurrences of geometric isomers is as follows: (*E*,*E*)>(*Z*,*E*)∼(*E*,*Z*)>(*Z*,*Z*), suggesting that of all these four isomers, *E*,*E*-germacranes are the most common in nature with few (*Z*,*Z*)-germacranes.



Scheme 2. Germacranes' geometrical isomers.

Recently, a regioisomer of (*E*,*E*)-germacrane with the isopropyl group at C_6 was reported[18,44] and it has been proposed to be biogenetic precursor of the rare gorgonanes, zieranes and *iso*-humulane sesquiterpenoids skeleton,[18] Scheme 1.

Germacrane sesquiterpenes have been reported to have various biological purposes and effects in nature.[10] These purposes range from biosynthetic intermediates of several sesquiterpenes[16a,b,13a,b,14a–c,15,45] to specific biological activities such as sex pheromones,[34a–c,46] alarm pheromone,[35a,b] anti-inflammatory activities,[47a,b] anti-cancer agents,[48a–c] antiplasmodial activity,[49] antibacterial and antifungal activities,[50a–c] antifeedant,[51] tubulin inhibitor,[52] phytotoxic activity,[53] inhibitor of tumour necrosis and interleukin-6,[54] PTP1B inhibitor,[55] NF-κB inhibitors,[56] inhibitors of preadipocyte differentiation,[57] inhibitors of germination and seedling growth in plant species,[58] moth antennal receptor neuron activator,[59] nematicidal activity,[60] cytotoxic activity,[61] tyrosinase inhibitory activities[62] and other various biological activities.

Interestingly, germacrene artefacts (elemenes) or the Cope rearrangement products isolated from the traditional Chinese medicinal herbs *Rhizoma zedoariae*, *Curcuma Wenyujin* Y. H. Chen et C. Ling and other higher plants have been reported to be effective in the treatment of leukemia and carcinomas of the brain, breast, liver and other tissues in China.[63a–i]

1.2. Identification and isolation

The identification of germacranes is usually accomplished by gas chromatography coupled with mass spectrometry (GC–MS) in electron ionization mode (EI). Several general mass spectral libraries such as the Wiley and the NIST library[64] are available, but specialized libraries for volatile compounds (e.g., MassFinder), which contains a large collection of mono- and sesquiterpenoids,[65] are sometimes more useful. These libraries offer tremendous identification opportunity, but they can also fool an inexperienced user, because a closest hit within the library might be taken as positive identification. In cases where germacrane related compounds generate similar mass spectra, for example, different positional and geometrical isomers, compound identification cannot be performed on the basis of the mass spectrum alone. Therefore, inclusion of additional data, such as gas chromatographic retention indices, is critical for structure determination[66a–e] (Table 1).[65]

Generally, gas chromatographic (GC) analyses of extracts or essential oils commonly show the co-existence of germacrenes and its thermal artefact (elemane). And sometimes, presence of a particular elemene-type serves as a reliable indicator of its precursor germacrane. Thus, in cases where germacrane is present in trace amounts the corresponding elemane allows accurate prediction because the elemane-type is usually more abundant or higher.[26,67a–h]

Often, higher plants have sesquiterpenes of opposite enantiomer to that of lower plants or microorganisms,[66d, 68a–h] for example, (−)-germacrene A (**2**) was first isolated from the gorgonian *Eunicea mammosa*[36] while its (+)-enantiomer is commonly widespread in the higher plants such as caraway herb and root,[23] and fresh costus roots (*S. lappa*).[24]

Only a few germacranes are readily available in their pure form. This is due to instability associated with their isolation during the sample handling procedures from their natural sources. The isolation difficulties originate from the sensitivity of their endocyclic double bonds, which sometimes undergo closures that give other bicyclic sesquiterpenes in slightly acidic conditions[2,24,69a–e] and elevated temperatures.[1,11e,m,14b,c,24,29,36,69e]

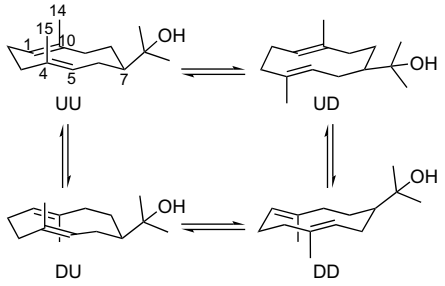
Table 1
Identified germacrene compounds, their Cope rearrangement product and related compounds detected by a non-polar polysiloxane CPSil-5 column under same experimental conditions. The compounds are listed in order of their retention indices and were identified by matching GC–MS retention indice and mass spectrum to authentic standard[65,66c]

Compound	Retention indice
Geijerene (**127**)	1139
Pregeijerene B (**128**)	1274
Pregeijerene A (**10**)	1288
Bicycloelemene (**120**)	1338
δ-Elemene (**79**)	1340
iso-β-Elemene (**53**)	1359
cis-β-Elemene (**37**)	1381
trans-β-Elemene (**36**)	1389
γ-Elemene (**59**)	1429
Isogeremacrene D (**97**)	1445
Isobicyclogermacrene (**121**)	1477
Germacrene D (**34**)	1479
Isolepidozene (**124**)	1483
Bicyclogermacrene (**119**)	1494
Isogermacrene A (**51**)	1502
Germacrene A (**2**)	1503
Helminthogermacrene (**19**)	1503
E,*Z*-Germacrene B (**78**)	1543
Germacrene B (**4**)	1552
Germacrene C (**33**)	ND
Germacrene E (**118**)	ND
Elemone (**134**)	1589
Furanodiene (**157**)	1624
Germacrone (**1**)	1684
Costunolide (**11**)	1914

Therefore, the isolation of germacrane requires mild conditions and methods used also depend on complexity of the sample. These methods include column chromatography on silica gel or Al_2O_3 or prep-TLC or prep-GC or HPLC or a combination of two to three of these methods. Isolations have been achieved on column chromatography using silica gel with eluent such as *n*-pentane or *n*-pentane–ethyl acetate at room temperature or at −25 °C,[2,11m,69e,70,71a–d] $AgNO_3$-impregnated silica gel with Et_2O and Et_2O–MeOH as eluents,[70,24] $AgNO_3$-impregnated Al_2O_3 with hexane–Et_2O as eluent,[1,20b] deactivated-Al_2O_3 with *n*-pentane–Et_2O as eluent,[18] 30% powdered sucrose and 70% florisil mixed as dry solids with *n*-hexane[36] and by prep-TLC (silica gel) at room temperature for further purification[11m] or at −25 °C.[69e] Other methods include prep-GC with SE-30 column,[2,18,29,72a] and prep-GC with enantioselective cyclodextrin columns such as heptakis(6-*O*-*tert*-butyldimethyl-silyl-2,3-di-*O*-methyl)-β-cyclodextrin and octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin.[2,29,72b] For germacranolides, which are less volatile and thermolabile, HPLC on reverse phase or sometimes normal phase may be preferable,[73] or at times a combination of silica gel column chromatography, Sephadex LH-20 and HPLC.[74] For more information on analytical techniques readers are forwarded to a review by Merfort.[75]

1.3. Conformational and stereochemical analyses

Of all the four germacrane geometric isomers, the conformational behaviour of (*E*,*E*)-germacranes has been studied intensively.[11d–g,11i–l,76a–c] These studies have shown that cyclodecadiene ring of germacranes in this case hedycaryol (**3**) can adopt four distinct conformations, which has been denoted as UU, DU, DU, and DD. U (up) and D (down) refer to the orientation of the methyl groups at C_4 and C_{10} (Scheme 3). The UU and DD conformations have a crossed endocyclic double bonds while UU and DD have a parallel endocyclic double bonds. The inversion of the C_7–C_8 unit in the cyclodecadiene ring is highly dependent of substituent at C_7, which preferably occupy an equatorial or pseudoequatorial position.[11d–g,j,m]



Scheme 3. Conformational behaviour of hedycaryol (**3**) in four distinct conformations, which has been denoted as UU, DU, DU, and DD.[11d]

Samek and Harmantha (1978) introduced an extensive notation to denote the cyclodecadiene conformers formed from *E*,*E*-, *E*,*Z*-, *Z*,*E*- and *Z*,*Z*-germacranes. [11g] The corresponding notations for the case of *E*,*E*-cyclodecadiene are as follows: UU=($_1D^{14}$, $^{15}D_5$), UD=($_1D^{14}$, $_{15}D^5$), DD=($^1D_{14}$, $_{15}D^5$), and DU=($^1D_{14}$, $^{15}D_5$).[11g]

In solution, most (*E*,*E*)-cyclodecadiene system have been reported to show a temperature dependent NMR spectra indicative of several interconvertible conformational isomers in equilibria.[11e,f,j,m,14b,c] This interconversion usually results in broadened or multiplet sets of NMR signals.[11d,f,m,14b,c,36,77]

Reliable predictions of most stable conformations of the germacranes have been achieved by molecular mechanics calculations (MMC), NMR (NOE) and X-ray studies or sometimes a combination of any of these methods. The molecular mechanics calculations (MMC) have been applied to study many hydrocarbons including cyclodecadiene rings and reliable predictions of conformations, heats of formation, steric energies, and in some cases estimates of energy barriers between conformers have been achieved.[11b,c,k–m,78a–c]

Before MMC, the most favourable transition state of (*E*,*E*)-cyclodecadiene system reported is the chair–chair (CC).[11a,f,69b] This observation was later confirmed when MMC was applied to the thermal isomerization products of (*E*,*E*)-1,5-cyclodecadiene.[11h,11i] Terada and Yamamura (1979) have evaluated the relative stabilities of each conformation of germacrene A (**2**), hedycaryol (**3**) and germacrene B (**4**) in their ground states and transition states. In these experiments they confirmed that elemenes are formed from the corresponding germacrenes through the most stable transition states (CC), regardless of the most stable conformers in each ground state. They also indicated that the two elemanes shyobunone (**5**) and *epi*-shyobunone (**6**), resulting from acoragermacrone (**7**), are formed from CC, and CC and CT, respectively.[11h,i] Molecular mechanics calculations (MMC) also revealed that germacrene B (**4**) has two comparably stable conformations.[76b]

Ground state conformation of all possible geometrical isomers of hedycaryol (**3**) (*E*,*E*-, *E*,*Z*-, *Z*,*E*-, *Z*,*Z*-) have also been estimated by MMC and all the four isomers are indicated to exist in more than two conformations in which the parallel conformation (TC or TT) is reported to be the most stable for all isomers.[76c,78c]

Using MMC, Tashkhodzhaev and Abduazimov (1997)[11l] have suggested a detailed probable structural types of *cis*/*trans*-guaianes and *cis*/*trans*-eudesmanes formed from the four conformers of *E*,*E*-germacranes via a transannular cyclization. They have also suggested the possibility of similar structural guaianes and eudesmanes type of compounds from (*E*,*Z*)- and (*Z*,*E*)-germacranes.[11l]

Intramolecular nuclear Overhauser effect (NOE) measurements have been used to deduce the stable conformation of germacrene-type sesquiterpenes in solution.[11e] In a few cases, NOE experiments, in combination with variable-temperature ^1H NMR spectra and/or molecular mechanic calculations, have been applied to establish the preferred conformation germacranes.[11a,79a–d] Wharton et al. (1973) concluded that hedycaryol (**3**) consists mainly of one crossed and two parallel conformations and that the conformational changes is rapid at 90 °C and slow at −30 °C, with the parallel conformations predominating to 75% at −30 °C and that they are favoured to the parallel forms at higher temperatures.[11d]

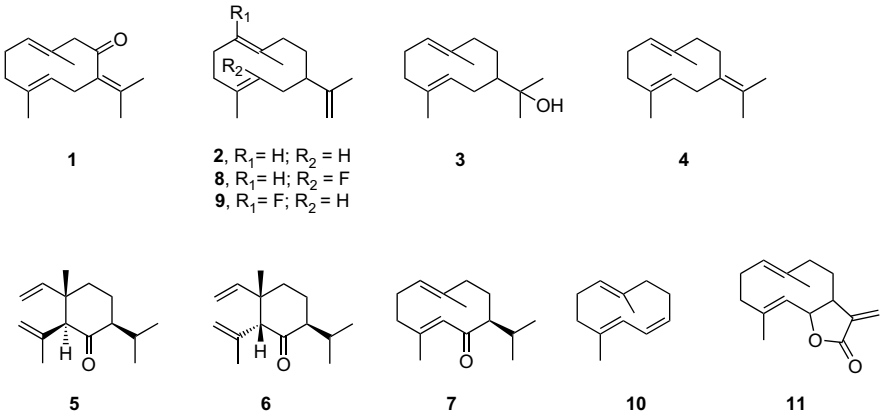
Recently, using variable-temperature 500 MHz ^1H NMR spectra in $CDCl_3$, the three NMR-distinguishable conformational isomers of (+)-germacrene A (**2**) were established to occur in the ratio 5:3:2 at or below ordinary probe temperature (25 °C) by Coate's group.[11m] They assigned 52% UU, 29% UD and 19% DU to the conformer structures based on ^1H NMR data comparison, NOE experiments and vicinal couplings.[11m]

Using a variable-temperature ^1H NMR spectroscopy, Allemann's group (2007) showed that 5-fluorogermacrene A (**8**) indicates the existence of two conformers in the ratio 3.22:1 that were in slow exchange at −60 °C, while at 90 °C the two isomers gave rise to averaged NMR signals.[14b] Consistent with **8**, ^1H NMR and ^9F NMR spectra of (−)-1-fluorogermacrene (**9**) at 25 °C also revealed the existence of a 7:3 mixture of UU and UD conformers in solution.[14c]

X-ray analysis of silver nitrate adducts of pregeijerene A (**10**),[80] costunolide (**11**),[81a] germacrene B (**4**)[81b] and germacrone (**1**)[82] have shown that the most stable chair–chair (CC) conformation is also the one that is preferred in the solid state. Recently, attempts to prepare X-ray quality crystals of the $AgNO_3$ adduct of (+)-germacrene A (**2**) using the literature methods have been reported to be unsuccessful.[11m]

1.4. Cope rearrangements

Cope rearrangement in germacranes is a stereospecific [3,3]-sigmatropic rearrangement that proceeds via the most stable chair-like transition state of 1,5-cyclodecadiene to give 1,2-divinylcyclohexane



1 **2**, R_1= H; R_2 = H; **8**, R_1= H; R_2 = F; **9**, R_1= F; R_2 = H **3** **4**

5 **6** **7** **10** **11**

system. The configuration of 1,2-divinylcyclohexane formed depends on most stable chair-like transition state conformation of the corresponding 1,5-cyclodecadiene.[11f,h,i,15,83] The mechanism of Cope rearrangement has been studied[84a–d] and various groups have contributed to the understanding of this rearrangement.[85a–i]

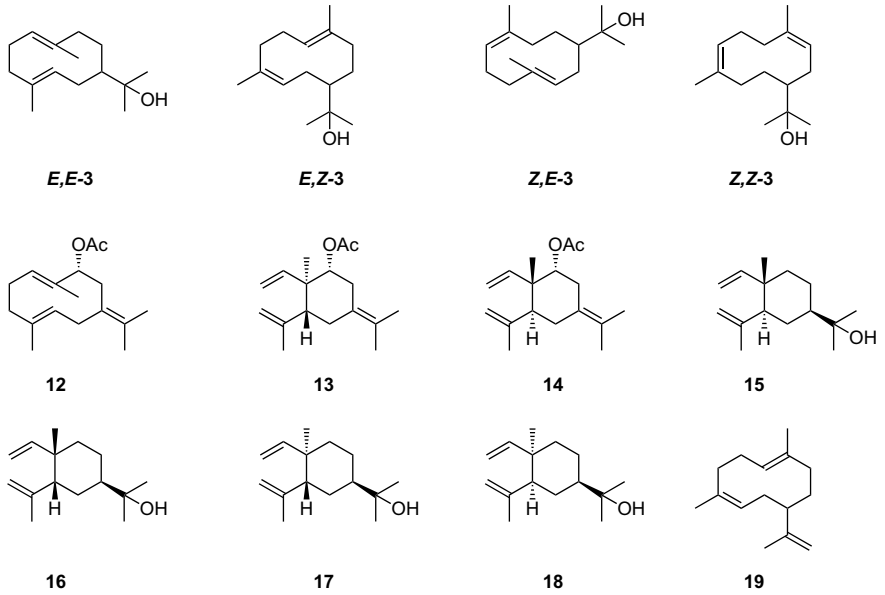
It is also well known that Cope rearrangement is a reversible process[86a–d] and that equilibrium between 1,5-cyclodecadiene and 1,2-divinylcyclohexane system depends on the nature and configuration of substituents.[85i,86d,87a,b] While *E*,*E*-cyclodeca-l,5-dienes are known to undergo Cope rearrangement to give *trans*-l,2-divinylcyclohexane,[11m,14b,c,36,69e] the *Z*,*E*-cyclodeca-1,5-dienes give *cis*-1,2-divinyl derivative[29,67a,76c,88] and it has been established that the presence of a fused five-membered ring at positions C_6 and C_7 in the *Z*,*E*-cyclodeca-1,5-diene derivatives influences the stereostructure of the 10-membered ring transition state, which has an important effect on the rearrangement.[88]

Recent investigation by Sezter (2008) on energetics of Cope rearrangement product of 17 germacrane sesquiterpenoids by density functional theory (B3LYP/6-31G*) and post Hartree–Fock (MP2/6-31G**) showed that different substitution patterns affect the relative energetics of the germacrene–elemene Cope rearrangement.[89] The results of these two calculations are in qualitative agreement with the experimentally observed Cope rearrangements, eventhough the two methods gave slightly different results.[89]

Generally, germacranes undergo Cope rearrangements to elemanes, and it is possible to detect variation in the amount of elemane produced from their germacrane precursor by variation of GC injector port temperature. The increase in temperature of GC injector port leads to an increase in the amount of elemane produced with a corresponding decrease in the precursor germacrane.[11m,17,24,29,69e,90] In few cases, small amount of diastereomeric elemanes could also be formed in addition to the major elemane produced at slightly high temperature.[29]

The existence of different germacrane conformations have been postulated to explain the formation of a small amount of diastereomeric elemanes during the thermal Cope rearrangement of a few cyclodecadienes such as acetyl caulesol (**12**), which rearranges into two elemanes **13** and **14** in ratio 5:3, respectively.[91] Thermal reactions conducted at higher temperatures (ca. 500 °C) with synthesized hedycaryol isomers *E*,*E*-(**3**), *Z*,*E*-(**3**), *E*,*Z*-(**3**) and *Z*,*Z*-(**3**) led to the formation of diastereomeric elemols (**15**, **16**, **17**, **18**) in addition to the low temperature formed elemols from corresponding hedycaryol isomer.[76c] They suggested that although the diastereomeric elemols can be explained as being formed from respective conformation of hedycaryols, and they also noted a few features against the explanation and as a result, an additional pathway involving the retro-Cope rearrangements of the preformed low temperature elemols was considered.[76c]

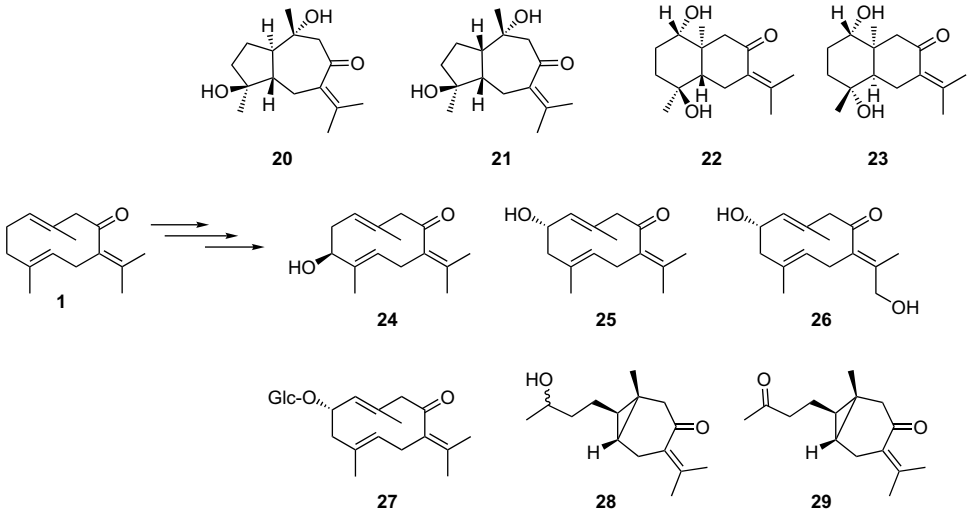
Occurrence of similar diastereomeric elemanes have also been reported for germacrene A (**2**),[24,69e] and it derivatives (alcohol, aldehyde and carboxylic acid),[24] and helminthogermacrene (**19**).[29] In 5-fluorogermacrene A (**8**) and 1-fluoro-germacrene A (**9**), which appear more stable than germacrene A (**2**), only the corresponding major fluoro-elemane were observed.[14b,c]



***E*,*E*-3** ***E*,*Z*-3** ***Z*,*E*-3** ***Z*,*Z*-3**

12 **13** **14** **15**

16 **17** **18** **19**



Scheme 4. Biotransformation of germacrone (**1**).[94–96]

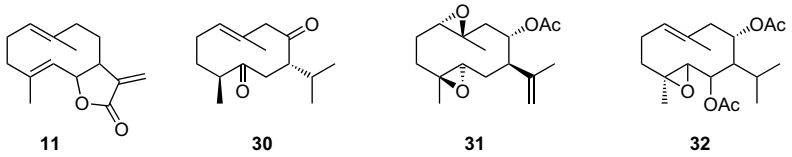
1.5. Acid induced transannular cyclizations

Germacranes undergo transformation to a large variety of products upon acid treatment. Acid induced cyclization of (*E*,*E*)-germacranes has been studied extensively,[14c,24,25,69a,b,d,e,76c,92a–e] whereas the induced transannular cyclizations of its geometric isomers such as (*Z*,*E*)-germacranes (melampolides),[76c,93a,b] (*E*,*Z*)-germacranes (heliangolides)[2,69e,76c,92d] and (*Z*,*Z*)-germacranes appear to be limited to a few studies.[111]

Commonly, induced transannular cyclization of (*E*,*E*)-germacranes system produced corresponding *trans*-selinane-type, while (*Z*,*E*)- and (*E*,*Z*)-germacranes system produced cadinane-type and *trans*- or *cis*-selinane-type or guaiane-type sesquiterpenes.[2,69e,92d]

From molecular mechanics calculations (MMC), a detailed probable *cis*/*trans*-guaianes and *cis*/*trans*-eudesmanes structural types that could result from transannular cyclization of (*E*,*E*)-germacranes have been reported by Tashkhodzhaev and Abduazimov (1997) and they have also suggested the possibility of having similar structural types of compounds from (*E*,*Z*)- and (*Z*,*E*)-germacranes.[111]

Several kinds of acidic reagents and solvents that have been used to induce cyclization include 80% aq AcOH, 80% aq HCOOH, $AlCl_3$ in absolute ether, AcOH in PhSH, 100% HCOOH in PhSH and concd H_2SO_4 in PhSH;[92d] 80% aq AcOH at 0 °C for 1 h;[93c] adsorption on SiO_2;[69e,92a] adsorption on SiO_2, acetic acid, *p*-toluene sulphonic acid, or Amberlyst® 15, BF_3, $AlCl_3$;[2] *p*-toluenesulfonic acid;[24] storage at 4 °C in $CDCl_3$ for at least one week, treated with BF_3 in diethyl ether, and acidic ion exchange resin Amberlyst® 15;[69e] treated with CF_3CO_2H in $CDCl_3$;[14c] and when subjected to basic treatment such as basic alumina.[93d,e]



The rearrangements products obtain from acid induced cyclizations depend on acid reagents or solvents use, reaction time and temperature,[2,69e,92d] while the percentage (%) yield of products is dependent of the overall reaction conditions.[2] With increasing reaction time, secondary rearrangement products could also be formed, which cannot be related to the starting material.[2]

1.6. Biotransformations

The studies on biotransformation of germacranes have led to the discovery of bio-activation and/or bio-inactivation metabolites with unique structures. Biotransformation of germacrone (**1**) by *Aspergillus niger*[94] and cultured plant cells of *Curcuma zedoaria*[95] produced similar as well as new sesquiterpenoid metabolites of hydroxylated guaiane-type (**20**, **21**), eudesmane-type (**22**, **23**, **24**, **25**), together with allylic alcohols (**26**) and glucosylated eudesmane (**27**) (Scheme 4). The configurations of some of the derivatives were opposite to those of the sesquiterpenes isolated from the Curcuma species, such as *Curcuma aromatica*, *Curcuma longa* and *C. zedoaria*.[95] Biotransformation of germacrone (**1**) examined by suspension cultured cells of *Lonicera japonica*, *Bulpleurum falcatum*, *Polygonumn tinctorium* and *S. altissima* afforded several types of sesquiterpenes, such as guaiane, eudesmane and *seco*-guaianes (**28**, **29**).[96]

Incubation of (+)-hedycaryol (**3**)[97] administered to a mortared root suspension of fresh chicory for four days gave cryptomeridiol[98] as its sole product.[69d] Biotransformation of germacrane epoxides by a suspension of fresh chicory root (*Cichorium intybus*) gave hydroxylated guaianes and eudesmane derivatives.[99]

Biotransformation have also been reported in other germacrane-type compounds such as curdione (**30**),[100a,b] costunolide (**11**),[100c–e] (1α,10β),(4β,5α)-diepoxygermacrane (**31**)[101] and shiromodiol diacetate (**32**).[102] Commonly, biotransformation increases the polarity and water solubility of germacrane metabolites via hydroxylation, oxidation and glucosylation.

1.7. Biosynthesis

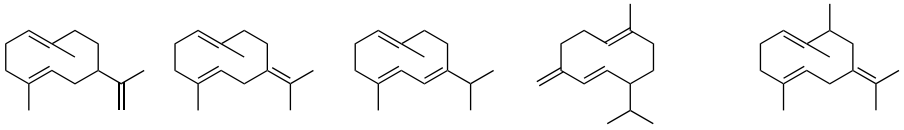
Germacrene A synthases have been isolated, purified and characterized from chicory roots.[15,103] For detailed recent review on germacrene A synthases and biosynthesis read a recent publication by Faraldos et al. (2007).[11m] In addition, the intermediacy of germacrene A (**2**) in the mechanism involving conversion of (*E*,*E*)-

farnesyl diphosphate (FPP) to aristolochene[14b] and *epi*-aristolochene[14c] have been indirectly confirmed with fluoro-FPP derivatives.[14b,c]

Biosynthesis of germacrene C (**33**) was confirmed by a preliminary radioactive labelling experiment involving an enzymatic conversion of 2-^{14}C-mevalonic acid lactone via *trans*,*trans*-farnesyl pyrophosphate (FPP).[104] The enzymatic solvolysis of farnesyl pyrophosphate (FPP) by prenyltranferase yielded **33** as part of the products.[105] The isolation, purification and characterization of germacrene C synthases from *Lycopersicon esculentum* cv. VFNT Cherry have been achieved.[106]

The biosynthetic pathway of germacrene D (**34**) was elucidated by incubation of isolated enzymes with isotopically labelled FDP[107] and mass spectrometric analysis of the products,[108] which indicated different steps for both enantiomers as already suspected by Niwa et al., 1980.[20b] The labelling experiments carried out on *S. canadensis* with 1-[5,5-D_2]deoxy-D-xylulose-5-phosphate (D_2-DOXP), [5-^{13}C]mevalonolactone (^{13}C-MVL) and [1-^{13}C]-D-glucose,[109] and *Tanacetum vulgare* (Asteraceae)[110] revealed that the biosynthesis of germacrene D (**34**) proceeds predominantly via the methylerythritol phosphate pathway. Enantiospecific (+)- and (−)-germacrene D synthases, cloned from 'goldenrod' *S. canadensis* showed a functionally active variant of the universal isoprenoid-biosynthesis aspartate-rich motif.[111]

germacrene A (**1**) from natural sources has met set backs due to its sensitivity to slight acidic conditions and thermal instability.[69e] The instability of germacrene A (**2**) upon storage at freezer temperatures over a particular period has been reported.[35b,36] During isolation and GC analysis, germacrene A (**2**) is known to undergo facile Cope rearrangement to *trans*-β-elemene (**36**).[11e,m,23,24,35b,36,69e] The *trans*-β-elemene (**36**) is commonly referred to as 'β-elemene or elemene' and is currently being reported to be effective in the treatment of leukemia and carcinomas of the brain, breast, liver, lungs and other tissues.[63a–i] The thermal decomposition of germacrene A (**2**) to *trans*-β-elemene is often characterized by broad hump in the baseline in the GC chromatogram. Diastereomers (ca. 2–7%) of *trans*-β-elemene (**36**) with similar mass spectrum to their 'true elemenes' were detected in germacrene A (**2**) and its derivatives at the GC-injection port during Cope rearrangements.[24] Recently, minor *cis*-β-elemene diastereomer (**37**) was detected along with (−)-*trans*-β-elemene (**36**) during Cope rearrangement experiment of (+)-germacrene A (**2**) isolated from *S. canadensis* in a ratio of 5:95, respectively. Compound **37** elutes before (−)-*trans*-β-elemene (**36**) and both increase with decreasing amount of rearranged (+)-germacrene A (**2**).[69e] The absolute configuration of (+)- and (−)-*trans*-β-elemene (**36**) has been established by means of Cope rearrangement on chiral GC columns, which is able to distinguish the enantiomers.[15,119]



2 **4** **33** **34** **35**

1.8. Synthesis

Generally, the synthesis of germacranes have met tremendous set backs because of their thermal instability[1,11e,24,35a,36,112a,b] and their sensitivity towards slight acidic conditions,[24,69a,b,d,e,92d] and UV radiations.[2] Despite these set backs many reports on germacrane syntheses have been published in the last 50 years. In 1999, an extensive review on synthesis of germacrane sesquiterpenes and related compounds has been reported by Minnaard et al.[6] therefore, only related chemical synthesis of compounds reported on or after this review will be mentioned briefly. Germacrene B (**4**) and (±)-9-methylgermacrene B (**35**) have been synthesized.[113a,b] 9-Methylgermacrene B (**35**) has also been synthesized enantiospecifically.[114] Recently, Mehta and Kumaran (2005) reported a short, flexible and enantioselective approach towards 10-membered germacratrienones from the commercially available monoterpene (−)-carvone.[115]

2. Germacrene A or (*E*,*E*)-1,5-cyclodecadiene, 1,5-dimethyl-8-(1-methylethenyl)- or (*E*,*E*)-germacra-1(10),4,11-triene (2)

(−)-Germacrene A (**2**) was first isolated from the gorgonian *E. mammosa* and characterized by Weinheimer et al.[36] Later it was isolated from the aphid *T. maculala*[35a,b] and from a soft coral of the genus *Lobophytum*,[116] termites *Reticulitermes lucifugus*,[117] and in several species of the primitive neotropical nasute genus *Synterme*.[118] The (+)-enantiomer of (**2**) is commonly widespread in the higher plants such as Caraway herb and root,[23] fresh costus roots (*S. lappa*),[24] and from *S. Canadensis*.[69e]

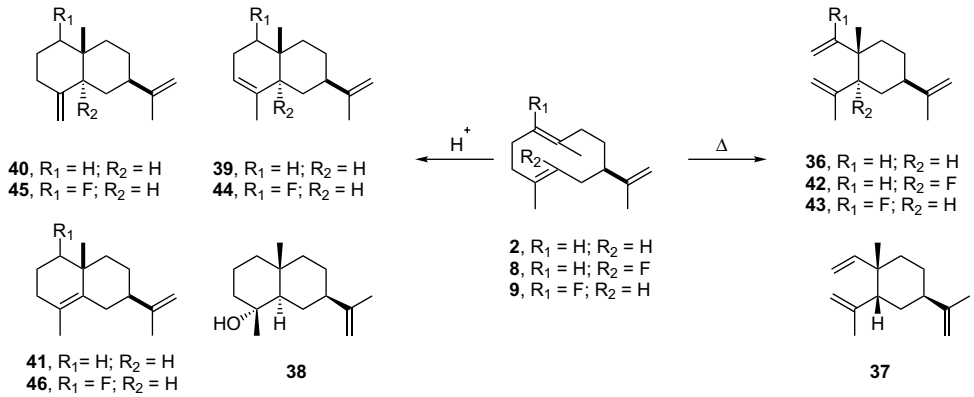
Recently, Coates' group and collaborators reported the isolation of a very pure form of (+)-germacrene A (**2**) for the first time from a genetically engineered yeast and its structure was characterized by chromatographic techniques (TLC, GC), MS, optical rotation, UV, IR, ^{1}H NMR and ^{13}C NMR data.[11m] Previously, the isolation of pure

In the presence of *p*-toluenesulfonic acid, (+)-germacrene A (**2**) and its derivatives (aldehyde, carboxylic acid and alcohol) were completely converted into their corresponding eudesmane analogues.[24] Adsorption of (+)-germacrene-A (**2**) isolated from *S. canadensis* on silica gel induces transannular cyclization to a mixture of eudesmanes; (−)-selin-11-en-4-ol (**38**, 4%), (−)-α-selinene (**39**, 41%), (+)-β-selinene (**40**, 45%) and (+)-selina-4,11-diene (**41**, 12%)[69e] (Scheme 5).

2.1. Fluorogermacrene A analogues

Allemann and Coates' groups independently synthesized different fluoro-germacrene A derivatives to probe the intermediacy of germacrene A (**2**) in the mechanism involving conversion of (*E*,*E*)-farnesyl diphosphate (FPP) to aristolochene[14b] and *epi*-aristolochene,[14c] respectively. 5-Fluorogermacrene A (**8**) was formed upon incubation of 5-fluoro-FPP with aristolochene synthase from *Penicillium roqueforti*.[14b]

Compared to germacrene A (**2**), no thermal rearrangement of 5-fluorogermacrene A (**8**) was observed at 200 °C temperature and only a small amount of rearranged product occurred at 250 °C but thermal rearrangement to 5-fluoroelemene (**42**) occurred at 300 °C.[14b] Another fluoro-compound (−)-1-fluorogermacrene (**9**) was obtained as the sole product from incubation of (2*E*,6*Z*)-6-fluoro-FPP with recombinant tobacco 5-*epi*-aristolochene synthase (TEAS) by Coates' group.[14c] (−)-1-Fluorogermacrene A (**9**) was characterized by chromatographic properties (TLC, GC), MS, optical rotation, UV, IR, ^{1}H NMR, and by heat-induced Cope rearrangement at 180 °C to (+)-1-fluoro-elemene (**43**). 1-Fluoroelemene (**43**) and *trans*-β-elemene (**36**) obtained by reflux (110 °C) under similar conditions took 3 h and 2 h, respectively.[14c] 1-Fluorogermacrene A (**9**) underwent trifluoroacetic acid-catalyzed cyclization to give three 1-fluoroselinene isomers (**44**, **45** and **46** in the ratio 2:2:1, respectively) at a rate estimated to be about 1000 times slower than that of the similar cyclization of



Scheme 5. Thermal and acid induced cyclization of germacrene A (**2**) and fluoro-germacrene A derivatives **8** and **9**.

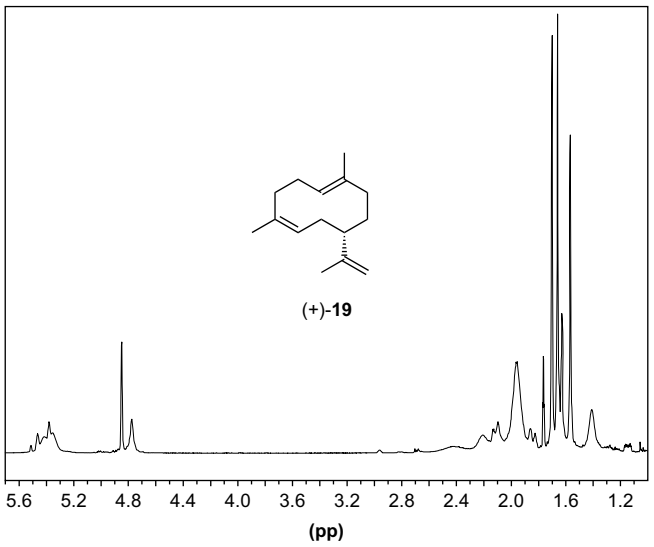


Figure 2. ^{1}H NMR spectrum (500 MHz, C_6D_6) of (+)-helminthogermacrene (**19**) at 20 °C.[69e,122]

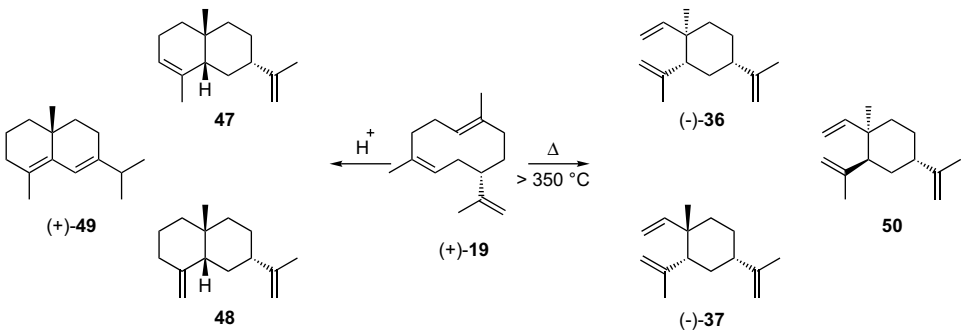
(+)-germacrene A (**2**) to the parent selinenes.[14c] Commonly, the presence of fluoro-substituent in **8** and **9** appear to slow their rate of Cope rearrangements[14b,14c] and acid induced transannular cyclization[14c] compared to germacrene A (**2**) (Scheme 5).

2.2. Helminthogermacrene (19)

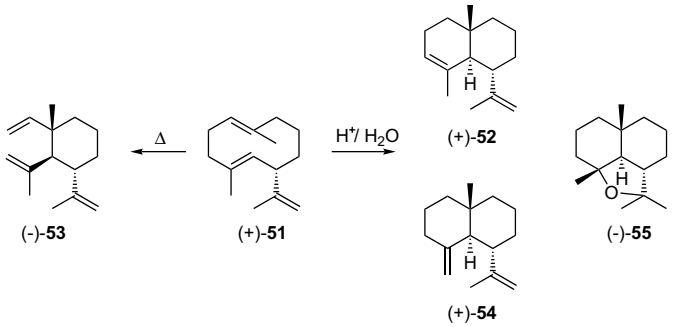
(±)-Helminthogermacrene (**19**), an (*E*,*Z*)-isomer of germacrene A (**2**), was first synthesized in a high yield via ring contraction of an (*E*,*Z*)-humulene derivative under the influence of an aluminium reagent of sufficient steric bulk.[120] Two years later, (−)-(**19**) was isolated from the fungus *H. sativum*[40] and subsequently from the defense secretion of the termite *A. wheeleri*[33a] and the (+)-enantiomer was isolated from the liverwort *S. undulata*.[29,69e] The unproven configuration of (−)-**19** was initially assigned 7*S* as concluded from the sesquiterpene congeners (−)-sativene and (−)-longifolene, which were also isolated from *H. sativum* by Winter et al.[40] The structure of (±)-helminthogermacrene (**19**) had been verified by total synthesis.[40,121] The absolute configuration of (+)-**19**, isolated from the liverwort *S. undulata*,[29] was recently assigned 7*S* via an indirect chemical correlation.[69e] Figure 2 represents the ^{1}H NMR spectrum (500 MHz, C_6D_6) of (+)-helminthogermacrene (**19**) at 20 °C.[69e,122]

Compound (+)-(**19**) undergoes rearrangement when stored in $CDCl_3$ at 4 °C for at least one week and on treatment with BF_3 in diethyl ether or upon interaction with acidic ion exchange resin Amberlyst® 15 to form a series of sesquiterpene hydrocarbons with mass 204. The major acid induced product gave ^{1}H NMR, ^{13}C NMR ($CDCl_3$) and MS data consistent with (−)-α-helmiscapene (**47**)[69e] earlier isolated from *S. undulata*,[123] and synthesized with known absolute configuration.[124a–c] β-Helmiscapene (**48**)[123,125a,b] was also detected in addition to δ-selinene (**49**). Compared to germacrenes A (**2**) and B (**4**), no significant rearrangement products were observed when **19** was treated with silica gel for 3 h under the same experimental conditions.[69e] McMurry and Kočovský (1985) have earlier reported that (+)-**19** undergoes Cope rearrangement at higher temperatures (>300 °C) compared to germacrene A (**2**), which undergoes Cope rearrangements at room temperature.[121]

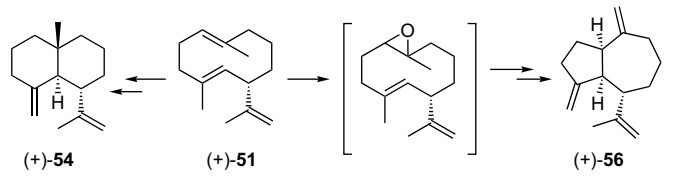
Recently, Cope rearrangement of (+)-**19** was achieved at temperature above 350 °C to afford (−)-*cis*-β-elemene (**37**), another β-elemene diastereomer (**50**) and a trace of 'normal' (−)-β-elemene (**36**) in the ratio of 8:1:~0.08, respectively (elution order from a non-polar polysiloxane CP-Sil-5). Compounds **37** and **50** exhibit mass spectra undistinguishable from that of *trans*-β-elemene (**36**) (Scheme 6).[29,69e]



Scheme 6. Acid induced and Cope rearrangement products of helminthogermacrene (+)-(**19**).[29,69e]



Scheme 7. Acid induced and Cope rearrangement products of isogermacrene (+)-(**51**).[18]



Scheme 8. Proposed biogenetic pathway of gorgonanes and zieranes from isogermacrene A (**51**).[18]

2.3. Isogermacrene A (51)

(+)-Isogermacrene A (**51**) was isolated for the first time from the liverwort *Saccogyna viticulosa*.[18] Compound **51** is a regioisomer of germacrene A (**2**) with an isopropyl group at C_6.[18,44] Isogermacrene A (**51**) has been proposed to be the biogenetic precursor of *iso*-α-humulene, α-gorgonene (**52**), gorgona-1,4(15),11-triene and gorgon-11-en-4-ol sesquiterpenes identified in the volatiles of *S. viticulosa*.[18] Compound **51** shows a less broadened ^{1}H NMR (acetone-d_6) with well separated multiplet signals at 10 °C and undergoes Cope rearrangement to (−)-*iso*-β-elemene (**53**). The treatment of **51** with an acidic ion exchange resin (Amberlyst® 15) at room temperature for 1 h gave (+)-α-gorgonene (**52**), (+)-β-gorgonene (**54**) and (−)-maalioxide (**55**) in the ratio 2:5:1, respectively, as major products.[18] The assigned absolute configuration of (+)-7*S*-isogermacrene A (**51**) was concluded indirectly from the absolute configuration of the acid induced cyclization products (Scheme 7).[18]

Biogenetically, isogermacrene A (**51**) has been proposed as the missing link between FPP and the gorgonanes and zieranes (e.g., zierene (**56**)) (Scheme 8).[18]

3. Germacrene B or (*E*,*E*)-1,5-cyclodecadiene, 1,5-dimethyl-8-(1-methylethylidene)- or (*E*,*E*)-germacra-1(10),4,7(11)-triene (4)

Germacrene B (**4**) was first isolated in the cold-pressed peel oil of the higher plant *Citrus junos*[92a,126] and subsequently from *Citrus aurantifolia*,[127] *Callicarpa japonica* Thunb,[128] *S. Canadensis*[69e] and liverwort *Preissia quadrata*.[90]

The structure of germacrene B (**4**) was established by X-ray-crystallographic analysis of its silver nitrate adduct by Allen and Rogers.[129] Compound **4** has been found to occur with selina-3,7(11)-diene (**57**), selina-4(14),7(11)-diene (**58**), α-selinene (**39**) and β-selinene (**40**) in the essential oil of hops *Humulus lupulus*.[130]

Germacrene B (**4**) is known to readily undergoe Cope rearrangement above 120 °C to give γ-elemene (**59**) and its sulfuric acid induced rearrangements gave eudesm-7(11)-en-4-ol (**60**), while percolation of **4** through alumina gave selina-3,7(11)-diene (**57**) and selina-4(14),7(11)-diene (**58**).[69b,131] Adsorption of **4** isolated from *S. canadensis* on silica gel induces similar transformations to a mixture of eudesmanes **57**, **58** and **60** at a rather slow manner with very low yield as compared to germacrene A (**2**) under the same experimental conditions (Scheme 9).[69e]

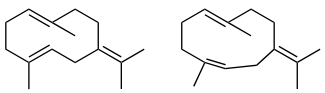
The oxidation of germacrene B (**4**) with 1 mol of peracetic acid gave an unexpected 1,10-, 4,5- and 7,13-monoxides in the ratio 30:70:2.[132] In contrast to epoxidation, reaction of $^1O_2$ with **4** led to the attack of isopropylidene double bond at ca. nine times more rapidly than the endocyclic double bonds.[133] Irradiation of **4** under singlet conditions results in the formation of **61**, **62**, **63** and **64** (Scheme 10).[134]

When 8-hydroxygermacrene B (**65**) and 8-methoxygermacrene B (**66**) were irradiated using a 500 W medium-pressure mercury lamp in methanol or *n*-pentane for 3 h, three major products **67**, **68** and **69** were formed in each case via **70** as a result of intramolecular reactions of the endocyclic double bonds and a photochemical [1,3]-OR shift (R=H, Me) of the allylic oxygen substituent (Scheme 11).[135]

Peijnenburg et al.[136] have demonstrated extensively the role of exocyclic double bond in isomerization of 1,5-cyclodecadiene system by irradiation of (4*SR*,8*SR*)-4,5-dihydro-germacrol (**71**) and (4*SR*,8*RS*)-4,5-dihydro-germacrol (**72**). This leads only to *E*-*Z* isomerization of the endocyclic double bonds (**73** and **74**) and to a photochemical [1,3]-allyl shift (**75**, **76** and **77**) (Scheme 12). They concluded that the ground state conformation of these molecules is known to play an important role in the observed photochemistry.[134,137a,b]

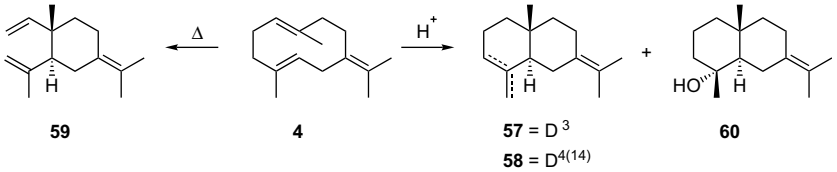
3.1. *E*,*Z*-Germacrene B or (*E*,*Z*)-germacra-1(10),4,7(11)-triene (78)

(*E*,*Z*)-Germacrene B (**78**) was first obtained as minor synthetic product via a ring contraction of a suitable (*Z*,*E*)-humulene isomer by Ito et al.[120] and later obtained in good yield.[138] Compound **78** has been tentatively identified as a product of the δ-selinene synthase from Grand fir (*Abies grandis*) based on an exact mass spectral match to (*E*,*E*)-**4** and a similar GC retention time.[139]

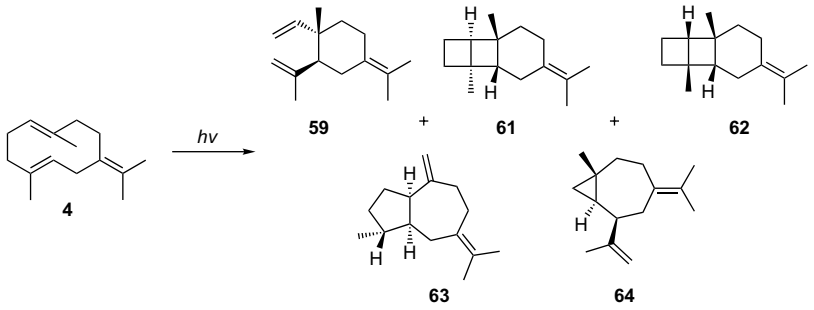


4. Germacrene C or (*E*,*E*)-germacra-1(10),4,6-triene (33)

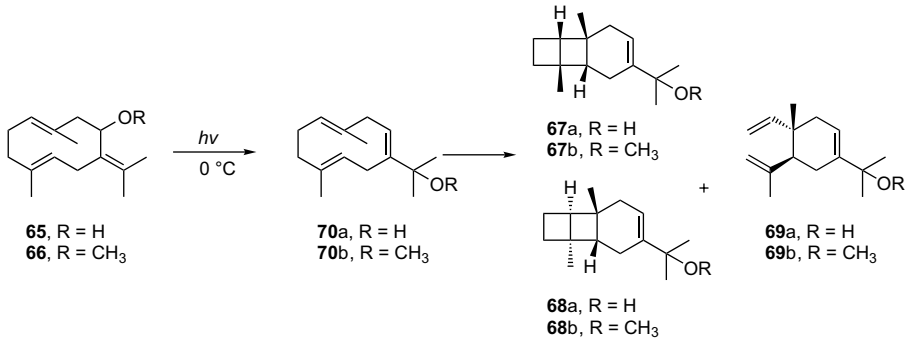
Germacrene C (**33**) was first isolated as the main constituent of the essential oil of the seed of *Kadsura japonica* by Morikawa and Hirose.[92a] Compound **33** is also the main constituent of the German liverworts *P. quadrata*.[90] Compound **33** readily undergoes Cope rearrangement at 100 °C in solution to form δ-elemene (**79**),[92a,140]



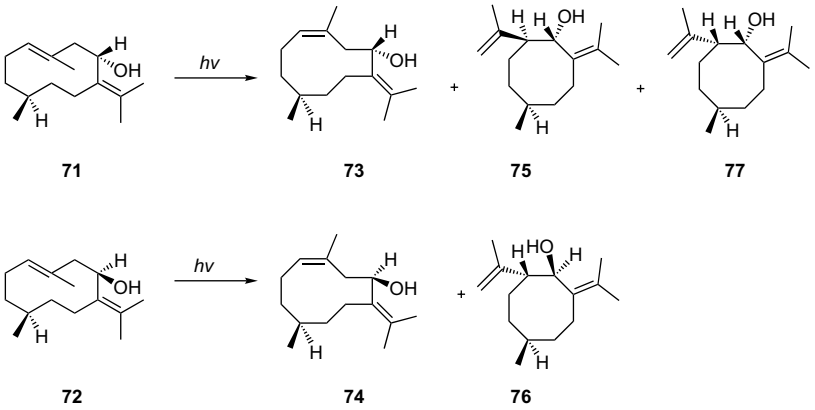
Scheme 9. Acid induced and Cope rearrangement products of germacrene B (**4**).



Scheme 10. Irradiation products of germacrene B (**4**).[134]



Scheme 11. Irradiation products of 8-hydroxygermacrene B (**65**) and 8-methoxygermacrene B (**66**).[135]



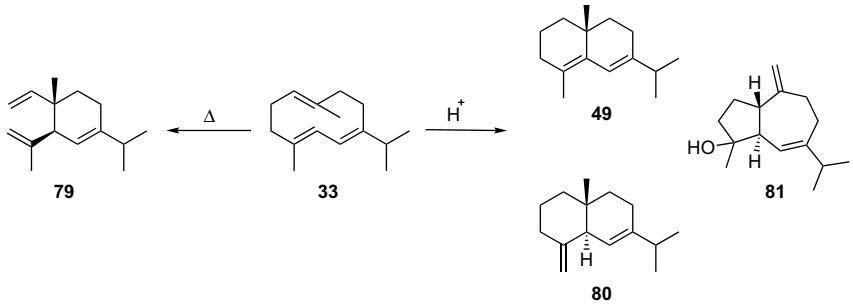
Scheme 12. Irradiation of (4*SR*,8*SR*)-4,5-dihydro-germacrol (**71**) and (4*SR*,8*RS*)-4,5-dihydro-germacrol (**72**).[136]

but when the injection port temperature was raised from 200 °C to 280 °C, germacrene C (**33**) thermally rearranged to (±)-δ-elemene (**79**) as observed by capillary gas chromatography using cyclodextrins as chiral stationary phases.[90]

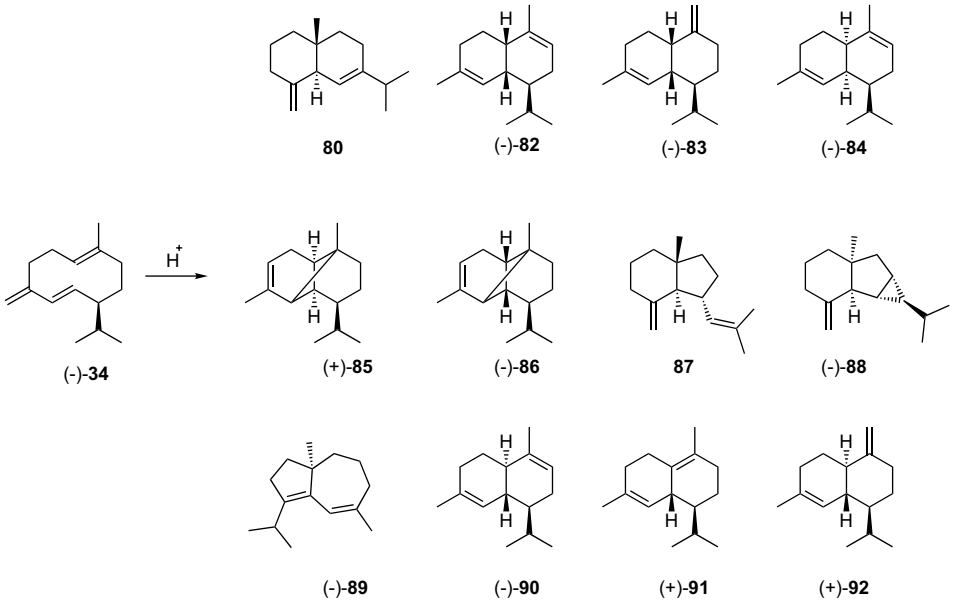
Germacrene C (**33**) was smoothly converted to δ-selinene (**49**) and selina-4(15),6-diene (**80**) under slightly acidic conditions with silica gel at room temperature.[92a] Other degradative products of germacrene C (**33**) formed during processing of the plant material include alismol (**81**)[141] and some of its derivatives[142] (Scheme 13).

5. Germacrene D or *E*,*E*-1,6-cyclodecadiene,1-methyl-5-methylene-8-(1-methylethyl) or *E*,*E*-germacra-1(10),4(15),5-triene (34)

(−)-Germacrene D (**34**) was first isolated from the essential oil of *Pseudotsuga japonica*.[1] It is widely detected in plant constituents especially in essential oils, such as *Pittosporum tobira*, *K. japonica* and *Piper Kadsura*,[1] *Falcaria vulgaris* Bernh.,[143] *S. altissima* L.,[20b] *Torilis japonica* D.C.,[144] *S. Canadensis*,[2,20a] *Araucaria bidwillii*,[145] and as a sex stimulant of the male American cockroach (*Periplanata Americana* L.).[146] In higher plants, **34** is present as (−)-enantiomer, while the (+)-enantiomer is more likely to occur in lower organisms.[90,147a,b] The occurrence of both enantiomers of **34** has been described and analyzed in the 'goldenrod' *S. canadensis* L. and *Solidago gigantea* Ait. by enantioselective gas chromatography.[20a,148] The proportions of (+)- and (−)-enantiomers of **34** have been reported to vary widely depending on the collection site and the part of the plant.[20a,148] Germacrene D (**34**) rearranges to different sesquiterpenes hydrocarbons upon treatment with acidic media over a period of time to give cadinanes, muurolanes, amorphanes, ylangane, eudesmanes, isodaucane, oppositane and axane.[2,92b,e] Major acid catalyzed rearrangements products of Germacrene D (**34**) include α-muurolene (**82**), (+)-γ-muurolene (**83**), (−)-α-amorphene (**84**), α-ylangene (**85**), α-copaene (**86**), selina-4(15),6-diene (**80**), opposite-4(15),7-



Scheme 13. Acid induced and Cope rearrangement products of germacrene C (**33**).



Scheme 14. Acid catalyzed products of germacrene D (**34**).[1,2]

diene (**87**), 4(15)-cycloaxene (**88**), isodauca-4,6-diene (**89**), α-cadinene (**90**), (+)-δ-cadinene (**91**) and (+)-γ-cadinene (**92**) with the cadinanes predominating (Scheme 14).[1,2]

The acid rearrangement products obtained depend on the acid reagents used (SiO_2, acetic acid, *p*-toluene sulphonic acid, or Amberlyst® 15, BF_3, $AlCl_3$) and the percentage (%) yield of rearrangement products is dependent of the reaction conditions.[2] With increasing reaction time a mixture of secondary rearrangement products are formed, which cannot be related to **34**. For detailed report on the role of germacrene D (**34**) as a precursor in sesquiterpene biosynthesis, reader is directed to the paper by Bülow and König.[2]

Recently, Setzer (2008)[149] carried out a computational ab initio investigation using both density functional theory (B3LYP/6-31G*) and post Hartree–Fock (MP2/6-31G**) on the acid-catalyzed cyclization products of **34**. The calculated energies are in general agreement with experimentally observed distribution of cadinane, muurolane, amorphane and selinane, from both acid-catalyzed cyclizations of **34** as well as in essential oils.[149]

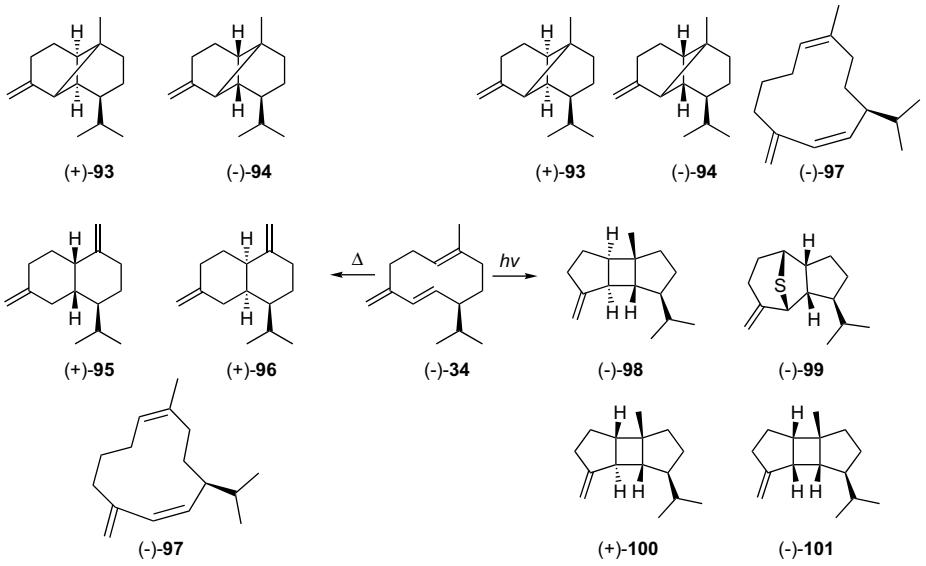
Compound **34** is stable up to ca. 180 °C but at 240 °C over several hours in hexane solution in a seal tube it rearranges to β-ylangene (**93**), β-copaene (**94**), ϵ-muurolene (**95**) and ϵ-amorphene (**96**) as the major products.[150] Identical thermal products were obtained in addition to isogermacrene D (**97**) when a solution of germacrene D (**34**) was injected into a gas chromatography with port injector at 400 °C (Scheme 15).[2]

Upon irradiation, germacrene D (**34**) gave β-bourbonene (**98**)[151] as the main irradiation product in addition to β-copaene (**94**),[152] β-ylangene (**93**), mintsulphide (**99**), isogermacrene D (**97**), mono-*epi*-β-bourbonene (**100**), 1,5-di-*epi*-β-bourbonene (**101**) and other unidentified components (Scheme 15).[2]

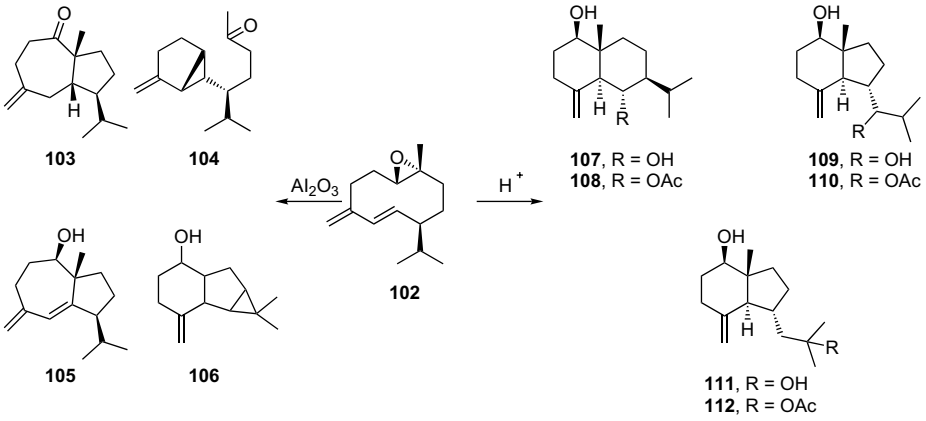
A biomimetic reactions of epoxygermacrene D (**102**) in hexane adsorbed on basic alumina at room temperature for 2.5 h afforded compounds **103**, **104**, **105** and **106**.[93d,e] But when epoxygermacrene D (**102**) was treated with 80% aq AcOH at 0 °C for 1 h, it was easily converted into two selinane-type compounds **107** (9.3%), **108** (11.6%), and four oppositol-type compounds **109** (9.6%), **110** (8.5%), **111** (5.1%) and **112** (5.9%) (Scheme 16).[93c]

5.1. Isogermacrene D (97)

Isogermacrene D (**97**) is a geometric isomer of germacrene D (**34**) and a side product formed during thermal and irradiation treatment of **34**.[2] Bülow and König reported that Isogermacrene D (**97**) does not rearrange under thermal conditions below 240 °C. To date no investigations has been carried out on the thermal rearrangement of isogermacrene D (**97**).[2] Treatment of isogermacrene D (**97**) with Amberlyst® 15 gave (−)-α-muurolene (**82**), (−)-cadina-1,4-diene (**113**), δ- and ω-cadinene (**91**, **114**), selina-4,7-diene (**115**), (−)-selina-3,5-diene (**116**), (+)-δ-selinene (**49**), (−)-isodauca-4,6-diene (**89**) and other unidentified compounds.[2] Photochemical reaction products of isogermacrene D (**97**) include δ-elemene (**79**),



Scheme 15. Main thermal and irradiated products of germacrene D (**34**).[1,2]

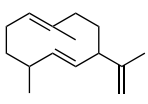


Scheme 16. Acid and basic induced products of epoxygermacrene D (**102**).[93c]

β-ylangene (**93**), β-copaene (**94**), β-bourbonene (**98**) and (+)-1,5-di-*epi*-β-bourbonene (**101**), which rearranged to 1,5-di-*epi*-α-bourbonene (**117**) in acidic condition, in addition to other unidentified components (Scheme 17).[2]

6. Germacrene E or 1,6-cyclodecadiene,1,5-dimethyl-8-(1-methylethenyl)-, or germacra-1(10),5,11-triene (118)

Germacrene E (**118**) was first isolated from the coral *Sinularia erecta*.[71c] To date there has been no report on its thermal rearrangement, acid induced cyclization and photochemical reaction.



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7. Bicyclogermacrene (119) and its isomers

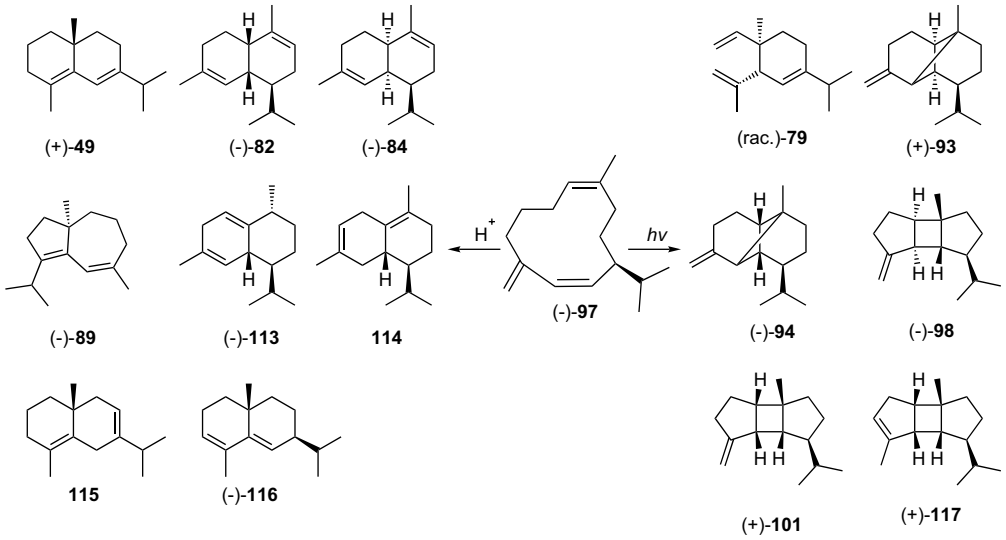
(+)-Bicyclogermacrene (**119**) was first isolated from the cold pressed peel oil of *C. junos*.[126] The (+)-enantiomer is commonly detected in essential oils of higher plants such as roots of *Panax ginseng* C. A. Meyer (Araliaceae),[153] *C. spicatus*,[22] while (−)-**119** has been identified as a constituent of many liverworts such as *Plagiochila asplenioides*,[154] *Diplophyllum albicans*,[155] *Mylia taylorii* and *Mylia nuda*.[156]

Bicyclogermacrene (**119**) has been suggested as a biogenetic precursor of a number of other sesquiterpenes containing a fused dimethylcyclopropane ring, such as maaliane, aristolane and aromadendrane derivatives[126] (Scheme 18).

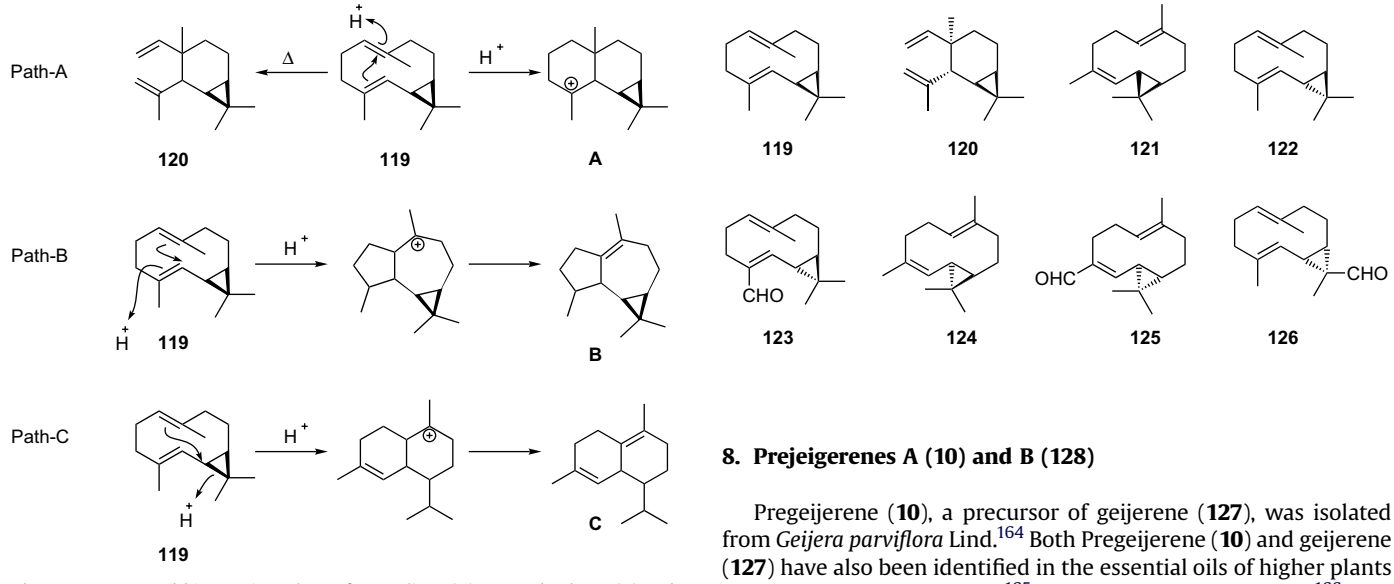
When (+)-bicyclogermacrene (**119**) was heated to 200 °C for 30 min, it gave a mixture of **119**, bicycloelemene (**120**)[157] and isobicyclogermacrene (**121**) in the ratio 5:4:1, respectively, which changed after 2 h to 1:1:8, respectively.[126] The configuration of endocyclic double bonds for **119** was assigned *trans*,*trans*-, while a *cis*,*trans*- or *cis*,*cis*-cyclodeca-1,5-diene was assigned to **121**.[126]

The stereostructure of (+)-**119** was postulated from the absolute configuration of **120** whose cyclopropane ring was assigned a β-configuration by Takeda et al.[158] The configurations of endocyclic double bonds and conformations of **119** and **121** was determined in solution by the use of intramolecular nuclear Overhauser effects and was assigned *trans*,*trans*-orientation and *trans*,*cis*-orientation, respectively.[159]

(−)-Lepidozene (**122**) is another isomer of bicyclogermacrene (**119**) prepared for the first time by degradation of (−)-lepidozenal (**123**).[160] Compound **122** contains a *trans*-fused dimethylcyclopropane ring with one *E*- and one *Z*- double bond whereas **119** contains



Scheme 17. Acid and irradiated products of isogermacrene D (**97**).[1,2]



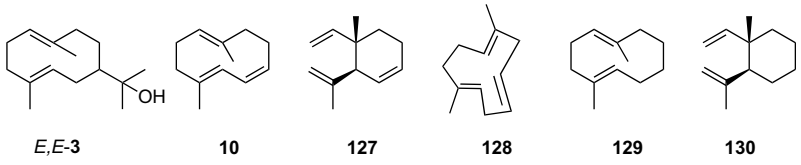
Scheme 18. Proposed biogenetic pathway for maaliane (**A**), aromadendrane (**B**) and cadinane (**C**).

a *cis*-fused dimethylcyclopropane ring with two *E*-double bonds.[160] Nine years later (+)-lepidozene (**122**) was isolated from the gorgonia, *Lophogorgia ruberrima*.[161] (−)-Isolepidozene (**124**), the fourth isomer of bicyclogermacrene (**119**), was later isolated from the liverworts *P. quadrata*, *Frullania tamarisci* and *Scapania aequiloba* by könig's group.[72a] Oxygenated bicyclogermacrene derivatives such as (−)-isobicyclogermacrenal (**125**) and bicyclogermacren-13-al (**126**) were isolated from the liverworts *Lepidozea vitrea*[162] and *Conoceohalum conicum*,[71b] respectively. McMurry and Bosch have reported the total syntheses of (+/−)-**119**, (+/−)-**121**, (+/−)-**122** and (+/−)-**124** by intramolecular carbonyl coupling.[163] Till date no Cope rearrangements have been reported yet for **121**, **122** and **124**.

8. Prejeigerenes A (10) and B (128)

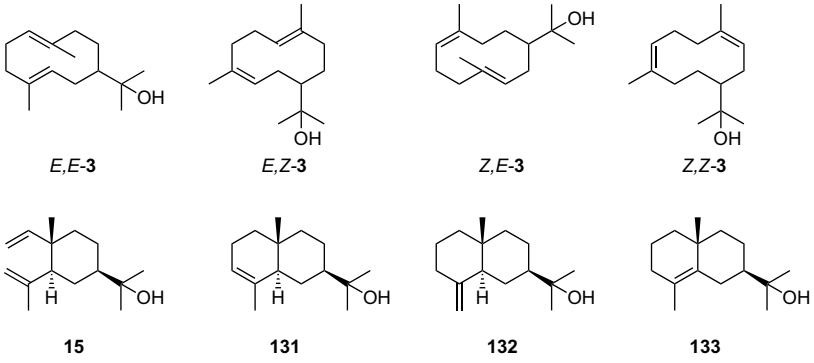
Pregeijerene (**10**), a precursor of geijerene (**127**), was isolated from *Geijera parviflora* Lind.[164] Both Pregeijerene (**10**) and geijerene (**127**) have also been identified in the essential oils of higher plants such as *Pimpinella anisum*,[165] *Chloroxylon swietenia* D.C.[166] and *Dictamnus dasycarpus*.[167]

Pregeijerene B [**128**, (*E*,*E*,*E*)-1,7-dimethylcyclodeca-1,4,7-triene], a geometric isomer of pregeijerene (**10**), was isolated for the first time from *Juniperus erectopatens* foliage.[19] Compound **128** has been reported to be stable[19] even at 280 °C compared to pregeijerene (**10**), which readily undergoes thermal rearrangement to geijerene (**127**).[164] Pregeijerene B (**128**) has been subjected to selective hydrogenation[168] to obtain known dihydropregeijerene (**129**),[169] which readily undergoes thermal Cope rearrangement to 7,8-dihydrogeijerene (**130**).[170] Cool and Adams proposed a trivial name pregeijerene B (**128**) for the *E*,*E*,*E*-**128**, with pregeijerene (**10**) been revised to pregeijerene A.[19] A possible biosynthetic pathway for pregeijerene B (**128**) had been proposed from a structurally related germacrane-type sesquiterpenoid, hedycaryol (**3**), via an enzymatic C-8 oxidation.[19]



9. Hedycaryol (3)

(+)-Hedycaryol (**3**) was first isolated from the essential oil of *H. angustifolia* A. Cunn.[25] Compound **3** is widespread in essential oils of various higher plants such as *Rubus rosifolius*,[171] *Thymus praecox* ssp. arcticus,[172] *Thymus praecox* Opiz arcticus[173] and *Xanthocyparis vietnamensis*.[174] Compound (+)-**3** undergoes Cope rearrangement to (−)-elemol (**15**), when heated at 100 °C.[25,175] Refluxing (+)-(*E*,*E*)-**3** with 1% toluene-*p*-sulphonic acid in ether for 2 h yielded a mixture of α-, β- and γ-eudesmols (**131**,**132** and **133**, respectively) and three minor unidentified products.[25]



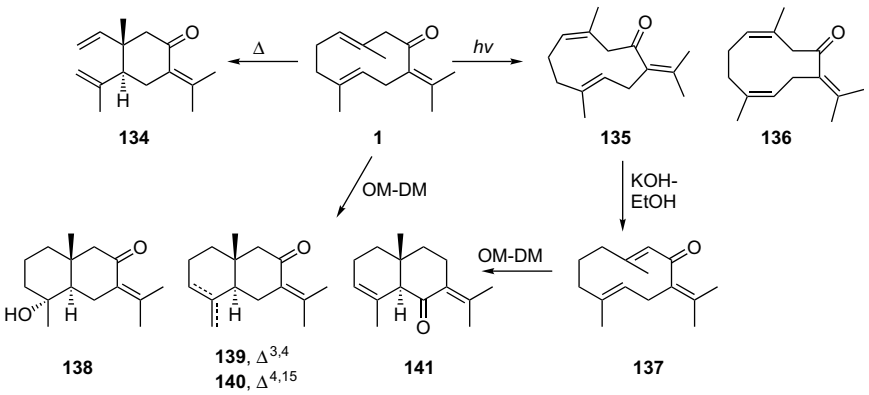
The treatment of *E*,*Z*-, *Z*,*E*- and *Z*,*Z*-hedycaryol (**3**) geometrical isomers with toluene-*p*-sulphonic acid and or formic acid yielded dihydrooccidentalol (α-eudesmol, **131**)[176] and traces of γ-eudesmol (**133**), and other dehydration and conjugation products.[76c] Ganter and Wojtkiewicz have carried out pyrolysis experiments at 195–200 °C on elemol (**15**) and its nitrobenzoate derivative in the presence of benzoic or *p*-nitrobenzoic acid to form mixture of elemane and eudesmane isomers.[177] For products of thermal rearrangements conducted at higher temperatures for *E*,*E*-**3** and its geometric isomers (*E*,*Z*-, *Z*,*E*- and *Z*,*Z*-), see Section 1.4 on Cope rearrangements.[76c]

10. Germacrone-type compounds

Germacrone (**1**) was first isolated from the essential oil of Bulgarian zdravets oil (*G. macrorrhizum* L.) and it is widespread in the essential oils of several plants such as Labrador tea (*Ledum groenlandicum*),[178] *Eugenia uniflora* L.,[67f] *Croton flavens* L.,[179] *Cyperus articulates* L.[180] and *Eugenia uniflora* L. (Brazilian Pitanga).[181]

Compound **1** undergoes smooth thermal rearrangement to β-elemenone (**134**).[182] Germacrone (**1**) was transformed into two photoisomers (**135**, *cis*,*trans*-1,5-germacrone, 27%) and (**136** *cis*,*cis*-1,5-germacrone, 48%) by irradiation in ether in the presence of acetophenone under an atmosphere of nitrogen at room temperature for 5 h, using a Pyrex apparatus with a 300 W high-pressure mercury-vapour lamp.[183] When **135** was heated under reflux in 1 N KOH–EtOH for 6.5 h it gave isogermacrone (**137**).[183] Germacrone (**1**) undergoes transannular cyclization by oxymercuration–demercuration (OM–DM) to form 4α-hydroxy-5αH-selin-7(11)-en-8-one (**138**), 5αH-selina-3,7(11)-diene-8-one (**139**) and 5αH-selina-4(15),7(11)-diene-8-one (**140**) derivatives. *trans*-Selinanes **138**, **139**, **140** and 5αH-selina-3,7(11)-diene-6-one (**141**) were also slowly formed when isogermacrone (**137**) was subjected to a similar OM-DM treatment[184a] (Scheme 19).

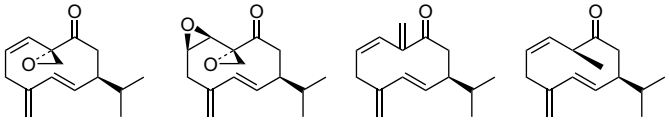
Tsankova and Enev[184b] have studied extensively other oxidative reactions of germacrone (**1**) including its first biomimetic chemical transformation into a humulane skeleton.[185]

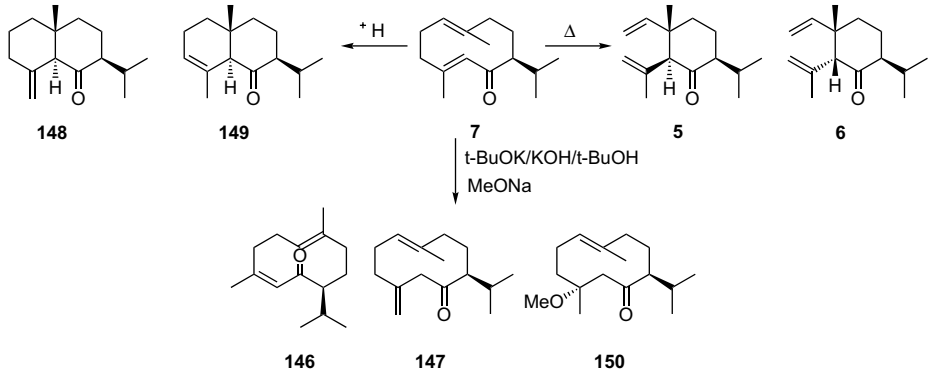


Scheme 19. Thermal, photochemical and oxymercuration–demercuration (OM–DM) products of germacrone (**1**) and isogermacrone (**137**).

10.1. Periplanones A–D (142–145)

Periplanones A, B, C (or D_1) and D (or D_2) (**142**,**143**,**144**,**145**) are sex pheromones isolated from female American cockroaches (*P. americana*).[34a–c,186] Their total syntheses have been achieved.[34b,c,186,187]





Scheme 20. Acid and thermal rearrangements products of acoragermacrone (**7**).

10.2. Other germacrone-type compounds

Acoragermacrone (**7**), isoacoragermacrone (**146**)[92c] and preioscalamendiol (**147**)[27a–c] are other germacrane-type sesquiterpenoids isolated from isolated from *A. calamus* L.

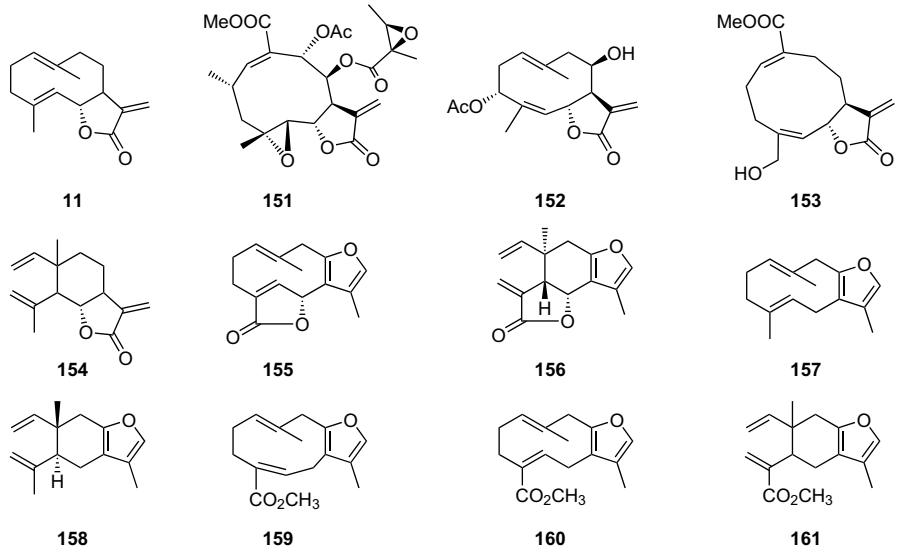
Cope rearrangement of **7** at temperatures more than 106 °C gave shyobunone (**5**) and *epi*-shyobunone (**6**) relatively in ratio 21:8, respectively.[92c] And upon repeated chromatography of **7** on silica gel it gives acolamone (**148**) and isoacolamone (**149**).[92c,188] Treatment of **7** with *t*-BuOK in *t*-BuOH for 30 min at room temperature under nitrogen gave isomer isoacoragermacrone (**146**, 95%) and treatment with 5% KOH in *t*-BuOH at room temperature for 24 h gave preisocalamendiol **147** (84%). Compound **7** gave a methoxy-adduct (**150**) when treated with MeONa (Scheme 20).[92c] The acid-catalyzed cyclizations of **7**, **146** and **147** have been carried out, using several kinds of reagents and solvents such as 80% aq AcOH, 80% aq HCOOH, $AlCl_3$ in absolute ether, AcOH in PhSH, 100% HCOOH in PhSH and concd H_2SO_4 in PhSH. In all cases, the stereospecific cyclizations gave cadinane-type, selinane-type or guaiane-type compounds depending on the kinds of reagents and solvents.[92d]

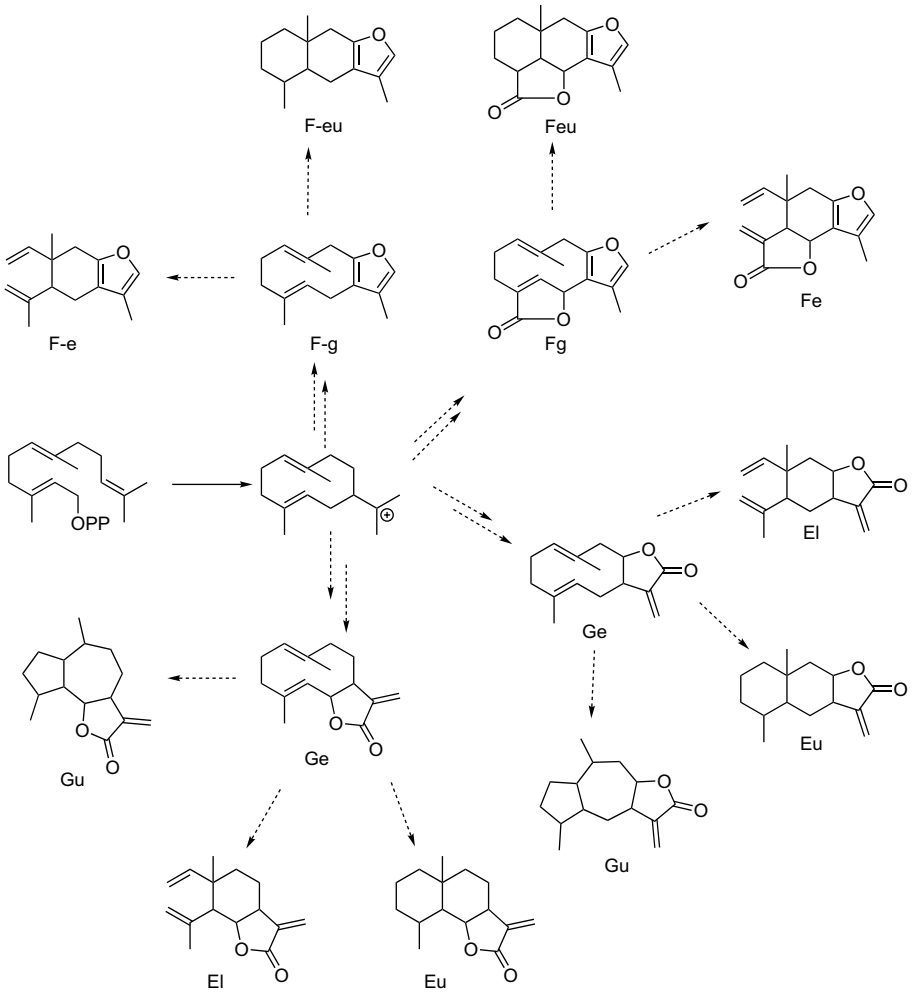
11. Germacranolides

The bibliographic search in SciFinder Scholar using the key word germacranolides (as of June 8th, 2007) gave a total of 961 journal articles. Germacranolides are the largest group of naturally occurring sesquiterpene lactone and can be considered as the biogenetic precursors for other related skeletal types of lactone. The germacranolides are classified into four possible geometric isomers,[189a,b] namely (*E*,*E*)-germacranolides (e.g., costunolide (**11**));[190,191] (*Z*,*E*)-germacranolides (melampolides, e.g., enyhdrin (**151**));[192] (*E*,*Z*)-germacranolides (heliangolides, e.g., euparoformonin (**152**))[193] and (*Z*,*Z*)-germacranolides (e.g., methyl-15-hydroxy-germacra-1(10)-*E*,4*E*,11(13)-triene-6α,12-olide-14-oic acid (**153**)).[194]

For annual update of newly isolated germacranolides see natural product reports by Fraga.[5a–u] Of these germacranolides structures, *trans*-12,6-lactones form the majority but *cis*-12,6-lactones as well as *cis*- and *trans*-12,8-lactones are also common.[195a,b] Scheme 21 shows the proposed biogenetic pathway of guainolides, germacranolides, elemanolides, eudesmanolides, furanogermacranolides, furanogermacranes, furanoelemanolides, furanoelemanes, furanoeudesmanolides and furanoeudesmanes from germacranyl cation.

Similar to germacrene A (**2**), germacranolides also undergo Cope rearrangement and acid induced cyclization to their corresponding elemane and eudesmane-type compounds, respectively.[191] Costunolide (**11**)[191] undergoes Cope rearrangement to dehydrosaussurea lactone (**154**),[196] and its acid catalyzed cyclization and pyrolysis products have earlier been reported.[197] Similarly, linderalactone (**155**) undergoes Cope rearrangement at 150–170 °C and at room temperature to isolinderalactone (**156**).[198]





Scheme 21. Proposed biogenetic pathway of guainolides (Gu), germacranolides (Ge), elemanolides (El), eudesmanolides (Eu), furanogermacranolides (Fg), furanogermacranes (F-g), furanoelemanolides (Fe), furanoelemanes (F-e) furanoeudesmanolides (Feu), furanoeudesmanes (F-eu) from germacranyl cation.

Furanogermacrene derivatives such as furanodiene (**157**)[39,199] is the proposed precursor of isogermafurene (**158**)[200] while sericenine (**159**) and neosericenine (**160**) are the precursors of isosericenine (**161**).[201a,b] For reviews on germacranolides,[202] eudesmanolides and guanolides readers are forwarded to the articles by Fraga[5a–u] and Zidorn.[203]

12. Conclusions

The germacranes are an important group of sesquiterpenes widely occurring in nature and are considered as important intermediates in sesquiterpene biosynthesis. Common to germacranes cyclodecadiene ring system are their ability to undergo conformational changes, their great tendency to undergo Cope rearrangement and transformation to a large variety of products upon acid or irradiation treatment. Most of these rearrangements or transformation products were eventually found as natural products.

Investigations into the natural products have yielded a large number of germacrane derivatives, some of which have shown fascinating biological activities. Considering recent reports of the activities of a thermal product of germacrene A (*trans*-β-elemene)[63a–i] against carcinomas of the brain, breast, liver, lungs and in the treatment of leukemia and other tissues in China, biological studies of other newly structural related elemene isomers could open up new sets of unprecedented plant-derived metabolites of medicinal values.

While the cope rearrangement of *E*,*E*-germacrenes have been extensively investigated, the general capability of *Z*,*Z*- or *Z*,*E*- for the production of elemenes have not been thoroughly explored because they are rare in nature.

Hence, the discovery of a stable fluoro-analogues of germacrene A[14b,c] should offer opportunity for more rearrangement works with different acid induced cyclization reagents, thermal rearrangement at higher temperature and photochemical reactions, which would eventually lead to the discovery of yet another new skeletons or compounds of biological importance.

Acknowledgements

This review is dedicated to the memory of Prof. Dr. Wilfried A. König, who introduced me to the germacrane research at the Universität Hamburg. He will long be remembered for his work on germacranes, liverworts and his extensive investigations on enantioselective cyclodextrin derivatives in separation of chiral molecules.

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References and notes

1. Yoshihara, K.; Ohta, Y.; Sakai, T.; Hirose, Y. *Tetrahedron Lett.* **1969**, *10*, 2263–2264.
2. Bülow, N.; König, W. A. *Phytochemistry* **2000**, *55*, 141–168.
3. Sorm, F. *J. Agric. Food Chem.* **1971**, *19*, 1081–1087.
4. Roberts, J. S.; Bryson, I. *Nat. Prod. Rep.* **1984**, *1*, 105–169.
5. (a) Fraga, B. M. *Nat. Prod. Rep.* **1985**, *2*, 147–161; (b) Fraga, B. M. *Nat. Prod. Rep.* **1986**, *3*, 273–296; (c) Fraga, B. M. *Nat. Prod. Rep.* **1987**, *4*, 473–498; (d) Fraga, B. M. *Nat. Prod. Rep.* **1988**, *5*, 419–450; (e) Fraga, B. M. *Nat. Prod. Rep.* **1990**, *7*, 515–537; (f) Fraga, B. M. *Nat. Prod. Rep.* **1992**, *9*, 557–580; (g) Fraga, B. M. *Nat. Prod. Rep.* **1993**, *10*, 397–419; (h) Fraga, B. M. *Nat. Prod. Rep.* **1994**, *11*, 533–554; (i) Fraga, B. M. *Nat. Prod. Rep.* **1995**, *12*, 303–320; (j) Fraga, B. M. *Nat. Prod. Rep.* **1996**, *13*, 307–326; (k) Fraga, B. M. *Nat. Prod. Rep.* **1997**, *14*, 145–162; (l) Fraga, B. M. *Nat. Prod. Rep.* **1998**, *15*, 73–92; (m) Fraga, B. M. *Nat. Prod. Rep.* **1999**, *16*, 711–730; (n) Fraga, B. M. *Nat. Prod. Rep.* **2000**, *17*, 483–504; (o) Fraga, B. M. *Nat. Prod. Rep.* **2001**, *18*, 650–673; (p) Fraga, B. M. *Nat. Prod. Rep.* **2002**, *19*, 650–672; (q) Fraga, B. M. *Nat. Prod. Rep.* **2003**, *20*, 392–413; (r) Fraga, B. M. *Nat. Prod. Rep.* **2004**, *21*, 669–693; (s) Fraga, B. M. *Nat. Prod. Rep.* **2005**, *22*, 465–486; (t) Fraga, B. M. *Nat. Prod. Rep.* **2006**, *23*, 943–972; (u) Fraga, B. M. *Nat. Prod. Rep.* **2007**, *24*, 1350–1381.
6. Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1999**, *55*, 2115–2146.
7. (a) Ognyanov, I.; Ivanov, D.; Herout, V.; Horak, M.; Pliva, J.; Sorm, F. *Chem. Ind. (London)* **1957**, 820–821; (b) Ognyanov, I.; Ivanov, D.; Herout, V.; Horak, M.; Pliva, J.; Sorm, F. *Collect. Czech. Chem. Commun.* **1958**, *23*, 2033–2045.
8. Treibs, W. *Justus Liebigs Ann. Chem.* **1952**, *576*, 116–124.
9. Naves, Y. R. *Parfums de France* **1929**, *7*, 304–314.
10. Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*. Mono- and Sesquiterpenoids; Chapman and Hall: London, 1991; Vol. 1, pp 214–285.
11. (a) Bhacca, N. S.; Fischer, N. H. *J. Chem. Soc., Chem. Commun.* **1969**, 68–69; (b) Allinger, N. L.; Tribble, M. T.; Sprague, J. T. *J. Org. Chem.* **1972**, *37*, 2423–2424; (c) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1972**, *94*, 5734–5747; (d) Wharton, P. S.; Poon, Y.-C.; Kluender, H. C. *J. Org. Chem.* **1973**, *38*, 735–740; (e) Takeda, K. *Tetrahedron* **1974**, *30*, 1525–1534; (f) Sutherland, J. K. *Tetrahedron* **1974**, *30*, 1651–1660; (g) Samek, Z.; Harmatha, J. *Collect. Czech. Chem. Commun.* **1978**, *43*, 2779–2799; (h) Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1979**, *35*, 3303–3306; (i) Terada, Y.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2495–2499; (j) Watson, W. H.; Kashyap, R. P. *J. Org. Chem.* **1986**, *51*, 2521–2524; (k) Tashkhodzhaev, B.; Makhmudov, M. K. *Chem. Nat. Compd.* **1997**, *33*, 289–292; (l) Tashkhodzhaev, B.; Abduazimov, B. Kh. *Chem. Nat. Compd.* **1997**, *33*, 382–388; (m) Faraldos, J. A.; Wu, S.; Chappell, J.; Coates, R. M. *Tetrahedron* **2007**, *63*, 7733–7742.
12. (a) Barton, D. H.; de Mayo, P. *Q. Rev. (London)* **1957**, *11*, 189–211; (b) Hendrickson, J. B. *Tetrahedron* **1959**, *7*, 82–89; (c) Parker, W.; Roberts, J. S.; Ramage, R. *Q. Rev., Chem. Soc.* **1967**, *21*, 331–363.
13. (a) Herz, W. *Isr. J. Chem.* **1977**, *16*, 32–44; (b) Banthorpe, D. V. *Natural Products: their Chemistry and Biological Significances*; Longman Scientific and Technical: Harlow, UK, 1994; Chapter 5.
14. (a) Cane, D. E. *Chem. Rev.* **1990**, *90*, 1089–1103; (b) Miller, D. J.; Yu, F.; Allemann, R. K. *ChemBioChem* **2007**, *8*, 1819–1825; (c) Faraldos, J. A.; Zhao, Y.; O'Maille, P. E.; Noel, J. P.; Coates, R. M. *ChemBioChem* **2007**, *8*, 1826–1833.
15. de Kraker, J.-W.; Franssen, M. C. R.; de Groot, A.; König, W. A.; Bouwmeester, H. J. *Plant Physiol.* **1998**, *117*, 1381–1392.
16. (a) Arigoni, D. *Pure Appl. Chem.* **1975**, *41*, 219–245; (b) Cane, D. E.; Tandon, M. *J. Am. Chem. Soc.* **1995**, *117*, 5602–5603.
17. He, X.; Cane, D. E. *J. Am. Chem. Soc.* **2004**, *126*, 2678–2679.
18. Hackl, T.; König, W. A.; Muhle, H. *Phytochemistry* **2004**, *65*, 2261–2275.
19. Cool, L. G.; Adams, R. P. *Phytochemistry* **2003**, *63*, 105–108.
20. (a) Bülow, N. Ph.D. Thesis, Universität Hamburg, Germany, 1999; (b) Niwa, M.; Iguchi, M.; Yamamura, S. *Chem. Pharm. Bull.* **1980**, *28*, 997–999.
21. Kasali, A. A.; Wintherhalter, P.; Adio, A. M.; Knapp, H.; Bonnlander, B. *Flavour Fragrance J.* **2002**, *17*, 247–250.
22. Tesso, H.; König, W. A.; Son, P. T.; Giang, P. M. *Flavour Fragrance J.* **2006**, *21*, 592–597.
23. Wichtman, E.-M.; Stahl-Biskup, E. *Flavour Fragrance J.* **1987**, *2*, 83–89.
24. de-Kraker, J.-W.; Franssen, M. C. R.; de Groot, A.; Shibata, T.; Bouwmeester, H. J. *Phytochemistry* **2001**, *58*, 481–487.
25. Jones, R. V. H.; Sutherland, M. D. *J. Chem. Soc., Chem. Commun.* **1968**, 1229–1230.
26. Mölleken, U.; Sinnwell, V.; Kubeczka, K.-H. *Phytochemistry* **1998**, *49*, 1709–1714.
27. (a) Iguchi, M.; Nishiyama, A.; Koyama, H.; Yamamura, S.; Hirata, Y. *Tetrahedron Lett.* **1968**, *9*, 5315–5318; (b) Iguchi, M.; Nishiyama, A.; Koyama, H.; Yamamura, S.; Hirata, Y. *Tetrahedron Lett.* **1969**, *10*, 3729–3732; (c) Iguchi, M.; Nishiyama, A.; Koyama, H.; Yamamura, S.; Hirata, Y. *Tetrahedron Lett.* **1970**, *11*, 855–857.
28. König, W. A.; Rieck, A.; Saritas, Y.; Hardt, I. H.; Kubeczka, K.-H. *Phytochemistry* **1996**, *42*, 461–464.
29. Adio, A. M.; Paul, C.; Kloth, P.; König, W. A. *Phytochemistry* **2004**, *65*, 199–206.
30. Paul, C.; König, W. A.; Wu, C.-L. *Phytochemistry* **2001**, *58*, 789–798.
31. Asakawa, Y. *Phytochemistry* **2004**, *65*, 623–669.
32. Saritas, Y.; Sonwa, M. M.; Iznaguen, H.; König, W. A.; Muhle, H.; Mues, R. *Phytochemistry* **2001**, *57*, 443–457.
33. (a) Scheffrahn, R. H.; Sims, J. J.; Lee, R. K.; Rust, M. K. *J. Nat. Prod.* **1986**, *49*, 699–701; (b) Quitana, A.; Reinhard, J.; Faure, R.; Uva, P.; Bagnéres, A.-G.; Massiot, G.; Clément, J.-L. *J. Chem. Ecol.* **2003**, *29*, 639–652.
34. (a) Talman, E.; Verwiel, P. E. J.; Titter, F. J.; Persoons, C. J. *Isr. J. Chem.* **1978**, *17*, 227–235; (b) Hauptmann, H.; Mühlbauer, G.; Walker, N. P. C. *Tetrahedron Lett.* **1986**, *27*, 1315–1318; (c) Hauptmann, H.; Mühlbauer, G.; Sass, H. *Tetrahedron Lett.* **1986**, *27*, 6169–6192.
35. (a) Nishino, C.; Bowers, W. S.; Montgomery, M. E.; Nault, L. R.; Nielson, M. W. *J. Chem. Ecol.* **1977**, *3*, 349–357; (b) Bowers, W. S.; Nishino, C.; Montgomery, M. E.; Nault, L. R.; Nielson, M. W. *Science* **1977**, *196*, 680–681.
36. Weinheimer, A. J.; Youngblood, W. W.; Washecheck, P. H.; Karns, T. K. B.; Ciereszko, L. S. *Tetrahedron Lett.* **1970**, *11*, 497–500.
37. Beechan, C. M.; Djerassi, C.; Eggert, H. *Tetrahedron* **1978**, *34*, 2503–2508.
38. Kashman, Y.; Loya, Y.; Bodner, M.; Groweiss, A.; Benayahu, Y.; Naveh, N. *Mar. Biol.* **1980**, *55*, 255–259.
39. Izac, R. R.; Bandurraga, M. M.; Waskylyk, J. M.; Dunn, F. W.; Fenical, W. *Tetrahedron* **1982**, *38*, 301–304.
40. Winter, R. E. K.; Dorn, F.; Arigoni, D. *J. Org. Chem.* **1980**, *45*, 4786–4789.
41. (a) Pollak, F. C.; Berger, R. G. *Appl. Environ. Microbiol.* **1996**, *62*, 1295–1299; (b) Schulz, S.; Dickschat, J. S. *Nat. Prod. Rep.* **2007**, *24*, 814–842.
42. (a) Ruzicka, L. *Experientia* **1953**, *9*, 357–367; (b) Ruzicka, L. *Pure Appl. Chem.* **1963**, *6*, 493–523.
43. Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*; Academic: New York, NY, 1972; Vol. 2, p 576.
44. König, W. A.; Adio, A. M.; Paul, C.; Hailemichael, T.; Hackl, T. Abstract of Papers, Stereochemistry of Germacrene Isomers, Future Trends in Phytochemistry, Phytochemical Society of Europe, 05–08 May, 2004, Gargnano, Italy.
45. Rising, K. A.; Starks, C. M.; Noel, J. P.; Chappell, J. *J. Am. Chem. Soc.* **2000**, *122*, 1861–1866.
46. Hamilton, J. G. C.; Hooper, A. M.; Ibbotson, H. C.; Kurosawa, S.; Mori, K.; Muto, S.-E.; Pickett, J. A. *Chem. Commun.* **1999**, 2335–2336.
47. (a) Chen, K. S.; Hsieh, P. W.; Hwang, T. L.; Chang, F. R.; Wu, Y. C. *Nat. Prod. Res.* **2005**, *19*, 283–286; (b) Stefani, R.; Schorr, K.; Tureta, J. M.; Vichnewski, W.; Merfort, I.; Da Costa, F. B. *Z. Naturforsch., C: Biosci.* **2006**, *61*, 647–652.
48. (a) Srivastava, S. K.; Abraham, A.; Bhat, B.; Jaggi, M.; Singh, A. T.; Sanna, V. K.; Singh, G.; Agarwal, S. K.; Mukherjee, R.; Burman, A. C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4195–4199; (b) Horiike, T.; Ohshiro, M.; Kuroyanagi, M. *Phytochemistry* **1997**, *44*, 627–632; (c) Ma, X.-C.; Zheng, J.; Wu, L.-J.; Guo, D.-A. *Magn. Reson. Chem.* **2007**, *45*, 90–92.
49. Garzón, S. P.; Rodráguez, A. D.; Sánchez, J. A.; Ortega-Barria, E. *J. Nat. Prod.* **2005**, *68*, 1354–1359.
50. (a) Dolara, P.; Corte, B.; Ghelardini, C.; Pugliese, A. M.; Cerbai, E.; Menichetti, S.; Nostro, A. L. *Planta Med.* **2000**, *66*, 356–358; (b) Satitpatipan, V.; Suwanborirux, K. *J. Nat. Prod.* **2004**, *67*, 503–505; (c) Luna-Herrera, J.; Costa, M. C.; González, H. G.; Rodrigues, A. I.; Castilho, P. C. *J. Antimicrob. Chemother.* **2007**, *59*, 548–552.
51. Reichardt, P. B.; Bryant, J. P.; Anderson, B. J.; Phillips, D.; Clausen, T. P.; Meyer, M.; Frisby, K. *J. Chem. Ecol.* **1990**, *16*, 1961–1970.
52. Gertsch, J.; Meier, S.; Tschopp, N.; Altmann, K.-H. *Chimia* **2007**, *61*, 368–372.
53. Macías, F. A.; Velasco, R. F.; Álvarez, J. A.; Castellano, D.; Galindo, J. C. G. *Tetrahedron* **2004**, *60*, 8477–8488.
54. Pae, H.-O.; Jeong, G.-S.; Kim, H.-S.; Woo, W. H.; Rhew, H. Y.; Kim, H. S.; Sohn, D. H.; Kim, Y.-C.; Chung, H.-T. *Inflamm. Res.* **2007**, *56*, 520–526.
55. Li, S.; An, T.-Y.; Li, J.; Shen, Q.; Lou, F.-C.; Hu, L.-H. *J. Asian Nat. Prod. Res.* **2006**, *8*, 281–286.
56. Nam, N.-H. *Mini-Rev. Med. Chem.* **2006**, *6*, 945–951.
57. Matsuura, N.; Yamada, M.; Suzuki, H.; Hasegawa, N.; Kurosaka, C.; Ubukata, M.; Tanaka, T.; Iinuma, M. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 2470–2474.
58. Shao, H.; Peng, S.; Wey, X.; Zhang, D.; Zhang, C. *J. Chem. Ecol.* **2005**, *31*, 1657–1668.
59. Rostelien, T.; Borg-Karlson, A. K.; Faldt, J.; Jacobsson, U.; Mustaparta, H. *Chem. Senses* **2000**, *25*, 141–148.
60. Hong, L.; Li, G.; Zhou, W.; Wang, X.; Zhang, K. *Pest Manag. Sci.* **2007**, *63*, 301–305.
61. Chen, W.; Tang, W.; Zhang, R.; Lou, L.; Zhao, W. *J. Nat. Prod.* **2007**, *70*, 567–570.
62. Wu, B.; He, S.; Wu, X.-D.; Pan, Y.-J. *Chem. Biodivers.* **2008**, *5*, 1298–1303.
63. (a) Wang, J. W.; Zhang, H. P.; Sun, Y. *Chin J. New Drugs* **1995**, *4*, 26–29; (b) Wang, J.; Zhang, H.; Sun, Y. *Zhongguo Lin Chuang* **1996**, *23*, 301–304; (c) Yang, H.; Wang, X.; Yu, L. L. *Chin. J. Cancer Res.* **1997**, *9*, 83–88; (d) Tan, P. G.; Zhong, W. J.; Cai, W. Q. *Zhongguo Zhongliu Linchuang* **2001**, *28*, 682–684; (e) Wang, G.; Li, X.; Huang, F.; Zhao, J.; Ding, H.; Cunningham, C.; Coad, J. E.; Flynn, D. C.; Reed, E.; Li, Q. Q. *Cell. Mol. Life Sci.* **2005**, *62*, 881–893; (f) Li, X.; Wang, G.; Zhao, J.; Ding, H.; Cunningham, C.; Chen, F.; Flynn, D. C.; Reed, E.; Li, Q. Q. *Cell. Mol. Life Sci.* **2005**, *62*, 894–904; (g) Wang, Y.; Deng, Y.; Mao, S.; Jin, S.; Wang, J.; Bi, D. *Drug Dev. Ind. Pharm.* **2005**, *31*, 769–778; (h) Xu, L.; Tao, S.; Wang, X.; Yu, Z.; Wang, M.; Chen, D.; Jing, Y.; Dong, J. *Bioorg. Med. Chem.* **2006**, *14*, 5351–5356; (i) Tao, L.; Zhou, L.; Zheng, L.; Yao, M. *Cancer Chemother. Pharmacol.* **2006**, *58*, 24–34.
64. McLafferty, F. W. *Wiley Registry of Mass Spectral Data* with NIST 2005 Spectral Data, 7th ed.; John Wiley & Sons: New York, NY, 2005.
65. Hochmuth, D. H.; Joulain, D.; König, W. A. *MassFinder 2.3, Terpenoids and Related Constituents of Essential Oils*; 2003; www.chemie.uni-hamburg.de/oc/koenig/massfinder.html.

66. (a) Davies, N. W. *J. Chromatogr., A* **1990**, *503*, 1–24; (b) Richmond, R.; Pombo-Villar, E. *J. Chromatogr. A* **1997**, *760*, 303–308; (c) Joulain, D.; König, W. A. *The Atlas of Spectral Data of Sesquiterpene Hydrocarbons*; E.B.: Hamburg, 1998; (d) König, W. A.; Bülow, N.; Saritas, Y. *Flavour Fragrance J.* **1999**, *14*, 367–378; (e) König, W. A.; Hochmuth, D. H. *J. Chromatogr. Sci.* **2004**, *42*, 423–439.
67. (a) Takeda, K.; Horibe, I.; Minato, H. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2212–2220; (b) Stahl, E.; Keller, K. *Planta Med.* **1983**, *47*, 75–78; (c) Skaltsa, H. D.; Demetzos, C.; Lazari, D.; Sokovic, M. *Phytochemistry* **2003**, *64*, 743–752; (d) Oliveira, M. J.; Campos, I. F. P.; Oliveira, C. B. A.; Santos, M. R.; Souza, P. S.; Santos, S. C.; Seraphin, J. C.; Ferri, P. H. *Biochem. Syst. Ecol.* **2005**, *33*, 275–285; (e) Bruni, R.; Pellati, F.; Bellardi, M. G.; Benvenuti, S.; Paltrinieri, S.; Bertaccini, A.; Bianchi, A. *J. Agric. Food Chem.* **2005**, *53*, 964–968; (f) Ogunwande, I. A.; Olawore, N. O.; Ekundayo, O.; Walker, T. M.; Schmidt, J. M.; Setzer, W. N. *Int. J. Aromath.* **2005**, *15*, 147–152; (g) Werka, J. S.; Boehme, A. K.; Setzer, W. N. *Nat. Prod. Commun.* **2007**, *2*, 1215–1219; (h) Cole, R. A.; Haber, W. A.; Setzer, W. N. *Biochem. Syst. Ecol.* **2007**, *35*, 877–886.
68. (a) Huneck, S.; Klein, E. *Phytochemistry* **1967**, *6*, 383–390; (b) Matsuo, A.; Nakayama, M.; Sato, S.; Nakamoto, T.; Uto, S.; Hayashi, S. *Experientia* **1974**, *30*, 321–322; (c) Dorn, F.; Arigoni, D. *Experientia* **1974**, *30*, 851–852; (d) See Ref. 37; (e) Matsuo, A.; Ishii, O.; Suzuki, M.; Nakayama, M.; Hayashi, S. *Z. Naturforsch.* **1982**, *37b*, 1636–1639; (f) Lorimer, S. D.; Weavers, R. T. *Phytochemistry* **1987**, *26*, 3207–3215; (g) König, W. A.; Bülow, N.; Fricke, C.; Melching, S.; Rieck, A.; Muhle, H. *Phytochemistry* **1996**, *43*, 629–633; (h) Adio, A. M.; Paul, C.; König, A. W.; Muhle, H. *Phytochemistry* **2002**, *61*, 79–91.
69. (a) Southwell, I. A. *Phytochemistry* **1970**, *9*, 2243–2245; (b) Brown, E. D.; Sam, T. W.; Sutherland, J. K.; Torre, A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2326–2332; (c) Niwa, M.; Iguchi, M.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3148–3154; (d) Piet, D. P.; Minnard, A. J.; van der Heyden, K. A.; Franssen, M. C. R.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1995**, *51*, 243–254; (e) Adio, A. M.; Paul, C.; Tesso, H.; Kloth, P.; König, W. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1631–1635.
70. Kitagawa, I.; Cui, Z.; Son, B. W.; Kobayashi, M.; Kyoyoku, Y. *Chem. Pharm. Bull.* **1987**, *35*, 124–135.
71. (a) Kubeczka, K.-H. *Phytochemistry* **1979**, *18*, 1066–1067; (b) Toyota, M.; Nagashima, F.; Fukuyama, Y.; Honda, S.; Asakawa, Y. *Phytochemistry* **1988**, *27*, 3317–3319; (c) Rudi, A.; Dayan, T. L.-A.; Aknin, M.; Gaydou, E. M.; Kashman, Y. *J. Nat. Prod.* **1998**, *61*, 872–875; (d) See Ref. 46.
72. (a) Hardt, I. H.; Rieck, A.; Konig, W. A.; Muhle, H. *Phytochemistry* **1995**, *40*, 605–606; (b) Hardt, I. H.; König, W. A. *J. Chromatogr. A* **1994**, *666*, 611–615.
73. Kery, A.; Turiak, G. Y.; Zambo, I.; Tetenyi, P. *Acta Pharm. Hung.* **1987**, *57*, 228–238.
74. Tori, M.; Takeichi, Y.; kuga, H.; Nakashima, K.; Sono, M. *Chem. Pharm. Bull.* **2002**, *50*, 1250–1254.
75. Merfort, I. *J. Chromatogr. A* **2002**, *967*, 115–130.
76. (a) Yamamura, S. *Tetrahedron Lett.* **1979**, *35*, 3303–3306; (b) Shirahama, H.; Ōsawa, E.; Matsumoto, T. *Tetrahedron Lett.* **1979**, *20*, 2245–2246; (c) Kodama, M.; Yokoo, S.; Matsuki, Y.; Itô, S. *Tetrahedron Lett.* **1979**, *20*, 1687–1690.
77. Kulkarni, G. H.; Kelkar, G. R.; Bhattacharyya, S. C. *Tetrahedron* **1964**, *20*, 1301–1315.
78. (a) White, D. N. J.; Bovill, M. J. *Tetrahedron Lett.* **1975**, *16*, 2239–2240; (b) White, D. N. J.; Bovill, M. J. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1610–1623; (c) Ōsawa, E.; Shimada, K.; Kodama, M.; Itô, S. *Tetrahedron Lett.* **1979**, *20*, 2353–2354.
79. (a) Horibe, I.; Tori, K.; Takeda, K. *Tetrahedron Lett.* **1973**, *14*, 735–738; (b) Inayama, S.; Gao, J. F.; Harimaya, K.; Iitaka, Y.; Guo, Y. T.; Kawamata, T. *Chem. Pharm. Bull.* **1985**, *33*, 1323–1326; (c) Ohkura, T.; Gao, J.; Harimaya, K.; Hikichi, M.; Iitaka, Y.; Kawamata, T.; Kuroyanagi, M.; Fukushima, S.; Inayama, S. *Chem. Pharm. Bull.* **1986**, *34*, 4435–4438; (d) Mori, M.; Okada, K.; Shimazaki, K.; Chuman, T.; Kuwahara, S.; Kitahara, T.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1769–1777.
80. Coggon, P.; McPhail, A. T.; Sim, G. A. *J. Chem. Soc. B* **1970**, 1024–1028.
81. (a) Šorm, F.; Suchý, M.; Holub, M.; Línek, A.; Hadinec, I.; Novák, C. *Tetrahedron Lett.* **1970**, *11*, 1893–1896; (b) Allen, F. H.; Rogers, D. *J. Chem. Soc. B* **1971**, 257–262.
82. Hikino, H.; Konno, C.; Nagashima, T.; Takemoto, T. *Tetrahedron Lett.* **1971**, *12*, 337–340.
83. Houk, K. N.; Gonzales, J.; Li, J. *Acc. Chem. Res.* **1995**, *28*, 81–90.
84. (a) Doering, W. V. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67–74; (b) Dewar, M. J. S.; Wade, L. E., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 4417–4424; (c) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1978**, *100*, 6268–6269; (d) Dewar, M. J. S.; Jie, C. *J. Am. Chem. Soc.* **1987**, *109*, 5893–5900.
85. (a) Dewar, M. J. S.; Ford, G. P.; McKee, M. L.; Rzepa, H. S.; Wade, L. E. *J. Am. Chem. Soc.* **1977**, *99*, 5069–5073; (b) Wehrli, R.; Schmid, H.; Bellus, D.; Hansen, H. J. *Helv. Chim. Acta* **1977**, *60*, 1325–1356; (c) Shea, K. J.; Phillips, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 3156–3162; (d) Osamura, Y.; Kato, S.; Morokuma, K.; Feller, D.; Davidson, E. R.; Borden, W. T. *J. Am. Chem. Soc.* **1984**, *106*, 3362–3363; (e) Dupuis, M.; Murray, C.; Davidson, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 9756–9759; (f) Hill, R. K. *Comp. Org. Syn.* **1991**, *5*, 785–826; (g) Hrovat, D. A.; Morokuma, K.; Borden, W. T. *J. Am. Chem. Soc.* **1994**, *116*, 1072–1076; (h) Staroverov, V. N.; Davidson, E. R. *THEOCHEM* **2001**, *573*, 81–89; (i) Black, K. A.; Wilsey, S.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 6715–6724.
86. (a) Fisher, N. H.; Mabry, T. J. *J. Chem. Soc., Chem. Commun.* **1967**, 1235–1236; (b) Jain, T. C.; Banks, C. M.; McCloskey, J. E. *Tetrahedron Lett.* **1970**, *11*, 841–844; (c) Gopalan, A.; Magnus, P. *J. Org. Chem.* **1984**, *49*, 2317–2321; (d) See Ref. 84c.
87. (a) Hrovat, D. A.; Borden, W. T.; Vance, R. L.; Rondan, N. G.; Houk, K. N.; Morokuma, K. *J. Am. Chem. Soc.* **1990**, *112*, 2018–2019; (b) Blavins, J. J.; Cooper, D. L.; Karadakov, P. B. *J. Phys. Chem. A* **2004**, *108*, 194–202.
88. Takeda, K.; Horibe, I. *J. Chem. Soc., Perkin Trans. 1* **1975**, 870–876.
89. Setzer, W. N. *J. Mol. Model.* **2008**, *14*, 335–342.
90. See Ref. 68g.
91. Endo, J.; Ogino, T.; Nagasawa, M. *Yakugaku Zasshi* **1972**, *92*, 874–878.
92. (a) Morikawa, K.; Hirose, Y. *Tetrahedron Lett.* **1969**, *22*, 1799–1801; (b) Lawrence, B. M.; Hogg, J. W.; Terhune, S. J. *Flavour Ind.* **1972**, 467–472; (c) Niwa, M.; Nishiyama, A.; Iguchi, M.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2930–2934; (d) See Ref. 69c; (e) Nishimura, H.; Hasegawa, H.; Seo, A.; Nakano, H.; Mizutani, J. *Agric. Biol. Chem.* **1979**, *43*, 2397–2398.
93. (a) González, A. G.; Galindo, A.; Afonso, M. M.; Mansilla, H.; López, M. *Tetrahedron* **1988**, *44*, 4585–4589; (b) Delgado, G.; Guzmán, S. *J. Chem. Soc., Chem. Commun.* **1992**, 606–607; (c) Niwa, M.; Iguchi, M.; Yamamura, S. *Tetrahedron Lett.* **1978**, *19*, 4043–4046; (d) Niwa, M.; Iguchi, M.; Yamamura, S. *Tetrahedron Lett.* **1979**, *20*, 4291–4294; (e) Yamamura, S.; Niwa, M.; Ito, M.; Saito, Y. *Chem. Lett.* **1982**, 1681–1684.
94. Asakawa, Y.; Takahashi, H.; Toyota, M. *Phytochemistry* **1991**, *30*, 3993–3997.
95. Sakui, N.; Kuroyanagi, M.; Ishitobi, Y.; Sato, M.; Ueno, A. *Phytochemistry* **1992**, *31*, 143–147.
96. Sakamoto, S.; Tsuchiya, N.; Kuroyanagi, M.; Ueno, A. *Phytochemistry* **1994**, *35*, 1215–1219.
97. Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1994**, *50*, 4755–4764.
98. Evans, F. E.; Miller, D. W.; Cairns, T.; Baddeley, G. V.; Wenkert, E. *Phytochemistry* **1982**, *21*, 937–938.
99. Piet, D. P.; Schrijvers, R.; Franssen, M. C. R.; de Groot, A. *Tetrahedron* **1995**, *51*, 6303–6314.
100. (a) See Ref. 48b; (b) See Ref. 48c; (c) Barrero, A. F.; Oltra, J. E.; Raslan, D. S. *J. Nat. Prod.* **1999**, *62*, 726–729; (d) Hashimoto, T.; Noma, Y.; Asakawa, Y. *Heterocycles* **2001**, *54*, 529–559; (e) Ma, X.-C.; Zheng, J.; Guo, D.-A. *Enzyme Microb. Technol.* **2007**, *40*, 1013–1019.
101. García-Granados, A.; Gutiérrez, M. C.; Martínez, A.; Rivas, F. *J. Org. Chem.* **2005**, *70*, 338–341.
102. Hayashi, K.-I.; Asano, K.-I.; Tanaka, M.; Takaoka, D.; Nozaki, H. *Phytochemistry* **1998**, *48*, 461–466.
103. Bouwmeester, H.; Kodde, J.; Verstappen, F. W. A.; Altug, I. G.; de Kraker, J. W.; Wallaart, T. E. *Plant Physiol.* **2002**, *129*, 134–144.
104. Morikawa, K.; Hirose, Y.; Nozoe, S. *Tetrahedron Lett.* **1971**, *16*, 1131–1132.
105. Saito, A.; Rilling, H. C. *Arch. Biochem. Biophys.* **1981**, *208*, 508–511.
106. Colby, S. M.; Crock, J.; Dowdle-Rizzo, B.; Lemaux, P. G.; Croateau, R. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 2216–2221.
107. Schmidt, C. O.; Bouwmeester, H. J.; de Kraker, J.-W.; Konig, W. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1400–1402.
108. Schmidt, C. O.; Bouwmeester, H. J.; Franke, S.; König, W. A. *Chirality* **1999**, *11*, 353–362.
109. Steliopoulosa, P.; Wüsta, M.; Adamb, K.-P.; Mosandl, A. *Phytochemistry* **2002**, *60*, 13–20.
110. Umlauf, D.; Zapp, J.; Becker, H.; Adam, K. P. *Phytochemistry* **2004**, *65*, 2463–2470.
111. Posser, I.; Altug, I. G.; Phillips, A. L.; König, W. A.; Bouwmeester, H. J.; Beale, M. H. *Arch. Biochem. Biophys.* **2004**, *432*, 136–144.
112. (a) See Ref. 70; (b) Schmaus, G.; Schultze, W.; Kubeczka, K.-H. *Planta Med.* **1989**, *55*, 482–487.
113. (a) Muto, S.-E.; Nishimura, Y.; Mori, K. *Eur. J. Org. Chem.* **1999**, 2159–2165; (b) Hooper, A. M.; Farcet, J.-B.; Mulholland, N. P.; Pickett, J. A. *Green Chem.* **2006**, *8*, 513–515.
114. Kurosawa, S.; Mori, K. *Eur. J. Org. Chem.* **2000**, 955–962.
115. Mehta, G.; Kumaran, R. S. *Tetrahedron Lett.* **2005**, *46*, 8831–8835.
116. Dunlop, R. W.; Wells, R. J. *Aust. J. Chem.* **1979**, *32*, 1345–1351.
117. Baker, R.; Parton, A. H.; Howse, P. E. *Experientia* **1982**, *38*, 297–298.
118. Baker, R.; Coles, H. R.; Edwards, S. M.; Evans, D. A.; Howse, P. E.; Walmsley, S. *J. Chem. Ecol.* **1981**, *7*, 135–145.
119. König, W. A.; Rieck, A.; Hardt, I.; Gehrcke, B.; Kubeczka, K.-H.; Muhle, H. *J. High Resolut. Chromatogr.* **1994**, *17*, 315–320.
120. Itoh, A.; Nozaki, H.; Yamamoto, H. *Tetrahedron Lett.* **1978**, *32*, 2903–2906.
121. McMurry, J. E.; Kočovský, P. *Tetrahedron Lett.* **1985**, *26*, 2171–2172.
122. Adio A. M. Ph.D. Thesis, Universität Hamburg, Germany, 2005.
123. Andersen, N. H.; Bissonette, P.; Liu, C.-B.; Shunk, B.; Ohta, Y.; Tseng, C. W.; Moore, A.; Huneck, S. *Phytochemistry* **1977**, *16*, 1731–1751.
124. (a) Caine, D.; Stanhope, B. *Tetrahedron* **1987**, *43*, 5545–5555; (b) Schinzer, D.; Fesserner, K.; Ruppelt, M. *Liebigs Ann. Chem.* **1992**, 139–143; (c) Baker, R.; Evans, D. A.; McDowell, P. G. *Tetrahedron Lett.* **1978**, *42*, 4073–4076.
125. (a) Tesso, H.; König, W. A.; Asakawa, Y. *Phytochemistry* **2005**, *66*, 941–949; (b) Adio, König, unpublished results.
126. Nishimura, K.; Shinoda, N.; Hirose, Y. *Tetrahedron Lett.* **1969**, *22*, 3097–3100.
127. Clark, B. C., Jr.; Chamblee, T. S.; Iacobucci, G. A. *J. Agric. Food Chem.* **1987**, *35*, 514–518.
128. Kobaisy, M.; Tellez, M. R.; Dayan, F. E.; Duke, S. O. *Phytochemistry* **2002**, *61*, 37–401.
129. Allen, F. H.; Rogers, D. *J. Chem. Soc., Chem. Commun.* **1967**, 558–591.
130. Hartley, R. D.; Fawcett, C. H. *Phytochemistry* **1969**, *8*, 1793–1796.
131. de Pascual Teresa, J.; Barrero, A. F.; Caballero, M. C. *An. Quim.* **1978**, *74*, 519–521.
132. Allen, F. H.; Brown, E. D.; Rogers, D.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1967**, 1116–1118.
133. Sam, T. W.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2336–2340.
134. Reijnders, P. J. M.; van Putten, R. G.; de Haan, J. W.; Koning, H. N.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 67–69.

135. Franssen, H. R.; Buck, H. M. *J. Chem. Soc., Chem. Commun.* **1982**, 786–787.
136. Peijnenburg, W. J. G. M.; Dormans, G. J. M.; Buck, H. M. *Tetrahedron* **1988**, *44*, 2339–2350.
137. (a) Peijnenburg, W. J. G. M.; Dormans, G. J. M.; Bezemer, G. J.; Buck, H. M. *Tetrahedron* **1984**, *40*, 4959–4962; (b) Jacobsson, U.; Norin, T.; Weber, M.; Tsankova, E. *Tetrahedron* **1985**, *41*, 2033–2036.
138. Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1997**, *62*, 7336–7345.
139. Steele, C. L.; Crock, J.; Bohlmann, J.; Croteau, R. *J. Biol. Chem.* **1998**, *273*, 2078–2089.
140. Goug, J. H.; Sutherland, M. D. *Aust. J. Chem.* **1964**, *17*, 1270–1281.
141. Oshima, Y.; Iwakawa, T.; Hikino, H. *Phytochemistry* **1983**, *22*, 183–185.
142. Yoshikawa, M.; Hatakeyama, S.; Tanaka, N.; Fukuda, Y.; Murakami, N.; Yamahara, J. *Chem. Pharm. Bull.* **1992**, *40*, 2582–2584.
143. See Ref. 71a.
144. Itokawa, H.; Matsumoto, H.; Mihashi, S. *Chem. Lett.* **1983**, 1253–1256.
145. Pietsch, M.; Konig, W. A. *Phytochem. Anal.* **2000**, *11*, 99–105.
146. Kitamura, C.; Takahashi, S.; Tahara, S.; Mitsutani, J. *Agric. Biol. Chem.* **1976**, *40*, 1965–1969.
147. (a) See Ref. 37; (b) See Ref. 68f.
148. Bülow, N.; König, W. A. In *Essential Oils: Basic and Applied Research. Proceedings of the 27th International Symposium on Essential Oils, Vienna*; Franz, C., Mathe, A., Buchbauer, G., Eds.; Allured: Carol Stream, IL, 1996; pp 209–213.
149. Setzer, W. N. *Int. J. Mol. Sci.* **2008**, *9*, 89–97.
150. Köster, F.-H.; Wolf, H.; Kluge, H. *Liebigs Ann. Chem.* **1986**, 78–92.
151. Tomioka, K.; Tanaka, M.; Koga, K. *Chem. Pharm. Bull.* **1989**, *37*, 1201–1207.
152. Kulkarni, Y. S.; Niwa, M.; Ron, E.; Snider, B. B. *J. Org. Chem.* **1987**, *52*, 1568–1576.
153. Richter, R.; Basar, S.; Koch, A.; König, W. A. *Phytochemistry* **2005**, *66*, 2708–2713.
154. Adio, A. M.; König, W. A. *Phytochemistry* **2005**, *66*, 599–609.
155. Adio, A. M.; König, W. A. *Tetrahedron: Asymmetry* **2007**, *18*, 1693–1700.
156. von Reuß, S. H.; Wu, C.-L.; Muhle, H.; König, W. A. *Phytochemistry* **2004**, *65*, 2277–2291.
157. Vlahov, R.; Holub, M.; Ognjanov, I.; Herout, V. *Collect. Czech. Chem. Commun.* **1967**, *32*, 808–821.
158. Takeda, K.; Horibe, I.; Minato, H. *J. Chem. Soc., Chem. Commun.* **1971**, 308.
159. Nishimura, K.; Hirose, Y.; Tori, K. *Tetrahedron Lett.* **1973**, *29*, 271–274.
160. Matsuo, A.; Kubota, N.; Nakayama, M.; Hayashi, S. *Chem. Lett.* **1981**, 1097–1100.
161. Norte, M.; Fernández, J. J.; González, R.; Rodríguez, M. L.; Ruiz-Pérez, C.; Rodríguez-Romero, V. *Tetrahedron* **1990**, *46*, 8237–8242.
162. Matsuo, A.; Kubota, N.; Uto, S.; Nakayama, M.; Hayashi, S.; Yamasaki, K. *Chem. Lett.* **1979**, 1383–1384.
163. McMurry, J. E.; Bosch, G. K. *J. Org. Chem.* **1987**, *52*, 4885–4893.
164. Jones, R. V. H.; Sutherland, M. D. *Aust. J. Chem.* **1968**, *21*, 2255–2274.
165. Santos, P. M.; Figueiredo, A. C.; Oliveira, M. M.; Barroso, J. G.; Pedro, L. G.; Deans, S. G.; Younus, A. K. M.; Scheffer, J. J. C. *Phytochemistry* **1998**, *48*, 455–460.
166. Ravi-Kiran, S.; Sita Devi, P. *Parasitol. Res.* **2007**, *101*, 413–418.
167. Lei, J.; Yu, J.; Yu, H.; Liao, Z. *Food Chem.* **2008**, *107*, 1205–1209.
168. Choi, J.-S.; Yoon, N.-M. *Synthesis* **1996**, 597–599.
169. Wharton, P. S.; Poon, Y.-C.; Kluender, H. C. *J. Org. Chem.* **1971**, *38*, 735–740.
170. Tolstikov, G. A.; Mikhailov, B. M.; Dzhemilev, U. M.; Dorokhov, V. A.; Gubaidullin, L. Yu.; Zelinskii, N. D. USSR Patent SU 791717, 1980.
171. Southwell, I. A. *Aust. J. Chem.* **1978**, 2527–2538.
172. Stahl-Biskup, E. *Planta Med.* **1986**, 36–38.
173. Schmidt, A.; Bischof-Deichnik, C.; Stahl-Biskup, E. *Biochem. Syst. Ecol.* **2004**, *32*, 409–421.
174. Adams, R. P.; Thomas, P.; Rushforth, K. *J. Essent. Oil Res.* **2007**, *19*, 30–33.
175. Hellyer, R. O. *Aust. J. Chem.* **1962**, *15*, 157.
176. Hortmann, A. G.; de Rood, J. B. *J. Org. Chem.* **1969**, *34*, 736–738.
177. Ganter, von C.; Wojtkiewicz, B. K. *Helv. Chim. Acta* **1971**, *54*, 183–206.
178. See Ref. 51.
179. Sylvestre, M.; Pichette, A.; Longtin, A.; Nagau, F.; Legault, J. *J. Ethnopharmacol.* **2006**, *103*, 99–102.
180. Olawore, N. O.; Usman, L. A.; Ogunwande, I. A.; Adeleke, K. A. *J. Essent. Oil Res.* **2006**, *18*, 604–606.
181. Melo, R. M.; Corrêa, V. F. S.; Amorim, A. C. L.; Miranda, A. L. P.; Rezende, C. M. *J. Braz. Chem. Soc.* **2007**, *18*, 179–183.
182. Ognyanov, I.; Herout, V.; Horak, M.; Sorm, F. *Collect. Czech. Chem. Commun.* **1959**, *24*, 2371–2377.
183. Takeda, K.; Horibe, I.; Minato, H. *J. Chem. Soc., Chem. Commun.* **1971**, 87–88.
184. (a) Tsankova, E.; Ognyanov, I.; Norin, T. *Tetrahedron* **1980**, *36*, 669–671; (b) Tsankova, E.; Enev, V. *Tetrahedron* **1987**, *43*, 4425–4432.
185. Enev, V.; Tsankova, E. *Tetrahedron Lett.* **1988**, *29*, 1829–1832.
186. Biendl, M.; Hauptmann, H.; Sass, H. *Tetrahedron Lett.* **1989**, *30*, 2367–2368.
187. Nishii, Y.; Watanabe, K.; Yoshida, T.; Okayama, T.; Takahashi, S.; Tanabe, Y. *Tetrahedron* **1997**, *53*, 7209–7218.
188. Niwa, M.; Nishiyama, A.; Iguchi, M.; Yamamura, S. *Chem. Lett.* **1972**, *9*, 823–826.
189. (a) Rogers, D.; Moss, G. P.; Neidle, S. *J. Chem. Soc., Chem. Commun.* **1972**, 142–143; (b) Fisher, N. H. In *Recent Advances in Phytochemistry*; Towers, G. H. N., Stafford, H. A., Eds.; Plenum: New York, NY, 1990; Vol. 24, pp 161–201.
190. Paul, A.; Bawdekar, A. S.; Joshi, R. S.; Rao, A. S.; Kelkar, G. R.; Bhattacharyya, S. C. *Perfume Essential Oil Rec.* **1960**, *15*, 115–120.
191. de Kraker, J.-W.; Franssen, M. C. R.; Dalm, M. C. F.; de Groot, A.; Bouwmeester, H. J. *Plant Physiol.* **2001**, *125*, 1930–1940.
192. Stefani, R.; Da Costa, F. B. *Biochem. Syst. Ecol.* **2006**, *34*, 757–759.
193. McPhail, A. T.; Onan, K. D.; Gross, P. M.; Lee, K. H.; Ibuka, T.; Huang, H. C. *Tetrahedron Lett.* **1974**, *15*, 3203–3206.
194. Stokes, S.; Castro, V.; Poveda, L.; Papastergiou, F.; Jakupovic, J. *Phytochemistry* **1992**, *31*, 2894–2896.
195. (a) Šorm, F. In *Fortschritte der Chemie Organischer Naturstoffe*; Zechmeister, L.,Ed.; Springer: Wien, 1961; Vol. 19, pp 1–31; (b) Šorm, F. *Pure Appl. Chem.* **1970**, *21*, 263–283.
196. Jain, T. C.; Banks, C. M.; McCloskey, J. E. *Tetrahedron Lett.* **1970**, *11*, 2387–2390.
197. See Ref. 77.
198. Takeda, K.; Minato, H.; Ishikawa, M. *J. Chem. Soc.* **1964**, 4578–4582.
199. Hikino, H.; Agatsuma, K.; Takemoto, T. *Tetrahedron Lett.* **1968**, *9*, 931–933.
200. Ishi, H.; Tozyo, T.; Nakamura, M.; Takeda, K. *Tetrahedron* **1968**, *24*, 625–631.
201. (a) Hayashi, N.; Hayashi, S.; Matsuura, T. *Tetrahedron Lett.* **1968**, *9*, 4957–4960; (b) Hayashi, S.; Hayashi, N.; Matsuura, T. *Tetrahedron Lett.* **1968**, *9*, 1999–2001.
202. Krishna, V.; Natani, K.; Singh, P. *J. Indian Chem. Soc.* **2003**, *80*, 971–977.
203. Zidorn, C. *Phytochemistry* **2008**, *69*, 2270–2296.

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