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(−)-*trans*-β-Elemene and related compounds: occurrence, synthesis, and anticancer activity

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Contents

1. Introduction

Elemanes are group of sesquiterpenes widely occurring in nature,[1,2] and are considered as Cope rearrangement products or thermal artifacts of germacranes.[3,4] One of the most significant and recent developments is the use of (−)-*trans*-β-elemene (**1**) in the treatment of leukemia and cancers of the brain, ovary, prostate, breast, lungs, liver, colon, and other tissues in China.[5] Previously, Roberts and Bryson (1984)[6] published a review on isolated sesquiterpenoids including elemanes and beginning from 1985, an annual update of the literature of newly isolated and synthesized sesquiterpenoids including elemanes is also being published in the natural product reports by Fraga.[2] In China, mini-reviews published in Chinese academic journals include a systematic review of elemene injections for pulmonary cancer,[7] basic study and clinical application of β-elemene (**1**) in the antitumor therapy of many malignant neoplasms,[8] and a review on the effectiveness and safety of elemene in the treatment of patients with lung cancer.[9] In 2009, a review on germacranes as the biogenetic precursors of elemanes was published by Adio.[4]

This review will focus on the general identification and occurrence, synthesis, and anticancer activity of (−)-*trans*-β-elemene (**1**) and related compounds. Other topics such as isolation, biotransformations, synergistic interactions, Cope rearrangements, computational studies, and oxidation reactions of (−)-*trans*-β-elemene (**1**) are also discussed.

A bibliographic search in SciFinder Scholar using the keyword elemene as of December 1, 2008 gave a total of 4664 journal

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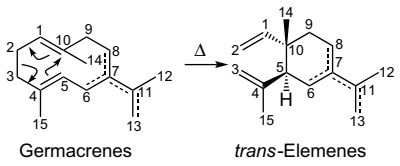
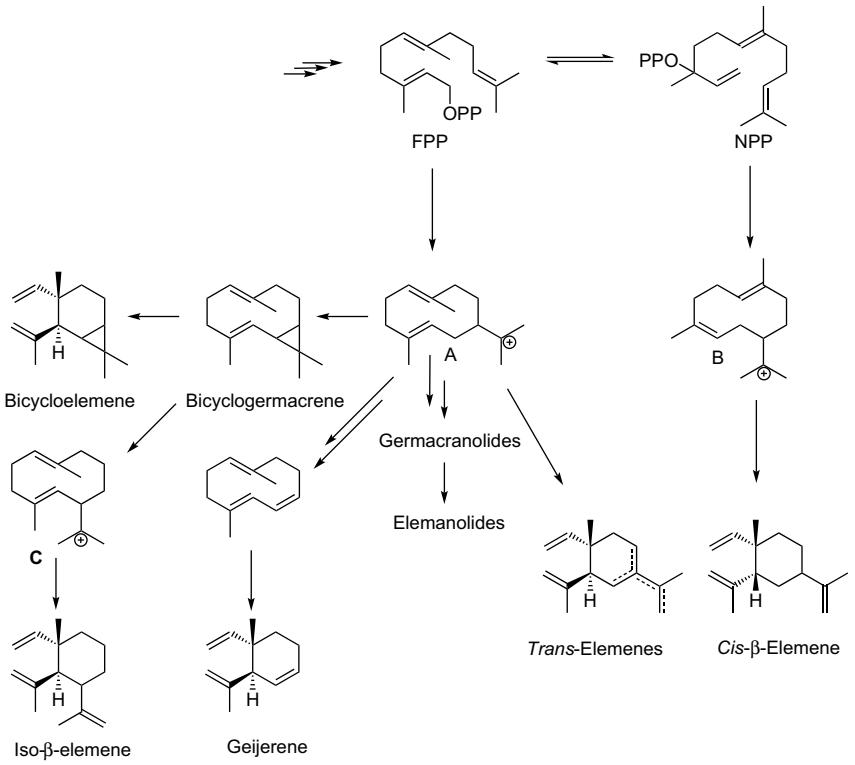


Figure 1. Chemical structure of *trans*-elemenes formed from *E,E*-germacranes.

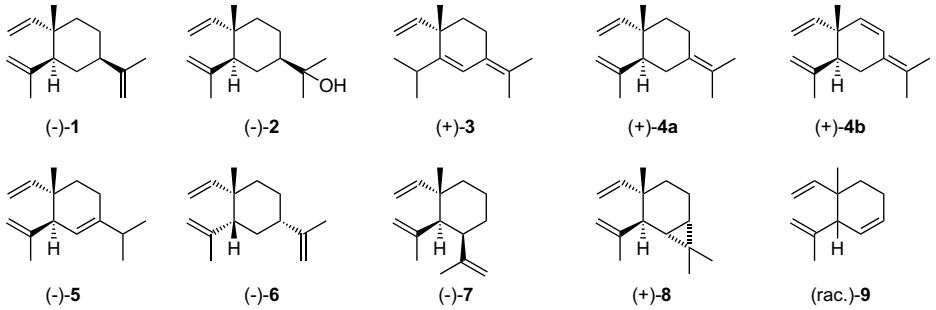
articles. While in 1916 only two articles contained the keyword elemene, the number has increased to 507 in 2006 and 526 in 2007. These journals range from isolation to synthesis, antitumor or antiproliferative activity, biotransformations, rearrangement reactions, etc. The increase in the number of publications and patents[10] filed in China and recently in the United States ranging from the synthesis of elemenes to their applications as anti-proliferatives in the treatment of broad spectrum of cancers demonstrates how widespread and interesting the compounds are. The name elemane is derived from the skeleton of (−)-elemol (**2**), the first monocyclic sesquiterpene alcohol isolated from the Manila elemi oil (*Canarium luzonicum*) in 1907.[11] The sesquiterpene hydrocarbon derivative named *trans*-β-elemene (**1**) was isolated from sweet-flag and juniper oils and also obtained by pyrolysis of elemyl benzoate, and its structure was correctly assigned by Sorm's group.[12] Figure 1 shows the chemical structure of *trans*-elemenes with a skeletal numbering system consistent with the germacrene precursors. Many earlier papers use a numbering system based on the cyclohexane ring, with the side chains being attached at carbons C-1, C-2, and C-4, but the difficulty with earlier literature is the inconsistent side chains numbering system. From a biogenetic point of view, many elemene-type sesquiterpenes are considered to be produced from the corresponding germacrenes or germacrones via Cope rearrangement (Scheme 1).[4] In Scheme 1, germacranyl cations (**A** and **B**) formed from both FPP and NPP could be responsible for the formation of the *trans*-elemenes, (β-, γ-, and δ-elemenes, **1**, **4a** and **5**, respectively),[3,13a–g] α-elemene (**3**),[13g] 8,9-didehydro-γ-elemene or elema-1,3,7(11),8-tetraene (**4b**),[13h] *cis*-β-elemene (**6**),[14] *iso*-β-elemene (**7**),[15] bicycloelemene (**8**),[16] and geijerene (**9**).[17] (Scheme 2).

1.1. Occurrence

Elemanes are widespread in nature,[1,2] in the essential oil or volatile compositions and extracts of the leaves, buds, flowers, fruits, stem or bark, and roots of various plants; in higher plants such as Caraway herb and root,[13d] *Manila Elemi* oil,[18] sweet-flag and juniper oils,[12] fresh costus roots (*Saussurea lappa*),[13a] *Solidago canadensis*,[14b] *Chloranthus spicatus* (Thunb.) Makino,[19a] *Hedycarya angustifolia* A. Cunn.,[19b] *Meum athamanticum*,[19c] *Evodia* species fruits,[19d] *Cyptotaenia japonica* Hassk 'Itomitsuba',[19e] *Laurus nobilis* L.,[19f] *Acorus calamus* L.,[20] Java citronella oil,[13g] *Kadsura japonica*,[21a,b] *Dysoxylum fraseranum* and *Gurjun balsam* oils,[13e,f] *Thujousis dolabrata* Sieb. et Zucc,[21c] *Petasites albus* rhizomes,[22a] *Murraya paniculata* (Linn) jack, syn. M. exotica Linn,[22b] sudachi (*Citrus sudachi* Hort. ex Shirai) and mochiyuzu (*Citrus inflata* Hort. ex Tanaka),[22c] black pepper *(Piper nigra)* oil,[23a] Polyscias fruticosa (L.) Harms,[23b] *Citrus unshiu Marc*,[23c] *Scutellaria lateriflora* L.,[23d] Salvia przewalskii Maxim,[23e] *Aloysia gratissima* (Gillies & Hook.) Tronc. var. *gratissima*,[24a] ve conifers,[24b] *Murraya exotica*,[24c] *Juniperus macropoda*,[24d] Salvia guaranitica,[24e] *Nigella orientalis* L. seeds,[25a] *Phlomis lanceolata*, *Phlomis anisodonta,* and *Phlomis bruguieri* Desf.,[25b] *Pilocarpus pennatifolius* Lemmaire (Rutaceae),[25c] *Cedrelopsis grevei* H. Baillon,[25d] *Curcuma caesia* Roxb.,[25e] *Piper friedrichsthalii* and *P. pseudolindenii,*[25f] Cedrela odorata L.,[26a] *Ocimum canum* Sims (basilic camphor) and *Ocimum urticifolia* Roth,[26b] *Lantana camara*,[26c] and *Eupatorium buniifolium* Hooker et Arnott;[26d] in the essential oils of liverworts such as *Scapania undulata*,[14a] *Lepidozia vitrea*,[27a] *Preissia quadrata*,[27b] and for more liverwort species read the review by Asakawa;[28] in arthropods such as termite (*Reticulitermes*),[29a] *Syntermes* soldiers,[29b] and aphids (*Therioaphis maculala*);[29c] in marine invertebrates such as *Eunicea mimosa*,[30a] *Pacifigorgia pulchra exilis*, *P. media* and *Tubipora musica*,[30b] gorgonian *Eunicea fusca*,[30c] and in



Scheme 1. Proposed biogenetic pathways for *trans*-β-elemene (**1**) and related hydrocarbon compounds from farnesyl diphosphate (FPP) and nerodily diphosphate (NPP) via germacranyl cations. The prefix *trans*- or *cis*- denotes the 1,2-divinyl relationship.



Scheme 2. Structure of *trans*-(−)-β-elemene (**1**), (−)-elemol (**2**), and related hydrocarbon compounds.

microorganisms such as *Streptomyces citreus*,[31a] and *Chondromyces crocatus* bacteria.[31b]

1.2. Identification, extraction, and isolation

The identification of elemanes 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[32] are available, but specialized libraries for volatile compounds (for example, databases such as MassFinder contain a large collection of mono- and sesquiterpenoids,[33] and are sometimes more useful). Generally, gas chromatographic (GC) analyses of extracts or essential oils commonly show the co-existence of germacrane and its thermal artifact (elemane) and the mass spectra of the germacrane precursors and their rearrangement products are practically similar.[34,35] As a result, 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.[35,36] Recently, Chen et al. (2008)[37] have reported a sensitive gas chromatography–mass spectrometry (GC–MS) assay that allowed the precise identification and quantification of (−)-β-elemene (**1**) and β-elemenal (**10**) in human plasma, which has been successfully applied in clinical trials.[37] Previously, elemenes **1**, **3**, **4a**, and **5** have been identified by comparison of infrared spectra with standards.[13f,g,23a] Commonly, one and two-dimensional NMR experiments have been employed in the structure elucidation of elemanes. An example is the complete assignment of the ^{1}H and ^{13}C NMR spectra of (−)-*trans*-β-elemene (**1**) from data generated from two-dimensional NMR experiments.[38] Figure 2 shows the ^{1}H NMR (500 MHz, C_6D_6) of (−)-*cis*-β-elemene (**6**), recently isolated from the liverwort *Scapania undulata*.[14,34] Another example is the ^{1}H and ^{13}C NMR data of furanoelemene (**11**).[39]

Often, higher plants have sesquiterpenes, which are antipodes to the same sesquiterpene hydrocarbons obtained from that of lower plants or microorganisms.[14a,27b,36c,40] For example (+)-*trans*-β-elemene (**1**) was isolated from the gorgonian *Eunicea mammosa*[30a] while its (−)-enantiomer is commonly widespread in the higher plants such as caraway herb and root,[13d] and fresh costus roots (*Saussurea lappa*).[13a] The absolute configuration of (+) and (−)-*trans*-β-elemene (**1**) has been established by means of thermal Cope rearrangement on chiral GC column, which is able to distinguish the enantiomers by König's group and collaborators.[13b,41] Figure 3 shows the separation of (−)-*cis*-β-elemene (**6**), another cis-diastereomer (**6**b), and both enantiomers of (±)-*trans*-β-elemene (**1**) with a 2,6-me-3-pe-γ-cyclodextrin phase at 100 °C (isothermal).[14b,34]

Several methods are used for the extraction of elemanes. These include hydrodistillation with clevenger hydrodistillator apparatus,[26a,38,39,41,42] steam distillation,[20a,21a,b,43] solvent extraction,[14b,44]

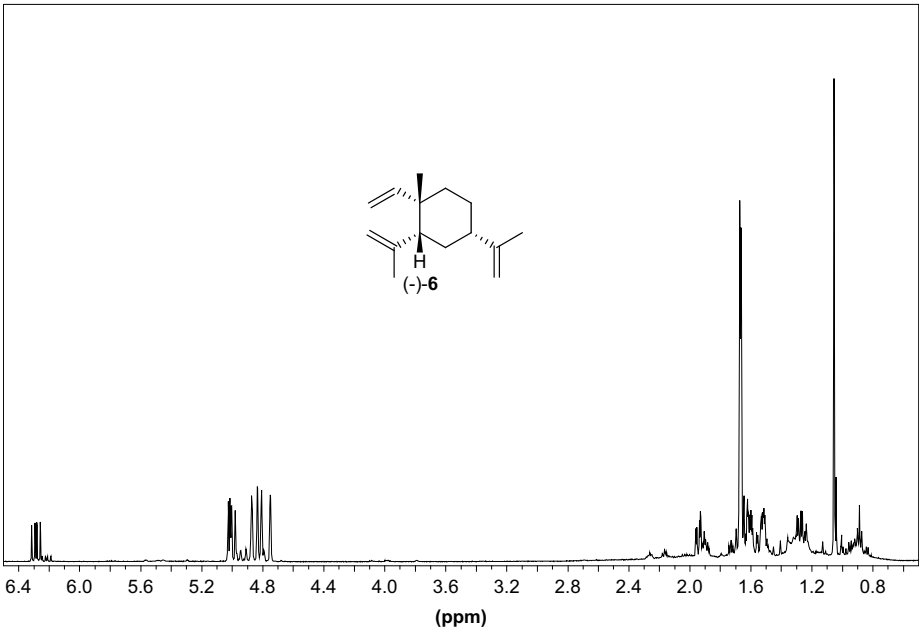


Figure 2. ^{1}H NMR (500 MHz, C_6D_6) of (−)-*cis*-β-elemene (**6**).[14,34]

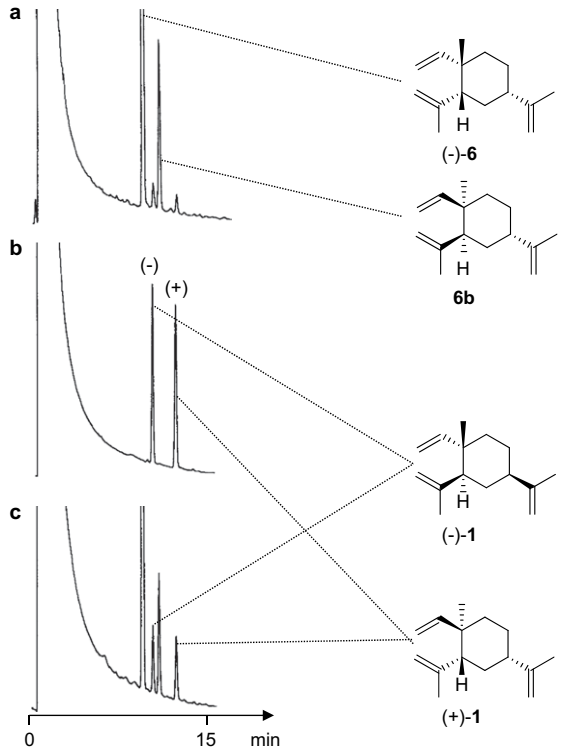


Figure 3. Separation of (a) (−)-*cis*-β-elemene (**6**) and another cis-diastereomer (**6b**), (b) (±)-*trans*-β-elemene (**1**) and co-injection of *cis*- and *trans*-β-elemenes, on 2,6-Me-3-Pe-γ-cyclodextrin at 100 °C isothermal.[14b,34]

cold expression,[22c] super critical carbon dioxide extraction processes,[45] and headspace solid-phase microextraction.[19d,46a,b] In general, many factors have been reported to influence the essential oil or volatile oil composition and production in plants.[46c] These factors include physiological variations such as organ development, pollinator activity cycle, type of plant material, type of secretory structure, seasonal variation, and mechanical or chemical injuries; environmental conditions such as climate, pollution, diseases, and pests; geographic variation (such as genetic factors and evolution), storage, and size of plant material.[46c] Therefore, isolation method used for elemane depends on complexity of the sample and the amount detected. These methods include column chromatography on silica gel, prep-TLC or prep-GC or HPLC or a combination of 2–3 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,[13a,c,14b,47] 5% silver nitrate–silica gel,[30c] silica gel,[20a,43,48] $AgNO_3$-impregnated silica gel with Et_2O and Et_2O–MeOH as eluents,[13a] prep-TLC (silica gel) at room temperature for further purification.[13c,47b] Other methods include prep-GC with SE-30 column,[14b,30a] 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.[14a] For elemenolides that are less volatile HPLC on reverse phases or normal phases may be preferable[49a] or at times a combination of silica gel column chromatography, Sephadex LH-20 and HPLC.[49b,c] For isolation techniques of sequiterpenoids refer to review by Merfort (2002).[50]

1.3. Elemanes from germacranes by Cope rearrangements

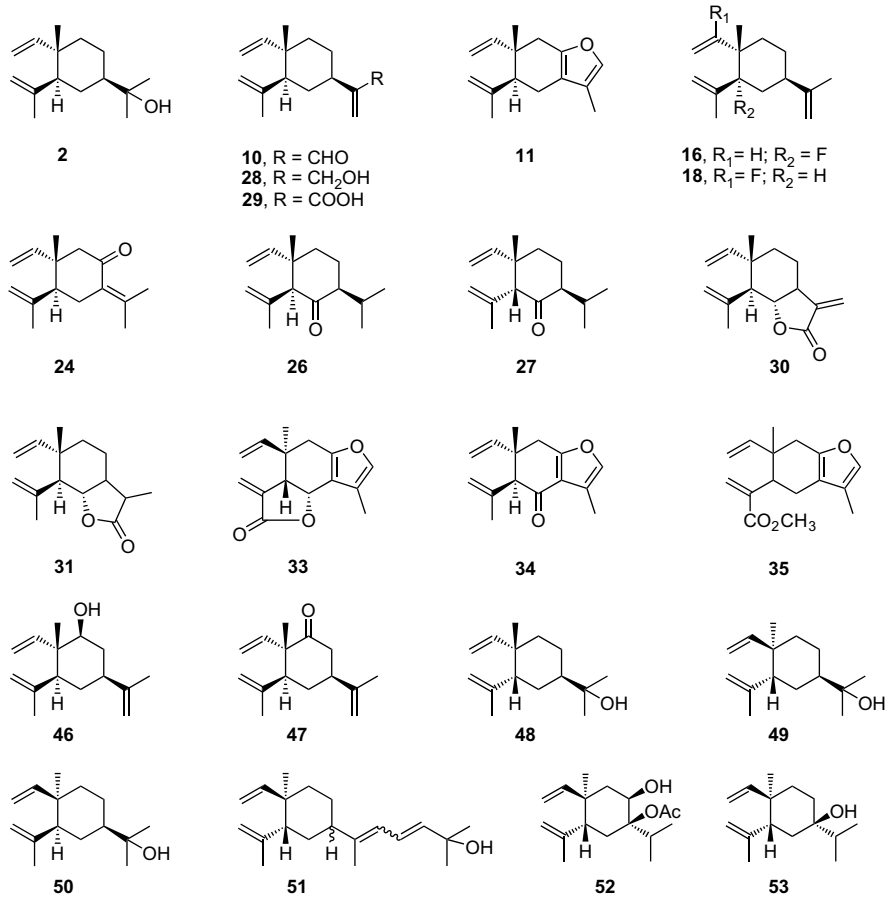
Germacranes undergo a stereospecific [3,3]-sigmatropic rearrangement that proceeds via the most stable chair-like transition state of 1,5-cyclodecadiene to give elemane, a 1,2-divinylcyclohexane system. The configuration of 1,2-divinylcyclohexane formed in turn depends on most stable chair-like transition state conformation of the corresponding 1,5-cyclodecadiene.[13b,51] It is also well known that Cope rearrangement is a reversible process[52] and that equilibrium between 1,5-cyclodecadiene and 1,2-divinylcyclohexane system depends on the nature and configuration of substituents.[53] While *E,E*-cyclodeca-l,5-dienes are known to undergo Cope rearrangement to give *trans*-l,2-divinylcyclohexane,[13c,14b,30a,47] the *Z,E*-cyclodeca-1,5-dienes give *cis*-1,2-divinyl derivative.[14a,53d,54] Commonly, 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.[13a–c,14,15,27b]

Table 1
Elemane compounds derived from their germacrane precursor via Cope rearrangement

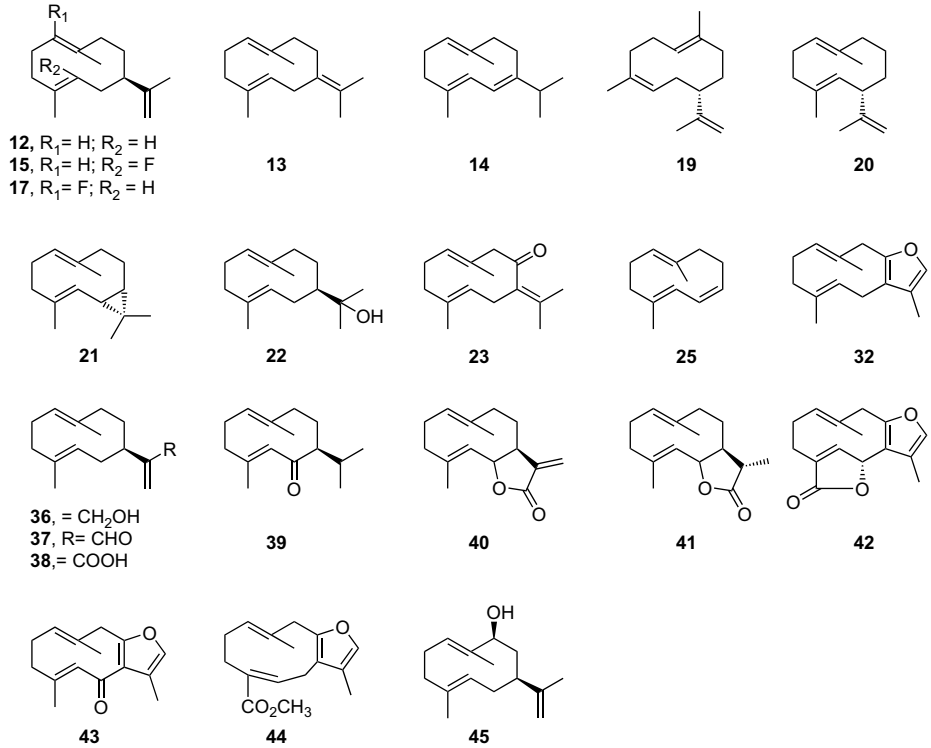
Germacrane/related compound	Elemane	Ref(s)
Germacrene A (**12**)	*trans*-β-Elemene (**1**)	13a,c,14b
Germacrene B (**13**)	γ-Elemene (**4**a)	55
Germacrene C (**14**)	δ-Elemene (**5**)	13f,21b,27b
Helminthogermacrene (**19**)	*cis*-β-Elemene (**6**)	14b
Isogermacrene A (**20**)	*iso*-β-Elemene (**7**)	15
Germacrone (**23**)	*trans*-β-Elemenone (**24**)	57a
Acoragermacrone (**39**)	Shyobunone (**26**) and *epi*-shyobunone (**27**)	56d
Hedycaryol (**22**)	Elemol (**2**)	17,56a
Bicyclogermacrene (**21**)	Bicycloelemene (**8**)	16
Costunolide (**40**)	Dehydrosaussurea lactone (**30**)	56e
Dihydrocostunolide (**41**)	Saussurea lactone (**31**)	57e
Furanodiene (**32**)	Furanoelemene (curzerene) (**11**)	30b,39,56g
Linderalactone (**42**)	Isolinderalactone (**33**)	56f
Furanodienone (**43**)	Curzerenone (**34**)	57d
Sericenine (**44**)	Isosericenine (**35**)	57b
Pregeijerene (**25**)	Geijerene (**9**)	17
1-Fluorogermacrene (**17**)	1-Fluoroelemene (**18**)	47b
5-Fluorogermacrene (**15**)	5-Fluoroelemene (**16**)	47a
Germacra-1(10),4,11(13)-trien-12-ol (**36**)	Elema-1,3,11(13)-trien-12-ol (**28**)	13a
Germacra-1(10),4,11(13)-trien-12-al (**37**)	Elema-1,3,11(13)-trien-12-al (**10**)	13a
Germacra-1(10),4,11(13)-trien-12-oic acid (**38**)	Elema-1,3,11(13)-trien-12-oic acid (**29**)	13a
Agerol (**45**)	β-Elemen-9β-ol (**46**)	56b,c

During isolation and GC analysis, germacrene A (**12**) is known to undergo facile Cope rearrangement to *trans*-β-elemene (**1**),[13a,c,14b] germacrene B (**13**) to γ-elemene (**4**a),[55] and germacrene C (**14**) to δ-elemene (**5**),[13f,21b,27b] 5-fluorogermacrene (**15**) to 5-fluoroelemene (**16**),[47a] 1-fluorogermacrene A (**17**) to 1-fluoroelemene (**18**),[47b] (+)-helminthogermacrene (**19**) to (−)-*cis*-β-elemene (**6**),[14b] (+)-isogermacrene A (**20**) to (−)-*iso*-β-elemene (**7**),[15] (+)-bicyclogermacrene (**21**) to bicycloelemene (**8**),[16] and hedycaryol (**22**) undergoes Cope rearrangement to (−)-elemol (**2**) when heated at 100 °C.[17,56a] Agerol (**45**) is the precursor of naturally occurring β-elemen-9β-ol (**46**) from *Achillea ageratum*, while β-elema-9-one (**47**) was obtained from the naturally occurring β-elemen-9β-ol (**46**).[56b,c] Germacrone (**23**) undergoes smooth thermal rearrangement to *trans*-β-elemenone (**24**)[57a] and pregeijerene (**25**) is a precursor of geijerene (**9**).[17]

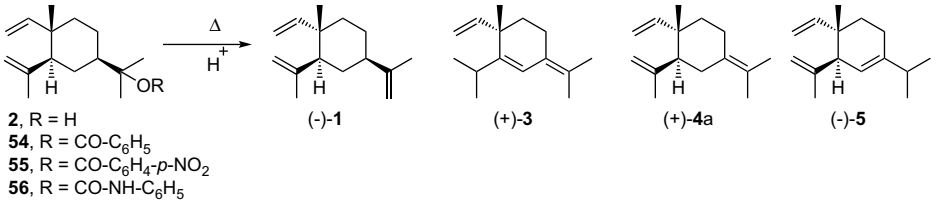
Structures of selected elemanes that occur in nature or through thermal rearrangement are also presented. These include, compounds **48**, **49**, and **50,** the diastereomeric elemols obtained from thermal reactions of synthesized hedycaryol (**22**) isomers conducted at higher temperatures (ca. 500 °C).[54b] See Table 1 for more corresponding elemane-type compound resulting from Cope rearrangements of germacranes, Schemes 3 and 4 show the structure of germacranes and elemanes mentioned in Table 1.



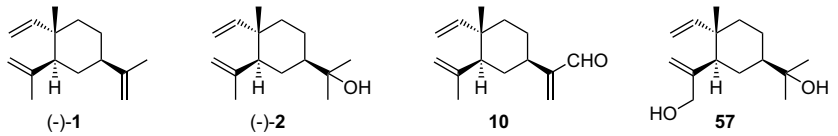
Scheme 3. Structures of elemanes in Table 1 and other related compounds.



Scheme 4. Structures of germacranes compounds in Table 1.



Scheme 5. Thermal and acid induced transformation products of elemane derivatives.



Scheme 6. Biotransformation products of (−)-*trans*-β-elemene (**1**) and (−)-elemol (**2**).

While fuscol (**51**) is an elemene-type diterpene alcohol isolated from the gorgonian *E. fusca*,[30c] 7-acetoxy-elema-1,3-dien-8-ol (**52**) and elema-1,3-dien-7-ol (**53**) are examples of antipodal sesquiterpenoid elemanes isolated from the liverwort *L. vitrea*.[27a]

The corresponding Cope rearrangement product of 17 germacrane sesquiterpenoids by density functional theory (B3LYP/6-31G*) and post-Hartree–Fock (MP2/6-31G**) have been reported by Setzer (2008).[3]

1.4. Thermal and acid induced transformations of elemane derivatives

The pyrolysis (195–200 °C) and/or acid induced transformation of elemol (**2**),[12,58] elemyl benzoate (**54**),[12,58] elemyl-*p*-nitrobenzoate (**55**),[58] and elemyl-phenyl-urethane (**56**)[13e,f] results in the formation of mixture of elemenes such as β-elemene or 1,3,11-elematriene (**1**), α-elemene or 1,5,7(11)-elematriene (**3**), γ-elemene or 1,3,7(11)-elematriene (**4**a), δ-elemene or 1,3,6-elematriene (**5**), and elemol (**2**) with β-elemene (**1**) as the major compound (Scheme 5). Several kinds of acidic reagents and solvents that have been used to induce transformation include formic acid[12] or perchloric/acetic acid[13g,i] or benzoic acid and *p*-nitrobenzoic acid.[58] Recently, the minor unidentified compounds from perchloric/acetic acid dehydration of **2** had been characterized as elemoxide and (+)-β-cyperone.[13i] The rearrangement products obtain and the percentage (%) yield of products from acid induce transformations depend on acid reagents or solvents used.[58] Depending on the reaction conditions secondary rearrangement products could also be formed, which cannot be related to the starting material.

1.5. Biotransformation and distribution of *trans*-(−)-β-elemene (1)

(−)-β-Elemene (**1**) has been reported to metabolize extensively before a rapid excretion in male Sprague-Dawley rats.[59,60] Wang et al.[59] have also reported that (−)-β-elemene (**1**) was eliminated primarily as metabolite and minimally as unchanged drug in cumulative fecal, biliary, and urinary excretion in 0.61%, 0.06%, and 0.003%, respectively, after 32 h of (75 mg/kg) dose administration.[59] They also suggested that the effectiveness of (−)-β-elemene (**1**) in crossing the blood–brain barrier holds promise for the treatment of malignant brain tumors.[59] (−)-β-Elemene (**1**) undergoes biotransformation in rat bile to an aldehyde derivative, elemenal (**10**)[59,61]and both compounds **1** and **10** can now be precisely identified and quantified in human plasma by GC–MS[37] (Scheme 6). Consistently, Wang and Su[62] have reported that (−)-β-elemene (**1**) was eliminated at a rapid rate and distributed widely in the body of Spraque-Dawley rats. (−)-β-Elemene (**1**) excreted via urine, feces, and bile were very few.[62] The excretion of (−)-β-elemene (**1**) from the respiratory tracts in male Spraque-Dawley rats also demonstrated that unchanged (−)-β-elemene (**1**) excretes from rat respiratory tracts, although this may not be the main elimination pathway in rats.[63]

Wang et al.[64] compared body distribution of intravenously administered solid–lipid nanoparticles (SLN) containing β-elemene (**1**) in rats with that of the commercial emulsion. They discovered that the in vitro release of β-elemene (**1**) from the solid–lipid nanoparticles (SLN) was slow and stable without obvious burst release and was found to follow the Higuich equation. After intravenous administration, the β-elemene (**1**) levels after 5 min of injection of SLN formulation were 1.5, 2.9, and 1.4 times higher than those of β-elemene emulsion in liver, spleen, and kidney, respectively, while the concentrations of β-elemene (**1**) were decreased 30% in heart and lung. They concluded that the solid–lipid nanoparticles (SLN) containing β-elemene (**1**) might be an attractive candidate for the treatment of liver cancer.[64]

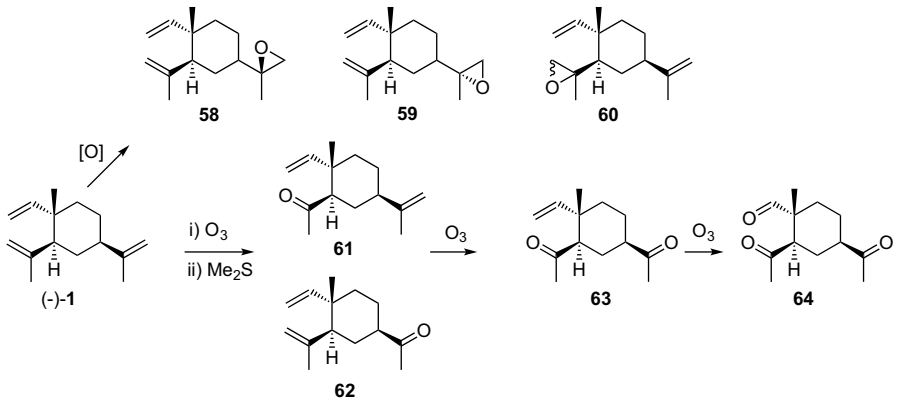
Compared to (−)-β-elemene (**1**), which undergoes oxidation to the aldehyde derivative at C-13 during biotransformation, (−)-elemol (**2**) undergoes hydroxylation at the allylic C-15 position to give 15-hydroxyelemol (**57**) in rabbit[65,66] (Scheme 6).

1.6. Epoxidation and ozonolysis of (−)-*trans*-β-elemene (1)

Treatment of (−)-*trans*-β-elemene (**1**) with peracetic acid occurs specifically on the isopropenyl group at C(7) resulting in a mixture of two epoxides **58** and **59**.[67] Subsequent oxidation of mixture of **58** and **59** with periodic acid gave their corresponding epimeric ketones and an additional ketone resulting from epoxides **60** (Scheme 7).[67] The reaction of compound **1** with ozone followed by decomposition of the ozonides with dimethyl sulfide gave two monoketones (**61** and **62**) in the first instance, and continued ozonolysis gave the diketone **63** as the major product. Further ozonolysis gave a complex end products being mostly the diketo-aldehyde **64** (Scheme 7). The epoxidation of (−)-β-elemene (**1**) is over 90% site specific, while its ozonolysis reaction is less specific because the ozone attacks the isopropenyl group at C(5) and C(7) and subsequently on the vinyl group at C(1).[67]

1.7. Computational chemistry of *trans*-β-elemene and derivatives

In enzyme–inhibitor interaction where the 3D structural data of the target enzyme are known, there is reliable information on which to base a study of these interactions. Therefore, in computer-



Scheme 7. Epoxidation and ozonolysis of (−)-*trans*-β-elemene (**1**).[67]

aided molecular design, the molecular modeling approach based on molecular interactions between ligands and target protein plays an important role.[68]

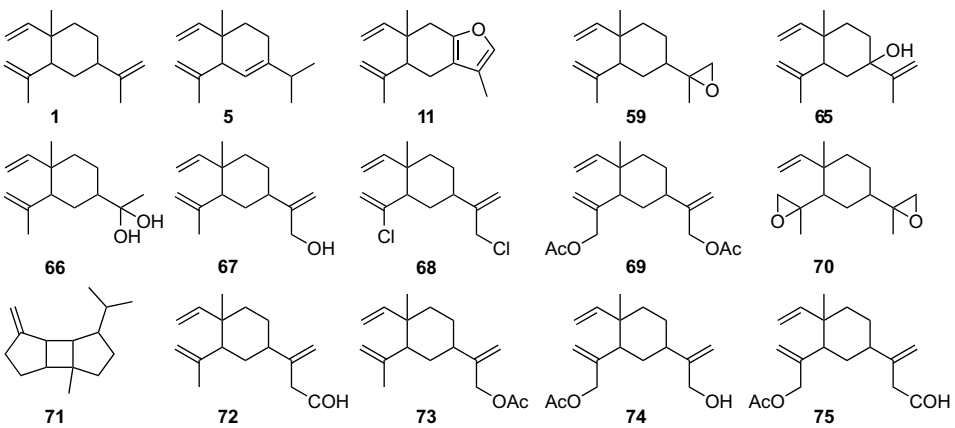
Pei et al. (2001)[69] have developed a Pseudo Atomic Receptor Model (PARM) software package to accommodate situations in which the 3D structure of the target receptor is not available. Considering the potential of elemenes as anticancer drugs, a set of 15 elemenes whose structures are shown in Scheme 8 have been analyzed by PARM.[69] These elemenes include synthesized compounds **1**, **5**, **11**, **59**, and **65**–**71** as well as four hypothetical compounds **72**–**75** selected for synthesis. Their results show that PARM can build models with favorable cross-validation statistics and give a helpful insight into structure–activity relationships (SAR) for drug design.[69]

Miao et al. (1994)[70] have investigated the internal motions of β-elemene (**1**) by using variable temperature ^{13}C NMR relaxation experiments. Their results show that the hexacyclic ring in **1** is almost rigid at an experimental temperature ranging from 298 K to 318 K, and the self-diffusion activation energy of overall motion of the molecule is 14 kJ/mol. In addition, all the internal rotation activation energies for the side chain groups (a vinyl and two isopropenyls) have been calculated with the three methyl groups on β-elemene (**1**) structure having different values possibly due to different space circumstances.[70] The ^{13}C NMR chemical shifts of β-elemene (**1**) have also been studied by quantum chemistry calculation.[71] Hu et al. (2001) have performed ab initio calculation of vibration spectrum of β-elemene (**1**) at RHF/6-31G* level. They have successfully assigned the normal modes for the fundamental frequency of **1** by its comparison with the experimental results. In addition, they have discussed the characteristic vibrations, and scaled theoretical frequencies empirically.[72]

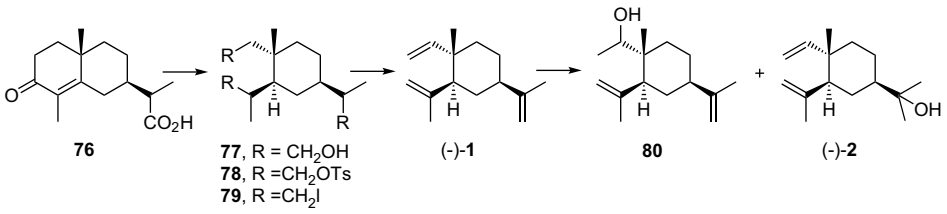
2. Syntheses of *trans*-β-elemene (1), elemol (2), and related hydrocarbon compounds

A number of elemane related compounds have been synthesized.[73,74,79] The synthesis of β-elemene (**1**)[76] and elemol (**2**)[75] has been reported.[76] Patil and Rao[76] carried out an indirect synthesis of elemol (**2**) from readily available (−)-α-santonin. The acid (**76**) prepared from (−)-α-santonin was converted to elemane-2,3,12-triol (**77**), followed by the tosylation of triol (**77**) to tritosylate (**78**). The treatment of **78** with sodium iodide in acetone, furnished the iodo-compound (**79**) on heating. Compound **79** undergoes elimination upon treatment with potassium *tert*-butoxide in dimethylsulfoxide to furnish β-elemene (**1**). Treatment of **1** with molar proportion of perbenzoic acid solution in chloroform at 0–10 °C for 20 h followed by lithium aluminum hydride reduction of the epoxidation product furnished a mixture of starting material and the alcohols (**80**) and elemol (**2**) (Scheme 9).[76] The structure and absolute configuration of elemol (**2**) have been established.[77]

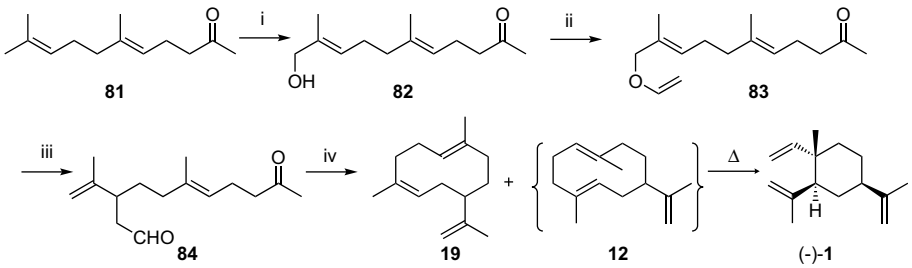
In 1985, McMurry and Kočovský[78] synthesized β-elemene (**1**) by a short route starting with the palladium-catalyzed allylic oxidation of commercially available geranylacetone (**81**) to provide keto alcohol (**82**). Compound **82** was converted to the vinyl ether (**83**), which was subjected to thermolysis at 200 °C to afford the key dicarbonyl cyclization substrate (**84**). In turn 3-isopropenyl-6-methyl-10-oxo-6*E*-undecenal (**84**) undergoes cyclization upon treatment with $TiCl_3$/Zn–Cu to yield a mixture of compounds



Scheme 8. Elemene derivatives analyzed with PARM.[69]



Scheme 9. Synthesis of β-elemene (**1**) and elemol (**2**).[76]



Scheme 10. Reagents and conditions for the synthesis of β-elemene (**1**) and helminthogermacrene (**19**): (i) benzoquinone, $Pd(CF_3COO)_2$, *o*-methoxyacetophenone, acetic acid, then KOH, H_2O, 55%; (ii) ethyl vinyl ether, $Hg(CF_3COO)_3$, rt, 75%; (iii) 200 °C, 6 h, 80%; (iv) $TiC1_3$, Zn–Cu, dimethoxyethane, reflux, 34 h addition, 60%.[78]

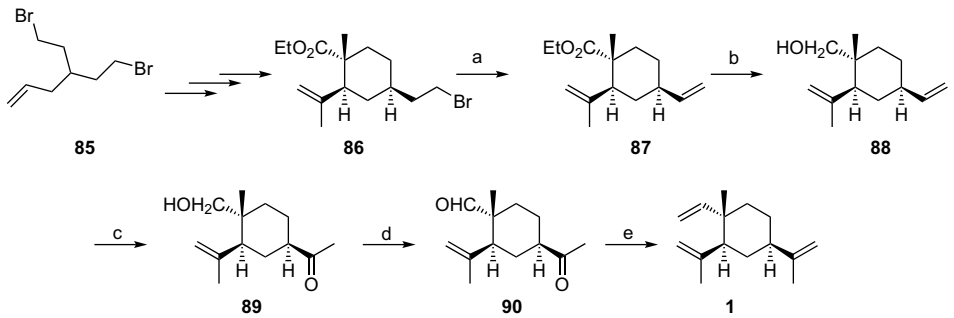
helminthogermacrene (**19**) and germacrene A (**12**). Compound **12** undergoes Cope rearrangement because of its thermal instablility to **1** to obtain a mixture of **19** and **1** (45:55) in 60% yield (Scheme 10).[78]

Recently, A total synthesis of the sesquiterpene (±)-β-elemene (**1**) has been achieved starting from a simple acyclic precursor 6-bromo-4-(2-bromoethyl)hex-1-ene (**85**).[80] The starting dibromide **85** was prepared from the known 2-allylpropane-1,3-diol in five steps. Ethyl (1*R**,2*S**,4*R**)-4-(2-bromoethyl)-2-isopropenyl-1-methyl-cyclohexane-1-carboxylate (**86**) obtained in five steps from dibromide **85** was treated with potassium *tert*-butoxide (THF, 0 °C) to give a olefin **87**, which was then subjected to DIBALH reduction to yield alcohol **88**. Treatment of the terminal alkenes **88** with $PdCl_2$ and $CuCl_2$ under oxygen atmosphere give compound **89**. Subsequent PCC oxidation of **89** led to the formation of a keto-aldehyde **90**. Finally, double Wittig methylenation of keto-aldehyde **90** provided the desired racemic-β-elemene (**1**) in 89% yield (Scheme 11).[80]

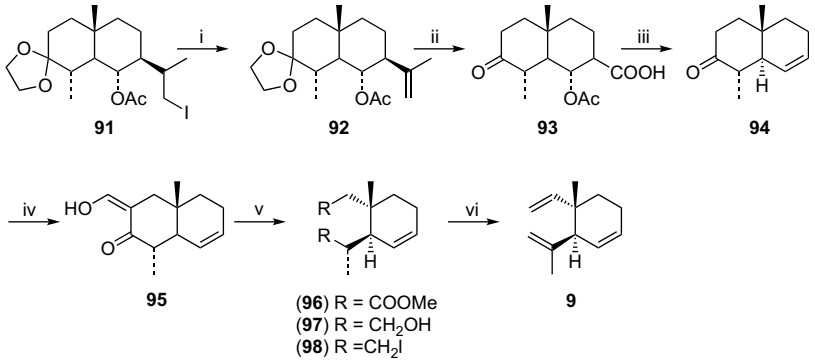
An enantioselective synthesis of sesquiterpene hydrocarbon (+)-α-elemene (**3**) from *R*-(+)-limonene has also been accomplished.[81] In addition, Kato et al. (1971)[82] have synthesized geijerene (**9**)[17] a nor-elemene-type sesquiterpene without an isopropenyl group, from the readily available (−)-santonin. Their approach involved a two-step dehydrohalogenation of **91** with AgF–pyridine via an olefin to compound **92**. Further ozonization of **92** at −78 °C followed by haloform reaction with NaOBr in dioxane gave a mixture of two acids, which were heated in aq AcOH to afford keto-acid (**93**). Compound **93** was refluxed with Br_2–HgO in dichloroethane for 1 h, and then treated with zinc powder in AcOH to give keto-olefin (**94**) in 40% yield. When **94** was treated with HCOOEt–NaH in benzene under nitrogen, **94** afforded a condensation product (**95**), which was oxidized with 30% H_2O_2–aq KOH, and then esterified with diazomethane to give diester (**96**), which was further converted in three steps by reduction of **96** with $LiAlH_4$ to the corresponding diol **97** that was treated with mesyl chloride–pyridine and then heated with a large excess of sodium iodide in acetone to afford an oily di-iodo-compound **98**. The last step involving dehydrohalogenation of **98** was effected with 1,5-diazobicyclo[5,4,0]undec-5-ene to give a mixture of three compounds, which were separated by Prep-GC to afford geijerene (**9**), in 20% yield (Scheme 12).[82]

2.1. Syntheses of β-elemene (1) derivatives

(−)-*trans*-β-Elemene (**1**) or (1*S*,2*S*,4*R*)-(−)-(1-methyl-1-vinyl-2,4-diisopropenyl-cyclohexane) has been structurally modified with various functional groups and conjugated with various compounds to improve the anti-proliferative activities and in some cases to increase the water solubility. These include the syntheses of a series of chlorinated-, hydroxylated-, and acetylated-β-elemene derivatives,[83] synthesis of aromatic heterocyclic derivatives of **1**,[84] (−)-β-elemene-monosubstituted amine derivatives,[85]



Scheme 11. Reagents and conditions for the synthesis of (±)-β-elemene (**1**): (a) *t*-BuOK, THF, 0 °C, 8 h, 89%; (b) DIBALH, toluene, −78 °C, 2 h, 92%; (c) CuCl, $PdCl_2$, O_2, DMF–H_2O, rt, 8 h, 93%; (d) (i) PCC, NaOAc, CH_2Cl_2, 0 °C, 2 h, 92%; (ii) separation; (e) $Ph_3P{=}CH_2$, THF, −78 °C to rt, 1 h, 89%.[80]



Scheme 12. Reagents and conditions for the synthesis of geijerene (**9**): (i) AgF–Py, 72%; (ii) O_3, −78 °C; NaOBr, (iii) Br_2–HgO, 1 h, Zn/AcOH; (iv) HCOOEt–NaH, (v) 30% H_2O_2–aq KOH, CH_2N_2; $LiAlH_4$; mesyl chloride–Py; NaI; (vi) 1,5-diazobicyclo[5,4,0]undec-5-ene, 20% yield.[82]

syntheses of β-elemene-13-yl esters,[86] β-elemene-glycoside derivatives,[87] synthesis and radiosynthesis of β-elemene–tricarbonyl rhenium complex,[88] synthesis and radiolabelling of β-elemene–TEG–Re $(CO)_3$ complex,[89] and β-elemene-monosubstituted polyethylene glycol (PEG) derivatives.[90] Other potential antitumor elemane derivatives 6α-acetoxy-5α*H*,4,6,11β*H*-elema-2,3-diene-12-ol (**99**) and 12-acetoxy-5α*H*,4,6,11β*H*-elema-2,3-diene-6α-ol (**100**) have also been synthesized from α-santonin by Choi et al.[91] The lactone ring of compound **101** obtained from α-santonin was opened by $LiAlH_4$ to give diol **102**, which was selectively protected by *tert*-butyldiphenylsilyl chloride (TBDPSCl). After acetylation of the secondary alcohol with Ac_2O–pyridine to **103**, the acetylated product **103** was ozonolyzed and reduced with $NaBH_4$ to give elemane derivative **104**. Compound **104** was converted in three steps to diolefin **108** via selenides, subsequent deprotection, and treatment with tetra-butylammonium fluoride to two compounds **99** and **100** (Scheme 13).[91]

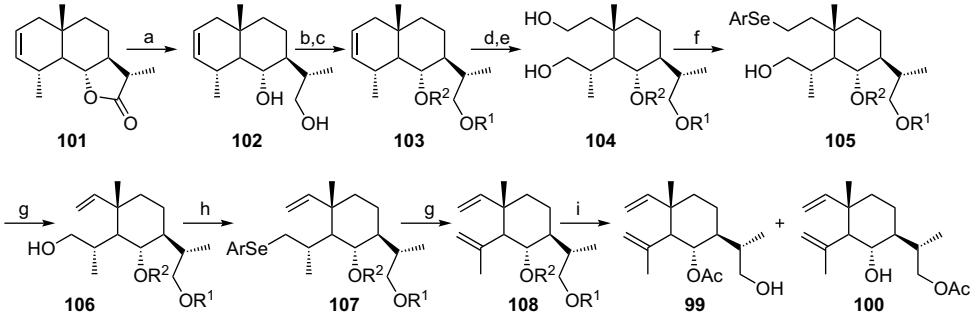
Fourteen *trans*-(−)-β-elemene (**1**) derivatives (**110**–**123**) containing a piperazine, a morpholine, a tetrahydropyrrole, a thiophenylethylamine, or a cyclohexamine group have been synthesized by Xu et al.[92] They have synthesized 13,15-dichloro-β-elemene (**109**), starting from *trans*-(−)-β-elemene (**1**), according to the procedures described by Jia et al. (1991).[93] The synthesized 13,15-dichloro-β-elemene (**109**) was subsequently treated with amine and triethylamine in dry *N*,*N*-dimethylformamide, and refluxed for 8–20 h to afford compounds **110**–**123** after purification on a silica gel column with petroleum ether–acetone.[92] All these 14 derivatives had been reported to have an increased anti-proliferative activity in human cervix epitheloid carcinoma HeLa, gastric carcinoma SGC-7901, and leukemia K562 cells compared to that of elemene. Of all these 14 derivatives the most potent derivatives include 13,15-bis(*cis*-3,5-dimethyl-1-piperazinyl)-β-elemene (**118**), 13,15-bis[2-(2-thiophenyl)ethylamino]-β-elemene (**122**),[92] and 13,15-bis(cyclohexamino)-β-elemene (**123**). Compounds **118**, **122**, and **123** have been reported to inhibit K562 cell growth with an IG_{50} below 5 μM that was correlated with *m*TOR activity inhibition (Scheme 14).[92]

Synthesized β-elemene–amino acid conjugates such as *N*-(β-elemene-13-yl)tryptophan methylester (ETME, **124**)[94] have been reported to induce apoptosis in human leukemia HL-60 and NB4 cells at concentrations less than 40 μM. Whereas the separate combination of (−)-*trans*-β-elemene (**1**) with tryptophan and tryptophan methylester has been reported to have only minimal cell growth inhibitory effects (Scheme 16).[94]

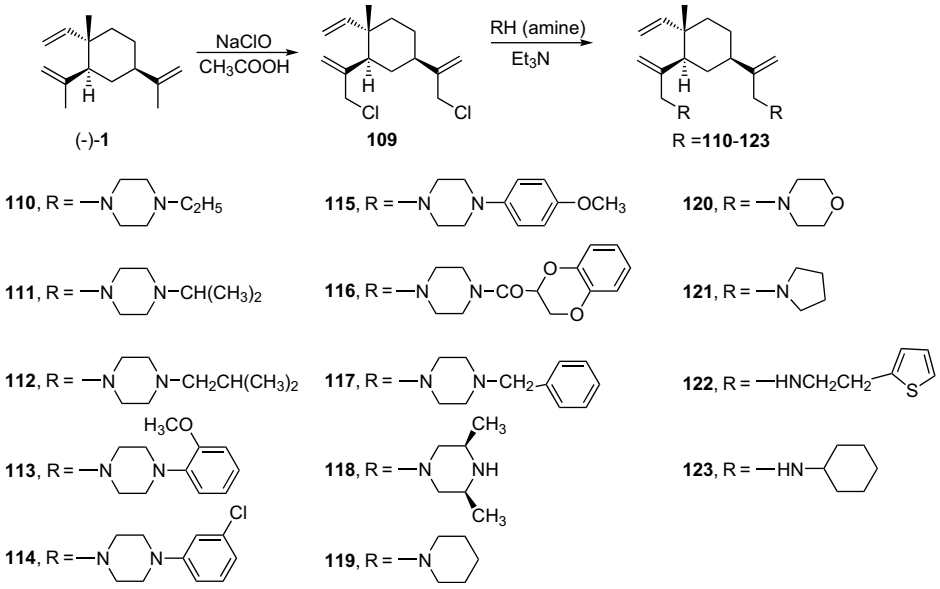
Sun et al. (2008)[95] have synthesized (−)-*trans*-β-elemene (**1**) monosubstituted ethers (**126**–**133**), amines (**134**–**141**), and rhenium coordinated complexes (**142**–**144**) (Schemes 15 and 16). They have reported that the in vitro anti-proliferative activity of β-elemene-monosubstituted amine and $Re(CO)_3$-β-elemene derivatives in human cervix epitheloid carcinoma HeLa cells was improved significantly compared with both ether derivatives and parent (−)-*trans*-β-elemene (**1**).[95] The synthetic routes in Scheme 15 involves the chlorination of (−)-*trans*-β-elemene (**1**) with NaClO to give 13-chloro-β-elemene (**125**), which was reacted further with alcohols or amine to yield the desired β-elemene-monosubstituted ether or amine derivatives **126**–**141**.[95]

3. Antitumor activities of (−)-*trans*-β-elemene (1) or 1,3,11-elematriene

(−)-*trans*-β-Elemene (**1**) or (1*S*,2*S*,4*R*)-(−)-(1-methyl-1-vinyl-2,4-diisopropenyl-cyclohexane) isolated from the Chinese medicinal herb *Curcuma Wenyujin* Y.H[45] and *Rhizoma Zedoariae*[96] has been reported to exhibit antitumor activity. Elemene or elemene emulsion is a mixture of β-, δ- and γ-elemene (**1**, **4a**, and **5**, respectively) with *trans*-β-elemene (**1**) as the main component.[97] (−)-*trans*-β-Elemene (**1**) has been a focus of attention in cancer research and many Chinese academic publications have reported the anticancer



Scheme 13. Reagents and conditions for the synthesis of elemane derivatives **99** and **100**: (a) $LiAlH_4$, ether; (b) *tert*-butyldiphenylsilyl chloride (TBDPSCl), imidazole, DMF; (c) Ac_2O, Py; (d) O_3, CH_2Cl_2, MeOH; (e) $NaBH_4$, MeOH; (f) *o*-nitrophenylselenocyanate (ArSeCN), tri-*n*-butylphosphine (Bu_3P), THF–Py; (g) 50% H_2O_2, THF; (h) ArSeCN, Bu_3P, THF; (i) tetra-butylammonium fluoride (TBAF),THF; (R^1=TBDPS, R^2=Ac, Ar=*o*-nitrophenyl).[91]



Scheme 14. The synthetic route and substitutes of *trans*-(−)-β-elemene (**1**) derivatives.[92]

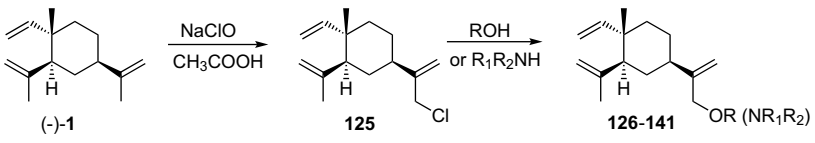
activities of (−)-*trans*-β-elemene (**1**) against cancer of the brain, liver, breast, lung, and other tissues as well as of leukemia in both in vitro and in vivo experiments.[5]

Reports indicate that elemenes can efficiently inhibit the growth of HL-60 cells and Hela cells in vitro, and the tumors of W-256 and Lewis in vivo;[98] suppresses telomerase activity through inhibiting expression of human telomerase reverse transcriptase (hTERT) promoter of gastric cancer cell;[99] inhibits human retinoblastoma HXO-RB44 cells by down-regulating the expression of survivin and suppressing telomerase activity in a concentration dependent manner;[100] inhibits human gastric cancer SGC-7901 cells, and the suppression of telomerase activity and induction of apoptosis would be a very important mechanism in treatment of gastric cancer;[101] inhibits the subcutaneous plantation of human laryngeal carcinoma in nude mice and its mechanism may be associated with inhibited expression of vascular endothelial growth factor-C (VEGF-C) and vascular endothelial growth factor receptor-3 (VEGFR-3);[102] inhibits the proliferation and migration of hepatic stellate cells (HSC) induced by Angiotensin II (ANG II);[103] inhibits tumor angiogenesis and tumor growth in Lewis lung carcinoma mouse through reducing the levels of vascular endothelial growth factor (VEGF) and inhibiting the expression of VEGF receptor;[104] and inhibits the growth of HEp-2 cells in vitro and in vivo.[51]

Wu et al. (1999)[105] indicated that (−)-*trans*-β-elemene (**1**) increases tumor cell immunogenicity partly by elevating the expression of heat shock protein 70 (HSP 70) on cancer cell surfaces, resulting in the induction and enforcement of host immunology reaction to tumor cells.[105] In addition, **1** may also change the immunogenicity of tumor cells in the level of gene, and may induce different immunogenic substances from tumor cells treated by heat shock.[106] Elemene also could reduce the expression of the multi-drug resistance gene (mdr1) and it is effective in killing tumors and also more effective when combined with a chemotherapeutic agent.[107] In the treatment of patients with malignant brain tumors, continuous infused *trans*-β-elemene (**1**) chemotherapy has been administered at an average dosage of 600 mg/day/human.[108]

Recent studies showed that *trans*-β-elemene (**1**) was found to trigger apoptosis in glioma SHG-44 cells and leukemia K562 cells.[5h,97,109] Li et al.[5b] suggest that *trans*-β-elemene (**1**) sensitizes chemoresistant ovarian carcinoma cells to cisplatin-induced growth suppression partly through modulating the cell cycle G2 checkpoint and inducing cell cycle G2-M arrest, which lead to blockade of cell cycle progression.[5b] Wang et al.[5a] indicate that the effect of *trans*-β-elemene (**1**) on lung cancer cell death may be through a mitochondrial release of the cytochrome c-mediated apoptotic pathway.[5a] Recently, Yao et al. (2008)[110] indicate that activation of p38 MAPK is critical for the anti-proliferation effect of *trans*-(−)-β-elemene (**1**) and that p38 MAPK might be a putative pharmacological target for glioblastoma therapy.[110]

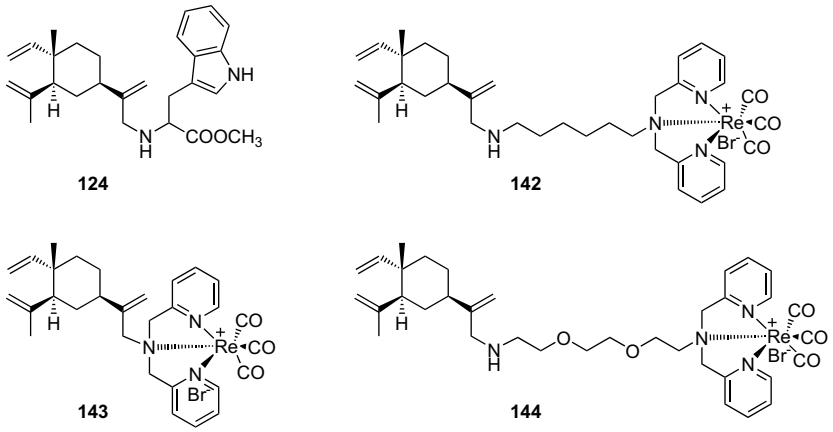
δ-Elemene (**5**) has also been reported to exhibit a markedly anti-proliferative effect on several tumor cell lines in a dose and time-dependent manner in vitro.[111,112] In addition, elemene was also



126, R = Me
127, R = Et
128, R = Bu
129, R = *t*-Bu
130, R = $(CH_2)_{10}CH_3$
131, R = Cyclohexyl
132, R = $PhCH_2$
133, R = $CH_2CH_2OCH_3$

134, R_1R_2 = BuH
135, R_1R_2 = *t*-BuH
136, R_1R_2 = H Cyclohexyl
137, R_1R_2 = H Cyclopentyl
138, R_1R_2 = H Cyclooctyl
139, R_1R_2 = Imidazole
140, R_1R_2 = Et
141, R_1R_2 = *i*-PrH

Scheme 15. The synthetic route to β-elemene-monosubstituted derivatives.[95]



Scheme 16. The synthesized monosubstituted β-elemene–rhenium complex derivatives[95] and *N*-(β-elemene-13-yl)tryptophan methylester (ETME, **124**).[94]

reported to be effective and safe in the treatment for patients with chylothorax.[113] More importantly, few side effects of elemene injection have been reported in clinical trials.[114] Possible side effects of (−)-**1** from intravenous injection include local pain, allergic and gastro-intestinal reactions, and slight fever.[5e,f] Peng et al. (2006)[115] reported that the methodological quality of randomized controlled trials (RCTs) of elemene injection against malignant tumors was low and suggested that the effect of elemene injection being used in clinical settings needs to be confirmed by further RCTs.[115]

3.1. Mechanism of anti-cancer activities of (−)-*trans*-β-elemene (1)

As mentioned in Section 3, there are several extant reports on the inhibitory effects and mechanism by which (−)-*trans*-β-elemene (**1**) inhibits tumor cells proliferation in vitro and in vivo, however, the mechanism still remains unclear. Reports indicate that it involves direct cytotoxic activities[5a] such as the induction of cell cycle arrest,[5b] the inhibition of oxygen free radical formation through the function of anti-lipid oxidization,[116] and several reports on apoptosis cell death,[117–119] and suppression of telomerase activity in a concentration-dependent manner.[101,120] In addition, the indirect induction and enforcement of host immunology reaction may also contribute to the antitumor activity of (−)-*trans*-β-elemene (**1**).[121a,b] Elemenes have also been reported to also significantly inhibit growth of C6 glioblastoma cells in vivo and in vitro through down-regulation of phosphorylated extracellular signal-regulated kinase (ERK).[121c]

3.2. Synergistic activity of (−)-*trans*-β-elemene (1)

Several combination therapies using one or more of the following anti-cancer agents and *trans*-β-elemene (**1**) have been reported. These include β-elemene-cisplatin intrapleural injection in treatment of malignant pleurisy,[122] interventional hepatic artery chemotherapeutic thrombosis treatment of late stage hepatoma by EFMA (elemene, 5-Fu, mitomycin, and adriamycin) and FMA regimens,[123] inhibitory effects of arsenic trioxide, ginseng saponin, and (−)-*trans*-β-elemene (**1**) on telomere-telomerase system in K562 cell line,[124] and the combination of tetramethylpyrazine (TMP) and (−)-*trans*-β-elemene (**1**) have been used to reverse the MDR (multidrug resistance) of K562/ADM cells.[125] Other inhibitory effects resulting in β-elemene (**1**) synergistic activities include the inhibitory effects of interleukin-23 (IL-23) gene-transfected dendritic cells (DCs) combined with (−)-*trans*-β-elemene (**1**) on the growth of mouse pancreatic cancer cells,[126] inhibitory effects of (−)-*trans*-β-elemene (**1**) combined with interleukin-23 gene-modified dendritic cells on murine pancreatic carcinoma,[127] inhibitory effects of antisense oligodeoxynucleotides and (−)-*trans*-β-elemene (**1**) on proliferation of breast cancer cell lines,[128] inhibitory effects of ginseng saponin, arsenic trioxide, (−)-*trans*-β-elemene (**1**) combined with cyclophosphamide (CTX) on telomere-telomerase system in K562 cell line,[129] effective immune and chemotherapeutic function of dendritic cell vaccines combined with (−)-*trans*-β-elemene (**1**) on murine pancreatic carcinoma,[130] suppression effect of combination treatments of (−)-*trans*-β-elemene (**1**) with taxanes (such as paclitaxel and docetaxel) against human lung carcinoma by enhancement of the apoptotic induction and inhibitory effect of the expression of the drug resistance genes induced by only taxanes,[5l] inhibitory effects of elemene combined with tamoxifen on breast cancer MCF-7 cell line,[131] inhibitory effect of elemene–piperazine on immune function in mice with tumor,[132] and *N*-(β-elemene-13-yl)tryptophan methylester induces apoptosis in human leukemia cells and synergism with arsenic trioxide through a hydrogen peroxide dependent pathway.[94]

4. Conclusions

The elemanes are an important group of sesquiterpenes widely occurring in nature[1,2] and are considered from a biogenetic point of view to be produced from germacranes via Cope rearrangements.[3,4] Commonly, (−)-*trans*-β-elemene (**1**) occurs in higher plants[13–26] and also arises from the Cope rearrangement of (+)-germacrene A (**12**) obtained from a genetically engineered yeast;[13c] it has been explored and synthesized in various derivatives.[10,84–92,94,95] Recent reports have shown that (−)-*trans*-β-elemene[5,94–132] possesses activity against a broad spectrum of cancers including, brain, breast, liver, lungs, prostate, and drug-resistance tumors. In addition (−)-*trans*-β-elemene (**1**) or elemene injection has been reported to show few side effects[114] and known to induced apoptosis.[117–132] Considering the fact that the metabolism or biotransformation of drugs is mainly caused by enzymes, which are chiral macromolecules and discriminate between substrate molecules of different stereochemistry, the use of antipodal elemene compounds may result in metabolites of different activity and in different pharmacokinetics, resorption, and excretion. It has been suggested that (+)- and (−)-enantiomers or racemic drugs should be looked at as two different compounds.[133] Therefore, (+)-*trans*-β-elemene, which is in turn present in lower plants or microorganisms and other structural related elemene isomers such as geijerene (**9**),[17] *cis*-(−)-β-elemene (**6**),[14] and (−)-*iso*-β-elemene (**7**)[15] could lead to a new set of unprecedented plant-derived metabolites of anticancer activity or compounds of medicinal values. In addition, furanodiene

(**32**), a natural product isolated from *C. wenyujin*, has been reported to produce cytotoxic effects and induced apoptosis,[134] and to possess anti-inflammatory, hepatoprotective, and antitumor activities.[135] Finally, the biological activity of other naturally occurring and synthesized elemanes and germacranes needs to be further explored, more so that the mechanism of action of (−)-*trans*-β-elemene (**1**) against cancer cells remains unclear.

Acknowledgements

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References and notes

1. Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman and Hall: London, 1991; Vol. 1, pp 205–213.
2. (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; Fraga, B. M. *Nat. Prod. Rep.* **2008**, *25*, 1180–1209.
3. Setzer, W. N. *J. Mol. Model.* **2008**, *14*, 335–342.
4. Adio, A. M. *Tetrahedron* **2009**, *65*, 1533–1552.
5. (a) Wang, G.; Li, X.; Huang, F.; Zhao, J.; Ding, H.; Cunningham, C.; Coad, J. E.; Flynna, D. C.; Reed, E.; Li, Q. Q. *Cell. Mol. Life Sci.* **2005**, *62*, 881–893; (b) 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; (c) Xu, L.; Tao, S.; Wang, X.; Yu, Z.; Wang, M.; Chen, D.; Jing, Y.; Dong, J. *Bioorg. Med. Chem.* **2006**, *14*, 5351–5356; (d) Fu, N. *Bull. Chin. Mater. Med.* **1984**, *9*, 83–87; (e) Tan, P.; Zhong, W.; Cai, W. *Chin. J. Integr. Tradit. Western Med.* **2000**, *20*, 645–648; (f) Wang, J.; Zhang, H.; Sun, Y. *Chin. J. Oncol.* **1996**, *18*, 464–467; (g) Zou, L.; Liu, W.; Yu, L. *Chin. J. Oncol.* **2001**, *23*, 196–198; (h) Zhou, H. Y.; Shen, J. K.; Hou, J. S.; Qiu, Y. M.; Luo, Q. Z. *Chin. J. Cancer* **2003**, *22*, 959–963; (i) Wang, J.; Zhang, H.; Sun, Y. *Chin. J. New Drug* **1995**, *4*, 26–29; (j) Wang, J.; Zhang, H.; Sun, Y. *Zhongguo Zhongliu Lin Chuang* **1996**, *23*, 301–304; (k) Zhao, J.; Li, Q. Q.; Zou, B.; Wang, G.; Li, X.; Kim, J. E.; Cuff, C. F.; Huang, L.; Reed, E.; Gardner, K. *Int. J. Oncol.* **2007**, *31*, 241–252; (l) Tao, L.; Zhou, L.; Zheng, L.; Yao, M. *Cancer Chemother. Pharmacol.* **2006**, *58*, 24–34.
6. Roberts, J. S.; Bryson, I. *Nat. Prod. Rep.* **1984**, *1*, 105–169.
7. Zhao, Y. L.; Peng, X. X.; Wang, Y. D.; Cui, S. Q. *Chin. J. EBM* **2005**, *5*, 216–223.
8. Hua, W.; Cai, S. *J. Chin. Med. Mater* **2006**, *29*, 93–97.
9. Taixiang, W.; Rui, D.; Xiaoyan, C. *Cochrane Database Syst. Rev.* **2006**. doi:10.1002/14651858.CD006054 Art. No.: CD006054.
10. (a) Lan, M. O; Wang, J.; Yuan, H.; Shen, P.; Zhang, Y.; Lin, Z.; Liu, Z.; Yu, W. CN Patent 2004–10018410, 2005; (b) Chen, A.-X. U.S. Patent 200,540,079, 2005; (c) Xu, L.; Huang J.; Jing Y.; Wang, M. CN Patent 1850779, 2006; (d) Huang, J.; Xu L.; Wang M. CN Patent 1844084, 2006; (e) Huang, J.; Xu, L.; Jing, Y.; Wang M. CN Patent 1844105, 2006; (f) Wan, B.; Xiao, Y.; Liang, X.; Wu, F. CN Patent 1736991, 2006; (g) Huang, L. WO Patent, 2005–US14699, 2005; (h) Huang, L. U.S. Patent 2,006,014,987, 2006; (i) Liu, M.; Wang, X.; Liu, Q.; Tang, S.; Ren, S.; Xu, H.; Du, L. CN Patent 1981749, 2007; (j) Shen, Y.; Ren, Y.; Cheng, K.; Sun, Y.; Wang, M. CN Patent 101239918, 2008; (k) Shen, Y.; Liu, G.; Cheng, K.; Sun, Y.; Ren, Y.; Feng, C. CN Patent 101239915, 2008; (l) Shen, Y.; Chen, K.; Liu, G.; Ren, Y.; Sun, Y.; Wang, M. CN Patent 101225049, 2008; (m) Shen, Y.; Ren, Y.; Cheng, K.; Sun, Y.; Liu, G. CN Patent 101200448, 2008; (n) Chen, R. CN Patent 101199498, 2008; (o) Shen, Y.; Liu, G.; Cheng, K.; Wang, M.; Sun, Y.; Ren, Y.; Feng, C. CN Patent 101165037, 2008; (p) Shen, Y.; Cheng, K.; Feng, C.; Sun, Y. CN Patent 101161290, 2008.
11. (a) Clover, A. M. *Phillipine J. Sci.* **1907**, *2*, 1; (b) Summler, F. W.; Liao, F. *Ber. Dtsch. Chem. Ges.* **1916**, *49*, 794–798.
12. (a) Herout, V.; Motl, O.; Sorm, F. *Collect. Czech. Chem. Commun.* **1954**, *19*, 990–1001; (b) Sykora, V.; Herout, V.; Sorm, F. *Collect. Czech. Chem. Commun.* **1956**, *21*, 267–268.
13. (a) de Kraker, J.-W.; Franssen, M. C. R.; de Groot, A.; Shibata, T.; Bouwmeester, H. J. *Phytochemistry* **2001**, *58*, 481–487; (b) de Kraker, J.-W.; Franssen, M. C. R.; de Groot, A.; König, W. A.; Bouwmeester, H. J. *Plant Physiol.* **1998**, *117*, 1381–1392; (c) Faraldos, J. A.; Wu, S.; Chappell, J.; Coates, R. M. *Tetrahedron* **2007**, *63*, 7733–7742; (d) Wichtman, E.-M.; Stahl-Biskup, E. *Flavour Fragrance J.* **1987**, *2*, 83–89; (e) Gough, J.; Powell, V.; Sutherland, M. D. *Tetrahedron Lett.* **1961**, *2*, 763–767; (f) Gough, J. H.; Sutherland, M. D. *Aust. J. Chem.* **1964**, *17*, 1270–1281; (g) Paknikar, K.; Bhattacharyya, S. C. *Tetrahedron* **1962**, *18*, 1509–1517; (h) Zdero, C.; Bohlmann, F.; King, R. M.; Robinson, H. *Phytochemistry* **1986**, *25*, 2841–2855; (i) Wahidulla, S.; Govenkar, M. B.; Paknikar, S. K. *Helv. Chim. Acta* **2006**, *89*, 496–501.
14. (a) Adio, A. M.; Paul, C.; Kloth, P.; König, W. A. *Phytochemistry* **2004**, *65*, 199–206; (b) Adio, A. M.; Paul, C.; Tesso, H.; Kloth, P.; König, W. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1631–1635.
15. (a) Hackl, T.; König, W. A.; Muhle, H. *Phytochemistry* **2004**, *65*, 2261–2275; (b) König, W. A.; Adio, A. M.; Paul, C.; Hailemichael, T.; Hackl, T. *Absract of Papers*, Stereochemistry of germacrene isomers, Future trends in Phytochemistry, Phytochemical Society of Europe, May 5–8, 2004; Phytochemical Society of Europe: Gargnano, Italy, 2004.
16. Vlahov, R.; Holub, M.; Ognjanov, I.; Herout, V. *Collect. Czech. Chem. Commun.* **1967**, *32*, 808–821.
17. Jones, R. V. H.; Sutherland, M. D. *Aust. J. Chem.* **1968**, *21*, 2255–2274; (b) Sutherland, M. D. *Aust. J. Chem.* **1964**, *17*, 75–91.
18. Villanueva, M. A.; Torres, R. C.; Baser, K. H. C.; Özek, T.; Kürkçüoglu, M. *Flavour Fragrance J.* **1993**, *8*, 35–37.
19. (a) Tesso, H.; König, W. A.; Son, P. T.; Giang, P. M. *Flavour Fragrance J.* **2006**, *21*, 592–597; (b) Jones, R. V. H.; Sutherland, M. D. *J. Chem. Soc., Chem. Commun.* **1968**, 1229–1230; (c) König, W. A.; Rieck, A.; Saritas, Y.; Hardt, I. H.; Kubeczka, K.-H. *Phytochemistry* **1996**, *42*, 461–464; (d) Pellati, F.; Benvenuti, S.; Yoshizaki, F.; Bertelli, D.; Rossi, M. C. *J. Chromatogr., A* **2005**, *1087*, 265–273; (e) Miyazawa, M.; Okamura, S.; Okuno, Y.; Morii, S. *Flavour Fragrance J.* **1999**, *14*, 273–275; (f) Fiorini, C.; Fouraste, I.; David, B.; Bessiere, J. M. *Flavour Fragrance J.* **1997**, *12*, 91–93.
20. (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.
21. (a) Hirose, Y. *Tetrahedron Lett.* **1968**, *24*, 2899–2901; (b) Morikawa, K.; Hirose, Y. *Tetrahedron Lett.* **1969**, *11*, 869–870; (c) Itô, S.; Endo, K.; Honma, H.; Ota, K. *Tetrahedron Lett.* **1965**, *12*, 3777–3781.
22. (a) Hochmannova, J.; Novotny, L.; Herout, V. *Collect. Czech. Chem. Commun.* **1962**, *27*, 2711–2714; (b) Rout, P. K.; Rao, Y. R.; Sree, A.; Naik, S. N. *Flavour Fragrance J.* **2007**, *22*, 352–357; (c) Njoroge, S. M.; Ukeda, H.; Kusunose, H.; Sawamura, M. *Flavour Fragrance J.* **1995**, *10*, 341–347.
23. (a) Muller, C. J.; Jennings, W. G. *J. Agric. Food Chem.* **1967**, *15*, 762–766; (b) Brophy, J. J.; Lassak, E. V.; Suksamrarn, A. *Flavour Fragrance J.* **1990**, *5*, 179–182; (c) Kekelidze, N. A.; Lomidze, E. P.; Janikashvili, M. I. *Flavour Fragrance J.* **1989**, *4*, 37–41; (d) Yaghmai, M. S. *Flavour Fragrance J.* **1988**, *3*, 27–31; (e) Liu, J.; Nan, P.; Tsering, Q.; Tsering, T.; Bai, Z.; Wang, L.; Liu, Z.; Zhong, Y. *Flavour Fragrance J.* **2006**, *21*, 435–438.
24. (a) Ricciardi, G. A. L.; van Baren, C. M.; Lira, P. D. L.; Ricciardi, A. I. A.; Lorenzo, D.; Dellacassa, E.; Bandoni, A. L. *Flavour Fragrance J.* **2006**, *21*, 698–703; (b) Su, Y.-C.; Ho, C.-L.; Wang, E. I.-C. *Flavour Fragrance J.* **2006**, *21*, 447–452; (c) Raina, V. K.; Verma, S. C.; Dhawan, S.; Khan, M.; Ramesh, S.; Singh, S. C.; Yadav, A.; Srivastava, S. K. *Flavour Fragrance J.* **2006**, *21*, 140–142; (d) Srivastava, D.; Haider, F.; Dwivedi, P. D.; Naqvi, A. A.; Bagchi, G. D. *Flavour Fragrance J.* **2005**, *20*, 460–461; (e) Vallverdú, C.; Vila, R.; Lorenzo, D.; Paz, D.; Dellacassa, E.; Davies, P.; Villamil, J.; Tomi, F.; Casanova, J.; Cañigueral, S. *Flavour Fragrance J.* **2005**, *20*, 421–424.
25. (a) Kokoska, L.; Havlik, J.; Valterova, I.; Nepovim, A.; Rada, V.; Vanek, T. *Flavour Fragrance J.* **2005**, *20*, 419–420; (b) Sarkhail, P.; Amin, G.; Surmaghi, M. H. S.; Shafiee, A. *Flavour Fragrance J.* **2005**, *20*, 327–329; (c) Santos, A. P.; Lopes, M. C.; Limberger, R. P.; Apel, M. A.; Henriques, A. T.; Moreno, P. R. H. *Flavour Fragrance J.* **2004**, *19*, 325–326; (d) Cavalli, J.-F.; Tomi, F.; Bernardini, A.-F.; Casanova, J. *Flavour Fragrance J.* **2003**, *18*, 532–538; (e) Pandey, A. K.; Chowdhury, A. R. *Flavour Fragrance J.* **2003**, *18*, 463–465; (f) Vila, R.; Mundina, M.; Tomi, F.; Cicció, J. F.; Gupta, M. P.; Iglesias, J.; Casanova, J.; Cañigueral, S. *Flavour Fragrance J.* **2003**, *18*, 198–201.
26. (a) Asekun, O. T.; Ekundayo, O. *Flavour Fragrance J.* **1999**, *14*, 390–392; (b) Chagonda, L. S.; Makanda, C. D.; Chalchat, J.-C. *Flavour Fragrance J.* **2000**, *15*, 23–26; (c) Khan, M.; Srivastava, S. K.; Syamasundar, K. V.; Singh, M.; Naqvi, A. A. *Flavour Fragrance J.* **2002**, *17*, 75–77; (d) Lorenzo, D.; Paz, D.; Davies, P.; Villamil, J.; Vila, R.; Cañigueral, S.; Dellacassa, E. *Phytochem. Anal.* **2005**, *16*, 39–44.
27. (a) Paul, C.; König, W. A.; Wu, C.-L. *Phytochemistry* **2001**, *58*, 789–798; (b) König, W. A.; Bülow, N.; Fricke, C.; Melching, S.; Rieck, A.; Muhle, H. *Phytochemistry* **1996**, *43*, 629–633.
28. Asakawa, Y. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C., Eds.; Springer: Vienna, New York, NY, 1995; Vol. 65, pp 1–618.
29. (a) Quitana, A.; Reinhard, J.; Faure, R.; Uva, P.; Bagnéres, A.-G.; Massiot, G.; Clément, J.-L. *J. Chem. Ecol.* **2003**, *29*, 639–652; (b) Baker, R.; Coles, H. R.; Edwards, M.; Evans, D. A.; Howse, P. E.; Walmsley, S. *J. Chem. Ecol.* **1981**, *7*, 135–146; (c) Nishino, C.; Bowers, W. S.; Montgomery, M. E.; Nault, L. R.; Nielson, M. W. *J. Chem. Ecol.* **1977**, *3*, 349–357.

30. (a) Weinheimer, A. J.; Youngblood, W. W.; Washecheck, P. H.; Karns, T. K. B.; Ciereszko, L. S. *Tetrahedron Lett.* **1970**, *11*, 497–500; (b) Izac, R. R.; Bandurraga, M. M.; Waskylyk, J. M.; Dunn, F. W.; Fenical, W. *Tetrahedron* **1982**, *38*, 301–304; (c) Gopichand, Y.; Schmitz, F. J. *Tetrahedron Lett.* **1978**, *19*, 3641–3644.
31. (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.
32. McLafferty, F. W. *Wiley Registry of Mass Spectral Data with NIST 2005 Spectral Data*, 7th ed.; John Wiley & Sons: New York, NY, 2005.
33. Hochmuth, D. H.; Joulain, D.; König, W. A. MassFinder 2.3, Terpenoids and Related Constituents of Essential Oils.www.chemie.uni-hamburg.de/oc/koenig/massfinder.html.
34. Adio, A. M. Ph.D. Thesis, Universität Hamburg, Germany, 2005.
35. Joulain, D.; König, W. A. *The Atlas of Spectral Data of Sesquiterpene Hydrocarbons*; E.B.: Hamburg, 1998.
36. (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) König, W. A.; Bülow, N.; Saritas, Y. *Flavour Fragrance J.* **1999**, *14*, 367–378; (d) König, W. A.; Hochmuth, D. H. *J. Chromatogr. Sci.* **2004**, *42*, 423–439.
37. Chen, Z.; Song, Y.; Che, J.; Liu, X.; Ning, Y.; Shan, C.; Hou, Y.; Liu, Y.; Miao, X.; Cheng, Y. *J. Chromatogr. B* **2009**, *877*, 408–414.
38. (a) Gaydou, E. M.; Faure, R.; Bianchini, J.-P.; Lamaty, G.; Rakotonirainy, O.; Randriamiharisoa, R. *J. Agric. Food Chem.* **1989**, *37*, 1032–1037; (b) Faure, R.; Gaydou, E. M. *J. Agric. Food Chem.* **1991**, *39*, 432; (c) Brauchli, R.; Thomas, A. F. *J. Agric. Food Chem.* **1991**, *39*, 431.
39. Baldovini, N.; Tomi, F.; Casanova, J. *Phytochem. Anal.* **2001**, *12*, 58–63.
40. (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) Beecham, C. M.; Djerassi, C. *Tetrahedron* **1978**, *34*, 2503–2508; (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) Adio, A. M.; Paul, C.; Konig, W. A.; Muhle, H. *Phytochemistry* **2002**, *61*, 79–91; (h) Adio, A. M.; von Reuss, S. H.; Paul, C.; Muhle, H.; Konig, W. A. *Tetrahedron: Asymmetry* **2007**, *18*, 1245–1253.
41. König, W. A.; Rieck, A.; Hardt, I.; Gehrcke, B.; Kubeczka, K.-H.; Muhle, H. *J. High Resolut. Chromatogr.* **1994**, *17*, 315–320.
42. Singh, G.; Marimuthu, P.; de Heluani, C. S.; Catalan, C. A. *J. Agric Food Chem.* **2006**, *54*, 174–181.
43. Yamamura, S.; Iguchi, M.; Nishiyama, A.; Niwa, M.; Koyama, H.; Hirata, Y. *Tetrahedron* **1971**, *27*, 5419–5431.
44. (a) Kilic, A.; Hafizoglu, H.; Kollmannsberger, H.; Nitz, S. *J. Agric. Food Chem.* **2004**, *52*, 1601–1606; (b) Yang, F. Q.; Li, S. P.; Chen, Y.; Lao, S. C.; Wang, Y. T.; Dong, T. T.; Tsim, K. W. *J. Pharm. Biomed. Anal.* **2005**, *39*, 552–558.
45. Chen, S. L.; You, J.; Wang, G. J. *Chin. J. Chromatogr.* **2001**, *19*, 179–181.
46. (a) Guo, F.; Huang, L.; Zhou, S. *Chin. J. Chromatogr.* **2007**, *25*, 43–47; (b) Jirovetz, L.; Buchbauer, G.; Ngassoum, M. B.; Geissler, M. *J. Chromatogr., A* **2002**, *976*, 265–275; (c) Figueiro, A. C.; Barroso, J. G.; Pedro, L. G.; Sheffer, J. J. C. *Flavour Fragrance J.* **2008**, *23*, 213–226.
47. (a) Miller, D. J.; Yu, F.; Allemann, R. K. *ChemBioChem* **2007**, *8*, 1819–1825; (b) Faraldos, J. A.; Zhao, Y.; O'Maille, P. E.; Noel, J. P.; Coates, R. M. *ChemBioChem.* **2007**, *8*, 1826–1833; (c) Rosselli, S.; Maggio, A.; Raccuglia, R. A.; Bruno, M. *Eur. J. Org. Chem.* **2003**, 2690–2694.
48. Guo, Y.; Wu, X.; Chen, Y. *J. Chin. Herbology* **1983**, *8*, 31.
49. (a) Bohlmann, F.; Castro, V.; Jakupovic, J. *Phytochemistry* **1983**, *22*, 1223–1225; (b) Ortega, A.; Maldonado, E. *Phytochemistry* **1985**, *24*, 2635–2639; (c) González, A. G.; Arteaga, J. M.; Bretón, J. *Phytochemistry* **1975**, *14*, 2039–2041.
50. Merfort, I. *J. Chromatogr., A* **2002**, *967*, 115–130.
51. (a) Sutherland, J. K. *Tetrahedron* **1974**, *30*, 1651–1660; (b) Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1979**, *35*, 3303–3306; (c) Terada, Y.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2495–2499; (d) Houk, K. N.; Gonzales, J.; Li, J. *Acc. Chem. Res.* **1995**, *28*, 81–90; (e) Takeda, K. *Tetrahedron* **1974**, *30*, 1525–1534.
52. (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) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1978**, *100*, 6268–6269.
53. (a) Black, K. A.; Wilsey, S.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 6715–6724; (b) 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; (c) Blavins, J. J.; Cooper, D. L.; Karadakov, P. B. *J. Phys. Chem. A* **2004**, *108*, 194–202; (d) Takeda, K.; Horibe, I. *J. Chem. Soc., Perkin Trans. 1* **1975**, 870–876.
54. (a) Takeda, K.; Horibe, I.; Minato, H. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2212–2220; (b) Kodama, M.; Yokoo, S.; Matsuki, Y.; Itô, S. *Tetrahedron Lett.* **1979**, *20*, 1687–1690.
55. (a) Brown, E. D.; Sam, T. W.; Sutherland, J. K.; Torre, A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2326–2332; (b) de Pascual Teresa, J.; Barrero, A. F.; Caballero, M. C. *An. Quim.* **1978**, *74*, 519–521.
56. (a) Hellyer, R. O. *Aust. J. Chem.* **1962**, *15*, 157; (b) Grandi, R.; Marchesini, A.; Pagnoni, U. M.; Trave, R. *Phytochemistry* **1972**, *11*, 3363–3365; (c) Grandi, R.; Marchesini, A.; Pagnoni, U. M.; Trave, R. *Tetrahedron Lett.* **1973**, *20*, 1765–1773; (d) Niwa, M.; Nishiyama, A.; Iguchi, M.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2930–2934; (e) Jain, T. C.; Banks, C. M.; McCloskey, J. E. *Tetrahedron Lett.* **1970**, *11*, 2387–2390; (f) Takeda, K.; Minato, H.; Ishikawa, M. *J. Chem. Soc.* **1964**, 4578–4582; (g) Hikino, H.; Agatsuma, K.; Takemoto, T. *Tetrahedron Lett.* **1968**, *9*, 931–933.
57. (a) Ognyanov, I.; Herout, V.; Horak, M.; Sorm, F. *Collect. Czech. Chem. Commun.* **1959**, *24*, 2371–2377; (b) Hayashi, N.; Hayashi, S.; Matsuura, T. *Tetrahedron Lett.* **1968**, *9*, 4957–4960; (c) Hayashi, S.; Hayashi, N.; Matsuura, T. *Tetrahedron Lett.* **1968**, *9*, 1999–2001; (d) Hikino, H.; Konno, C.; Takemoto, T.; Tori, K.; Otsuru, M.; Horibe, I. *Chem. Commun.* **1969**, 662–663; (e) Rao, A. S.; Kelkar, G. R.; Battaacharyya, S. C. *Tetrahedron* **1960**, *9*, 275–283.
58. Ganter, v. C.; Wojtkiewicz, B. K. *Helv. Chim. Acta* **1971**, *54*, 183–206.
59. Wang, K.; Li, Z.; Chen, Y.-R.; Su, C.-Y. *Biopharm. Drug Dispos.* **2005**, *26*, 301–307.
60. Wang, K.; Li, Z.; Chen, Y.-R.; Su, C.-Y. *Asian J. Drug Metab. Pharmacokinet.* **2005**, *5*, 195–201.
61. Li, Z.; Wang, K.; Chen, Y.-R.; Wu, X.-Y.; Su, C.-Y. *Acta Pharm. Sinica* **2000**, *35*, 829–831.
62. Wang, K.; Su, C.-Y. *Acta Pharm. Sinica* **2000**, *35*, 725–728.
63. Wang, K.; Li, Z.; Chen, Y.-R.; Wu, X.-Y.; Li, S.-Y.; Su, C.-Y. *Acta Pharm. Sinica* **2005**, *40*, 54–56.
64. Wang, Y.; Deng, Y.; Mao, S.; Jin, S.; Wang, J.; Bi, D. *Drug Dev. Ind. Pharm.* **2005**, *31*, 769–778.
65. Asakawa, Y.; Ishida, T.; Toyota, M.; Takemoto, T. *Xenobiotica* **1986**, *16*, 753–767.
66. Ishida, T. *Chem. Biodivers.* **2005**, *2*, 569–590.
67. Thomas, A. F.; Vial, C.; Ozainne, M.; Ohloff, G. *Helv. Chim. Acta* **1973**, *56*, 2270–2279.
68. (a) Böhm, H. J. *J. Comput. Aided Mol. Des.* **1992**, *6*, 61–78; (b) Böhm, H. J. *J. Comput. Aided Mol. Des.* **1992**, *6*, 593–606; (c) Moon, J. B.; Howe, W. J. *Proteins, Struct. Funct. Genet.* **1991**, *11*, 314–328.
69. Pei, J.; Zhou, J.; Xie, G.; Chen, H.; He, X. *J. Mol. Graph. Model.* **2001**, *19*, 448–454.
70. Miao, X.; Han, X.; Hu, J.; Xu, Y. *Chin. J. Magn. Reson.* **1994**, *11*, 265–271.
71. Ye, J.; Cheng, G.; Hu, J. *Chin. J. Magn. Reson.* **2000**, *17*, 115–120.
72. Hu, J.; Ye, J.; Cheng, G.; Long, X. *Spectrosc. Spect. Anal.* **2001**, *21*, 163–168.
73. Simonovíc, D. M.; Rao, A. S.; Bhattacharyya, S. C. *Tetrahedron* **1963**, *19*, 1061–1071.
74. Kulkarni, K. S.; Rao, A. S. *Tetrahedron* **1965**, *21*, 1167–1173.
75. Corey, E. J.; Broger, E. A. *Tetrahedron Lett.* **1969**, *22*, 1779–1782.
76. Patil, L. J.; Rao, A. S. *Tetrahedron Lett.* **1967**, *2*, 2273–2275.
77. Wagh, A. D.; Paknikar, S. K.; Bhattacharyya, S. C. *Tetrahedron* **1964**, *20*, 2647–2654.
78. McMurry, J. E.; Kočovský, P. *Tetrahedron Lett.* **1985**, *26*, 2171–2172.
79. Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193–196.
80. Kim, D.; Lee, J.; Chang, J.; Kim, S. *Tetrahedron* **2001**, *57*, 1247–1252.
81. Mehta, G.; Acharyulu, P. V. R. *J. Indian Chem. Soc.* **1998**, *75*, 601–612.
82. Kato, K.; Hirata, Y.; Yamamura, S. *Tetrahedron Lett.* **1971**, *38*, 3513–3515.
83. Jia, W.; Yang, L.; Li, Z.; Hu, J. *Chin. J. Org. Chem.* **1991**, *11*, 608–610.
84. Xu, L.; Tao, S.; Zhang, X.; Wang, X.; Wang, M.; Dong, J. *Chin J. Med. Chem.* **2006**, *16*, 277–280.
85. Liu, G.; Sun, Y.; Cheng, K.; Shen, Y. *J. Chin. Pharm.* **2007**, *38*, 396–399.
86. Zhang, X.; Xu, L.; Tao, S.; Wang, X.; Chen, G.; Wang, M.; Dong, J. *Chin. J. Med. Chem.* **2007**, *17*, 13–17.
87. Yang, L.-Y.; Zhang, S.-J.; Zheng, X.-F.; Yin, H.-X. *Chin. J. Org. Chem.* **2008**, *28*, 1797–1802.
88. Ren, Y.-F.; Cheng, K.-M.; Liu, G.-F.; Sun, Y.-H.; Shen, Y.-M. *Acta Chim. Sinica* **2008**, *66*, 459–464.
89. Ren, Y.-F.; Liu, G.-F.; Sun, Y.-H.; Shen, Y.-M. *Gaodeng Xuexiao Huaxue Xuebao* **2008**, *29*, 1765–1768.
90. Cheng, K.-M.; Sun, Y.-H.; Feng, C.-L.; Shen, Y.-M. *Chin. J. Org. Chem.* **2008**, *28*, 65–68.
91. Choi, B. G.; Kwak, E. Y.; Chung, B. H.; Cho, W. J.; Cheon, S. H. *Arch. Pharm. Res.* **1999**, *22*, 575–578.
92. See Ref. 5c.
93. See Ref. 83.
94. Yu, Z.; Wang, R.; Xu, L.; Dong, J.; Jing, Y. *Cancer Lett.* **2008**, *269*, 165–173.
95. Sun, Y.; Liu, G.; Zhang, Y.; Zhu, H.; Ren, Y.; Shen, Y.-M. *Bioorg. Med. Chem.* **2009**, *17*, 1118–1124.
96. Zheng, S.; Yang, H.; Zhang, S.; Wang, X.; Yu, L.; Lu, J.; Li, J. *J. Cell. Biochem.* **1998**, *67*, 106–112.
97. Yang, H.; Wang, X.; Yu, L.; Zheng, S. *Chin. Clin. Cancer* **1999**, *26*, 4–7.
98. (a) Zheng, S.; Yang, H.; Zhang, S.; Wang, X.; Yu, L.; Lu, J.; Li, J. *J. Cell Biochem. Suppl.* **1997**, *27*, 106–112; (b) Yang, H.; Wang, X.; Yu, L. *Chin. J. Oncol.* **1996**, *18*, 169–172.
99. Fan, Y.; Zhang, Y.; Li, H. *Jiangsu Daxue Xuebao, Yixueban* **2006**, *16*, 413–415.
100. Wei, W.; Tang, L.; Yang, Y.; Li, L.; Qu, C. *Yanke Yanjiu* **2007**, *25*, 651–654.
101. Fan, Y.; Lin, G.; Qian, L.; Li, H.; Zhu, H.; Yan, J. *Fudan Xuebao, Yixue Kexueban* **2001**, *28*, 5–8.
102. Cao, Z.; Ji, W. *Lin Chung Er Bi Yan Hou Tou Jing WaiKe ZaZhi* **2007**, *21*, 417–420.
103. Yang, L.; Zhu, Q. J.; Zhou, W.; Ye, J.; Qian, W.; Zhu, R.; Hu, T. H.; Hou, X. H. *Chin. J. Hepatol.* **2008**, *16*, 748–751.
104. Zhang, Z.; Chen, J.; Lin, X.; Lin, X. *Xiandai Zhongxiyi Jiehe Zazhi* **2008**, *17*, 4685–4687.
105. Wu, W.; Liu, K.; Tang, X. *Chin. J. Oncol.* **1999**, *21*, 405–408.
106. Gao, Z.; Huang, L.; Shi, G.; Guo, L.; Shen, J.; Qian, Z. *Chin. J. Microbiol. Immunol.* **2002**, *22*, 375–378.
107. Zou, D.; Ba, J.; Ji, Y.; Lu, P. *World Chin. J. Diges.* **2007**, *15*, 2931–2933.
108. Tan, P.; Zhong, W.; Cai, W. *Chin. J. Clin. Oncol.* **2001**, *28*, 682–684.
109. See Ref. 5g.
110. Yao, Y.-Q.; Ding, X.; Jia, Y.-C.; Huang, C.-X.; Wang, Y.-Z.; Xu, Y.-H. *Cancer Lett.* **2008**, *264*, 127–134.
111. Xi-Sha, W.; Wei, Y.; Shu-Juan, T.; Karen, L.; Ming, L.; Jin-Hua, D.; Min-Wei, W. *Yakugaku Zasshi* **2006**, *126*, 979–990.
112. Qiansha, W.; Wei, Y.; Ming, L.; Jinhua, D.; Min-Wei, W. *Zhonghua Yiyao Zazhi* **2006**, *6*, 841–843.

113. Jianjun, Q.; Song, Z.; Yin, L.; Jia, Z.; Donglei, L. *J. Thorac. Cardiovasc. Surg.* **2008**, *56*, 103–105.
114. (a) Hu, J.; Jin, W.; Yang, P. *Chin. J. Oncol.* **2004**, *26*, 268–270; (b) Zhang, W.; Wang, H.; Li, L. *Chin. J. Clin. Oncol.* **1996**, *23*, 75–77; (c) Xiao, L.; Zhu, W. *Chin. J. Clin. Oncol.* **1996**, *23*, 757–759; (d) Liu, X.; Hua, B. J. *Chin. J. Integr. Tradit. Western Med.* **2008**, *28*, 105–107.
115. Peng, X.; Zhao, Y.; Liang, X.; Wu, L.; Cui, S.; Guo, A.; Wang, W. *Contemp. Clin. Trials* **2006**, *27*, 70–82.
116. Wang, G. X.; Wu, L. Y.; Tang, S. T.; Yin, T. Y. *J. Chin. Med. Mater.* **2007**, *30*, 1407–1410.
117. (a) See Ref. 98b; (b) See Ref. 98a; (c) Yang, H.; Wang, X.; Yu, L.; Zheng, S. *Chin. J. Cancer Res.* **1997**, *9*, 83–88; (d) Yuan, J.; Gu, Z.; Zhou, W.; Guo, C. *Zhongguo Yaolixue Tongbao* **1998**, *14*, 410–412; (e) Xu, X.; Zhou, Z.; Luo, Y.; Lu, R.; Men, R.; Fang, D. *Di-San Junyi Daxue Xuebao* **1999**, *21*, 268–271; (f) Zou, L.; Wang, Q.; Shao, S.; Yu, L.; Zhang, C.; Yang, P. *Chin. J. Clin. Oncol.* **1999**, *26*, 616–619.
118. (a) Ma, D.; Xiao, J.; Tong, S.; Hu, B.; Shi, Q.; Hu, L. *Shanghai Dier Yike Daxue Xuebao* **2000**, *20*, 484–487; (b) See Ref. 5g; (c) Li, W.; Zhou, L.; Jin, X. *Shanghai Dier Yike Daxue Xuebao* **2002**, *22*, 306–308; (d) Huang, F.; Fan, Y.; Lin, G.; Qian, L.; Xu, Z.; Li, H. *Fudan Xuebao, Yixueban* **2003**, *30*, 49–51.
119. (a) Zhou, H.; Shen, J.; Hou, J.; Qiu, Y.; Luo, Q. *Chin. J. Cancer* **2003**, *22*, 959–963; (b) Guan, W.; Fan, Y.; Guo, X.; Lin, G.; Qian, L.; Xu, Z.; Li, H. *Fudan Xuebao, Yixueban* **2003**, *30*, 434–438; (c) Li, C.; Li, M.; Shu, X.; Liu, Y.; Yang, C. *Zhonghua Yixue Zazhi* **2004**, *84*, 416–417; (d) Xu, Y. H.; Dong, B.; Luo, Q. Z.; Zhou, H. Y.; Jia, Y. C.; Yang, Y. F.; Wang, Y. Z. *Zhonghua Yi Xue Za Zhi* **2005**, *85*, 1700–1703; (e) See Ref. 119d; (f) Yang, W.; Chen, C.; Shi, S.; Wang, C.; Yang, X.; Wang, R. *Chin. J. Clin. Oncol.* **2005**, *32*, 763–766; (g) See Ref. 111; (h) Zou, D.; Ba, J.; Ji, Y.; Lu, P. *World Chin. J. Diges.* **2007**, *15*, 2931–2933.
120. (a) Fan, Y.; Lin, G.; Qian, L.; Li, H.; Zhang, Z. *Chin. J. Clin. Oncol.* **2001**, *28*, 848–851; (b) Fan, Y.; Lin, G.; Qian, L.; Xu, Z.; Li, H. *Shanghai Yixue* **2001**, *24*, 490–492; (c) Fan, Y.; Lin, G.; Qian, L.; Xu, Z.; Li, H. *Fudan Xuebao, Yixue Kexueban* **2001**, *28*, 378–381; (d) Huang, F.-C.; Fan, Y.; Zheng, S. *Yiyao Daobao* **2004**, *23*, 712–714; (e) Wang, Y.; Fang, M.-Y.; Jiang, F.; Peng, H.-J. *Zhongguo Shiyan Xueyexue Zazhi* **2004**, *12*, 315–320.
121. (a) See Ref. 106; (b) See Ref. 105; (c) Yao, Y.; Xu, Y.; Zhou, H.; Cui, C.; Wang, Y. *Zhongliu* **2007**, *27*, 777–779.
122. Jiang, Y.; Ding, H.; Liu, X.; Yin, X. *Jiangsu Yiyao* **1997**, *23*, 218–219.
123. Wang, Z.; Chen, L.; Xu, Y.; Chen, J.; Zhang, H.; He, Q.; Li, X. *Chin. J. Oncol.* **1998**, *20*, 198.
124. See Ref. 120e.
125. Hao, L.; Zhao, J.; Yang, P. *Chin. J. Clin. Oncol.* **2005**, *32*, 25–28.
126. Tan, G.; Lin, L.; Wang, Z.; Yin, S. *Zhonghua Shiyan Waike Zazhi* **2006**, *23*, 113.
127. Tan, G.; Wang, Z.-Y.; Wang, X.-G.; Cheng, L.; Yin, S. *Chin. J. Cancer* **2006**, *25*, 1082–1086.
128. Sun, J.; Jiang, S.; Xiao, W.; Zhu, J.; Jiang, Z.; Song, H.; Song, S. *Chin. J. Clin. Oncol.* **2006**, *33*, 661–664.
129. Wang, Y.; Fang, M. Y. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* **2006**, *14*, 1089–1095.
130. Yin, S.; Tan, G.; Luo, H.-F.; Cheng, L.; Wang, Z.-Y. *Zhongguo Aizheng Zazhi* **2007**, *17*, 50–53.
131. Zhou, X.; Zheng, Q.; Zhao, X.; Ma, H. *Xi'an Jiaotong Daxue Xuebao, Yixueban* **2007**, *28*, 74–77.
132. Chen, G.; Ding, X.-F.; Xiao, J.-F.; Han, Z.; Wang, M.-W.; Dong, J.-H. *Shenyang Yaoke Daxue Xuebao* **2007**, *24*, 238–241.
133. König, W. A. In *Drug Stereochemistry: Analytical Methods and Pharmacology*, 2nd ed.; Wainer, I. W., Ed.; Marcel Dekker: New York, NY, 1993; pp 107–137.
134. Ma, E.; Wang, X.; Li, Y.; Sun, X.; Tai, W.; Li, T.; Guo, T. *Cancer Lett.* **2008**, *271*, 158–166.
135. Xiao, Y.; Yang, F.; Li, S.; Gao, J.; Hu, G.; Lao, S.; Conceicao, E.; Fung, K.; Wang, Y.; Lee, S. *Cancer Biol. Ther.* **2007**, *6*, 1044–1050.

Biographical sketch

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