HETEROCYCLES, Vol. 90, No. 2, 2015, pp. 741 - 810. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 8th July, 2014, Accepted, 22nd September, 2014, Published online, 1st October, 2014
DOI: 10.3987/REV-14-SR(K)3

TERPENOIDS BEARING THE 7-OXABICYCLO[2.2.1]HEPTANE (7-OXANORBORNANE) SKELETON. NATURAL SOURCES, BIOLOGICAL ACTIVITIES AND CHEMICAL SYNTHESIS

Silvia Roscales[a] and Joaquín Plumet[b,*]

Multidisciplinary Institute, Complutense University, "Campus de Excelencia Internacional Moncloa", University City, 28040-Madrid, Spain, silviaroscales@ucm.es

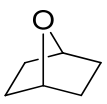
Complutense University, "Campus de Excelencia Internacional Moncloa", Faculty of Chemistry, Organic Chemistry Department, University City, 28040-Madrid, Spain, plumety@ucm.es

Abstract – Compounds bearing the 7-oxabicyclo[2.2.1]heptane (7-oxanorbornane) subunits have been used extensively in the synthesis of a large array of complex organic structures. The ease of synthesis of compounds having this substructure in enantiomerically pure form, using Diels-Alder chemistry, is today an almost routinely experimental work. Moreover, the reactivity of these compounds, easily controllable and almost always associated to its ring-strain, makes them particularly valuable chiral building blocks. However, the presence of compounds showing this bicyclic skeleton in Nature has attracted less attention despite its relatively broad distribution. Many of these compounds have been shown to possess important biological activities presenting, in cases, unprecedented biogenetic origin. In addition, some of them have been considered as convenient synthetic targets enabling the development of new synthetic methodologies. In this article we have reviewed different families of terpenoids having in its structure this bicyclic subunit, paying particular attention to their natural sources, biosynthesis, biological activity and chemical synthesis.

CONTENTS

1. INTRODUCTION. SCOPE OF THE REVIEW

Compounds derived from the 7-oxabicyclo[2.2.1]heptane (7-oxanorbornanes) **1** (Figure 1) are useful intermediates or starting material for the synthesis of more complex molecules including natural products and analogues also being valuable building blocks for polymers and material science.



1

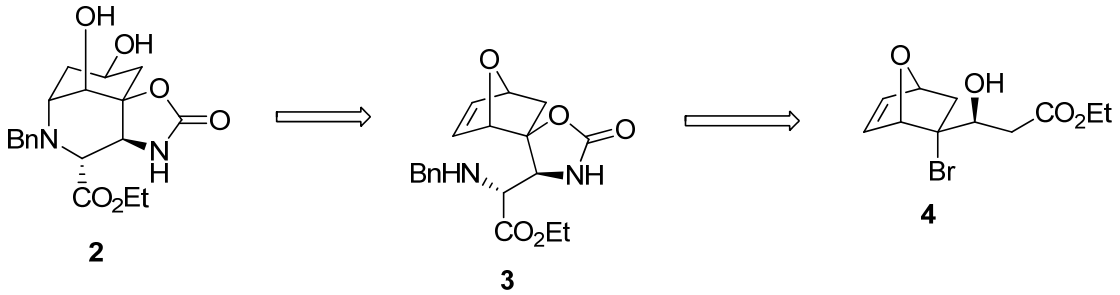
Figure 1. The 7-oxanorbornane ring system

The usefulness of this bicyclic system is consequence, at least, of two facts: first, because their syntheses –even in enantiomerically pure form- is relatively easy using, among other methods, Diels–Alder chemistry. Second, because the chiral information stored in the rigid skeleton may be transferred to their transformation products.

To the best of our knowledge, the more complete review on the chemistry of 7-oxanorbornane derivatives was published in 1999.[1] Since then and to date a number of excellent reviews have been published, covering various specific aspects on the synthesis and synthetic applications of these compounds. An account of those, in our opinion more significant, is summarized in the following paragraphs:

1. Synthesis of cyclohexyl systems including hydroxycyclohexyl-β-amino acids and other cyclohexyl subunits, constitutive of a wide array of organic compounds. The synthetic methodology here described lies on the base- and acid-mediated fragmentation and transition-metal catalyzed ring-opening reactions of the oxygen-bridge of the oxanorbornene ring system.[2]

2. Synthesis of complex natural products starting from 7-oxanorbornene derivatives as well as the synthetic way to these building blocks.[3] The utility of these transformations was highlighted in the enantioselective route to the central core **2** of banyaside and suomilide natural products (Scheme 1). Banyasides and suomilide are novel natural products belonging to the *Aeruginosin* family of serine protease inhibitors.[4]



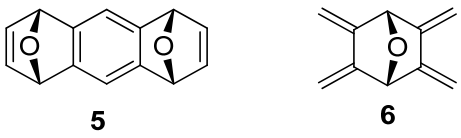
Scheme 1. Retrosynthetic analysis of the central core of banyaside and suomilide, **2** from simple 7-oxanorbornene derivative **4**

3. Use of optically pure 7-oxanorbornene derivatives in the efficient synthesis of rare sugars,[5] glycomimetics, polypropionates,[5,6] anthracyclinone[7] and aza-disaccharides.[8]

4. Synthetic applications of Ring-Rearrangement Metathesis (RRM) in 7-oxanorbornene derivatives and the related aza-analogues.[9] Ring-rearrangement metathesis (RRM) refers to the combination of several metathetical transformations into a domino process, in which an endocyclic double bond of a cycloolefin reacts with an exocyclic alkene.

5. Synthesis of [6]n cyclacenes,[10] the simplest subunits of carbon nanotubes. Cyclacenes has been defined as *"Hoop-shaped systems composed of conjugated rings"*. The necessary curved shape of the belt

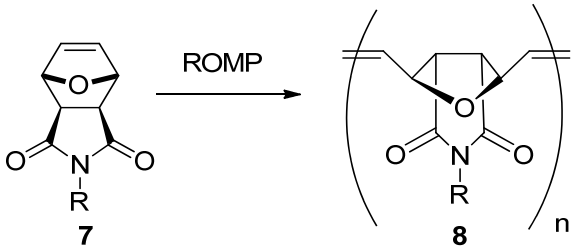
was achieved using the 7-oxanorbornene precursors **5** and **6** (Figure 2).



5 **6**

Figure 2. Oxanorbornene starting materials for the synthesis of [6]n-cyclacenes derivatives

6. Synthesis of new functional polymers such as liquid crystals polyoxanorbornenes **8** from enantiomerically pure 7-oxanorbornenes **7** via Ring-Opening Metathesis Polymerization (ROMP) (Scheme 2).[11]



7 **8**

Scheme 2. ROMP of 7-oxanorbornene monomer **7**

In addition, several 7-oxanorbornane derivatives are also found in Nature showing, in several cases, interesting biological activities. Only in reference 1 (see p. 13529-13546) this topic has been briefly mentioned and, on the best of our knowledge, no other review on this point can be found in the literature. In this account we intend to fill this gap considering this aspect under the points of views of the natural sources, biosynthesis, and biological activity of these compounds. In addition, the more recent chemical synthesis of some of them will be conveniently detailed.

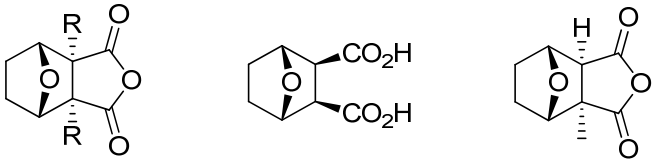
We should indicate that our attention has focused on compounds bearing terpenic structure. Other related family of natural products such as carotene derivatives and some other natural products featuring the 7-oxanorbornene skeleton will not be considered here. The literature has covered until March 2014.

2. CANTHARIDIN AND ANALOGUES

Cantharidin **9** (2,6-dimethyl-4,10-dioxatricyclo[5.2.1.02,6]decane-3,5-dione, CTD, Figure 3)[≠,12] was first

[≠]Some cantharidin derivatives have been named as pseudocantharidins. Also norcantharidin **10** (Figure 3) has been designed as isocantharidin. This type of "nomenclature" will not be considered in this report. See reference 12.

isolated in 1810 by Pierre Robiquet,[¥,13] from *Lytta vesicatoria* (Spanish fly) sometimes incorrectly called *Cantharis vesicatoria.*



9, R = Me
10, R = H

11

12

Figure 3. Structure of cantharidin and analogous

This compound is the principle responsible for the aggressively vesicant properties of the coating of the eggs of the insect. Cantharidin shows potent antitumor activity and it seems to be the result of that CTD is a strong inhibitor of protein phosphatase type 1 (PP1) and type 2A (PP2A). Protein phosphatase PP2A, is an enzyme with broad substrate specificity and diverse cellular functions. Among the targets of PP2A are some proteins responsible of oncogenic signalling cascades. Protein phosphatase 1 (PP1) belongs to a certain class of phosphatases known as protein serine-threonine phosphatases. The PP1 has been found to be important, among others, in the control of cell division, apoptosis and protein synthesis.[14] However, and due to its toxicity,[15] the clinical application of this compound is limited.[16] Diluted solutions of CTD can also be used as a topical medication in dermatology[17] and their insecticidal activity[18] and aphrodisiac properties[19] have also been documented.

Norcantharidin **10** (NCTD, *exo*-7-oxabicylo-[2.2.1]heptane-2,3-dicarboxylic anhydride, Figure 3), the demethylated analog of CTD, causes fewer side effects than CTD and, like CTD, has been demonstrated as a potential agent against certain cancers.[20] The NCTD is preferentially, but not always,[21] toxic to cancer cells rather than normal cells, making this small molecule promising in cancer treatment.

Sodium salt of 7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid, **11** (Figure 3) also inhibit serine/threonine phsphatases.[22] In particular is inhibitor of PP2B (calcineurin), a proteinphosphatase which is involved in a large variety of biological processes. The compound **11**, designed in reference 12 as "desmethylcantharate" is a well-known synthetic herbicide named "endothall". It should be pointed out that the compound "endothall" has been incorrectly formulated in reference 12 and in the reference 1a, p 13530.[ϒ,23]

[¥]Pierre-Jean Robiquet (1780-1840) is the author of important contributions in the field of natural products. For a summary of the contributions of Robiquet, see: J. Wisniak, *Educacion Quimica*, 2013, **24**, 139.

[ϒ]The names assigned to endothall constitute an authentic puzzle. Trade names for the acid form of endothall include Aquathol, Hydrothal-47 and Hydrothal-191. Trade names for the disodium salt of endothall include Accelerate, Des-I-Cate, and Niagrathol among others. See: "The Agrochemicals Handbook", Third Edition. Royal Society of Chemistry Information Systems, Surrey, England, 1994.

Calcineurin is also known as protein phosphatase 3, and calcium-dependent serine-threonine phosphatase. Inhibition of calcineurin is associated with inmunosuppresion, and, in fact, calcineurin is inhibited by drugs such as cyclosporine.[24]

Organometallic complexes of **11** with Mn(II),[25] Pt(IV)[26] and La(III)[27] have been reported that possesses important anticancer activity. On the other hand, metal complexes containing the subunit **11** and heterocyclic compounds showed interesting biological properties. That is the case of complex of [Ni(II)-2-aminomethylbenzimidazole],[28] [rare earth-phenanthroline],[29] [Co(II) and Zn (II)-2-amino-1,2,3-thiadiazole],[30] [Co(II) and Ni(II)-2-aminothiazole],[31] [Co(II)-imidazole],[32] [Mn(II), Ni(II) and Cu(II)-2-aminopyridine,[33] [Cd(II)-2,2-bipyridine and phenanthroline],[34] [transition metals-2-amino-benzothiazole],[35] and [Mn(II), Ni(II) and Zn(II)-2,2'-bipyridine].[36]

Although cantharidin never seems to have been isolated from plant sources, the demethyl derivative palasonin **12** (3-methyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxyxlic anhydride), which lacks one of the angular methyl groups of cantharidin, (Figure 3), was initially isolated from the seeds of the Indian tree, *Butea frondosa (Leguminoseae)*.[37] The anthelmintic properties of **12** are well documented.[38]

Cantharimides are compounds in which the anhydride oxygen atom of cantharidine has been replaced by a N-substituted derivative. From the Chinese beetle *Mylabris phalerata* PALLAS,[ξ] cantharimides **13**-**15** have been isolated.[39] In these compounds the *N*-substituents are L-lysine, L-ornithine and L-arginine moieties respectively. Later and from the same insect five cantharimide-derivatives **16**-**20** were also isolated.[40] Three of them were cantharimide dimers (compounds **18**-**20**) which consists of two units of cantharimide combined with a tri-, tetra- and penta-methylene group. Other simple cantharimides have been previously isolated from natural sources. It is the case of the *N*-phenyl and *N*-hydroxyimides **21** and **22**. Compound **21** was isolated from *Butea monosperma*[41] whereas compound **22** is an ingredient of *Mylabris phalerata*[42] (Figure 4).

Before the isolation of compounds **13**-**20** several cantharimide derivatives were rationally designed,[43] synthesized and evaluated as inhibitors of PP1 and PP12A.[44] More recently[45] thirty-two cantharimides containing aryl, pyridyl, azolyl, thiadiazolyl, diaminophenyl, aminosulfanyl, sulfamethoxazolyl, or sulfadiazine moieties were synthesized by heating cantharidine at 200 °C in toluene and Et_3N along with the corresponding amines. All compounds were tested for their capability to suppress growth of several human carcinoma cell lines, concluding that the cytotoxic effects were produced by many different structural features of the cantharidinimide derivatives. For instance, the *in vitro* results suggested that decreasing electron negativity on the substituent-donating group might increase their cytotoxicity.

[ξ]This insect has been used in traditional Chinese medicine for the treatment of cancer. See: "The Dictionary of Chinese Drugs". Shanghai Science and Technological Publishers, Tokyo, 1985**,** Vol. III, pp. 2196-2198.

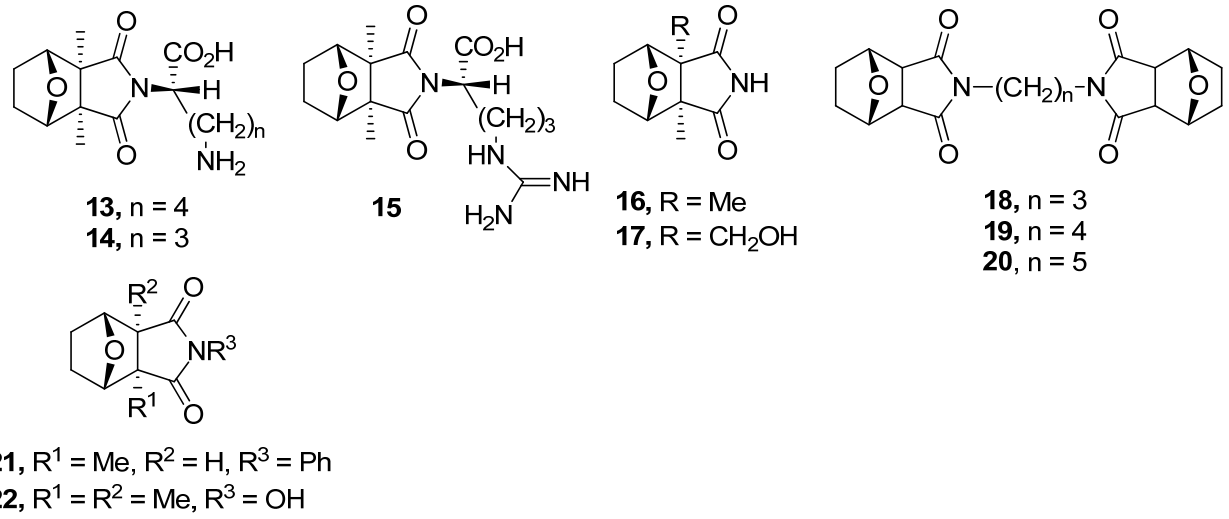
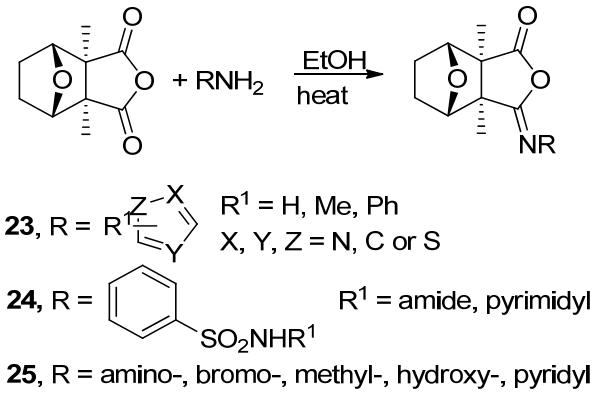


Figure 4. Natural cantharimides

Eighteen biologically active cantharidinimines with general structures **23**-**25** (Scheme 3) were prepared by heating cantharidin with the appropriate azolamines, sulfanils, and pyridinamines in ethanol.[46] The cytotoxic effects of these cantharidinimines seemed to be better than others cantharimides previously synthesised.



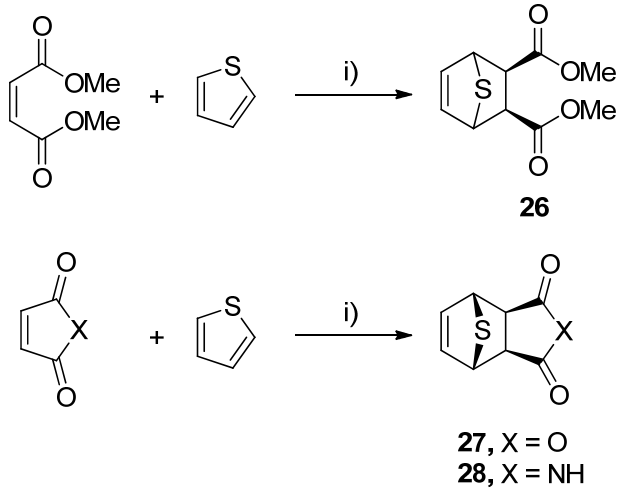
Scheme 3. Synthesis of cantharidinimines **23**-**25**

The mechanism of the biosynthesis of cantharidin is not exactly known although appears to be clear that it implicates some unprecedented transformations of farnesol.[47]

From 1953,[48] different synthetic approaches to cantharidin have been carried out using Diels-Alder chemistry. Among them, the synthesis of Stork,[49] Schenk[50] and, more recently, Dauben (using high-pressure conditions)[51] and Grieco ($LiClO_4$-promoted Diels-Alder cycloaddition)[52] should be emphasized. These synthetic efforts as well as the chemical transformations of cantharidin in others related, biologically active compounds, have been recently summarized in the appropriate reviews.[53]

Nevertheless, some recent, significant aspects of this chemistry applied to the synthesis of cantharidin analogs are highlighted as follows.

The 7-*S* analogues of cantharidin derivatives **26-28** were synthesized in acceptable yields (ca 60%) using high-pressure Diels-Alder reaction of tiophen with dimethyl maleate, maleic anhydride and maleimide respectively[≠] (Scheme 4).[54]



Scheme 4. High-pressure synthesis of sulphur analogues of cantharidin derivatives. *Reaction conditions*: thiophene (2 equiv.), CH_2Cl_2, 40 ºC, 17 kbar, 71 h

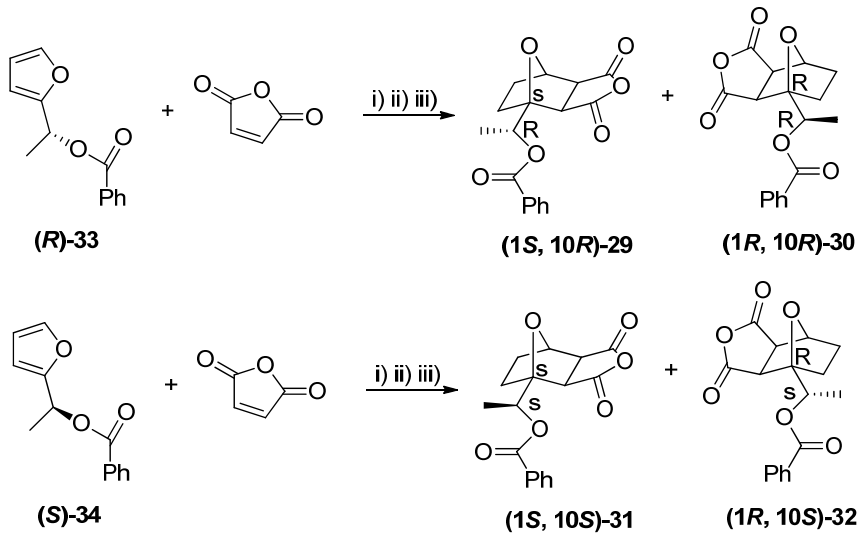
High-pressure synthesis of compounds **26** and **27** has been previously reported in ca 40% isolated yields.[55] Also compound **26** was synthesized in $LiClO_4$-Et_2O mixtures albeit in lower yield.[54]

Optically pure norcantharidin derivatives **29-32** were synthesized[56] by reaction of (*R*)-and (*S*)-2-benzyloxyethyl)furan **33** and **34** respectively and maleic anhydride followed by hydrogenation (Scheme 5).

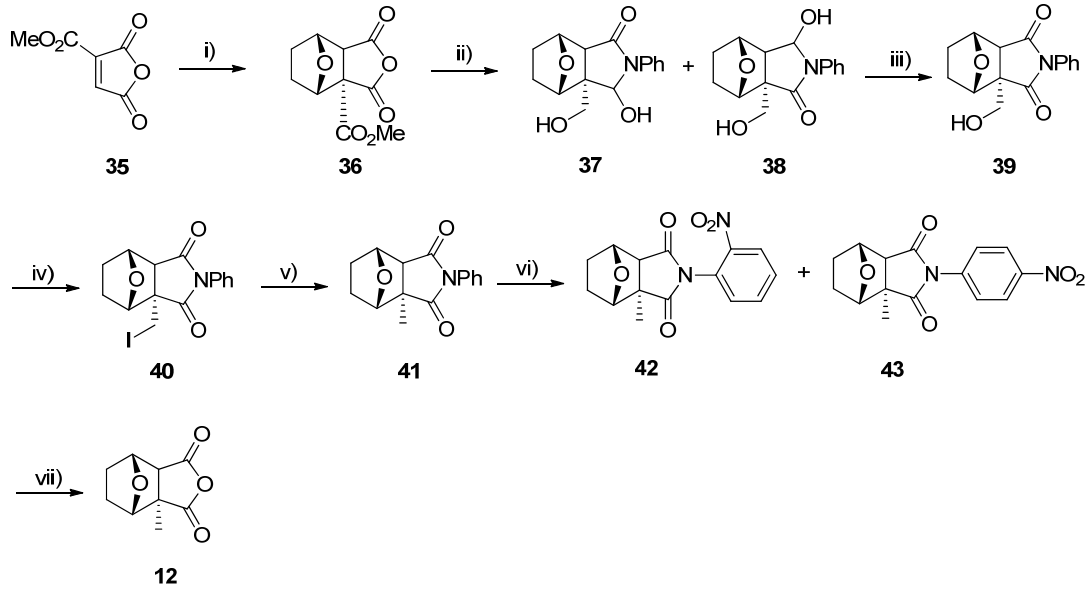
Compounds **33** and **34** were prepared by reaction of (*R*)- and (*S*)-1-(2 furyl)-ethanol, respectively, with benzoyl chloride (Et_3N, DMAP, CH_2Cl_2). Interestingly it was observed that (1*R*)-isomers **30** and **32** inhibit PP1 and PP2A whereas the (1*S*)-isomers **29** and **31** have negligible inhibitory activity for PP1 and PP2A.

Racemic palasonin **12** was synthesized[57] from furan and methoxycarbonyl maleic anhydride **35** using the lineal, nine-step sequence (6% overall yield) depicted in Scheme 6.

[≠] Interestingly compound **28** was found to be >30-fold selective than **27** vs. PP2A. See reference 54.



Scheme 5. Synthesis of optically pure norcantharidin derivatives **29**-**32**. *Reagents and reaction conditions*: i) neat, rt; ii) H_2, 10% Pd-C, THF; iii) Fractional crystallization

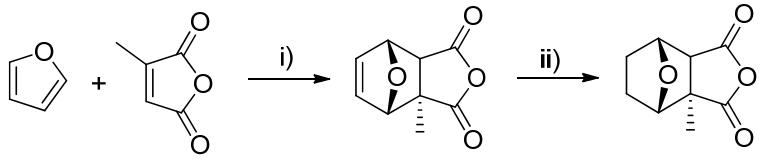


Scheme 6. Meinwald's synthesis of racemic palasonin **12**. *Reagents and reaction conditions*: i) furan, H_2, Pd-C, 69%; ii) a: aniline, CH_2Cl_2; b: TFAA, 0 ºC; c: $NaBH_4$, EtOH, 25 ºC; 49% for **37**; 10% for **38**; iii) $CeSO_4 \cdot 2H_2O$, $KBrO_3$, MeCN:H_2O (7:3), 80 ºC; 48%; iv) a: Et_3N, MsCl, CH_2Cl_2, 0 ºC; b: acetone, NaI, reflux; 69%; v) $[Me_3Si]_3SiH$, AIBN, C_6H_6, 80 ºC, 96%; vi) Ac_2O, HNO_3, 10-15 ºC, 80%; vii) a: NaOH, EtOH, H_2O, 80 ºC; b: TFAA, CH_2Cl_2, reflux, 69%

Two comments appear to be opportune regarding this synthetic approach: firstly, the concomitant reduction of the resulting adduct of the Diels-Alder reaction of **35** and furan to give anhydride **36** under the reaction conditions i). However, the reaction of citraconic anhydride (3-methylmaleic anhydride) **44** (see Scheme 7) with an excess of furan under hydrogenation conditions afforded only methylsuccinic

anhydride.[58] On the other hand, direct transformation of **41** into **12** appears to be an appealing possibility. Nevertheless, all attempts to achieve this transformation were unsuccessful mainly due to the vigorous conditions necessary to hydrolyze the *N*-phenylimide ring. In contrast, the nitrophenylimides **42** and **43** were easily hydrolyzed to give **12**. The purification of **12** was achieved by preparative GC.

In the same paper, Dauben *et al*.[58] reported a two-step synthesis of racemic **12** (92% overall yield) by high-pressure Diels-Alder reaction of furan and citraconic anhydride **44** followed by catalytic hydrogenation (Scheme 7).



44 **45** **12**

Scheme 7. Dauben's synthesis of racemic palasonin **12**. *Reagents and reaction conditions*: i) 8 kbar, 138 h, 97%; ii) H_2, 10% Pd-C, THF, 99%

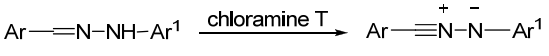
It should be pointed out that, under pseudo-first order conditions (furan as solvent), adduct **45** was obtained in 1.7% yield (at 20 ºC) and 1.5% yield (at 40 ºC). The values of the equilibrium constant at both temperatures were determined as K= $1.1\times10^{-3}M^{-1}$ (20 ºC) and K= 8×10^{-4} M^{-1} (40 ºC). Other kinetic parameters are: $k_1= 1.1\times10^{-9}$ $M^{-1}s^{-1}$ (20 ºC) and $k_1= 4.7\times10^{-8}M^{-1}s^{-1}$ (40 ºC); $k_{1\phi}= 3.7\times10^{-6}$ s^{-1} ($t_{1/2}$ = 52 h, 20 ºC); $k_{1\phi} = 5.9\times10^{-5}$ s^{-1} ($t_{1/2}$ = 3.3 h, 40 ºC).

On the other hand, and under catalysis by 5.0M $LiClO_4$-Et_2O (Grieco's conditions), the reaction of **44** and furan gave less than 10% yield of **45** with K= $1.0\times10^{-2}M^{-1}$ at rt.[58]

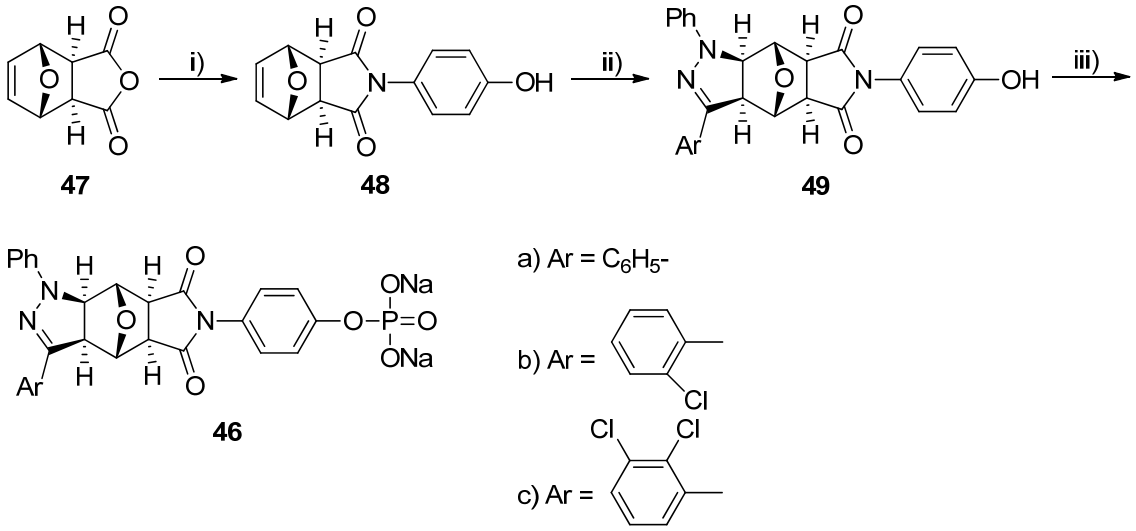
Racemic palasonin was resolved by reaction with (*S*)-2-methylbenzylamine followed by separation of the diastereomeric amides, saponification to the diacids and further reaction of the individual diacids with thionyl chloride. The combination of a pyrazole ring[≠,59] fused to the norcantharidin framework in one single structure such as **46** (Scheme 8) constitutes an appealing possibility in order to improve the antiproliferative activities of norcantharidin derivatives. Also the introduction of a phosphate group should improve the aqueous solubility of these compounds. with *in situ*-generated diarylnitrilimines.[ξ,60]

[≠]Although pyrazoles are rarely found in nature probably due to difficulty in the formation of N-N bond by living organisms, they exhibit numerous biological activities. For recent reviews, see reference 59.

[ξ]Catalytic oxidation of aldehyde hydrazones **50** with chloramine T leads to the formation of nitrilimines **51**. See reference 60.



50 **51**



Scheme 8. Synthesis of norcantharidin derivatives **46**. *Reagents and reaction conditions*: i) *p*-aminophenol, Et_3N, Ac_2O, $Mn(OAc)_2$. Yields not specified; ii) ArCH=N-NHPh, EtOH, chloramine T. Yields: **49a** 85.2%; **49b** 85.2%; **49c** 91.7%; iii) $POCl_3$, Et_3N, NaOH. Yields: **46a**, 57.0%; **46b**, 46.0%; **46c**, 43.0%

Cell-growth inhibition assay shows that compounds **46b** and **46c** where even more potent than cantharidin with aqueous solubility greatly improved.

3. MONOTERPENOIDS. THE 1,4-CINEOLE AND ANALOGUES

The cyclic monoterpene 1,4-cineole (1-isopropyl-4-methyl-7-oxabicyclo[2.2.1]heptane **52** (Figure 5), first described in 1907,[61] is widely distributed in nature. Their use as fragrance and flavoring agent is well documented. For instance, compound **52** is a major component of lime (*Citrus aurantifolia*) and eucalyptus (*Eucalyptus polybractea*) being also present in apricot (*Prunus armoniaca*), orange juice (*Citrus sinensis L. Osbeck*), grapefruit juice (*Blettaria cardamomum Matum*), laurel (*Laurus nobilis L.*) and rosemary (*Rosmarinus officinalis L.*).[62]

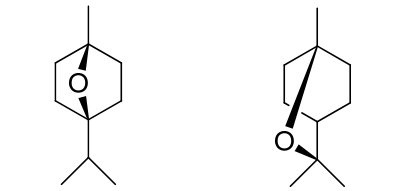
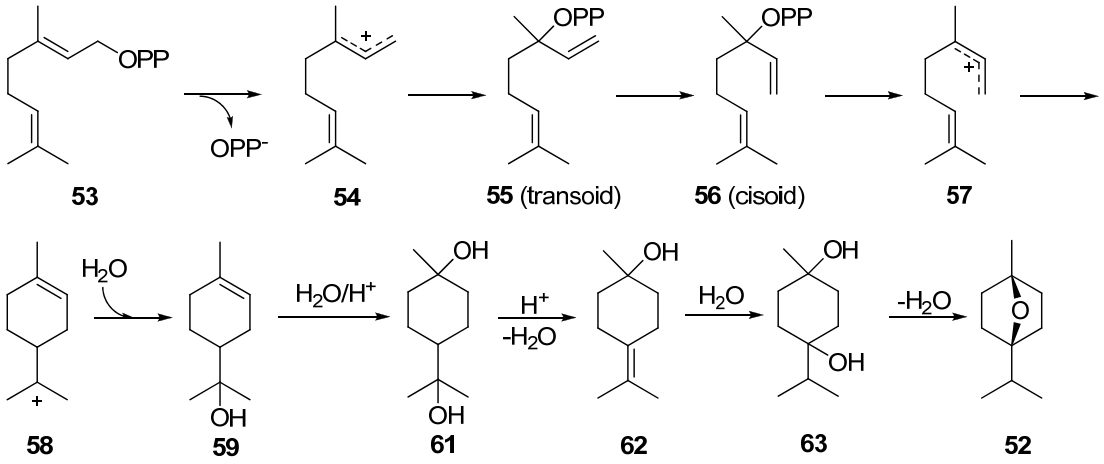


Figure 5. Structures of 1,4-cineole (**52**) and 1,8-cineole (eucalyptol) **60** (see text)

The biosynthesis of 1,4-cineole **52** (Scheme 9) has been determined by feeding to plants with radioactively labeled acetate and subsequent determination of the labeling pattern in the terpene (Scheme 9).[63] Thus, transformation of geranyl diphosphate **53** into α-terpineol **59**, *via* α-terpinyl cation **58**,[64] followed by a sequence hydration-dehydration of the intermediates 1,8-terpin **61**, γ-terpineol **62**, and 1,4-terpin **63**, afforded finally **52**. It should be indicated that the isomerization of α-terpineol **59** to 1,8-cineole **60** and 1,4-cineole **52**, catalyzed by $H_3PW_{12}O_{40}$ in homogeneous and heterogeneous systems, has been reported.[65]



Scheme 9. Biosynthesis of 1,4-cineole **52**

On the other hand, the α-terpinyl cation **58** can undergo a range of cyclizations, rearrangements, and hydride shifts which conforms the biogenetic way for most of the cyclic monoterpenes such as camphene **64**, α– and β-pinene (**65** and **66**) fenchol **67**, terpinolene **68**, limonene **69**, car-3-ene **70**, β-phellandrene **71**, γ-terpinene **72** and sabinene **73** besides the already mentioned α-terpineol **59**. Moreover, the geranyl **54** and linalyl **57** cations also are precursors of the acyclic monoterpenes geraniol **74**, linalool **75**, myrcene **76** and (E)-β-ocymene **77** (Figure 6).[66]

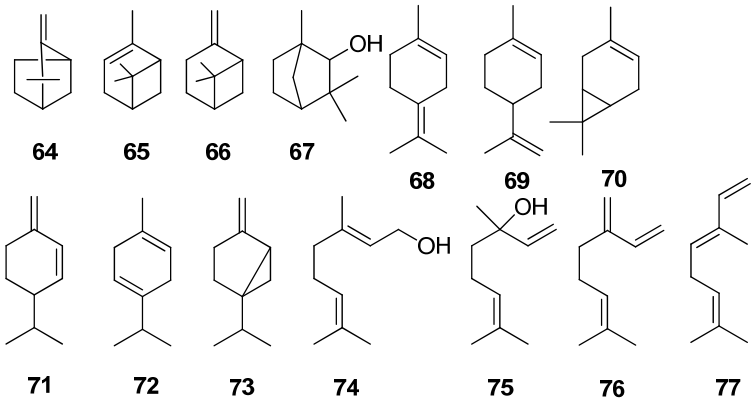
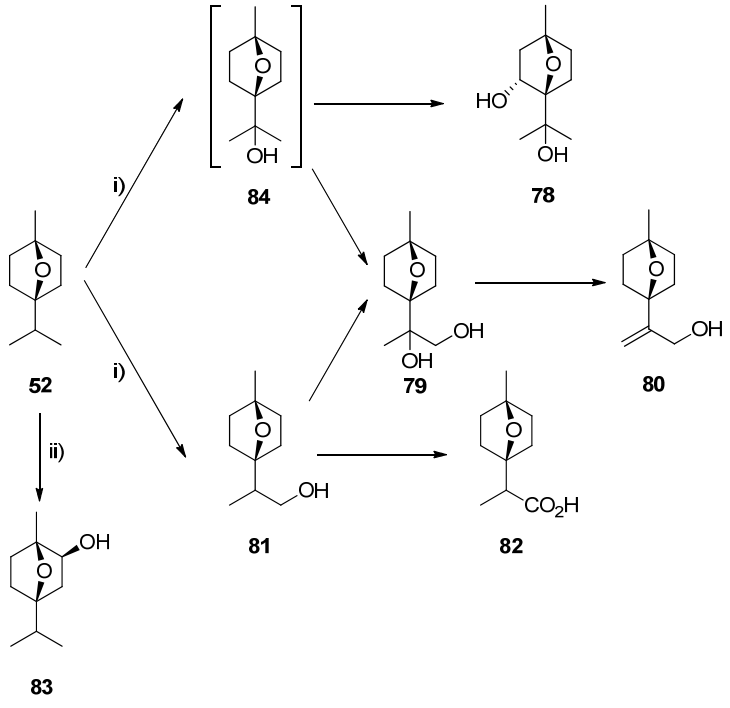


Figure 6. Monoterpenes derived from α-terpinyl cation **58**

The α-terpineol **59** is also the biogenetic precursor of 1,8-cineole (1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane, eucalyptol) **60**, an isomer of 1,4-cineole (Figure 5). The use of 1,8-cineole as flavoring, fragrance and cosmetic,[66] insecticide[67] and repellent[68] is well known. In contrast, eucalyptol is attractive to males of various species of orchid bees.[69] Compound **60** was also found to control airway mocus hypersecretion and asthma[70] and inhibit cytokine[≠,71] production in cultured human limphocytes and monocytes.[72] This compound was found effective in the treatment for non-purulent rhinosinusitis with minimal side effects.[73] Reduction of inflammation and pain when applied topically[74] and activity against leukemia cells in some cultured leukemia human cells has also been reported.[75]

As a consequence of their applications as flavoring agent in alimentation and cosmetic, the metabolism of **52** has been considered.[76] Although there are not *in vivo* studies in humans, after oral applications to rabbits, rats and human liver microsomes, the following metabolites have been identified (Scheme 10): 3,8-dihydroxy-1,4-cineole **78**, 8,9-dihydroxy-1,4-cineole **79**, 1,4-cineole-8-en-9-ol **80**, 9-hydroxy-1,4-cineole **81**, 1,4-cineole-9-carboxylic acid **82** and 2-*exo*-hydroxy-1,4-cineole **83**. Probably, 3-hydroxy-1,4-cineole **84** is the metabolic precursor of **78** and **79**.



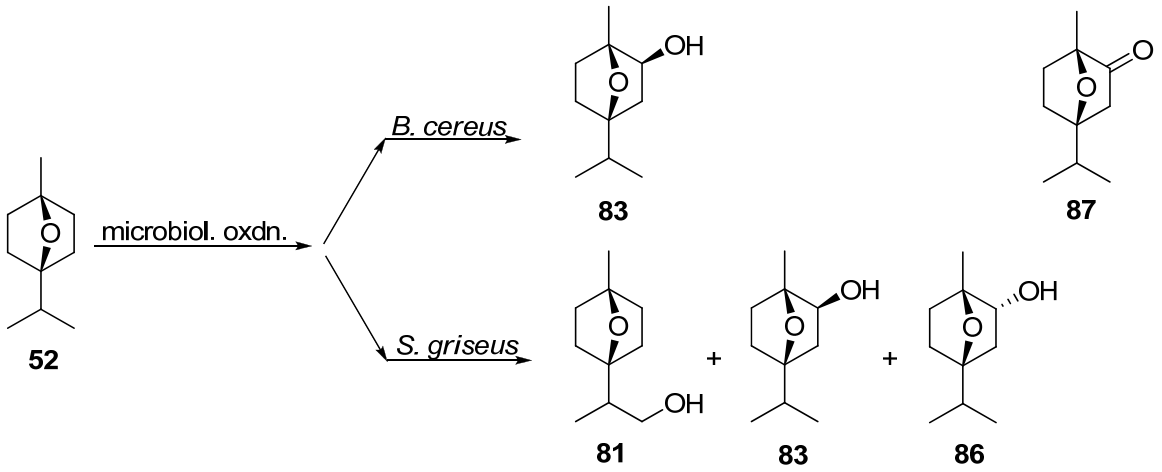
Scheme 10. Metabolism of 1,4-cineole **52**: i) metabolism in rabbit *in vivo*; ii) metabolism in rat *in vivo* and in human liver microsomes

[≠]Cytokines constitute a category of small proteins that are important in cell signalling, being produced by broad range of cells, including immune cells as well as endothelial cells, fibroblasts, and various stromal cells. They are important in connection with some diseases and, specifically, in host responses to infection, immune responses, inflammation, trauma, sepsis, cancer, and reproduction. See reference 73.

The 1,4-cineole **52** possesses important herbicidal activity.[77] In this context the 2-hydroxy derivative (*exo*-2-hydroxy-1,4-cineole) **83**, a constituent of the essential oil of *Ferula jaeschikeana*[78] is of interest as starting material for the synthesis of the 2'-methylbenzyl ether derivative **85**, a commercial herbicide known as cinmethylin (see Figure 7, see below).[≠]

The microbial oxidation of 1,4-cineole **52** was considered using different microorganism (Scheme 11). For instance, *Streptomyces griseus* yielded 8-hydroxy-1,4-cineole **81** as the major hydroxylation product together **83** and **86**.[79] *Bacillus cereus* and *Penicillium frequentatis* yield changing ratios of **83** and **86**.[80] In the case of *P. frequentatis*, both enantiomers of ketone **87** were also produced. Using *Aspergillus niger*, compound **86** was established as the major product.[81] In addition, different oxidases present in plant cultured cells of *Catharantus roseus* produced mixtures of secondary and tertiary alcohols.[82]

The chemo- and stereoselectivity of this microbial oxidation has been studied in deep using *Bacillus cereus* and *Streptomyces griseus* as biocatalysts. The hydroxylation with *B. cereus* displays high face stereoselectivity yielding only 2(*R*)-*exo*-hydroxy-1,4-cineole **83** whereas *S. griseus* gives 8-hydroxy-1,4-cineole **81** as major product together enantiomeric mixtures of **83** and **86** (Scheme 11).[83]



Scheme 11. Microbial oxidation of 1,4-cineol **52**

It was hypothesized[84] that the mode of action of 1,4-cineole derivatives as herbicides consists in blocking the conversion of tyrosine to 4-hydroxyphenylpyruvate (4-HPP). This transformation is catalyzed by tyrosine aminotransferase.[ξ, 85] In the prenylquinone pathway, tyrosine aminotransferase provides

[≠]Cinmethylin **85** is apparently a proherbicide that requires metabolic bioactivation *via* cleavage of the benzylether side chain.

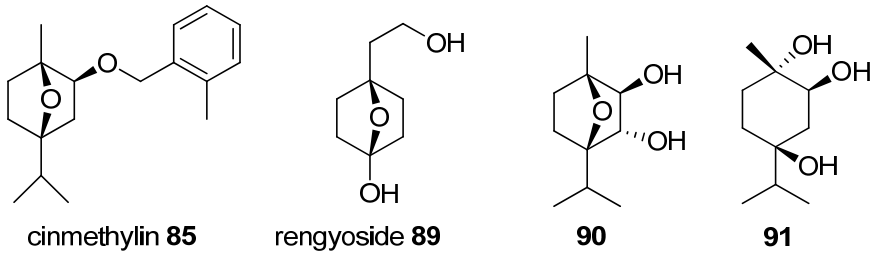
[ξ]For detailed studies on the role of tyrosine aminotransferase in plants see reference 85.

plastoquinone[Υ, 86] a cofactor of phytoene desaturase, an oxidoreductase involved in carotenoid biosynthesis.[87]

On the other hand, 1,4-cineole and the metabolic conversion product of the synthetic herbicide cinmethylin, are potent inhibitors[88] of asparagine synthetase, the key enzyme in asparagine biosynthesis.[≠] Asparagine synthetase plays an important role in nitrogen mobilization.[89] The biological activities of 1,4-cineole as anxiolytic,[90] antimicrobial[91] and permeation agent for percutaneous absorption of drugs[92] have also been reported.

Related with 1,4-cineole is the eight-carbon system rengyoxide **89** (Figure 7), originally isolated from *Forsythia suspensa* fruits[93] and more recently from the wastewaters of *'Megaritiki'*,[94] an olive cultivar widely used in Greece for the production of low polyphenol olive oil and table olives.

Finally it should be indicated that, in reference 1 p. 13531, the structure **90** was attributed to mullilam diol, isolated from *Zanthoxylum rhetsa*, a plant which show antibiotic activity and prescribed in dyspepsia and diarrhoea. This structure has been revised and conclusively verified to possess a structure, (±)-p-menthan-1α,2β,4β-triol **91** (Figure 7).[95]



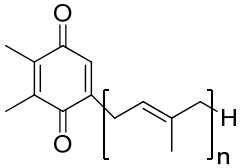
cinmethylin **85** rengyoside **89** **90** **91**

Figure 7. Structures of cinmethylin, rengyoside, putative mullilam diol, **90** and true mullilam diol, **91**

4. OXANORBORNYL-COUMARINS

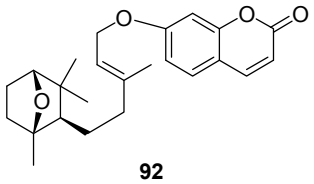
Farnesiferol C **92** (Figure 8) has been isolated from species of the genus *Ferula* such as *F. assafoetida*,[96] *F. szowitsiana*[97] and *F. sinkiagensis*.[98] Compound **92** show antiviral,[99] antiangiogenesis[100] and anticancer activity.

[Υ]Compounds with structure of 2,3-dimethyl-1,4-benzoquinone showing isoprenyl side chains of different length in position 5 (compounds with structure **88**) are designated as plastoquinone-n (PQ-n) where n varying from 6 to 9.



88

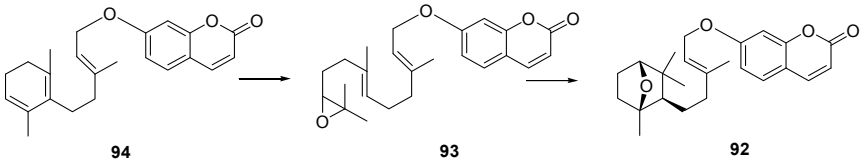
[≠]Asparagine synthetase catalyzes the synthesis of asparagine from glutamine and aspartate through an amidotransferase reaction



92

Figure 8. Structure of (-)-farnesiferol C, **92**

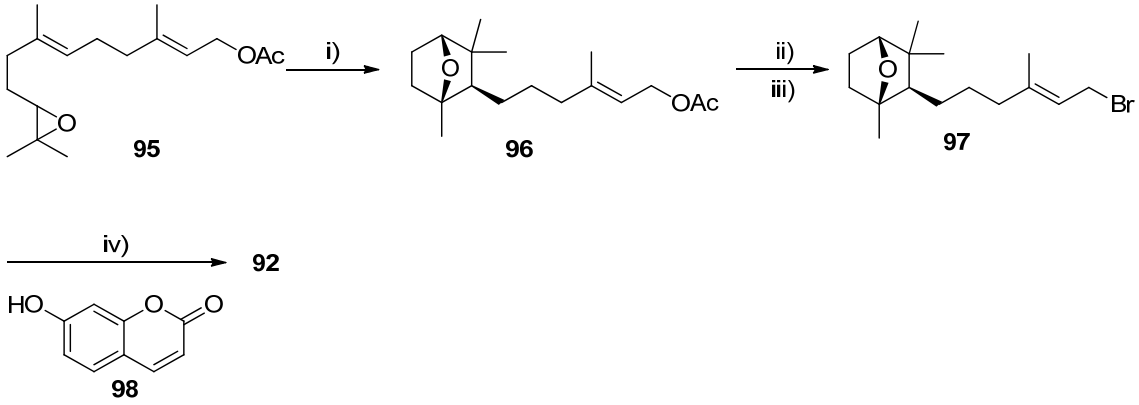
Several biogenetic-type syntheses of **92** by acid-catalyzed cyclizations of epoxy polyenes[≠,101] have been reported. For instance, acid-catalyzed cyclizations[102] of *trans*, *trans* umbelliprepin oxide **93**, easily prepared from the natural coumarin umbelliprepin,[ϒ,103] **94**, afforded **92** albeit in low yield (Scheme 12).



94 **93** **92**

Scheme 12. Biogenetic-type synthesis of farnesiferol **92**

Other convenient biogenetic-type synthesis of **92** was carried out from 10,11-epoxyfarnesyl acetate **95**[104] using a key step a zeolite[105] NaY-catalyzed cyclizations to give **96**. Further standard transformations of **96** into bromide **97** and final coupling of **97** with umbelliferone **98** yielded **92** (Scheme 13).[106] Attempts to perform the direct transformation of **93** into **92** using zeolite NaY were unsuccessful.



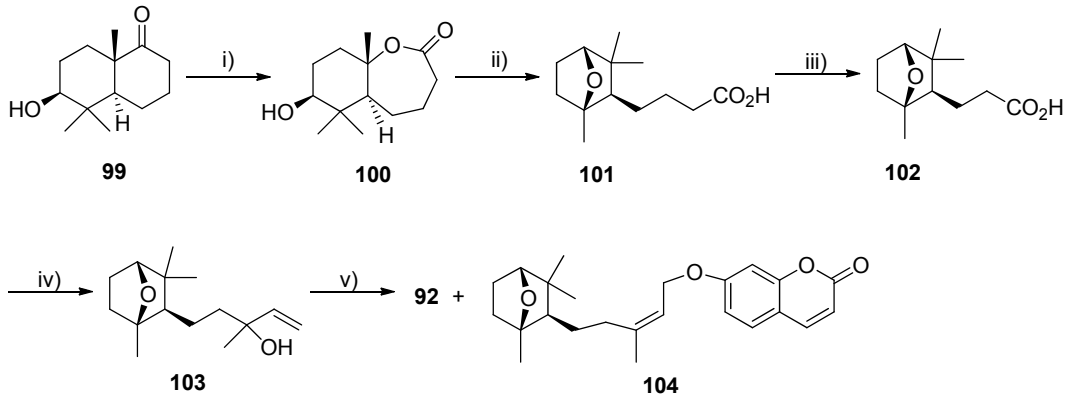
95 **96** **97** **98**

Scheme 13. Synthesis of farnesiferol **92** from 10,11-epoxyfarnesyl acetate **95**. *Reagents and reaction conditions*: i) NaY, 20 ºC, 15 min, 30%; ii) K_2CO_3, MeOH, 99%; iii) PBr_3, Et_2O, 94%; iv) **98**, K_2CO_3, acetone, 20 ºC, 12 h, 87%

≠The acid-catalyzed cyclization of epoxi polyenes has attracted much attention due to the discovery that analogous enzyme-catalyzed reaction are involved in the biosynthesis of a large array of terpenoids. See reference 101

ϒCompound **94** was isolated from *Ammi majus L.* fruits. See reference 103.

A non biogenetic-type synthesis of racemic **92** together the *Z*-isomer **104** has also been reported (Scheme 14).[107] The key step was the Baeyer-Villiger oxidation of decalone **99**[≠] to give lactone **100** which rearranges to the 7-oxanorbornane derivative **101**. Standard Barbier-Wieland degradation of this compound to **102** followed by ketone formation and vinylmagnesium bromide addition gave **103**. Further sequence of bromination and coupling with **98** afforded a mixture of **92** and **104** in ratio 3:1.



Scheme 14. Synthesis of farnesiferol **92** and the *Z*-isomer **104** from ketone **99**. *Reagents and reaction conditions*: i) CF_3CO_3H/CF_3CO_2H; ii) H^+; iii) a. CH_2N_2; b. PhMgBr; c. H_3O^+; d. $KMnO_4/NaIO_4$; iv) a. MeLi; b. vinylmagnesium bromide; v) a. PBr_3/Py; b. $AcOH/K_2CO_3$/**98**

The optical antipode of the natural product, (+)-farnesiferol C **105** was synthesized from the magnesium salt of the phenylglycinol derivative **106** by means of an intramolecular furan Diels-Alder (IMDAF) reaction. (Scheme 15).[108] In this way, a mixture of compounds **107** and **108** (ratio **107**:**108** = 78:12) was obtained. From **107,** a 15 step sequence afforded **109** which, by formation of the bromide and reaction with the potassium salt of **98**, gave **105**.

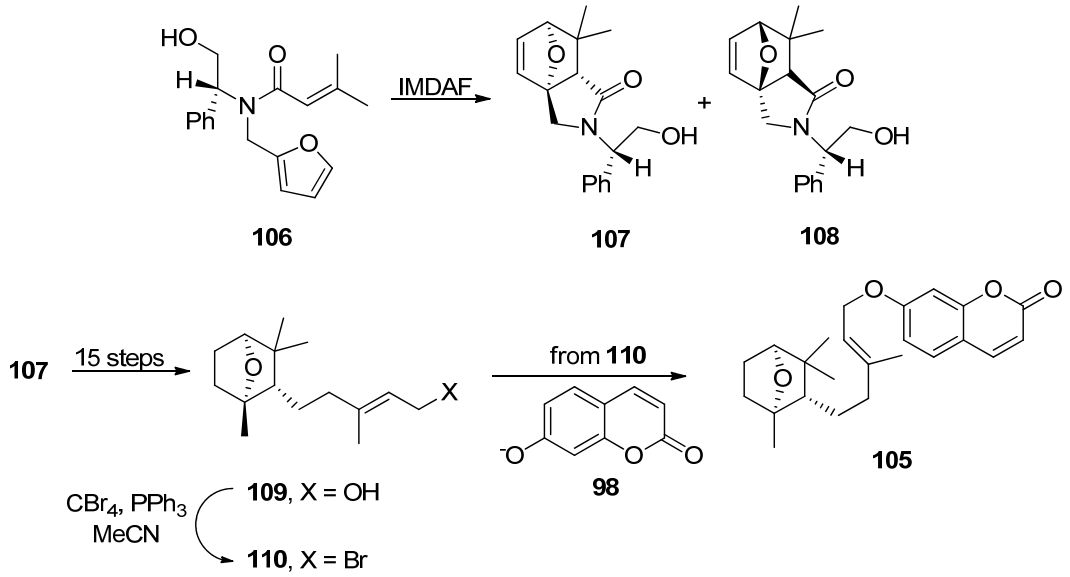
Creticacoumarin **111**, an oxidized form of **92** (Figure 9)[109] was isolated from *Anthemis cretica.* On the other hand, the natural coumarin (-)-3', 6'-epoxyauraptene was first isolated[110] from various *Aster* species (genus of flowering plants of the family of *Asteraceae*) and its structure determined as **112** (Figure 9) both chemically[111] and by X-ray analysis.[112]

The biomimetic synthesis of **112** has been carried out starting from the 7-geranyloxycoumarin **113** (auraptene) which, in turn, was synthesized from geraniol **74** *via* geranyl bromide **115** and further reaction with the sodium salt of umbelliferone **98** (Scheme 16).[113]

In the last decade auraptene was seen to exert important biological activivities such as anticancer, anti-bacterial, anti-protozoal, anti-fungal, anti-inflammatory and anti-oxidant.[114]

[≠]Compound **99** was synthesized by Robinson annelation of 2-methyl-cyclohexanedione with ethylvinyl ketone and further elaboration of the resulting product. See: D. L. Snitman, M. Y. Tsai, and D. S. Watt, *J. Org. Chem*., 1979, **44**, 2838.

The transformation of **113** into **112** was carried out by way of the terminal epoxide **114**, also isolated from the same natural source.[112]



Scheme 15. Synthesis of (+)-farnesiferol C **105**

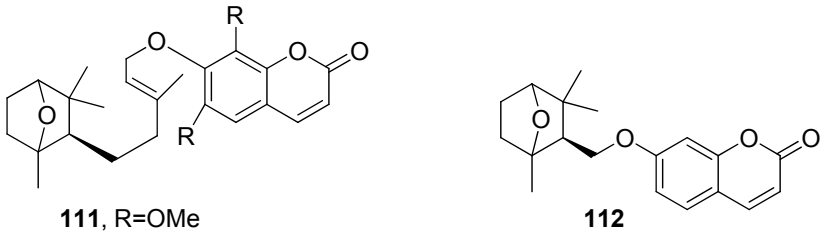
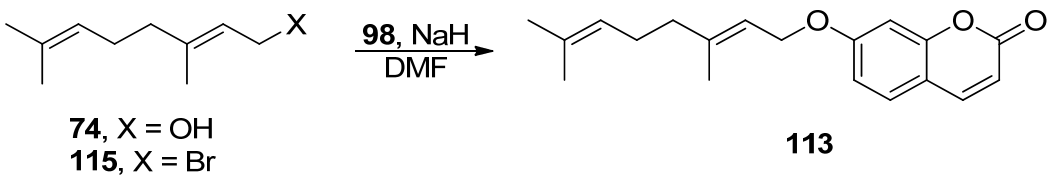
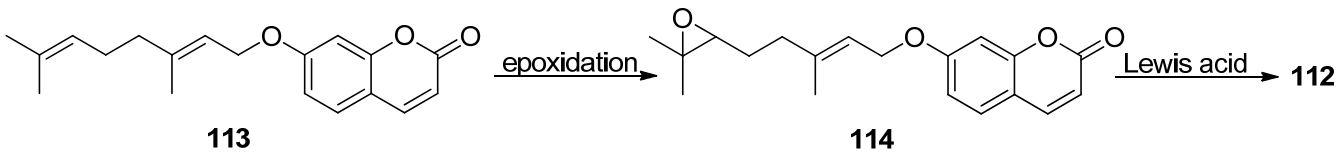


Figure 9. Structure of creticacoumarin, **111** and 3',6'-epoxiauraptene, **112**



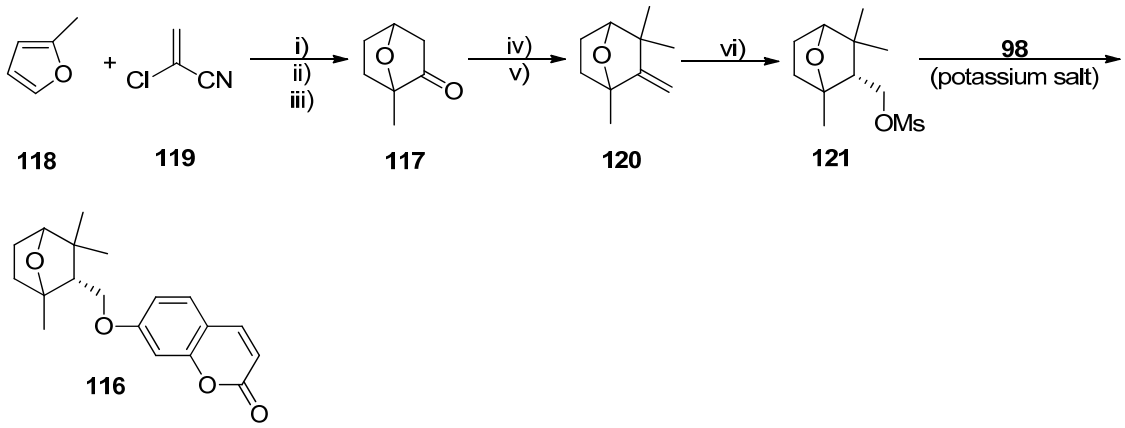
Scheme 16. Synthesis of geranyloxycoumarin **113** (auraptene) from geraniol **74**

Epoxide **114** has been synthesized in racemic form *via* a sequence hydroxylation-hypobromination[115] or in optically pure form using Sharpless asymmetric epoxidation[116] or microbial dihydroxylation.[117] Treatment of **114** with Lewis acid, in particular $SnCl_4$, afforded **112** (Scheme 17). The best yield reported was 60%.[113]



Scheme 17. Synthesis of (-)-3',6'-epoxyauraptene **112** from 7-geranyloxycoumarin **113**

The racemic 2-epimer of **112**, compound **116**, has been synthesized from ketone **117**[≠,118,119] easily accessible by Diels-Alder cycloaddition of 2-methylfuran **118** and 2-chloroacrylonitrile **119** (Scheme 18).[120] Double methylation of **117** at C-3 followed by Wittig olefination gave **120** which, by oxidative hydroboration followed by mesylation and reaction with the potassium salt of **98**, gave **116**.



Scheme 18. Synthesis of compound **116** from 2-methylfuran **118**. *Reagents and reaction conditions*: i) ZnI_2, 0 ºC, 14 d; ii) H_2/Pd-C; iii) KOH, *t*-BuOH; iv) MeI, *t*-BuOK; v) Ph_3PCH_2; vi) a. BH_3·THF; b. $H_2O_2/^-OH$; c. MsCl/Py

5. SESQUITERPENOIDS

5.1 . Epoxy-2,5-megastigma-6,8-dienes and related compounds.

These compounds, as 6(*E*),8(*E*)-, **122** and 6(*E*)-8(*Z*)-, **123** diatereoisomers (Figure 10) were first isolated[121] from *Osmanthus absolute* and their structures determined by synthesis from ethyl α-safranate (see below). Both compounds have been also detected as aroma component of *Malphigia glabra*.[122] The 6(*E*),8(*E*) diastereoisomer **122** was detected[123] in the essential oils of *Centaurea sericeae* and *Centaurea ensiformis* and in the volatile flavor of *Malpighia emarginata.*[124] The basic structure, but with

≠The use of ketone **117** in the synthesis of natural products containing the 1,3,3-trimethyl-7-oxabiyclo[2.2.1]heptane moiety has been reviewed. See reference 118. On the other hand, compound **117** serves as versatile template for the synthesis of other subunits of natural products and analogues. See reference 119.

undetermined stereochemistry, has been also detected as volatile component of honey bush (*Cyclopia subternata*).[125]

The first synthesis of compounds **122** and **123** was achieved starting from ethyl α-safranate **124** (Scheme 19).[121,ϒ]

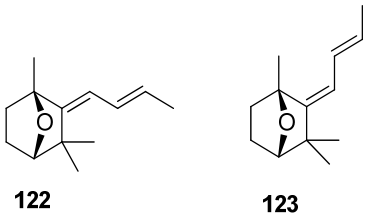
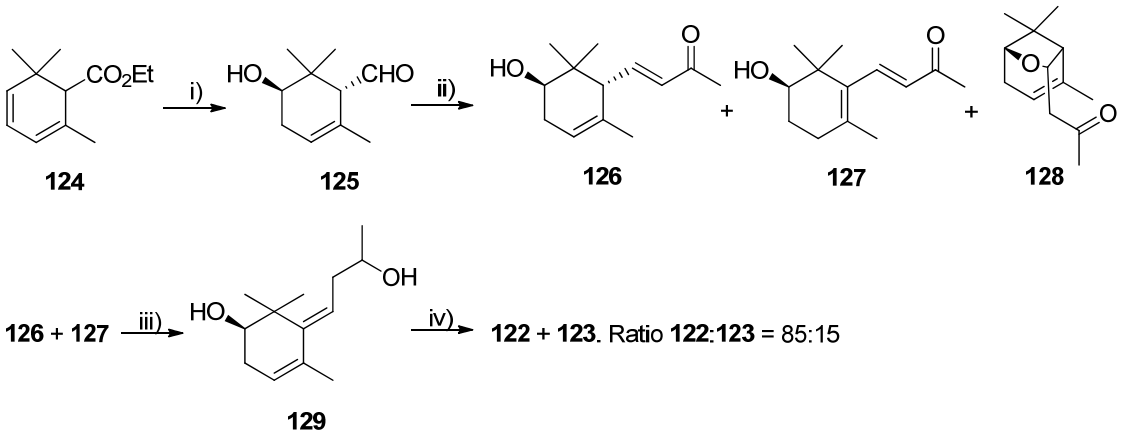


Figure 10. Structures of epoxy-2,5-megastigma-6,8-dienes **122** and **123**

This compound was transformed into 2-hydroxy-α-cyclocitral **125** through a five-steps sequence, including sensitized photooxidation, catalytic hydrogenation, dehydration, reduction with litium aluminium hydride and re-oxidation with pridinium chlorochromate. The base-catalyzed condensation of **125** with acetone afforded a mixture of compounds **126**, **127** and **128**, this later probably arising from intramolecular Michael addition of **126**. After purification, the hydroxyketones **126** and **127** were transformed into diol **129**. Acid treatment of **129** gave a mixture of **122** and **123** in ratio 85:15 and 50% overall yield in this last step.

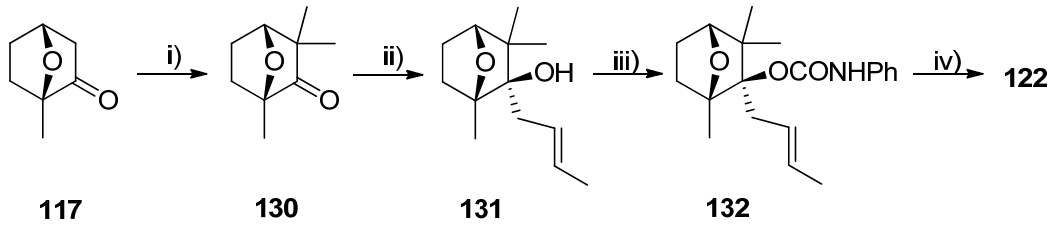


Scheme 19. Synthesis of epoxy-2,5-megastigma-6,8-dienes **122** and **123** from ethyl α-safranate **124.** *Reagents and reaction conditions*: i) a. O_2, hν, Rose Bengal, EtOH; b. H_2/PtO_2; c. TsOH, toluene; d. $LiAlH_4$, THF; e. pyridinium chlorochromate, CH_2Cl_2; ii) Acetone, KOH; iii) isopropenyl acetate, $LiAlH_4$; iv) TsOH

[ϒ]Interestingly, this synthetic sequence, reproduced by Mori *et al*., confirms that the natural, minor compound **123** (see reference 121) was isolated in only 11% e.e. See : K. Mori and H. Tamura, *Tetrahedron*, 1986, **42**, 2643.

A convenient synthesis of **122** has been carried out[126] from ketone **117**. This compound was transformed into ketone **130** which, after reaction with the Grignard reagent derived from (*E*)-1-bromo-2-butene and dehydration of the resulting product **131** *via* phenyluretane **132**, afforded **122** (Scheme 20).

Alcohol **133** (Figure 11) has been found as trace component in *Osmanthus absolute* and can be also obtained (10%) in the acidic treatment of compound **129**.[121] On the other hand, alcohol **134** (Figure 11) was found as component of essential oil of Lank[127] and Japanese *Saifu* tobacco[128] and has been also isolated from *Saussurea cordifolia*.[129] This compound constitutes the aglycon (C-9-O-β-D)-of the glucosyde Crotanoloside C, from *Crotalaria zanzibarica*.[130]



Scheme 20. Synthesis of epoxy-2,5-megastigma-6,8-diene **122** from ketone **117.** *Reagents and reaction conditions*: i) MeI, *t*-BuOK; ii) C_4H_7MgBr, Et_2O; iii) C_6H_5NCO, Py; iv) 225 ºC

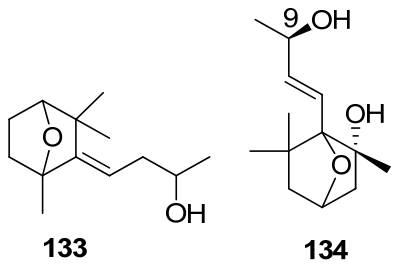


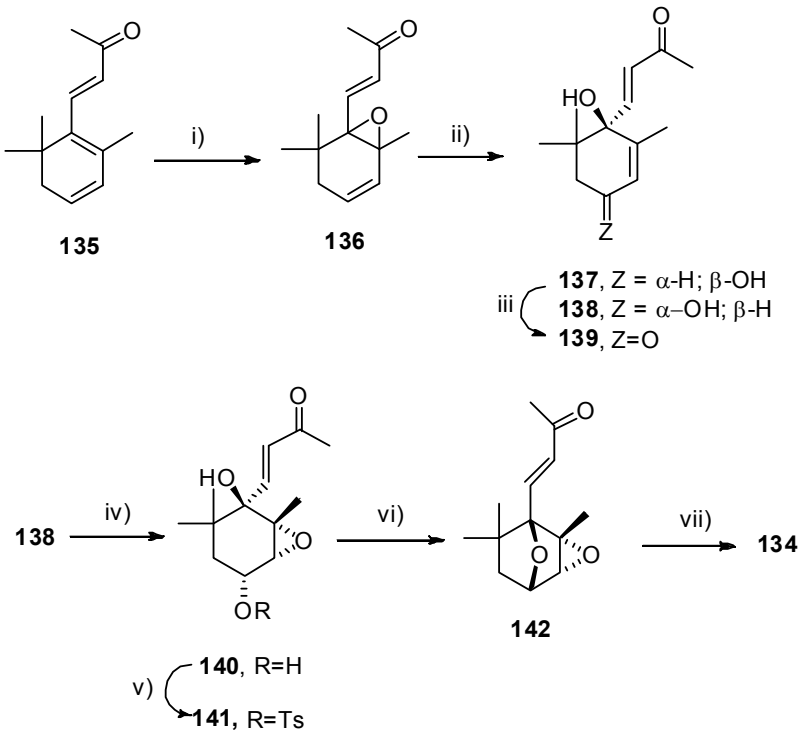
Figure 11. Structure of alcohols **133** and **134**.

The synthesis and structure confirmation by X-ray analysis of compound **134** has been accomplished[131] starting from dehydroionone derivative **135**[132] (Scheme 21).

5.2. Chamigrene derivatives.

Compounds **143** (oxachamigrene) and **144** were isolated from *Laurentia obtuse*.[133] Two others halogenated sesquiterpenoids, compounds **145** and **146**, were also isolated from *L. obtuse*[134] and *L. pannosa*[135] respectively (Figure 12).[≠]

[≠]For an exhaustive review on the halogenated organic molecules of *Rhodomelaceae* origin, see: B. G. Wang, J. B. Gloer, N. J. Ji, and J. C. Zhao, *Chem. Rev*., 2013, **113**, 3632. The *Rhodomelaceae* is the largest marine red algal family. A total of 1058 naturally occurring compounds were isolated and characterized from *Rhodomelaceae* (1960-early 2012). Of these, 76% were halogenated molecules.



Scheme 21. Synthesis of alcohol **134** from dehydroionone derivative **135**. *Reagents and reaction conditions:* i) Reference 132; ii) H_2O, dioxane; iii) CrO_3, H_2SO_4, H_2O; iv) *m*CPBA, CH_2Cl_2; v) TsOH, py; vi) NaH, THF; vii) $LiAlH_4$, THF

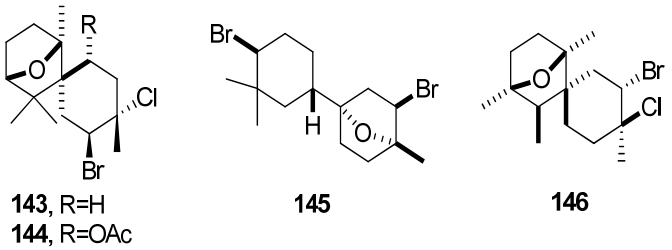
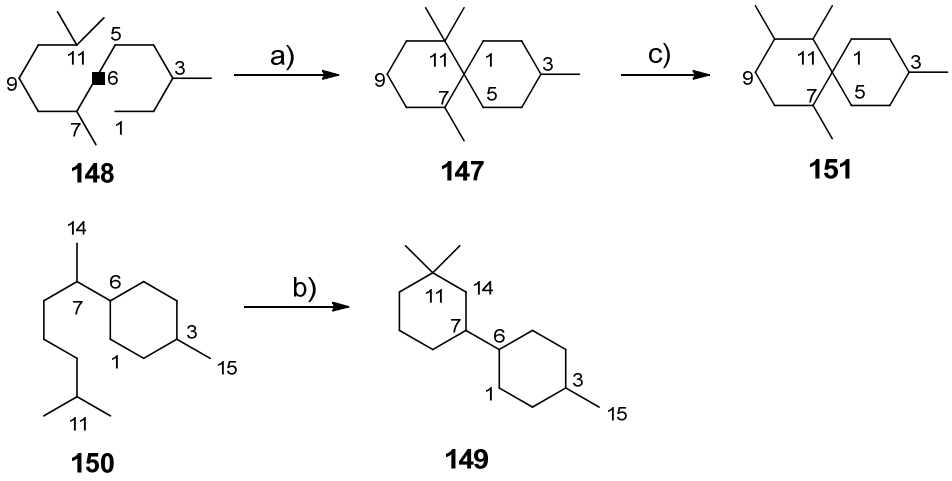
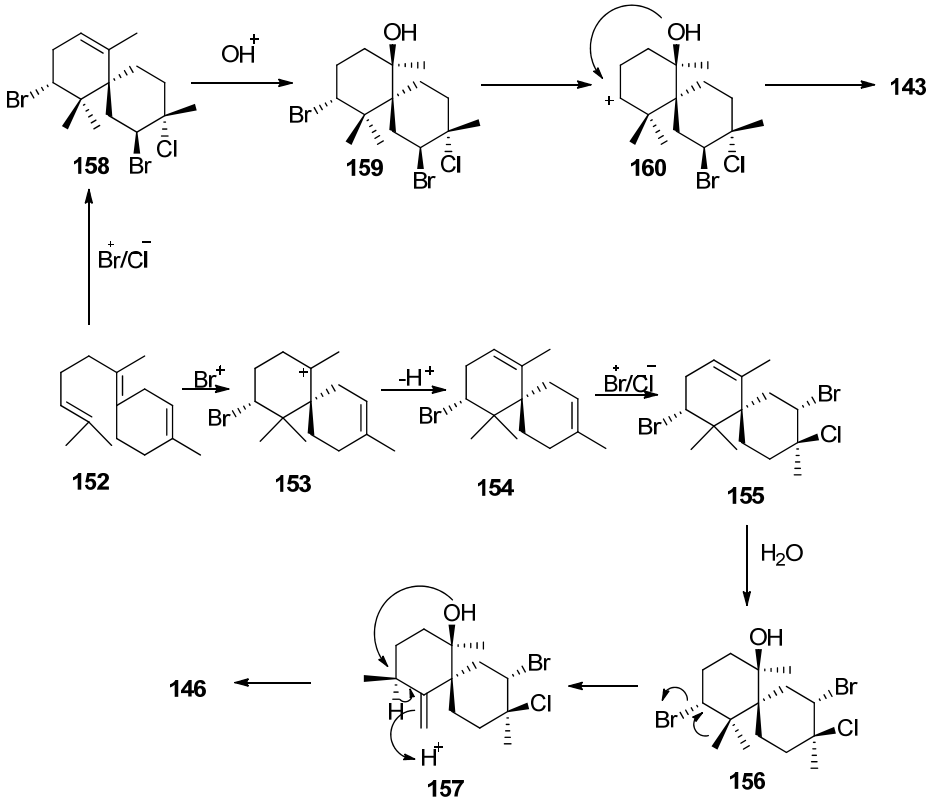


Figure 12. Structures of compounds **143**-**146**

Compounds **143** and **144** show the chamigrene (spiro [5,5]undecane) skeleton **147**, formally originate from linking the bonds C1-C6 and C6-C11 of farnesane **148** (Scheme 22a) whereas compound **145** representing a new class of cyclohexylcyclohexane-containing carbon skeleton **149** that may be rationalized as arising from C11−C14 cyclization of the bisabolane framework **150** (Scheme 22b). Finally, compound **146** (pannosane) possessing a new carbon skeleton **151** appears to result from a methyl migration from C11 to C10 of chamigrene framework **147** (Scheme 22c).[136] For compounds **143**, **144** and **146** two biogenetic pathways have been proposed starting from γ-bisabolene **152**. Both sequences are outlined in Schemes 23 and 24.



Scheme 22. Biogenetic origin of compounds **143-146**

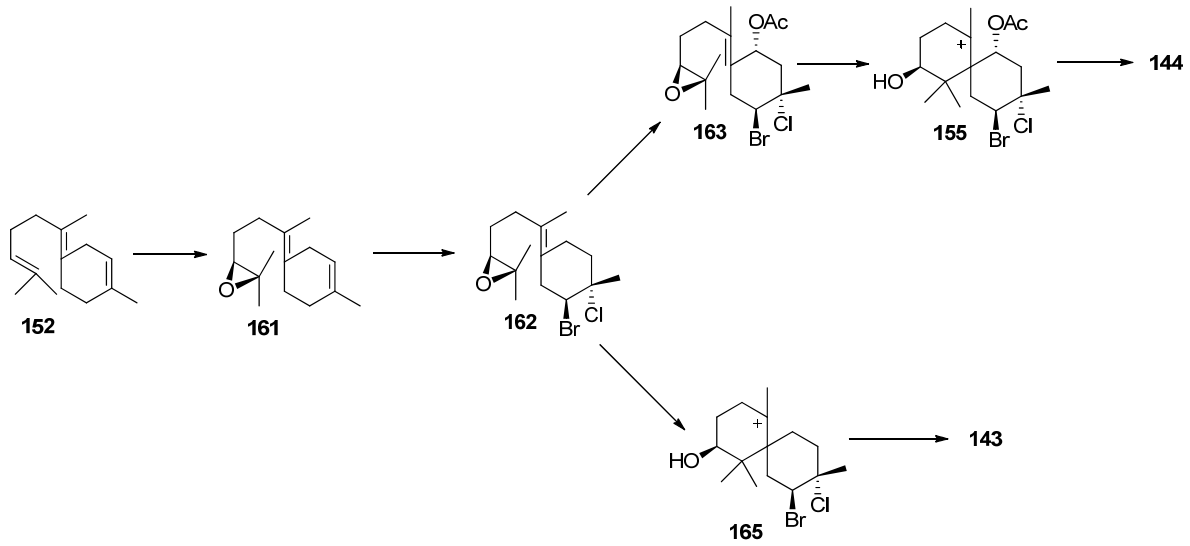


Scheme 23. Proposed biogenetic pathway for compounds **143** and **146** (I) (see references 133 and 135)

5.3. Laurenditerpenol and derivatives.

(-)-Laurenditerpenol **166** (Figure 13), isolated from the red alga *Laurencia intrincata,*[137] was shown to inhibit activation of hypoxia inducible factor 1 (HIF-1). The HIF-1 plays an important role in cellular and systemic responses to hypoxia (condition in which the body or a region of the body is deprived of

adequate oxygen supply). This inhibitory activity constitutes a valuable alternative for the late-stage cancer therapy.[138]



Scheme 24. Proposed biogenetic pathway for compounds **143** and **144** (II) (see reference 133)

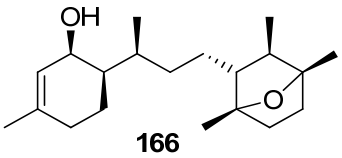
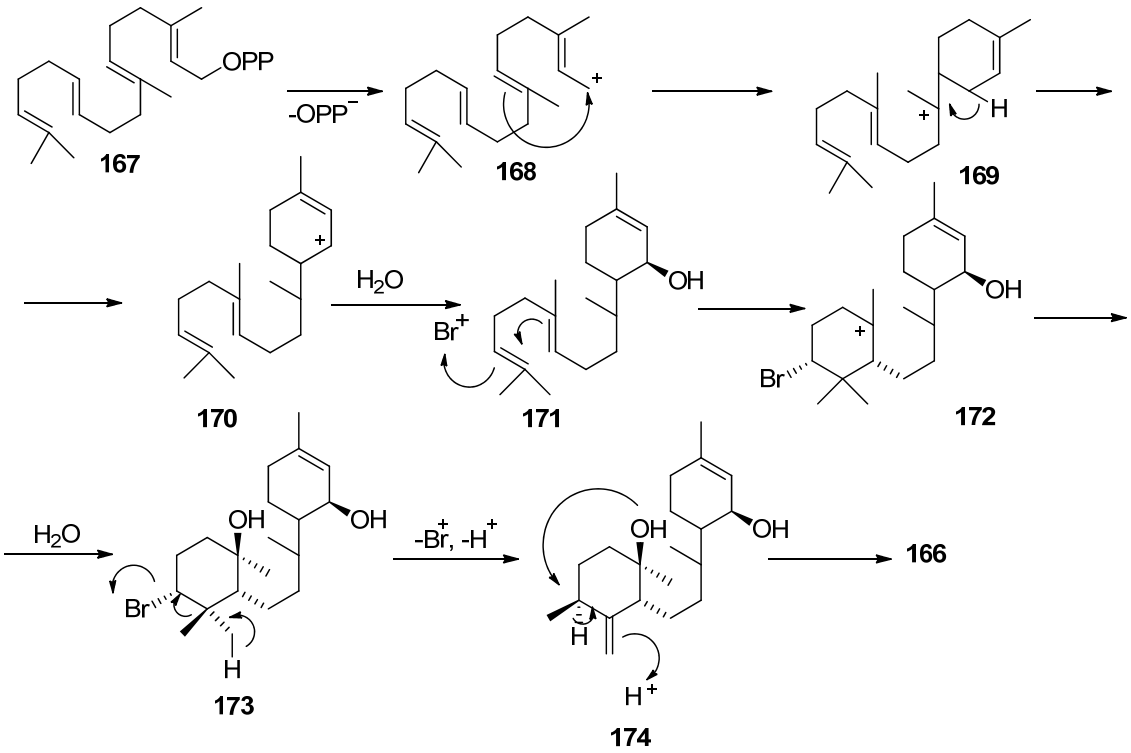


Figure 13. Structure of (-)-laurenditerpenol, **166**

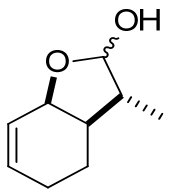
Considering that brominated terpenes are among the most common natural products produced by *Laurencia* spp. seems logical to assume that the compound **166** may be biogenetically formed from farnesyl pyrophosphate **167** through a sequence bromine assisted-cyclization-debromination of a diterpene precursor **171** as indicate in Scheme 25.[137]

A synthesis of racemic **166** and its diastereomer **175** was achieved[139] in a convergent fashion (Scheme 26) by coupling fragments **176** and **177** *via* Julia olefination procedure followed by reduction and deprotection of the dehydro derivatives **180** and **181**. Aldehyde **176** was synthesized from enone **178**[140] in a nine-steps sequence whereas sulfone **177** was prepared from the DA adduct of 2,5-dimethylfuran and maleic anhydride[141] **179** in eight steps. Coupling of **176** and **177** yielded a mixture of *cis*-and *trans*-products **180**-**183** from which the desired *E*-products could be separated by flash chromatography and submitted to diimide reduction to give a 1:1 mixture of **184** and **185**.



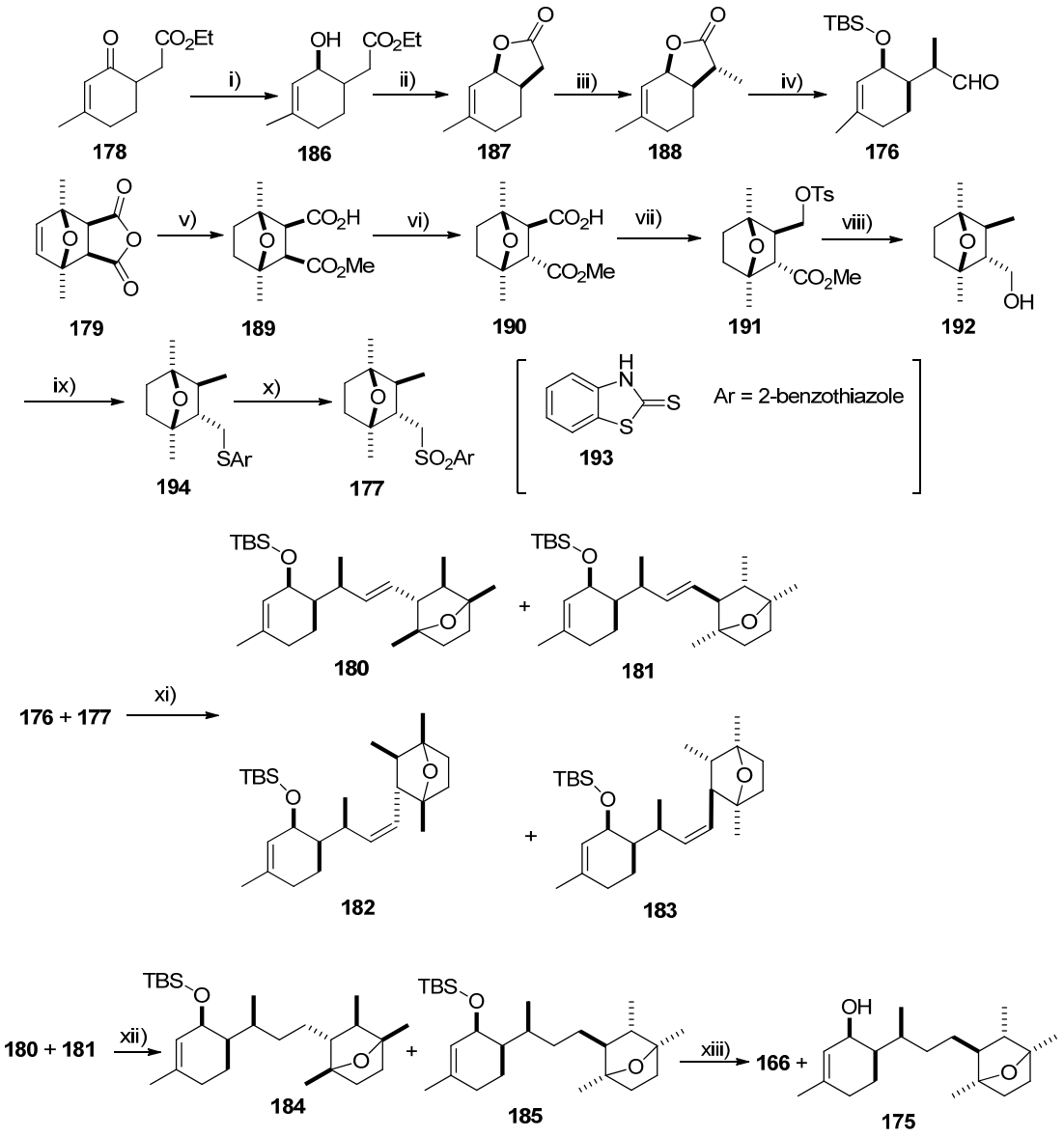
Scheme 25. Proposed biosynthesis of (-)-laurenditerpenol **166**

Treatment of this mixture with TBAF afforded **166** and **175** which were partially separated by chromatography. In the context of the synthetic sequence depicted in Scheme 26, two comments are pertinent: a) Unfortunately the Julia-Kocienski olefination between lactol **203**, prepared from **188** by reduction with DIBAL, and sulfone **177** failed probably because the lactol exits mainly in the cyclic form (Figure 14); b) Compound **188** is known as wine lactone. Wine lactone was found in white wines. There are 8 possible isomers of wine lactone being the (3*S*, 3a *S*, 7a*R*) isomer the only one that has been found in wine. The odour threshold of the wine lactone is 0.00001-0.00004 ng/l in air.[142]



203

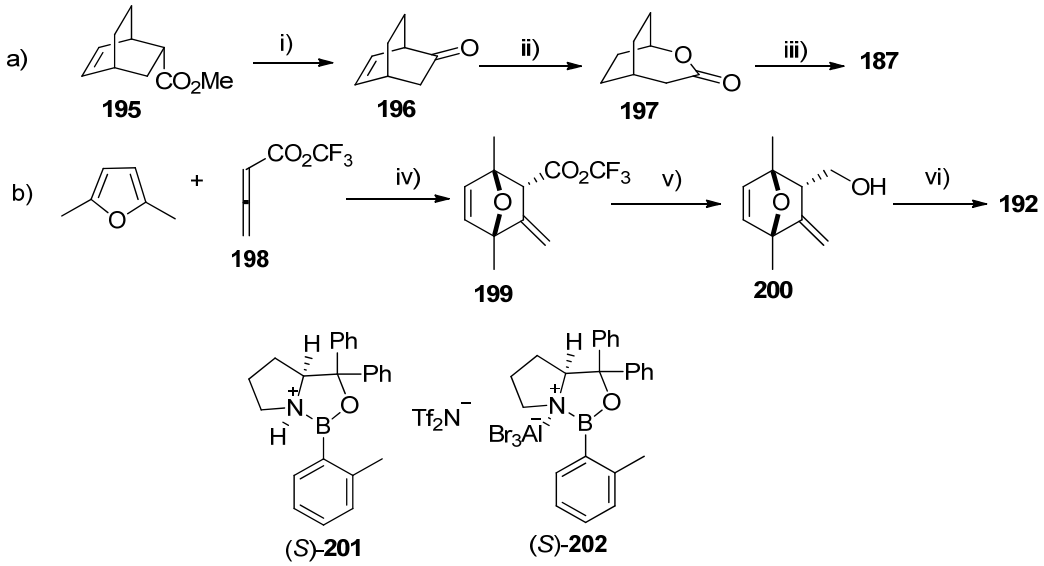
Figure 14. Structure of compound **203**



Scheme 26. Synthesis of racemic Laurenditerpenol **166** and isomer **175**. *Reagents and reaction conditions*: i) $NaBH_4$, $CeCl_3$, MeOH, 88%; ii) a. KOH, EtOH; b. DCC, DMAP, 38% (two steps); iii) LDA, MeI, -78 ºC, 85%; iv) DIBAL, -78 ºC, 84%; v) a. $LiAlH_4$, 0 ºC; b. PivCl, py; c. TBSCl, Im-H; d. DIBAL, -78 ºC; e. TPAP, NMO; 51% (five steps); vi) a. H_2, Pd/C, AcOEt; b. MeOH, heat; 79% (two steps); vii) MeONa, MeOH, 95%; viii) a. BH_3-THF; b. TsCl, py, CH_2Cl_2; 79% (two steps); ix) DIAD, PPh_3, CH_2Cl_2, 25 ºC, Ar-SH, 96%; x) *m*CPBA 0 ºC, 95%; xi) LiHMDS, -78 ºC, SiO_2, 88%, *Z:E*=1:1 xii) $KCO_2N{=}NCO_2K$, py, AcOH, MeOH, SiO_2, 33%; xiii) TBAF, 72%

Compounds **187** and **192** have been synthesized[143,144] in 99%ee and 87%ee respectively according with the following protocols (Scheme 27): starting from the DA adduct of 1,3-cyclohexadiene and methyl

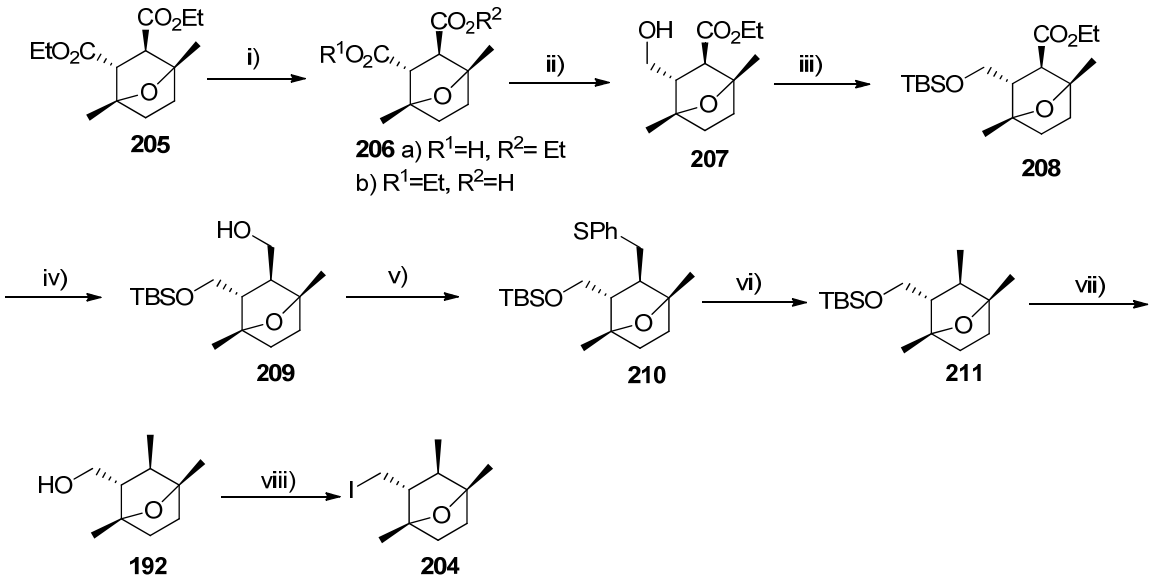
acrylate **195,**[≠] the nitrosobenzene-mediated transformation into ketone **196** followed by Baeyer-Villiger oxidation, ring-opening reaction and MeMgBr addition, cleany afforded **187** without any loss of optical purity (Scheme 27a). On the other hand, the synthesis of **192** was achieved by Diels-Alder reaction of 2,5-dimethylfuran and allenic ester **198** in the presence of catalyst (*S*)-**201**, followed by reduction and catalytic hydrogenation in the presence of Willkinson's catalyst (Scheme 27b). Thus, this procedure constitutes a convenient enantioselective approach to (-)-**166**.



Scheme 27. Enantioselective synthesis of compounds **187** and **192** *Reagents and reaction conditions*: i) a. LDA, PhNO, THF, -78 ºC. b. LiOH, dioxane-H_2O, 35 ºC; 68%; ii) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 ºC, 85%; iii) a. LiOH, THF-H_2O, rt; b. DMP, THF-CH_2Cl_2, 0 ºC-rt; c. MeMgBr, THF-Et_2O, 0 ºC; d. 4M H_2SO_4, 0 ºC-rt; 59% iv) Catalyst (*S*)-**201** (5 mol%), toluene, -63 ºC, 95%, ratio *endo*:*exo* = 87:13, 87% ee; v) $LiAlH_4$, Et_2O, 0 ºC-rt 99%; vi) H_2, 5 mol% $[Rh(PPh_3)]Cl$, CH_2Cl_2, rt, 88% (dr 83:17)

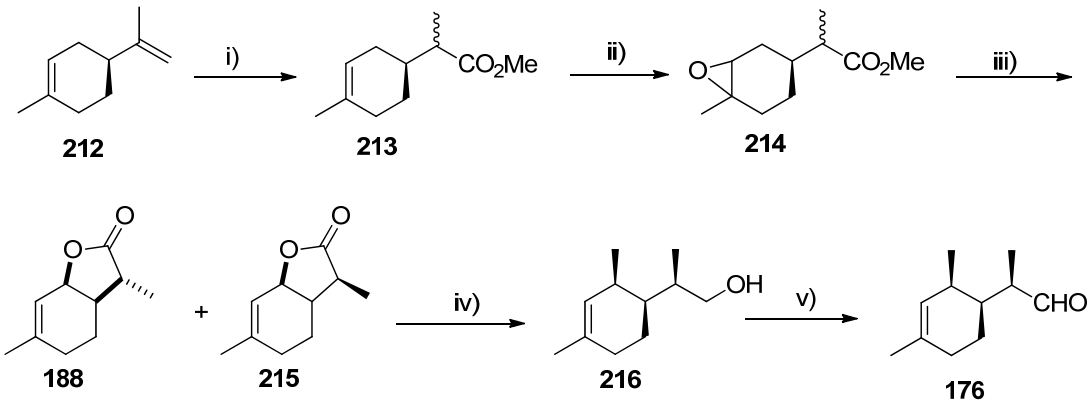
A related approach to (-)-**166** has been accomplished[145] through the addition of the organolithium compound derived from **204** to aldehyde **176** (see Scheme 26). The oxanorbornane derivative **204** was prepared from **192** which was in turn synthesized in seven steps from **205** (Scheme 28a). This compound had been previously prepared by catalytic enantioselective Diels-Alder reaction of diethyl fumarate and 2,5-dimethylfuran[146] followed by hydrogenation of the resulting cycloadduct.

[≠]Compound **195** has been previously synthesized by DA reaction of 1,3-cyclohexadiene and methyl acrylate (90% yield, 99%ee) using the chiral oxazaboralidinone triflate **201** as catalyst. See Scheme 27 and reference 143. On the other hand, the catalytic DA reaction of **198** has also been carried out in the presence of catalyst (S)-**202** using cyclopentadiene and furan as diene components and several acrylic esters as dienophilic counterparts. In most cases, (S)-**202** was found to be superior to catalyst (S)-**201**. See reference 144.



Scheme 28a. *Reagents and reaction conditions*: i) LiOH, EtOH-H_2O, 0 ºC; ii) BH_3.THF, THF, 74%; iii) TBSCl, imidazole, DMF, rt; iv) DIBAL, THF, -78 ºC, 90% two steps; v) PhSSPh, *n*Bu_3P, toluene, rt, 95%; vi) Raney Ni, MeOH, rt; vii) AcOH, THF, H_2O, rt, 89% two steps; viii) I_2, PPh_3, imidazole, CH_2Cl_2, 0 ºC-40 ºC, 92%

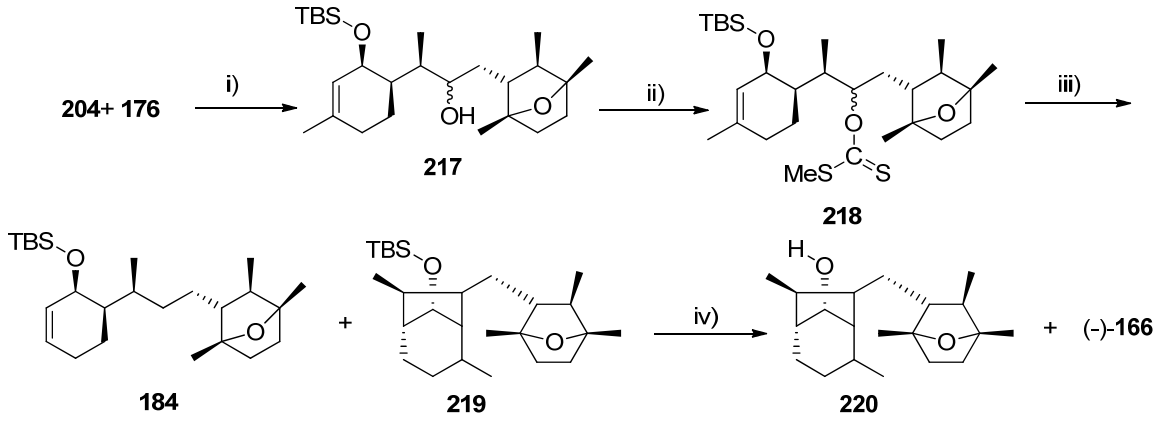
On the other hand, aldehyde **176** was synthesized in this approach from compound **213** (eight steps, Scheme 28b).



Scheme 28b. *Reagents and reaction conditions* i) Reference 147; ii) *m*CPBA, Na_2HPO_4, CH_2Cl_2, 0 ºC, 86%; iii) a. PhSeBr, $NaBH_4$, MeOH, rt to 65 ºC; b. 30% H_2O_2, THF, 0 ºC to 65 ºC; 44%; iv) a. $LiAlH_4$, THF, 0 ºC; b. PivCl, DMAP, Py, 0 ºC; c. TBSCl, imidazole, DMF, rt; d. DIBAL, CH_2Cl_2, -78 ºC, 67%; v) NMO, TPAP, MS 4A, CH_2Cl_2, rt, 85%

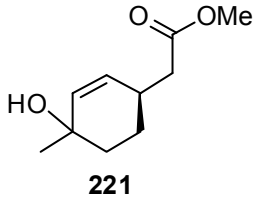
Compound **213** was obtained in three steps as a 1:1 mixture of diastereomers from *S*-limonene **212**.[147] Lithiation of **204** followed by slow addition of a solution of **176** in diethyl ether led to the formation of

alcohols **217** in 30% yield as a 3:1 mixture of C(8) epimers. After a further three-steps sequence, compound (-)-**166** was obtained in 31% yield over the last four steps (Scheme 28c).



Scheme 28c. *Reagents and reaction conditions* i) *t*BuLi, pentane-Et_2O, 30 min. Then, addition of **176**, -100 ºC, 30%, epimeric mixture 3:1, 45% recovered **176**; ii) NaHDMS, THF, CS_2, MeI, -78 ºC to rt; iii) $n$$Bu_3SnH$, Et_3B, toluene, rt, 80%; ratio **184**:**219**=2:1; iv) TBAF, CH_2Cl_2, 40 ºC, 77%

It should be pointed out that the mixture of epimeric lactones **188** and **215** arises from the non isolated compound **221** (Figure 15), *via* allylic rearrangement and lactonization.

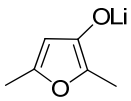


221

Figure 15. Structure of the non-isolated compound **221**

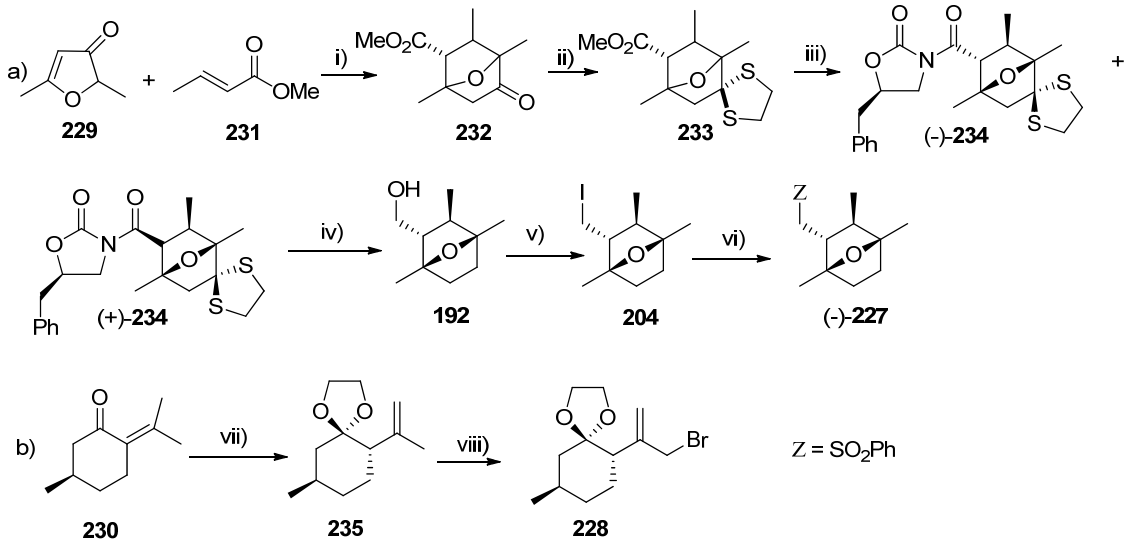
The absolute stereochemistry of **166** was determined through an asymmetric total synthesis as well as their distereomers **222-226**.[148] The synthetic scheme was based on the coupling of the optically pure sulfone (-)-**227** and the halide **228** which were in turn prepared from 2,5-dimethyl-3(2*H*)-furanone **229** and *R*-(+)-pulegone **230** respectively. The preparation of compounds **227**and **228** are outlined in Scheme 29. Reaction of **229** with methyl crotonate **231** produced racemic **232**[ξ,149] which, after thioketalization and hydrolysis afforded racemic **233**. Resolution of this compound via *N*-acyloxazolidinones (-) and

[ξ] The formation of **232** may be due to either an "anion-assisted" DA cycloaddition through intermediate **254** or a sequential Michael additions. See reference 149.



254

(+)-**234** followed by standard transformations gave pure sulfones (-)-**227** and (+)-**227** (Scheme 29a). The synthesis of both sulfones (-)-**227** and (+)-**227** were carried out starting from (-)-**234** and (+)-**234** respectively, through the same reaction sequence. Only the stereostructure of the "natural" moiety [from (-)-**234**] is showed. The crystal structure of (-)-**234** established the absolute configuration of the oxanorbornene ring system of **166**, previously proposed on the basis of NMR experiments.

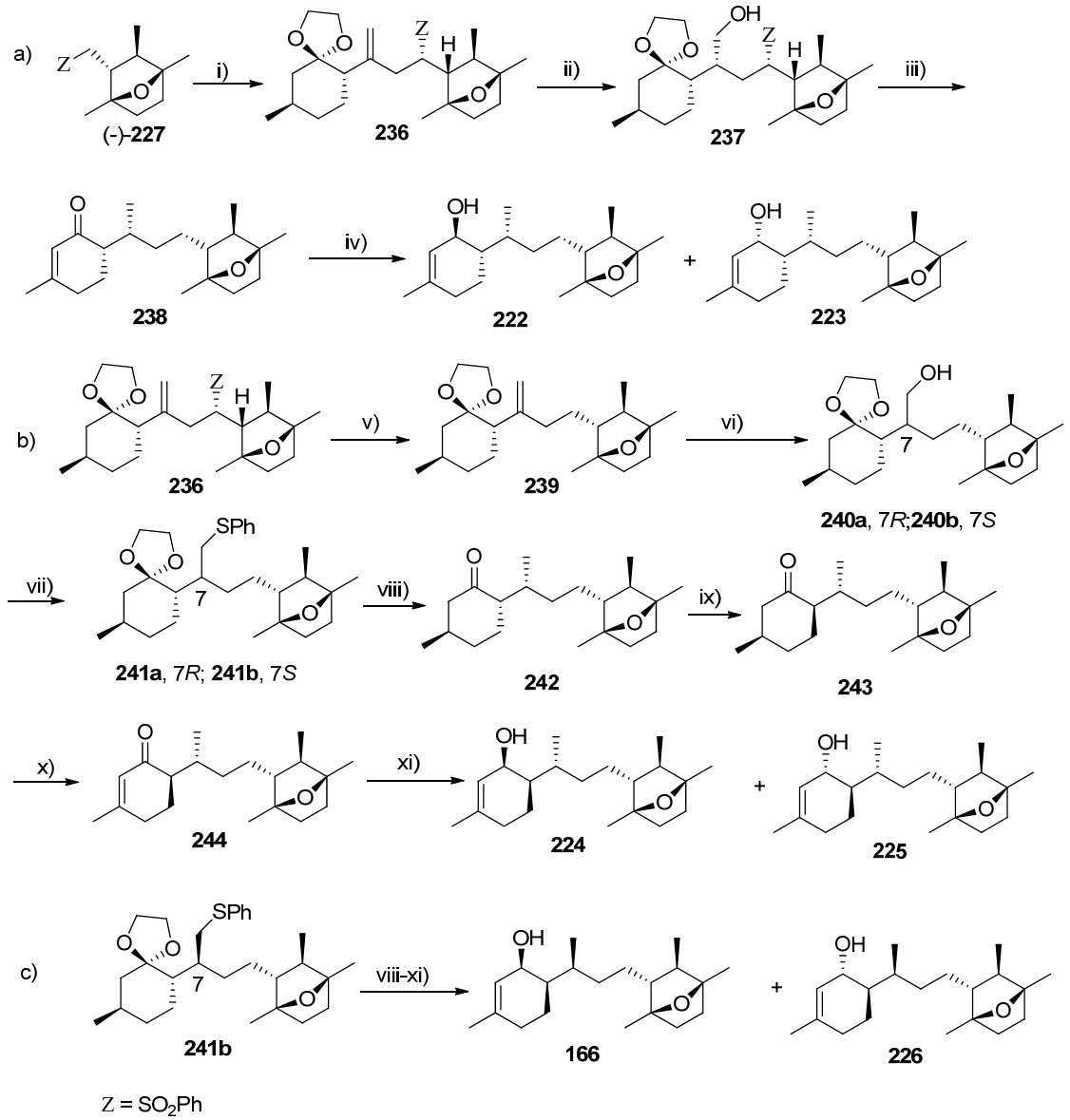


Scheme 29. Synthesis of intermediates **227** and **228**. *Reagents and reaction conditions*: i) LDA, Et_2O, cyclohexane, -78 ºC, then **221**, 69%; ii) a. ethanedithiol, *p*-TsOH, benzene, reflux, b. LiOH, aq. MeOH, 92% two steps; iii) TEA, trimethylacetyl chloride, LiCl, (S)-4-benzyl-2-oxazolidinone, CH_2Cl_2, rt, separation of distereomers (SiO_2 chromatography): (-)-**234**, 40%; (+)-**234**, 42%; iv) a. Raney Ni, EtOH, reflux, 98%, b. $LiBH_4$, THF, 0 ºC, (-)-**192**, 93%; (+)-**192**, 94%, v) Ph_3P, I_2, imidazole, CH_2Cl_2, rt, (-)-**204**, 94%; (+)-**204**, 92%; vi) $PhSO_3Na$, DMF, 60 ºC, (-)-**227**, 90%; (+)-**227**, 91%; viii) $(CH_2OH)_2$, CSA, benzene, reflux, 24 h., 73%, dr = 92:8; viii) NBS, $Yb(OTf)_3$, TMSCl, CH_2Cl_2, 0 ºC, 15 min, 48%

The coupling of (-)-**227** and bromide **228** afforded the sulfone **236** which was transformed into alcohol **237** in a stereo-and regioselective fashion *via* a sequence hydroboration-oxidation. The stereochemistry of this reaction may be explained in terms of electrophilic borane addition according with the Felkin-Anh-Houk hypothesis.[150] Further transformation of **237** into ketone **238** was accomplished through a six-step sequence. Regioselective reduction of **238** gave a chromatographically separable C1 epimers **222** and **223** (Scheme 30a).

The remaining stereoisomers **166** and **224**-**226** were synthesized from sulfone **236** following the previously developed synthetic strategy but altering the reaction sequence (Scheme 30b). Thus, considering that the observed stereoinduction in the hydroboration reaction of **236** was consequence of the presence of the phenylsulfone functionality, compound **236** was first desulfonylated. After reduction

and further sulfinylation, a chromatographically separable mixture of diastereomers **241** was obtained.



Scheme 30. Synthesis of compounds **224**, **225** and **166**, **226**. *Reagents and reaction conditions*: i) *n*BuLi, HMPA, THF, -40 ºC, then **228**, 98% (dr 95:5); ii) a. $BH_3 \cdot S(CH_3)_2$, THF, 10 h; b. H_2O_2, NaOH, 0 ºC, 87%, two steps; iii) a. $(PhS)_2$, $(n\text{Bu})_3P$, toluene, rt, 94%; b. Raney Ni, EtOH, reflux, 90%; c. $PdCl_2(MeCN)_2$, acetone, rt, 92%; d. Na-Hg (10%), MeOH, rt, 68%; e. LDA, PhSeCl, THF, -78 ºC; f. Py, H_2O_2, CH_2Cl_2, H_2O, 0 ºC, 78%; iv) $CeCl_3$, $NaBH_4$, MeOH, 0 ºC, 72%; v) Na-Hg, MeOH, rt, 6 h, 78%; vi) a. $BH_3 \cdot$DMS, THF, then H_2O_2, NaOH, 0 ºC, 86%; vii) $(PhS)_2$, $(n\text{Bu})_3P$, toluene, rt, 90%. Ratio **241a**:**241b**=3:1; viii) a. Chromatographic separation; b. Raney Ni, EtOH, reflux, 94% for **233a**, 90% for **242b**; ix) KOH, MeOH, rt, 12 h, 30% epimerization for **242a**; 35% epimerization for **242b**; x) a. LDA, -78 ºC; HMPA, THF, 1 h. Then PhSeCl, 2 h; b. H_2O_2, THF, 30 min, 72% **244a**; 68% **244b**, two steps; xi) $CeCl_3$, $NaBH_4$, MeOH, 0 ºC, 84% (ratio **224**:**225**= 2:3), 80% (ratio **166**:**226**= 2:3)

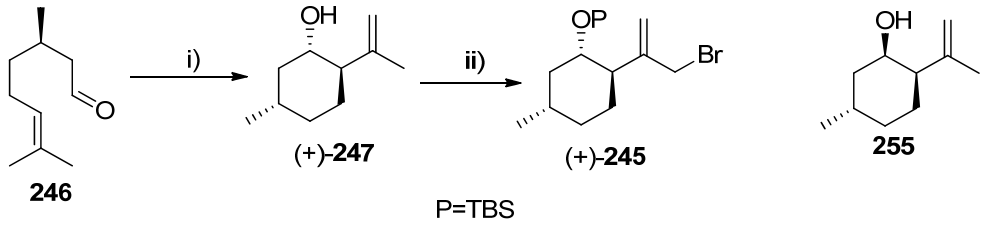
Separation of both C7 epimers, reductive elimination of phenyl sulfide in **241** and deketalization yielded ketone **242** which, after epimerization to **243**, dehydrogenation to enone **244** and regioselective reduction, produced stereoisomers **224** and **225** in ratio **224**:**225** = 2:3.

Following the same synthetic sequence, stereoisomers **166** and **226** were also synthesized from **241b** (Scheme 30c). Synthetic **166** shows ^{1}H- and ^{13}C-NMR spectra, rotation value and TLC behaviour identical to a sample of the natural product.

Compounds **223** and **224** were evaluated for their ability to inhibit hypoxia-induced HFI activation, showing that the inversion of configuration at C7 (compound **224**) was associated with a 76% drop in potency relative to synthetic **166** whereas inversion of configuration at C1, C6 and C7 (compound **223**) results in total loss of biological activity.

A notable improvement of this synthetic sequence applied to the total synthesis of both enantiomers of laurenditerpenol has been achieved[151] by modification of the following original features:

* Bromide **228** was substituted by bromide (+)-**245**. This compound was synthesized in four steps from (*S*)-citronellal **246** via $ZnCl_2$-catalyzed intramolecular Prins cyclizations[152] to give (+)-isopulegol **247** following by silyl protection and regioselective allylic bromination (Scheme 31). In the synthesis of (+)-**247** from **246**, minor amounts (11%) of (-)-neo-isopulegol **255** were also obtained. The mixture of (+)-**247** and (-)-**255** was easily purified by SiO_2 column chromatography.

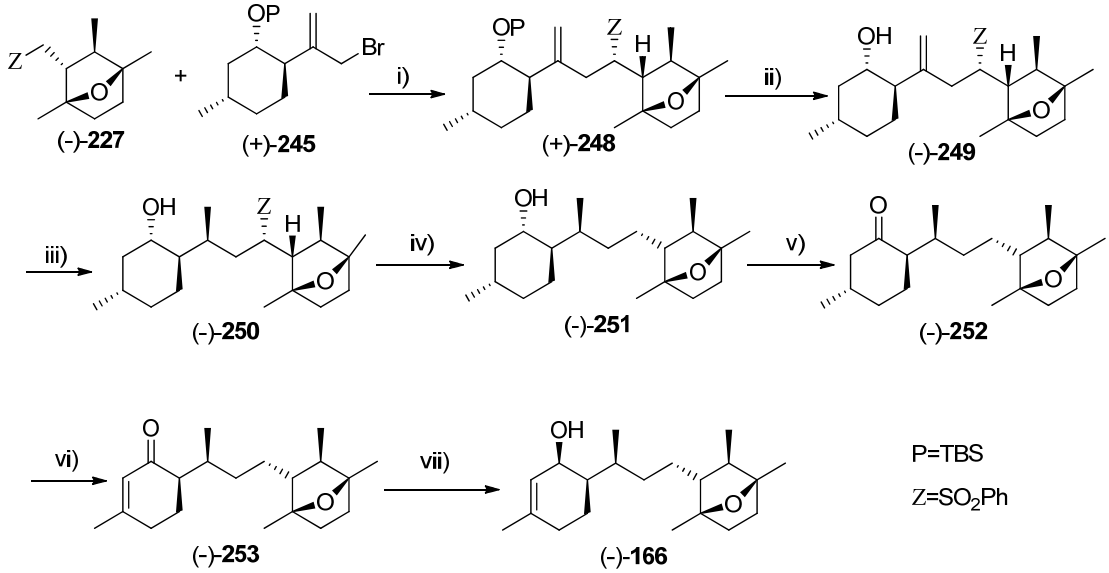


Scheme 31. Synthesis of bromide **245**. *Reagents and reaction conditions*: i) $ZnCl_2$, Et_2O-CH_2Cl_2, -78 ºC to rt, 14 h, 70%; ii) a. TBSOTf, imidazole, 0 ºC to rt, 5 h, 98%; b. NBS, $Yb(OTf)_3$, DCM-THF, 0 ºC to rt, 92%

* Coupling of (+)-**245** with sulfone (-)-**227**[148] (Scheme 32) gave (+)-**248** which, after TBS deprotection, afforded **249**. Hydroxy-directed hydrogenation[≠,153] of this compound using Crabtree's catalyst[154] yielded (-)-**250** which was desulfonylated to (-)-**251**. The transformation of (-)-**251** into (-)-**166** was achieved via the ketone (-)-**252** and enone (-)-**253** using the same synthetic protocols depicted in Scheme 30. The

[≠]The stereochemistry of this directed-hydrogenation reaction appears to be a consequence of simultaneous coordination of Ir to the hydroxyl group at C1 and the alkene between C7-C19, forming a rigid, chair-like intermediate. In this context, see reference 153.

unnatural (+)-**166** was synthesized following the same synthetic sequence starting from sulfone (+)-**227**[148] and bromide (-)-**245** prepared from commercially available (-)-isopulegol.



Scheme 32. Synthesis of laurenditerpenol **166**. *Reagents and reaction conditions*: i) *n*BuLi, HMPA, THF, -40 ºC, 5 h, dr 85:12; ii) TFA, CH_2Cl_2, 0 ºC, 2 h, 90%; iii) Crabtree's catalyst, CH_2Cl_2, rt, 3 h, 90%; iv) Na-Hg, MeOH, rt, 30 min, 85%; v) DMP, CH_2Cl_2 0 ºC, rt, 3 h, 92%; vi) a. LDA, PhSeCl, THF, -78 ºC, 5 h; b. Py, H_2O_2, CH_2Cl_2, 0 ºC, 2 h, 85% two steps; vii) $CeCl_3$, $NaBH_4$, MeOH, 0 ºC, 82%

6. C -15 ACETOGENINS. MANOENENE AND ISOMANOENENE GROUP

The C-15 acetogenins[ϒ,155] belong to a large family of halogenated[ξ] compounds commonly found in species of the family *Rhodomelaceae*. The manoene group features a skeleton of hexahydro-2,6-methanofuro[3,2-*b*]furan **256** whereas the biscarbocyclic skeleton of isomaneonenes consist in a system of octahydro-1,3-dioxa-2,4-mathanocyclopenta[*cd*]pentalene **257** (Figure 16).

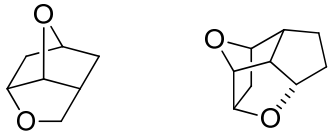


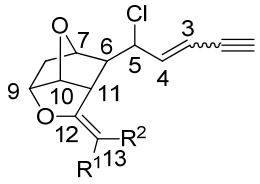
Figure 16. The basic skeleton of manoenenes **256** and isomanoenenes **257**

[ϒ]The difference between C-15 acetogenins and sesquiterpenes consists in their different biogenetic pathway. The sesquiterpenes, like all terpenoids, are formed by condensation of isopentenyl pyrophosphate (see reference 64) whereas C-15 acetogenins arise biogenetically from a common C-15 precursor which derives from a C 16 fatty acid. See reference 155.

[ξ]In these halogenated compounds as well as in halogenated sesquiterpenes the role of marine haloperoxidases appears to be well documented: A. Butler and J. N. Carter-Franklyn, *Nat. Prod. Rep.*, 2004, **21**, 180.

All manoenene derivatives isolated up the date are quoted in Table 1. All of them have been isolated from *Laurentia* species and, as common characteristic, each manoenene derivative features terminal ethyl and *cis*- or *trans* enyne units. In addition, all maneonene are bromochlorinated with chlorine at C5 and bromine at C13.

Table 1. The maneonene group



R^1, R^2 = Et, Br

----------Stereochemistry----------

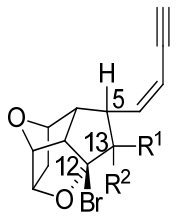
Comp.nº(a)	C3,4	C5	C6	C7	C9	C10	C11	C12,13	Source(c)	Reference
258	*Z*	*R*	*S*	*R*	*R*	*R*	*S*	*E*	L. n.	156 157
259	*Z*	*R*	*S*	*R*	*R*	*R*	*S*	*Z*	L. n.	156 157
260	*E*	*R*	*S*	*R*	*R*	*R*	*S*	*Z*	L. n.	156 157
261	*Z*	*R*	*R*	*R*	*R*	*R*	*S*	*E*	L. n.	157 158
262	*E*	*R*	*S*	*R*	*R*	*R*	*S*	*Z*	L. p.	159
263	*E*	*R*	*R*	*R*	*R*	*R*	*S*	*E*	L. p; L. o.	159 160
264 (b)	*Z*	*R*	*R*	*R*	*R*	*R*	*S*	*Z*	L. o.	160
265 (b)	*Z*	*S**	*R**	*R**	*R**	*R**	*S**	*Z*	L. sp	161
266	*Z*	*S**	*R**	*R**	*R**	*R**	*S**	*E*	L. m.	162

(a). Names assigned: **258**, *cis*-maneonene A; **259**, *cis*-maneonene B; **260**, *trans*-maneonene B; **261**, *cis*-maneonene C; **262**, 12-*Z*-*trans*-maneonene B; **263**, 12-*E*-*cis*-maneonene E; **264**, 12-*Z*-*trans*-maneonene C; **265**, Lembyne A; **266**, 12-*E*-lembyne A. (b) Relative stereochemistry. (c) L. n.: *Laurecia nidifica*; L. P.: *Laurencia papillosa*; L. o.: *Laurencia obtusa*; L. sp.: unidentified *Laurencia* species, L. m.: *Laurencia mariennensis*

The biological activity of some of these compounds has been evaluated. Thus, compound **263** induces apoptosis and may be involved in regulation of programmed death in the initiation and propagation of

inflammatory responses.[160] Also this compound showed high potential as a natural insecticide against the beetle larvae *Tribolium confusus* and against the larvae of mosquito *Culex pipiens*.[159] On the other hand, compounds **265** and **268** show antibacterial activity against some marine bacteria.[161]

Regarding the isomaneonenes, also isolated from *Laurencia* species, these compounds are all dibrominated at C-12 and C-13 showing, as the manoenene derivatives, the terminal ethyl and *cis*- or *trans*-enyne units (Figure 17).



R^1, R^2 = Et, Br

267, isomaneonene A,[157,158] 5*S*, 13*R*; **268**, lambyne B,[161] 5*R*,* 13*R*;* **269**, isomaneonene B,[158] 5*S*, 13*S*.

Figure 17. Structures of isomaneonenes **267**-**269**

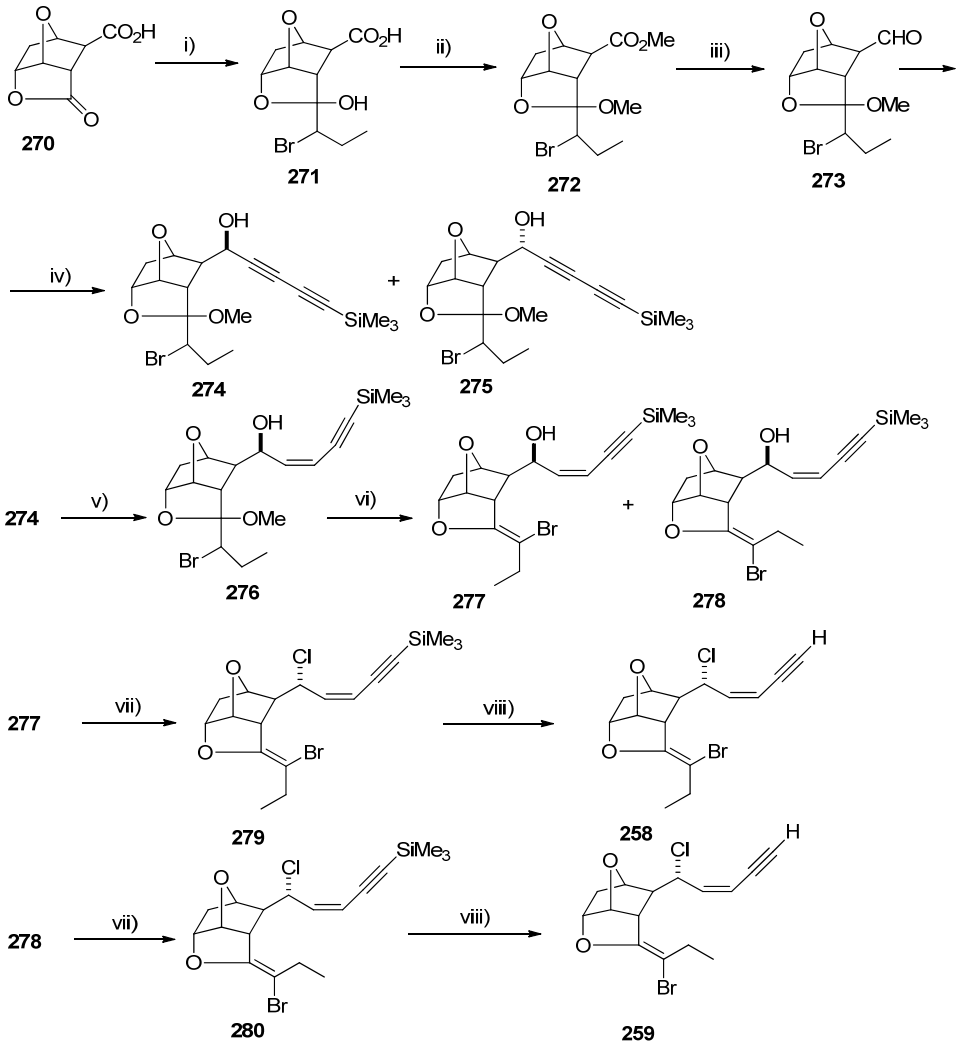
To the best of our knowledge only the synthesis of *cis*-maneonenes A **258** and B **259** and *trans*-manoenene B **260** have been described in racemic form.

In both synthetic approaches (Scheme 33, a and b) the starting material was the readily available lactone **270**.[163] For the synthesis of **258** and **259** (Scheme 33a)[164] lactone **270** was transformed into hemiacetal **271**. Bromination of this masked carbonyl group afforded the bromoacetal ester **272** as a mixture of stereoisomers. This compound was converted into aldehyde **273** which reacts with 4-lithio-1-trimethylsilyl-butadiyne[165] yielding a mixture of diastereoisomers **274** and **275**. Partial catalytic hydrogenation[166] of **274** gave **276** which, under pyrolytic conditions, gave a mixture of bromoenol ethers **277** and **278** in 20% and 30% yield respectively. After separation by column chromatography, independent reaction of **277** and **278** with (1-chloro-2-methyl-propenyl)-dimethylamine[167] produced alcohols **279** and **280** which were desilylated to **258** and **259** respectively. For the synthesis of *trans*-maneonene B, the reduction of **275** was accomplished with $LiAlH_4$ to give **281** which after the same reaction sequence furnished **260**. (Scheme 33b).[168]

7. OTHER SESQUITERPENOIDS

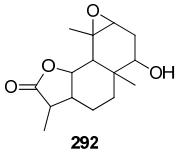
Oxanorbornane derivatives **285-288** as well as the rearranged sesquiterpenoid **289** (Figure 18) have been isolated from different natural sources.[169]

On the other hand the eudesmanolide **290**[≠,170] has been isolated from *Artemisia caerulescens* and is probably generated by acid-catalyzed cyclization of shonachalin A **291** (Scheme 34).[171]

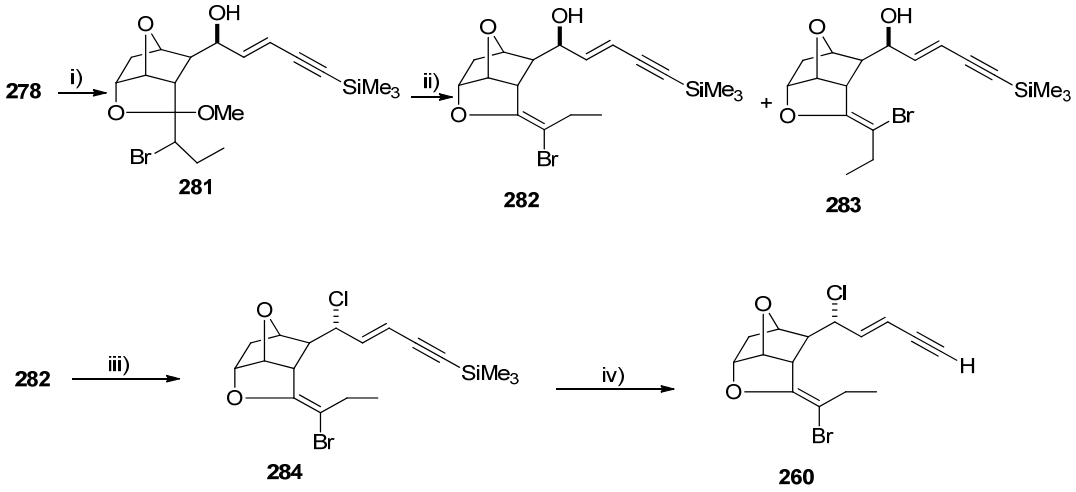


Scheme 33a. *Reagents and reaction conditions*: i) PhMgBr, $Me_2NCH_2CH_2NMe_2$, THF, -78 ºC, 76%; ii) Br_2, MeOH, rt, 70%; iii) a. $LiBH_4$, THF, reflux, 4 h; b. pyridinium chlorochromate, CH_2Cl_2, rt, 4 h, 67%; iv) $MgBr_2$, LiC_4SiMe_3, Et_2O, -78 ºC to rt, 1 h; b. flash chromatography; v) H_2, 5% Lindlar catalyst, hexane-MeOHl-EtOAc, 30-40% yield, 50% **274** recovered; vi) 200 ºC, 0.1 mm. Hg, 30 min, 20% **277**, 30% **278**; vii) $Me_2NC(Cl)=CMe_2$, CH_2Cl_2, 0 ºC, 0.5 h, 59% for **279**, 59% for **280**; viii) Bu_4NF, THF, rt, 30 min, 40% for **258**; 40% for **259**

≠In reference 1, p. 13538 compound **290** was named as shonacholin B. However the correct structure of shonacholin B is **292** (stereochemistry not determined). See reference 170.



The oxanorbornane derivative **293** (1,4-epoxycadinane) was isolated from the brown alga *Dilophus fasciola*.[172] The total synthesis of this compound (Scheme 35)[173] constitutes a nice example of the application of the intramolecular furan Diels-Alder reaction (IMDAF) to the synthesis of epoxydecalin systems.[174]



Scheme 33b. *Reagents and reaction conditions*: i) $LiAlH_4$, THF, reflux, 90 min, 65%; ii) *N,N*-dimethyl-acetamide, reflux, 30 min, 65%; iii) $Me_2NC(Cl)=CMe_2$, CH_2Cl_2, propylene oxide, 0 ºC to rt, 45 min, 55%; iv) Bu_4NF, THF-H_2O (99:1), 0 ºC, 30 min, 35%

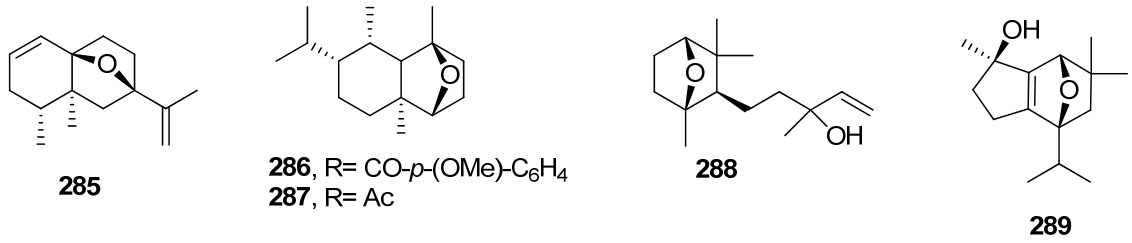
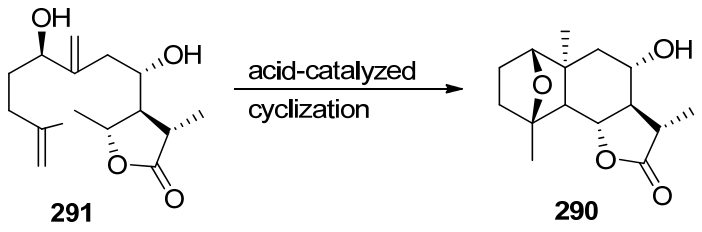


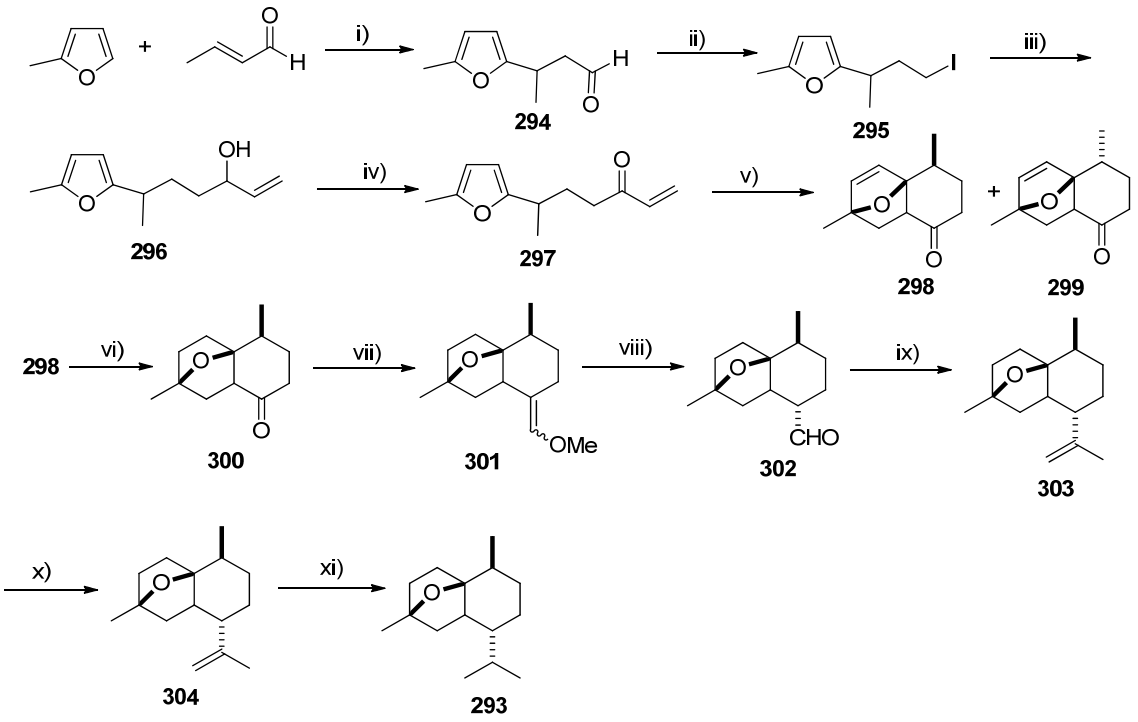
Figure 18. Structure of sesquiterpenoids **285**-**289**



Scheme 34. Acid-catalyzed cyclization of shonachalin A **291**

The Friedel-Crafts alkylation of 2-methylfuran with (2*E*)-but-2-enal provided aldehyde **294** which was converted into iodide **295** in a three-steps sequence: reduction with $NaBH_4$, conversion of the resulting

alcohol into tosylate and reaction with NaI in acetone. Treatment of **295** with 2.2 equivalents of *t*-butyllithium followed by reaction with acroleyn provided allylic alcohol **296** as a mixture of diastereomers which were oxidized with DMSO, $(COCl)_2$, Et_3N (Swern) to furnished enone **297**. Reaction of **297** with 1.1 equivalents of methylaluminium dichloride gave a mixture of cycloadducts **298** and **299** in ratio **298**:**299**= 90:10.



Scheme 35. Synthesis of racemic 1.4-epoxycadinene **293**. *Reagents and reaction conditions*: i) hydroquinone, 1 drop H_2SO_4, 53%; ii) a. $NaBH_4$, EtOH, b. TsCl, DMAP, CH_2Cl_2, c. NaI, acetone, reflux. overall yield not specified in reference 173; iii) a. 2.2 equiv. *t*BuLi, Et_2O, -78 ºC; b. CH_2=CH-CHO, 70%; iv) Swern oxidation, 90%; v) a. $MeAlCl_2$, 1.1 equiv., -78 ºC, 15 min; b. flash chromatography, 88% yield for **298**; vi) H_2, 1 atm, 10% Pd-C, AcOEt, 95%; vii) Ph_3PCH_2OMeCl, LDA, THF, 82%; viii) 10% HCl:THF (1:1), 63%; ix) a. 20 equiv. MeLi, THF, -78 ºC, b. Swern oxidation. Overall yield 87%; x) Ph_3PCH_3Br, *n*BuLi, THF, 76%; xi) H_2, 1 atm, PtO_2, AcOEt, 93%

After column chromatography, compound **298** was isolated in 88% yield. The hydrogenation of **298** followed by Wittig reaction of the resulting ketone **300** with the ylid of (methoxymethyl)triphenyl-phosphonium chloride afforded compound **301** as a mixture of *E*- and *Z*-diastereomers. This mixture was treated with dilute HCl in THF giving aldehyde **302**. This compound was converted into methyl ketone **303** in two steps. Reaction of **303** with the ylid of methylentriphenyl phosphorane gave vinyl derivative **304** which was finally hydrogenated to **293**.

Note that, in the major isomer **298**, the methyl group at position 2 (axial) is *syn* oriented regarding the oxygen bridge (Figure 19).

It should be pointed out that, from ketone **300**, a shorter-three steps route to **293** was tried. However, treatment of compound **305**, generated by reaction of **300** with isopropyllithium in the presence of CuI, did not provide **293** under a variety of conditions (Scheme 36).

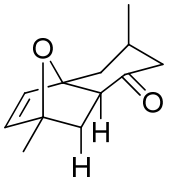
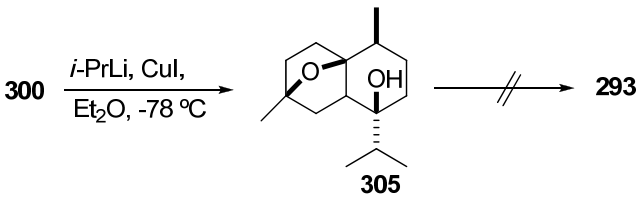


Figure 19. Preferred conformation of compound **298**



Scheme 36. Attemps to synthesis of compound **293** from ketone **300**

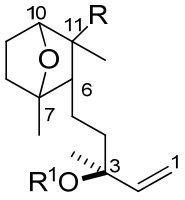
8. DITERPENOIDS

8.1 The dactylomelane group.

Diterpenes bearing the 3*S*,6*S*,7*S*,10*R*,11*S*-oxanorbornane **306** constitutes the so-called dactylomelane group.[175] Up the date eight members of this group have been isolated from different natural sources (Table 2).

Regarding the biogenesis of the basic skeleton of dactylomelane it can be envisaged as resulting of a brominium ion-assisted C6-C11 cyclization of geranylgeraniol pyrophosphate **316** (*via* **317**) to give intermediate **318**. Further S_N2-like reaction on bromine at C-10 give puctatene **308** which could diverges to the formation of dactylomlelol **307** or produce compounds **310**-**314** by the action of peroxidases (Scheme 37).[175]

Table 2. The dactylomelane group

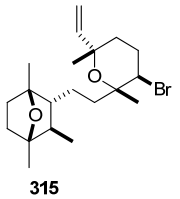


306

Comp.nº(a)	Source	R, R^1	Reference
307	*Aplysia dactylomella* (mollusc)	R=$(CH_2)_2$-C^{14}H(Br)-C(Me)$_2$Cl Conf. C14-*S*; R^1=H.	176
308	*Laurencia sp*.	R=$(CH_2)_2$-CH=C(Me)$_2$;R^1=H	175
309	*Aplysia punctata* (sea hare)	R=$(CH_2)_2$-CH=C(Me)$_2$; R^1=Ac	177
310	*Laurencia sp*.	R=CH_2-CH=CH-C(Me)$_2$-OOH; R^1=H. Conf. C13=C14 *E*	175
311	*Laurencia sp.*	R=CH_2-CH=CH-C(Me)$_2$-OOH ; R^1=H Conf. C13=C14 *Z*	175
312	*Laurencia sp.*	R=$(CH_2)_2$-C^{14}H(OOH)-C(Me)=CH_2 Conf. C14-*S*; R^1=H	175
313	*Laurencia sp.*	R=$(CH_2)_2$-C^{14}H(OH)-C(Me)=CH_2 Conf. C14-*S*; R^1=H	175
314	*Laurencia sp.*	R=$(CH_2)_2$-CO-C(Me)$_2$-OOH; R^1=H	175

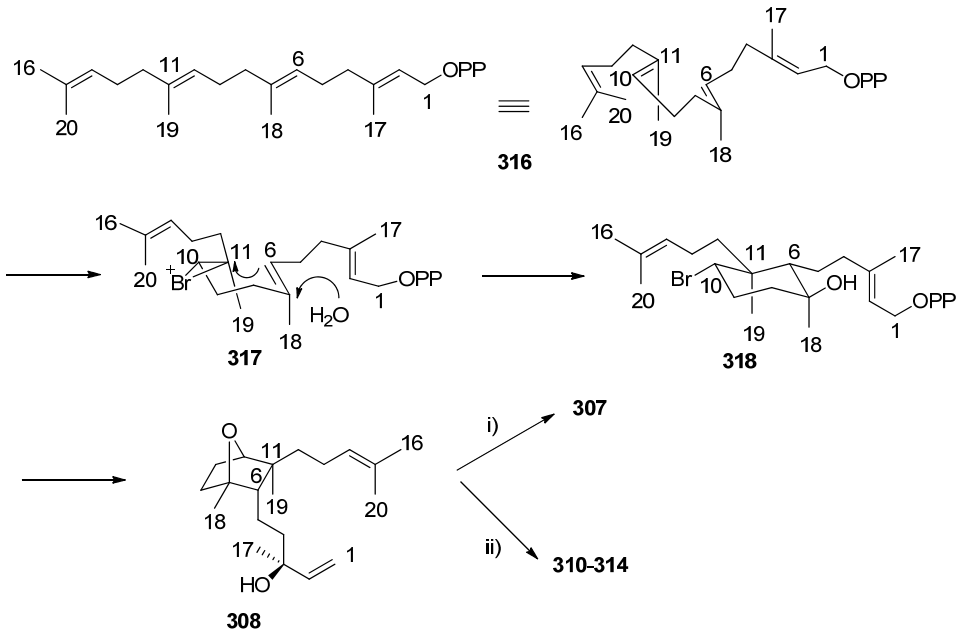
(a). Names assigned: **307**, dactylomelol; **308**, puctatene; **309**, puctatene acetate; **310**, *E*-dactylohydroperoxide A; **311**, *Z*-dactylohydroperoxide A; **312**, dactylohydroperoxide B; **313**, dactylo-3,14-diol; **314**, dactylohydroperoxide C

Related with these compounds, metabolite **315** -dactylopyranoid (Figure 20)- has also been isolated from *Aplysia dactylomella*.[178]



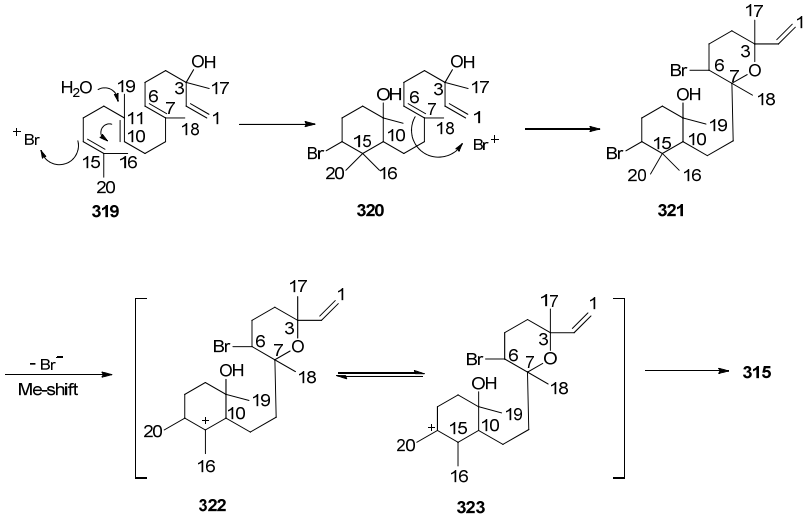
315

Figure 20. Structure of dactylopyranoid **315**



Scheme 37. Proposed biosynthesis of compounds of the dactylomelane group. Reagents: i) $Br^{+}Cl^{-}$, see Scheme 23; ii) Peroxidases.

A related pathway has been proposed for the biosynthesis of **315**[178] (Scheme 38). In this case the first bromine ion-assisted cyclization of **319** occurs between C10-C15 to give intermediate **320**. On **320** takes place the formation of the pyrane ring of **315** through a second bromine ion-assisted cyclizations between the oxygen at C-3 and C-7 (**321**). Bromine ionization and 1,2-methyl shift form **322** in equilibrium (1,2-hydrogen-shift) with **323**. Final intramolecular collapsing of **323** by cyclizations between oxygen at C-11 and C-14 generates the oxanorbornane subunit of **315**.



Scheme 38. Proposed biosynthesis of dactylopyranoid **315**

Compound **307** has been proposed as a potentially useful defensive substance.[176]

8.2. Diterpenoids with ent-clerodane (neo-clerodane) and dolastane skeleton.

The basic structure of *ent*-clerodane (*neo*-clerodane) diterpenoids family, **324** (Figure 20) is named as decahydro-1,2-4a,5-tetramethyl-1-(3-methyl-pentyl)naphtalene.[179] On the other hand the dolastane basic skeleton, **325** (Figure 21) is named as tetradecahydro-3a,5,8a-trimethyl-1-(1-methylethyl) benz[f]azulene.[180]

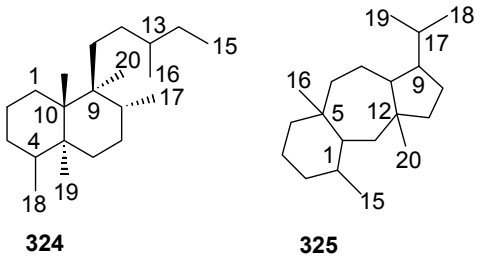


Figure 21. Basic skeleton of ent-clerodane (neo-clerodane), 3**24**, and dolastane, **325**, diterpenoids

Teupestalin **326** (Figure 22) is a C-10 oxygenated neo-clerodane diterpenoid isolated from *Teucrium pestalozzae*.[181] On the other hand the 1,4-epoxy-13-dolastene **327** has been isolated from a brown alga *Dictyota* sp.[182] A second dolastane diterpene (1,4-epoxy-17-dolastene) **328** has been isolated from the brown alga *Dilophus spiralis*.[183]

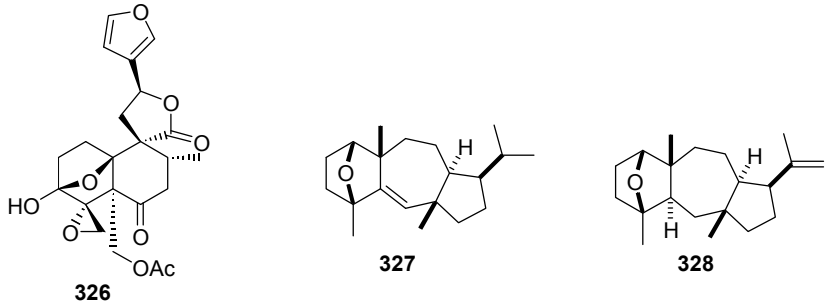


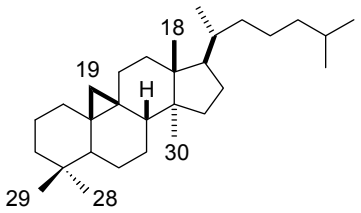
Figure 22. Structure of neo-clerodane and dolastane derivatives, **326-328**

9. TRITERPENOIDS

9.1. Cycloartane triterpenes.

Cycloartane triterpenoids[184] feature the basic skeleton of 17-(1,5-Dimethyl-hexyl)-4,4,13,14-tetramethyl-tetradecahydro-cyclopropa[9,10]cyclopenta[a]phenanthrene **329** (Figure 23).

These compounds exist widely in nature[185] and possess various bioactivities.[186] *Cimicifuga* (currently *Actaea* in Europe and USA) species have been used for many years as medicinal herb worldwide. Previous chemical and biological studies on *Cimicifuga* species led to isolation of various bioactive compounds.[187]

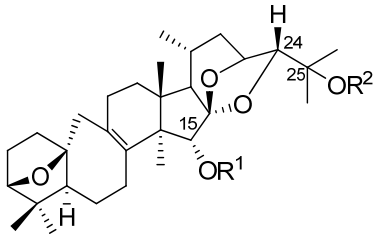


329

Figure 23. The basic skeleton of cycloartane triterpenoids, **329**

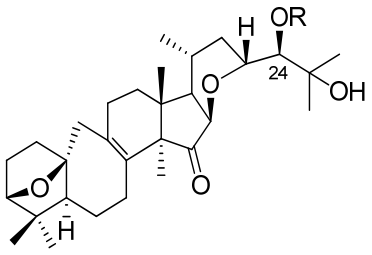
In fact, the roots of some of these species such as *C. foetida*, *C. dahurica*, and *C. heracleifolia* are important elements of Traditional Chinese Medicine (TCM) and have been officially listed in the Chinese Pharmacopoeia.[188] Several modified cycloartane triterpenoids isolated from these natural sources as well as semi- synthetic analogues showing a 7-oxanorbornane framework (**230**-**244**) are quoted in Tables 3-6 and Figure 24.

Table 3. Acerinol derivatives **230**-**233**



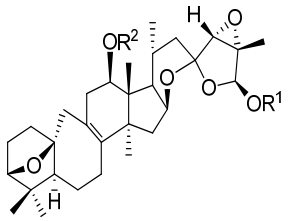
Compound	Structure	Reference
Acerinol, **230**	24S, R^1=R^2=H	189
Epi-acerinol, **231**	24R, R^1=R^2=H	190, 191
25-OMe-acerinol, **232**	24S, R^1=H, R^2=Me	190
15-Acetylacerinol, **233**	24S, R^1=Ac, R^2=H	190

Table 4. Acerionol derivatives **234**, **235**



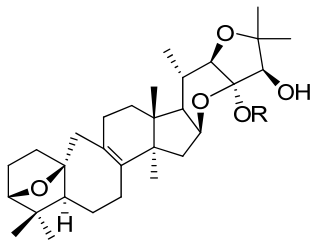
Compound	Structure	Reference
Acerionol **234**	R=H	192
24-Acetylacerionol **235**	R=Ac	192

Table 5. Cimicifugenin derivatives **236**-**239**

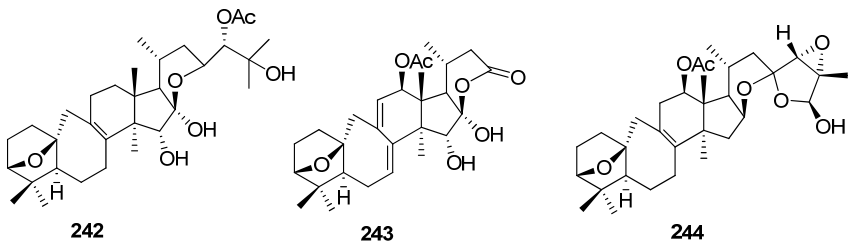


Compound	Structure	Reference
Cimicifugenin C **236**	R^1=R^2=H	193
Cimicifugenin A **237**	R^1=H, R^2=Ac	193
26-OMe-cimicifugenin A **238**	R^1=Me, R^2=Ac	193
26-OEt-cimicifugenin A **239**	R^1=Et, R^2=Ac	193

Table 6. Cimiacerol derivatives **240, 241**



Compound	Structure	Reference
Cimiacerol **240**	R=H	194
OMe-cimiacerol **241**	R=Me	195



242 **243** **244**

Figure 24. Structures of heracleifolinol **242,**[194] cimicilactone **243**[196] and cimifugenin D **244**[196]

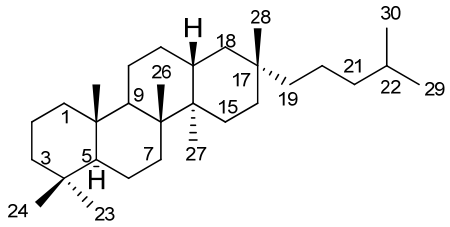
On the point of view of the biological activity of these compounds, it is known that active ingredients derived from traditional Chinese medicinal herbs have been reported to reverse multidrug resistance mediated by ATP-binding cassette sub-family B member 1 (ABCB1).[ξ] In this context, acerinol (**234**) was tested for its potential to modulate the ABCB1 transporter. The results indicate that this compound could be developing as a new multidrug resistance reversal agent.[197]

Compounds **230**-**233**, **235** and its epimer at C-24 and **241** have been evaluated as potential antitumor promoters by inhibition of Epstein-Bar virus[ϒ] early antigen concluding that these compounds might be valuable anti-tumor promoters.[198]

Finally, the antilipenic[199] and antimalarial[200] activities, among others[201] have also been considered.

8.2. Baccharane triterpenes.

The baccharane-type triterpenes features the basic skeleton **245** (Figure 25)[202] derived from octadecahydro chrysene.



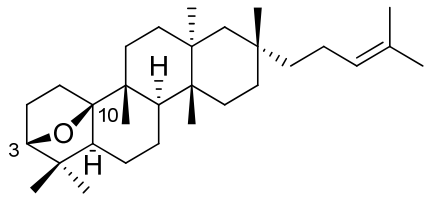
245

Figure 25. The baccharane skeleton

Baccharis oxide **246** (Figure 26) is a triterpene oxide first isolated[203] from *Baccharis halimifolia* being also common in many *Baccharis* species[204] This compound together campanulin (dendropanoxide, see below) are the only natural triterpenes showing a 3,10-oxide bridge in the A ring,[205] within the family of the baccharane-type triterpenes.[206]

[ξ]The ABCB1 is an important glycoprotein (170 kDa) of the cell membrane that pumps many foreign substances out of cells. In 2009, the first structure of a mammalian ABCB1 protein was solved. See: S. Aller, J. Yu, A. Ward, Y. Weng, S. Chittaboina, R. Zhug, P. M. Harrell, Y. T. Trinh, Q. Zhang, I. L. Urbatsch, and G. Chang, *Science*, 2009, **323**, 1718.

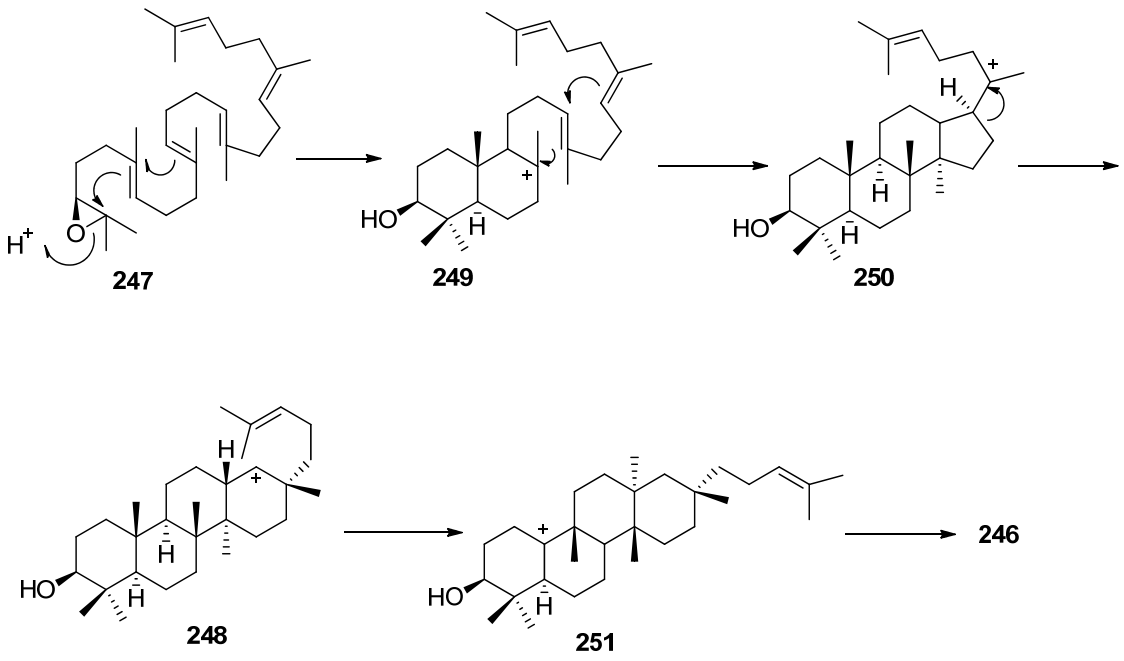
[ϒ]The Epstein–Barr virus (EBV) is one of the most common viruses in human. It is associated with several particular forms of cancer. See: E. Maeda, M. Akahane, S. Kirgu, N. Kato, T. Yoshikawa, N. Hayashi, S. Aoki, M. Minami, H. Llozaki, M. Fukuyama, and K. Ohtomo, *Jpn. J. Radiol.,* 2009, **27**, 4. As consequence, many compounds that inhibit EBV-EA induction by tumor promoters have been shown to act as inhibitors of tumor promotion in vivo. See: J. Ishida, M. Kozuka, H. K. Wang, T. Konoshima, H. Tokuda, M. Okuda, X. Y. Mou, H. Nishino, N. Sakurai, K. H. Lee, and M. Nagai, *Cancer Lett.,* 2000, **159**, 135.



246

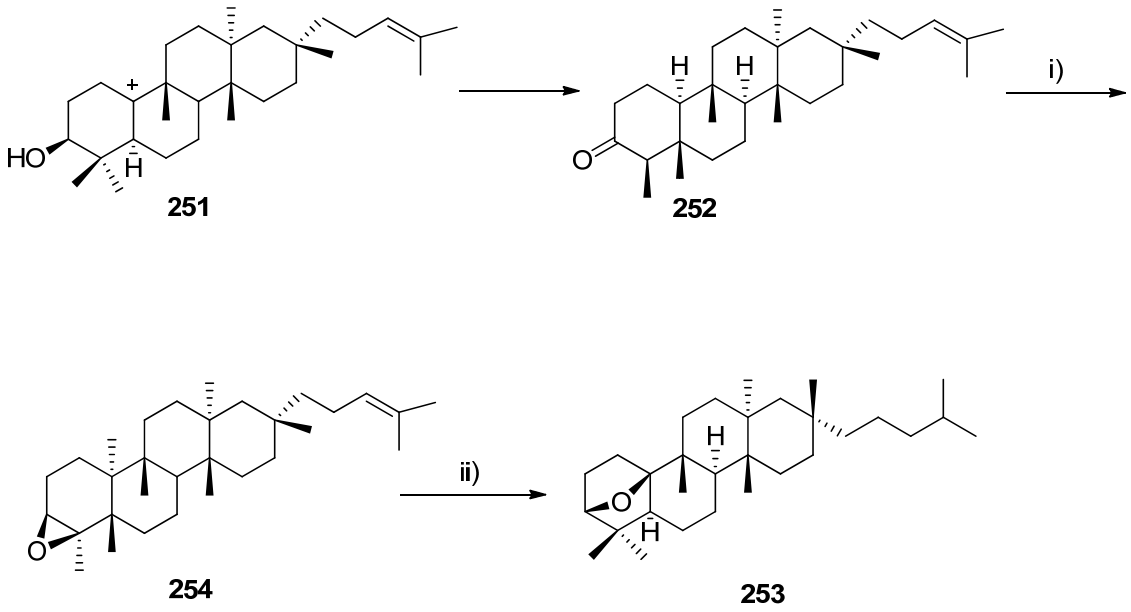
Figure 26. Structure of baccharis oxide, **246**

Biogenetically compound **246** arises from squalene oxide **247** *via* baccharenyl cation **248** which was in turn generated through a sequence involving intermediates **249** and **250**. Successive 1,2-shifts and conformational changes afford cation **251**. Final intramolecular attack of 3β-hydroxyl group yields **246**. (Scheme 39).[207]



Scheme 39. Biosynthesis of **246** from squalene oxide **247**

The ketone shinone **252**[208] appears to be derived from the same cation **251**.[207] Compound **252** was transformed into dehydrobaccharis oxide **253**[209] *via* formation of 3β,4β-epoxyshionane **254** followed by reaction with $BF_3 \cdot OEt_2$ at -30 ºC (Scheme 40).



Scheme 40. Biosynthesis of **252** and transformation of **252** into **253**. *Reagents and reaction conditions*: i) See reference 210; ii) $BF_3 \cdot OEt_2$, Et_2O, -30 ºC, 1 h, 17%

In this reaction the following baccharane derivatives **255**-**258** (Figure 27) were also generated.

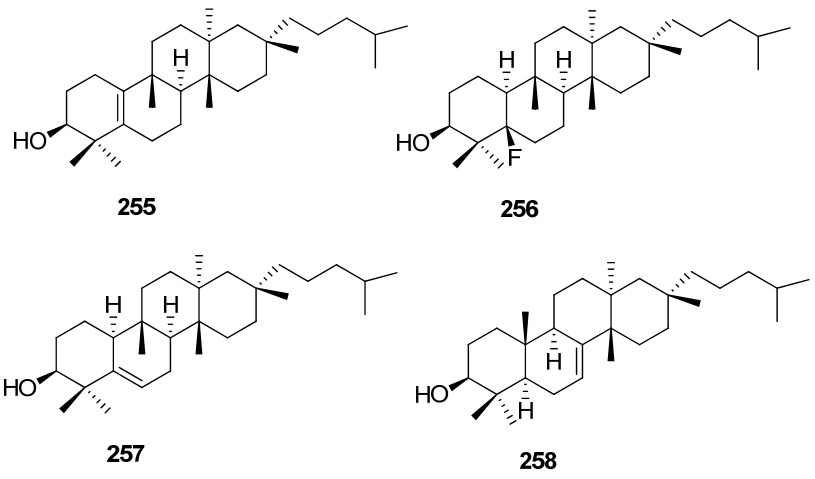
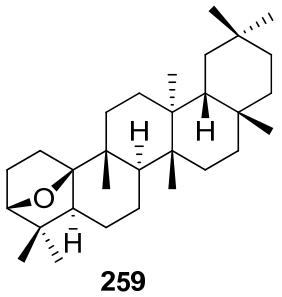


Figure 27. Baccharane-type triterpenoids **255**-**258**

Recent studies have revealed the macrophag,[211] trypanocidal,[212] and antimicrobial[213] activities of compound **246**.

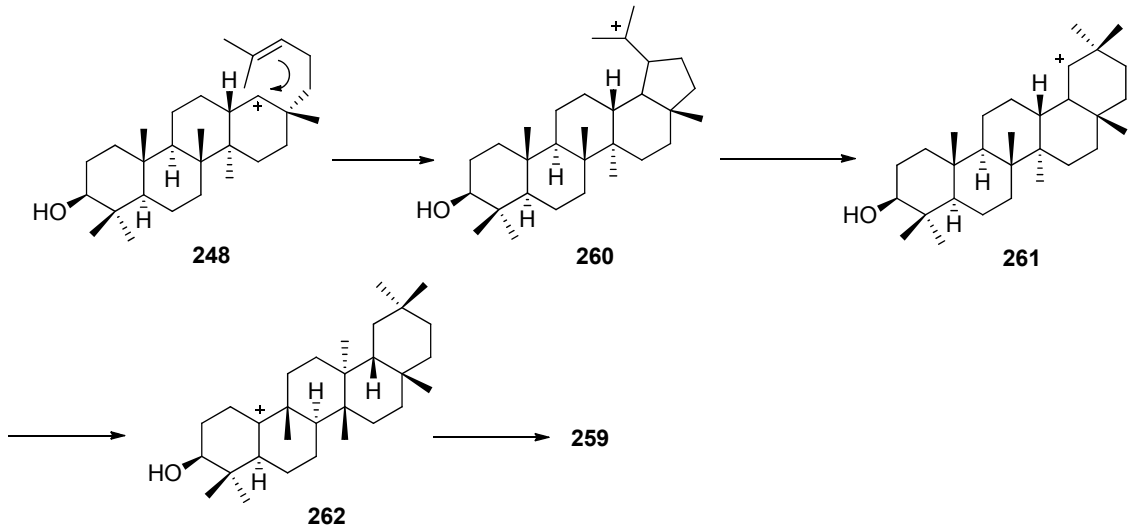
Dendropanoxide (campanulin) **259** (Figure 28) was first isolated from the leaves of *Rhododendron grande*[214] as well as from others *Rododendron* species.[215]



259

Figure 28. Structure of dendropanoxide (campanulin) **259**

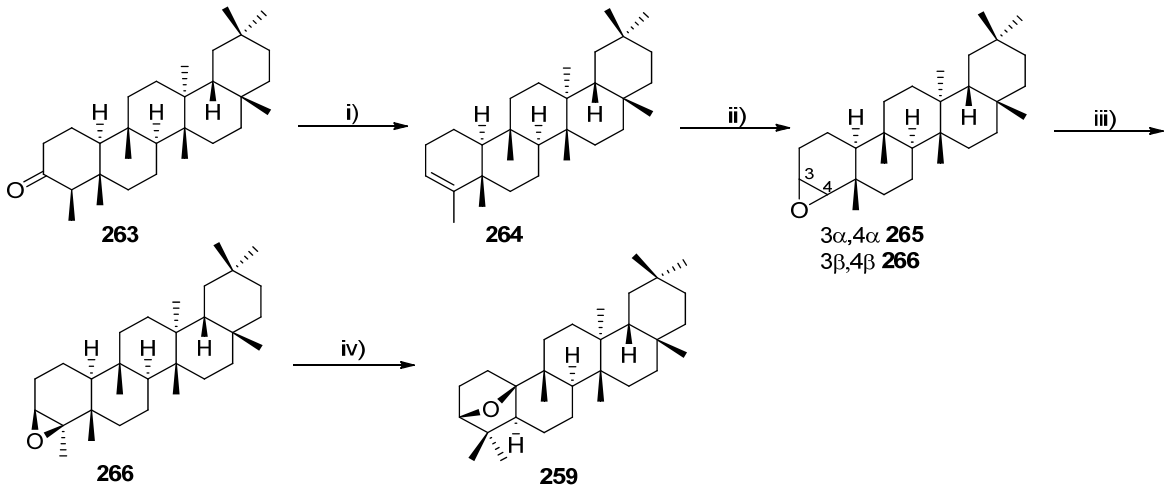
On the biosynthetic point of view dandropanoxide arises from baccharenyl cation **248** *via* lupanyl cation **260**. After a sequence of 1,2-shifts catalyzed by oxidosqualene cyclases (OSCs),[≠,216] **260** is transformed into **261**. Quenching of **261**with the hydroxyl group at C-3 finally produced **259** (Scheme 41).[207]



Scheme 41. Biosynthesis of dendropanoxide **259** from baccharenyl cation **248**

A synthesis of **259** starting from friedelin **263** has been carried out[217] as indicate in Scheme 42. Friedelin was transformed into friedel-3-ene **264** following previously reported synthetic protocol.[218] Epoxidation of **264** with *m*CPBA gave the epoxides **265** and **266** in ratio **265**:**266** = 2:1. After separation, **266** was treated with $BF_3 \cdot OEt_2$ to give **259** in 22% yield.

≠The first committed step in triterpenoid biosynthesis is the cyclization of epoxysqualene into various triterpene alcohol isomers, a reaction catalyzed by oxidosqualene cyclases (OSCs). The different OSCs have characteristic product specificities, which are mainly due to differences in the numbers of high-energy intermediates the enzymes can stabilize. See reference 216.



Scheme 42. Synthesis of **259** from friedelin **263.** *Reagents and reaction conditions*: i) Reference 218; ii) *m*CPBA, $CHCl_3$; iii) Chromatographic separation; iv) $BF_3{\cdot}OEt_2$, Et_2O, -10 ºC, 22%

In addition of **259**, products **267**-**269** (Figure 29) were also identified in the last reaction depicted in Scheme 42.

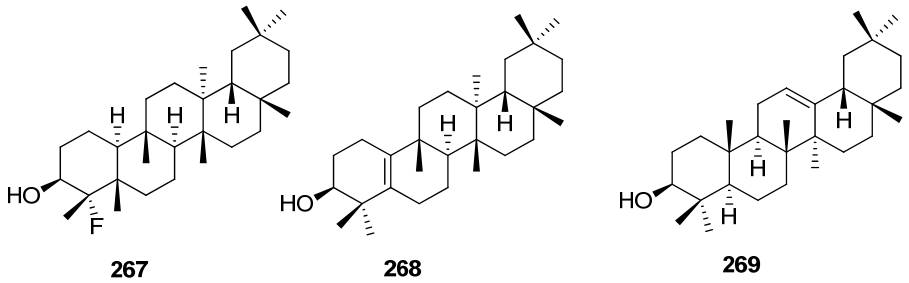
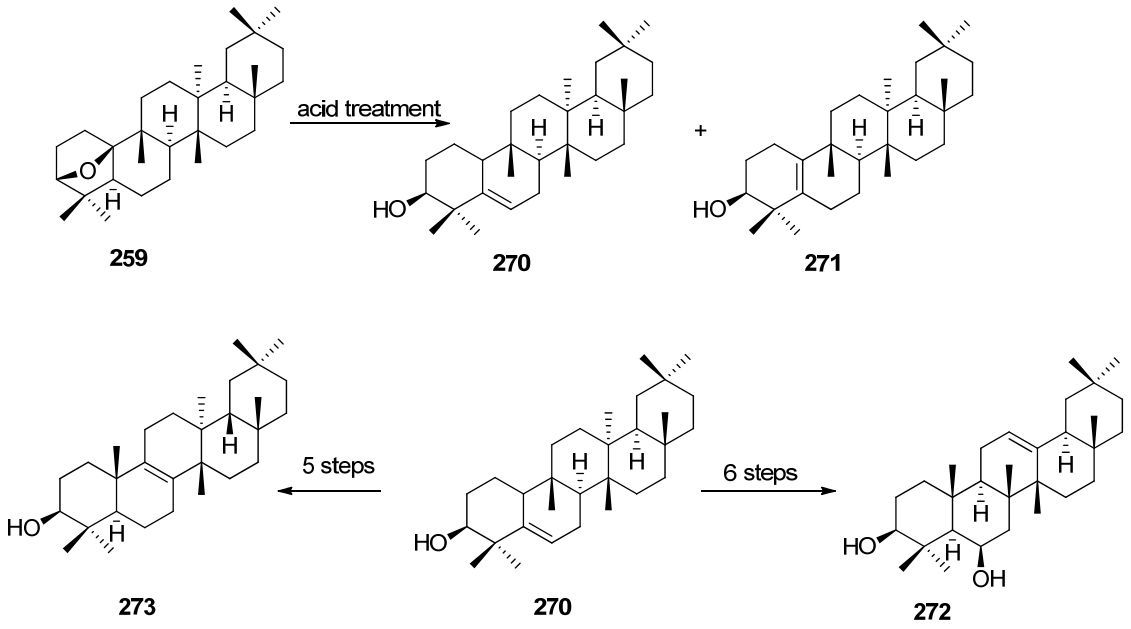


Figure 29. Structure of compounds **267**-**269**

Dendropanoxide **259** has been used as starting material for the preparation of other triterpenoids. Thus, acid treatment[219] of **259** afforded a mixture of **270** and **271**. After separation, **270** was converted into daturadiol **272**[220] or isomultiflorenol **273** (Scheme 43).[221,222]



Scheme 43. Synthesis of daturadiol **272** and isomultiflorenol **273** from dendropanoxide **259**

The antiplasmodial[223] and antidiabetic[224] activity of **259** have been evaluated. On the other hand, this compound inhibits cell-proliferation and induces apoptosis in MG-63 human osteosarcoma cells.[225] In this way, **259** constitutes a promising strategy for human osteosarcoma control.[≠,226]

9.3. The glycinoeclepins.

The glycinoeclepins A (**274**), B (**275**) and C (**276**) (Figure 30) are nortriterpenoids isolated from the soybean cyst nematode *Heteropdena glycines* (**274**)[227] and from the dried root of the kidney bean *Phasedus vulgaris* (**274**-**276**).[228] These compounds, especially **274**, are potent hatching stimulus for the soybean cyst nematodes.[ξ,229] The biosynthetic precursor of **274** appears to be the plant sterol cycloartenol **277**[230] and this was the basis for a biomimetic synthesis of 12-deoxyglycinoeclepin **278**[231] starting from abietospiran **279**[232] (Figure 30).

[≠]Dendropanoxide induces autophagy through ERK1/2 activation in MG-63 human osteosarcoma cells and autophagy inhibition enhances dendropanoxide-induced apoptosis. See reference 226.

[ξ]Cyst nematodos (more than 40 species) are devastating pests for many crops. The infection causes various symptoms that may include chlorosis of the leaves and stems, root necrosis, loss in seed yield and suppression of root and shoot growth. By this reason the ecological eradication of the nematode constitutes a target of primary importance. See reference 229.

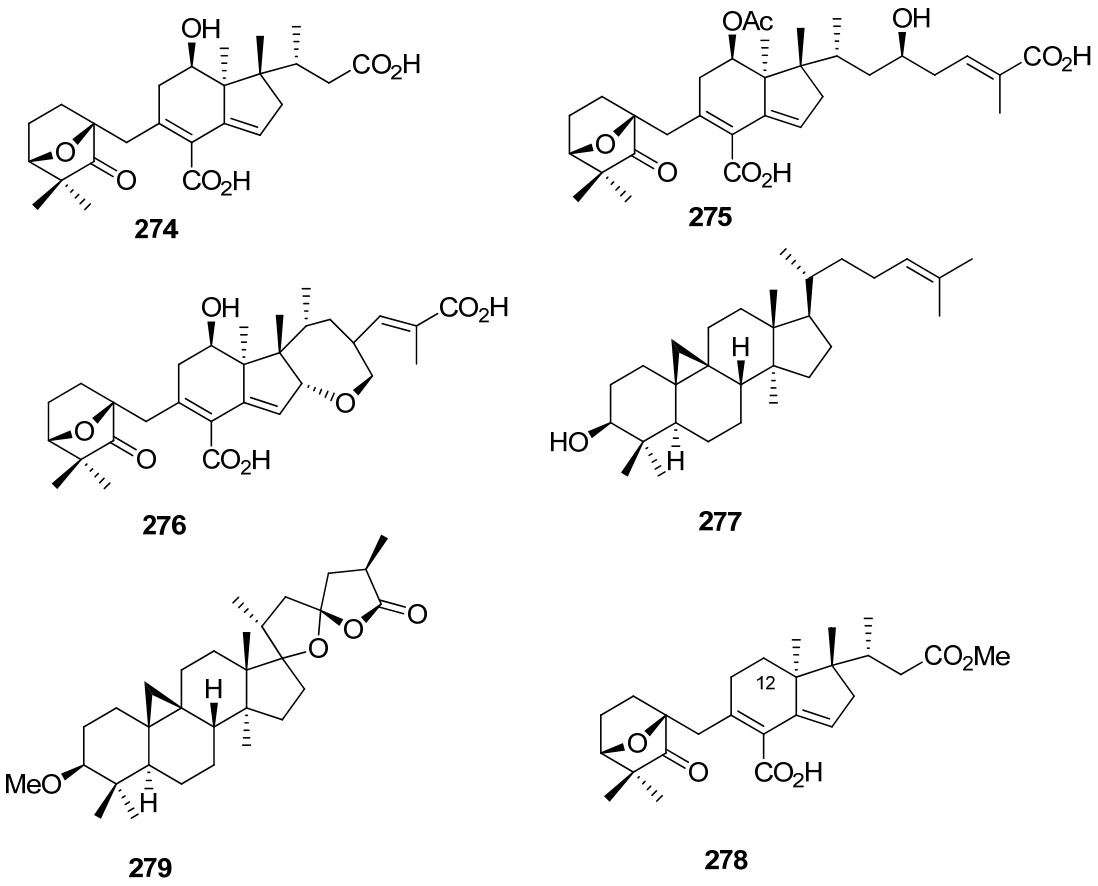
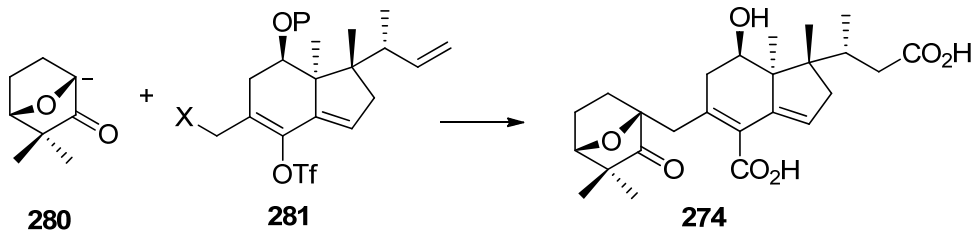


Figure 30. Structures of glycinoeclepins A-C (**274-276**), cycloartenol **277**, abietospiran **279** and 12-deoxyglycinoeclepin **278**

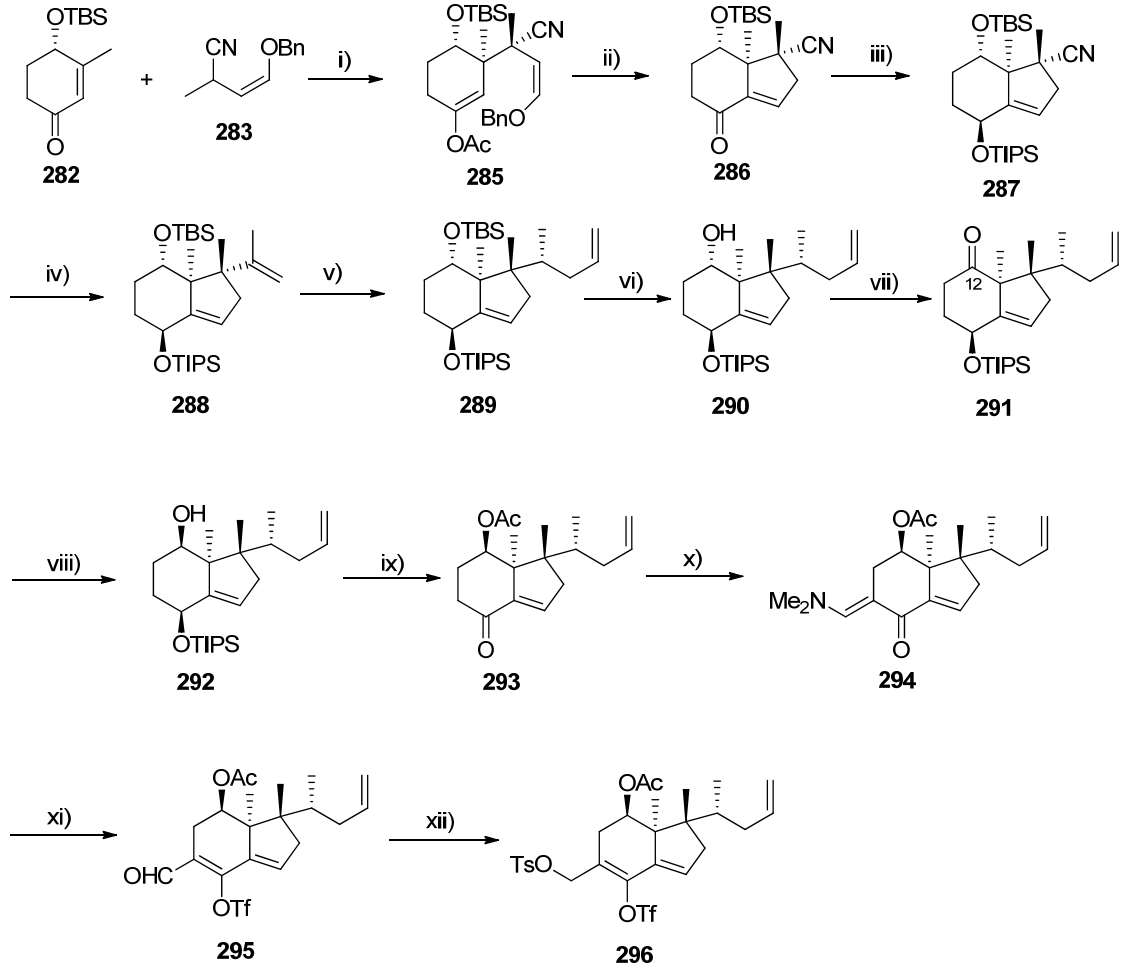
Until 1991 three total syntheses of **274** have been reported.[233] These synthetic approaches were described in detail in several reviews[234] and they will not be discussed here. A total synthesis of **274** based on the coupling of the fragments **280** and **281**, Scheme 44, has been reported.[235]



280: carbanion specie
X: leaving group
P: protecting group

Scheme 44. Proposed synthetic approach to **274**

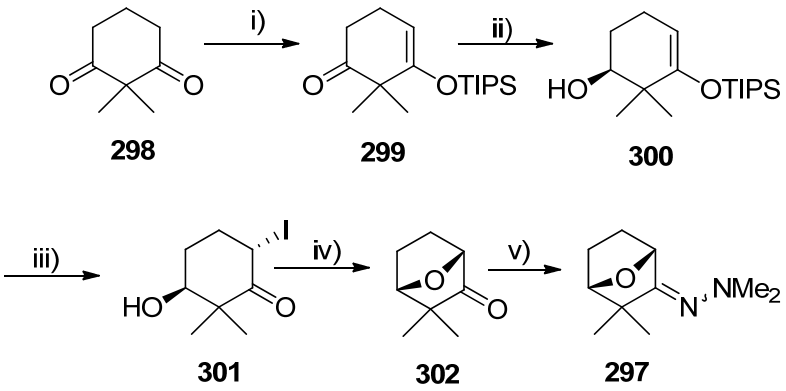
The synthesis of fragment **281** (compound **296**) was achieved as summarized in Scheme 45.



Scheme 45. Synthesis of fragment **281** (compound **296**). *Reagents and reaction conditions*: i) From nitrile **283**, KHDMS, THF, -78 ºC, then **282**, -78 ºC, then Ac_2O, -78 ºC to -50 ºC; ii) AcOH-H_2O (3:1), 100 ºC; 62% from **282** iii) a. $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, -78 ºC to rt; b. TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 ºC; 85% two steps; iv) a. MeLi, Et_2O, rt, then AcOH-H_2O-THF (1:1:2); b. Ph_3PCH_3Br, *t*BuOK, toluene-*t*BuOH (1:1), 80 ºC; 89% two steps; v) 9-BBN, THF, 0 ºC-rt, then $Pd(PPh_3)_4$, $BrCH{=}CH_2$, NaOH aq., rt; 97%, dr=94:6 vi) a. TBAF, DMF, 80 ºC; b.TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 ºC; 97% two steps; vii) TPAP, NMO, MS 4A, CH_2Cl_2, rt; 90%; viii) $LiEt_3BH$, toluene, -78 ºC to -15 ºC, 88%; ix) a. Ac_2O, DMAP, pyridine, rt; b. TBAF, THF, rt; c. Swern oxidation, 88% three steps; x) *t*BuOCH$(NMe_2)_2$, benzene, 50 ºC; xi) Tf_2O, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, -78 ºC then aq. $NaHCO_3$, rt, 89% from **293**; xii) a. $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 ºC to rt; b. *p*-TsCl, Et_3N, $Me_3N \cdot HCl$, toluene, 0 ºC, 93% two steps

Optically pure γ-silyloxyenone **282** reacted with the anion generated from nitrile **283**[Υ] to give **285** with high diastereoselectivity. Transformation of **285** into ketone **290** was achieved using standard procedures. Compound **290** have the *S*-configuration at the C-12 position, opposite that **274**. Attempts to invert alcohol **290** using Mitsunobu protocols failed and, by this reason, alcohol **290** was converted into ketone **291**. Stereoselective reduction of **291** to alcohol **292** was carried out with excellent distereoselectivity (92:8, 88% yield) using $LiEt_3BH$ as bulky reducing agent. Compound **292** was finally converted into allyl tosylate **296** in seven steps and 73% overall yield.

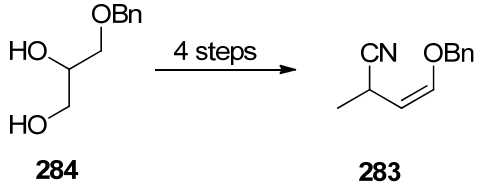
Anionic specie **280** was generated from hydrazone **297** prepared in turn from diketone **298**[236] as depicted in Scheme 46.

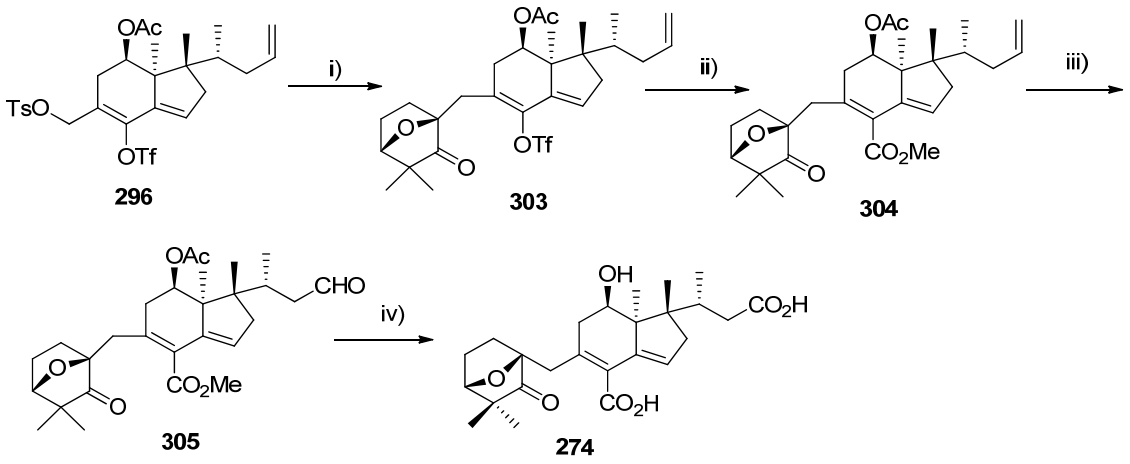


Scheme 46. Synthesis of hydrazone **297**. *Reagents and reaction conditions*: i) KHDMS, TIPSOTf, -78 ºC to 0 ºC, 90%; ii) (-)-DIPCl, 59%, 99% ee; iii) NIS, CH_2Cl_2, -40 ºC, to rt, dr 91:9; iv) AgOTf, 2,6-lutidine, CH_2Cl_2, 40 ºC; v) Me_2NNH_2, AcOH, EtOH, 70 ºC. 60% from **300**

Final coupling of **296** and **297** afforded **303** which was transformed into **304** by Pd-catalyzed carbonylation reaction.[237] Conversion of **304** into **274** was carried out in three steps and 77% yield from **304** (Scheme 47).

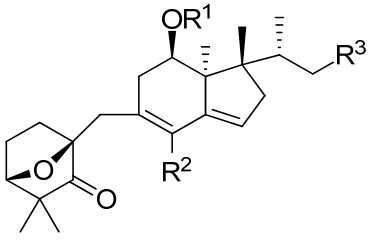
[Υ]Nitrile **283** was prepared from glycerol monobenzyl ether **284** in four steps and 56% overall yield.



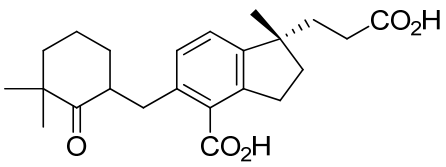


Scheme 47. Synthesis of glycinoeclepin A, **274**. *Reagents and reaction conditions* : i) a. Compound **297**, *n*BuLi , THF, 0 ºC then $CuBr{\cdot}SMe_2$, -40 ºC, then **296**, -40 ºC; b. AcOH-H_2O (1:1), 130 ºC, 65% two steps; ii) CO (1 atm), $Pd(OAc)_2$, 1,1'bis(diphenylphosphino)ferrocene, nBu_3N, DMF-MeOH (2:1), 80 ºC, 87%; iii) OsO_4, NMO, *t*BuOH-H_2O (3:1), 0 ºC, 81%; iv) a. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH-H_2O (3:1), 0 ºC; b. LiI, 2,4,6-collidine, 120 ºC, then LiOH, THF-H_2O (1:1), 60 ºC, then dil. H_2SO_4 95% two steps

It should be pointed out that as consequence of the important biological activity of **274**, different simpler analogues of this compound have been designed and synthesized. In the Figure 31 those which keep the 7-oxanorbornane moiety (**307**-**310**)[238] were indicated together the benzenoid analogue **311**.[239,240]



307, R^1=Ac, R^2=R^3=CO_2Me
308, R^1=Ac, R^2=CO_2Me, R^3= CO_2H
309, R^1=H, R^2=CO_2Me, R^3= CO_2H
310, R^1=Ac, R^2=H, R^3=CO_2Me

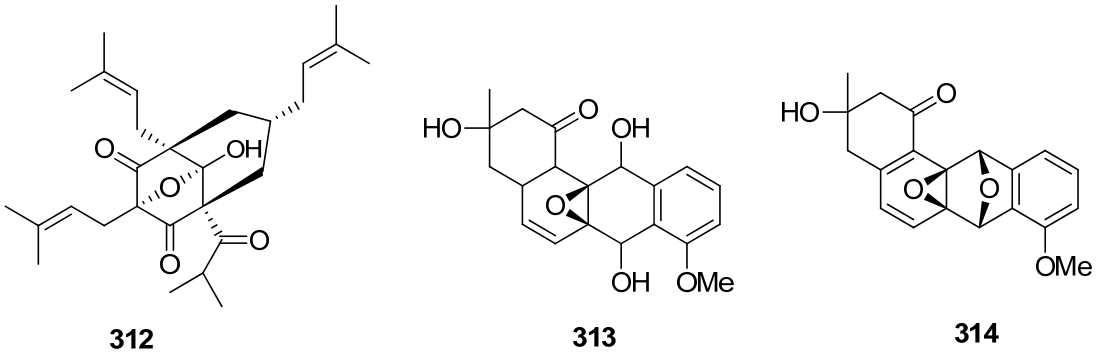


311

Figure 31. Some synthetic analogues of glycinoeclepin A **274**

10. OTHERS TERPENOID DERIVATIVES

Subellinone **312** is a polyisoprenylated phloroglucinol derivative isolated from *Garnicia subelliptica*.[241] This compound represents a novel type of phloroglucinol featuring a 10-oxatricyclo[3.3.1.1^{3,9}]decane skeleton. On the other hand compound **313**, an inhibitor of farnesyl protein transferase known as SCH 58450 isolated from *Streptomyces* sp.,[242] was initially formulated as **314**. This initial proposed structure was later corrected. (Figure 32).[243]



312 **313** **314**

Figure 32. Structure of compounds **312-314**

11. CONCLUDING REMARKS

As discussed above, several organic molecules incorporating an 7-oxanorbornene skeleton not only have interesting molecular structures but also possess, in some cases, a variety of biological activities including cytotoxic, antimicrobial, enzyme-inhibitory, as well as potential ecological relevant functions, such as insecticidal activity. However, biological evaluations of these molecules have been limited. Therefore, much more extensive testing of these molecules seems warranted. Further investigation of the structure-activity relationships, as well as mode-of-action studies, could result in the discovery of promising analogues with potential clinical application.

Additional studies in this area could contribute to a better understanding of their mechanisms of action which would be beneficial in the ongoing development and structure optimization of this class of compounds, and could lead to the discovery of novel pharmacophores and heretofore news mechanisms of drug action. On the other hand, development of new strategies and efficient methods for the synthesis of these molecules are also necessary in light of the interesting structures and biological properties displayed by such compounds as well as, in some cases, the difficulties in obtaining large quantities of them from the natural sources.

12. ACKNOWLEDGEMENTS

The Spanish Ministerio de Ciencia e Innovación (MICINN) is thanked for financial support (project CTQ-2010-16170). S. R. is thankful to the Government of Spain for a Formación del Profesorado Universitario (FPU) Grant (AP20090051).

13. REFERENCES AND NOTES

1. P. Vogel, J. Cossy, J. Plumet, and O. Arjona, *Tetrahedron*, 1999, **55**, 13521.
2. I. B. Masesane, *Trends Org. Chem*., 2010, **14**, 13.
3 C. S. Schindler and E. M. Carreira, *Chem. Soc. Rev.,* 2009, **38**, 3222.
4. For a review on the chemistry of the aeruginosins, see: K. Ersmark, J. R. Del Valle, and S. Hanessian, *Angew. Chem. Int. Ed*., 2008, **47**, 1202.
5. P. Vogel, *Chimia*, 2008, **62**, 519.
6. P. Vogel, *Curr. Org. Chem*., 2000, **4**, 455.
7. P. Vogel, *Topics in Current Chem*., 2008, **282** (Anthracycline Chemistry and Biology I), 187.
8. I. Robina and P. Vogel, *Synthesis*, 2005, 675.
9. O. Arjona, A. G. Csákÿ, and J. Plumet, *Eur. J. Org. Chem*., 2003, 611; N. Holub and S. Blechert, *Chem. Asian J*., 2007, **2**, 1064.
10. R. Gleiter, B. Esser, and S. C. Kornmayer, *Acc. Chem. Res.,* 2009, **42**, 1108.
11. V. Lapinte, L. Fontaine, V. Montembault, I. Campistron , and D. V. Lapinte-Reyx, *J. Mol. Catalysis, A*, 2002, **190**, 117.
12. Z. Zhang, O. Kelemen, M. A. van Santen, S. M. Yelton, A. Wendlandt, V. M. Sviripa, M. Bollen, L. Beullens, H. Urlaub, R. Luehrmann, D. S. Watt, and S. Stamm, *J. Biol. Chem*., 2011, **286**, 10126.
13. J. P. Robiquet, *Ann. Chem*., 1810, **76**, 302.
14. Selected, recent reviews: D. Perrotti and P. Neviani, *Lancet Oncol*., 2013, **14**, 229; P. Seshacharyulu, P. Pandey, K. Datta, and S. K. Batra, *Cancer Lett.,* 2013, **335**, 9; R. Visconti, L. Palazzo, A. Pepe, R. Della Monica, and D. Grieco, *Cell Cycle,* 2013, **12**, 17; B. Ewald, J. Lesage, M. Goernemann, L. Beullens, M. Van Meervelt, and M. Bollen, *FEBS J*., 2013, **280**, 584; L. K. Nguyen, D. Matallanas, D. R. Croucher, A.von Kriegsheim, and B. N. Kholodenko, *FEBS J*., 2013, **280**, 751; V. Kolupaeva and V. Janssens, *FEBS J*., 2013, **280**, 627; W. Peti, A. Nairn, C. Angus, and R. Page, *FEBS J.*, 2013, **280**, 596; P. Tsaytler and A. Bertolotti, *FEBS J.*, 2013, **280**, 766; S. Munter, M. Kohn, and M. Bollen, *ACS Chem. Biol.*, 2013, **8**, 36; T. Hunt, *Adv. in Biol. Regulation*, 2013, **53**, 173.
15. See, for instance: M. J. Graziano, A. L. Waterhouse, and J. E. Casida, *Biochem. Biophys. Res. Commun*., 1987, **149**, 79; W. Li, L. Xie, Z. Chen, Y. Zhu, Y. Sun, Y. Miao, Z. Xu, and X. Han,

Cancer Sci., 2010, **101**, 1226.

16. C. E. Puerto Galvis, L. Y. Vargas Méndez, and V. V. Kouznetsov, *Chem. Biol. Drug Design,* 2013, **82**, 477.
17. M. Peng and Y. Yang, *Acta Chromatogr.*, 2011, **23**, 611; M. A. Adatto, S. Halachmi, and M. Lapidoth, *Current Prob. Dermat*., 2011, **42**, 97; H. Vidal Jr., C. J. Luiz Costa, L. Omar, and S. K. Tyring, *J. Am. Acad. Dermat*., 2012, **67**, 331; J. O. Levitt, B. R. Keeley, and R. G. Phelps*, J. Am. Acad. Dermat.,* 2013, **69**, 254; D. T. Pompei, K. S. Rezzadeh, K. V. Viola, D. H. Lee, D. O. Schairer, L. A. Chismar, and S. R. Cohen, *J. Am. Acad. Dermat.,* 2013, **68**, 1045.
18. W. Sun, Z. Liu, and Y. Zhang, *Int. J. Mol. Sci*., 2013, **14**, 1; R. Maryam, R. A. Khan, Y. Zhang, and L. Ya, *Int. J. Agric. Biol*., 2013, **15**, 993; M. Rashid, A. R. Khan, and Y. Zhang, *J. Economic Entomology*, 2013, **106**, 2177; B. E. Campbell, A. Hofmann, A. McCluskey, and R. B. Gasser, *Biotechnol. Adv*., 2011, **29**, 28.
19. A. Rudo, H. U. Siehl, K. P. Zeller, S. Berger, and D. Sicker, *Chem. in Unserer Zeit,* 2013, **47**, 310.
20. For selected, recent reviews, see: L. Deng, J. Dong, and W. Wang, *Mini-Rev. Med. Chem.,* 2013, **13**, 1166; L. P. Deng, J. Dong, H. Cai, and W. Wang, *Curr. Med. Chem*., 2013, **20**, 159; L. Deng and S. Tang, *Expert Opinion on Therapeutic Patents*, 2011, **21**, 1743.
21. Y. C. Chen, S. C. Chang, M. H. Wu, K. A. Chuang, J. Y. Wu, W. J. Tsai, and Y. C. Kuo, *Life Sci*., 2009, **84**, 218.
22. A. Enz, G. Zenke, and E. Pombo-Villar, *Bioorg. Med. Chem. Lett.,* 1997, **7**, 2513.
23. For a review on endothall, see: R. C. Lord, *Med. Biochem*., 2001, **1**, 315. For others selected references concerning this compound, see also: J. Bajsa, Z. Pan, D. Zhiqiang, E. Franck, D. K. Owens, and S. O. Duke, *Pest. Biochem. Physiol.,* 2012, **102**, 38; S. Tresch and J. Schmotz, *Pest. Biochem. Physiol.*, 2011, **99**, 86.
24. Z. Liu, J. Zhang, J. Yuan, Y. Dang, C. Yang, X. Chen, J. Xu, and L. Yu, *Mol. Biol. Rep*., 2005, **32**, 41.
25. Y. Y. Wang, R. D. Hu, Q. Y. Lin, Y. L. Zhao, and N. Wang, *Asian J. Chem*., 2010, **22**, 5993.
26. M. R. Reithofer, S. M. Valiahdi, M. Galanski, M. A. Jakupec, V. B. Arion, and B. K. Keppler, *Chem. Biodivers.*, 2008, **5**, 2160.
27. F. L. Yin, J. J. Zou, L. Xu, X. Wang, and R. C. Li, *J. Rare Earths*, 2005, **23**, 596.
28. S. K. Li, Q. Y. Lin, L. Tx, Y. J. Wang, and D. Chen, *Chinese J. Struct. Chem.,* 2010, **29**, 1632.
29. F. Zhang, W. Z. Zhu, Q. Y. Lin, W. D. Guo, L. L. Zhang, and S. K. Li, *J. Rare Earths*, 2011, **29**, 297.
30. N. Wang, Q. Y. Lin, J. Feng, Y. L. Zhao, Y. J. Wang, and S. K. Li, *Inorg. Chim. Acta*, 2010, **363**,

3399.

31. N. Wang, Q. Y. Lin, Y. H. Wen, L. C. Kong, S. K. Li, and F. Zhang, *Inorg. Chim. Acta,* 2012, **384**, 345.
32. Q. Y. Li, Y. Y. Wang, Y. L. Zhao, D. M. Yan, F. J. Wang, and F. Zhang, *J. Coord. Chem*., 2011, **64**, 920.
33. F. Zhang, X. L. Zhang, Q. Y. Lin, X. L. Zheng, L. L. Zhang, Q. Y. Yang, and J. Y. Gu, *J. Fluoresc*., 2012, **22**, 1395.
34. F. Zhang, X. L. Zheng, Q. Y. Lin, P. P. Wang, and W. J. Song, *Inorg. Chim. Acta*, 2013, **394**, 85.
35. F. Zhang, Q. Y. Lin, S. K. Li, Y. L. Zhao, P. P. Wang, and M. M. Chen, *Spectrochim. Acta*, 2012, **98A**, 436.
36. F. Zhang, Q. Y. Lin, W. L. Hu, W. J. Song, S. T. Shen, and P. Gui, *Spectrochim. Acta*, 2013, **110A**, 100.
37. Isolation : J. S. Chandra and M. Sabir, *Indian J. Pharm. Sci*., 1978, **40**, 97. Structural determination: R. J. Bochis and M. H. Fisher, *Tetrahedron Lett.,* 1968, **16**, 1971. Absolute configuration: M. G. Meter, G. Snatzke, F. Snatzke, K. N. Nagarajan, and H. Schmid, *Helv. Chim. Acta,* 1974, **57**, 32.
38. R. Raj, R. Kaleysa, and P. A. Kurup, *Indian J. Med. Res.,* 1968, **56**, 1818.
39. T. Nakatani, T. Konishi, K. Miyahara, and N. Noda, *Chem. Pharm. Bull*., 2004, **52**, 807.
40. T. Nakatani, K. Jimpo, and N. Noda, *Chem. Pharm. Bull*., 2007, **55**, 92.
41. P. K. Guha, R. Poi, and A. Bhattaacharyya, *Phytochemistry*, 1990, **29**, 2017.
42. Z. Wang, H. L. Leng, K. Sha, and J. Liu, lit. cit. in 1a, reference 46 quoted in this paper.
43. A. McCluskey, S. P. Ackland, E. Gardiner, C. C. Walkom, and J. A. Sakoff, *Anti-Cancer Drug Design,* 2001, **16**, 291.
44. For selected references see: A. McCluskey, C. C. Walcom, M. C. Bowyer, S. P. Ackland, E. Gardiner, and J. A. Sakoff, *Bioorg. Med. Chem. Lett*., 2001, **11**, 2941; S. H. L. Kok, C. H. Chui, W. S. Lam, J. Chen, F. Y. Lau, S. M. Raymond, G. Y. M. Cheng, W. K. Tang, Y. T. N. Teo, F. Cheung, C. H. Cheng, A. S. C. Chang, and J. C. O. Tang, *Int. J. Mol. Med*., 2006, **18**, 1217; S. H. Kok, C. H. Chui, W. S. Lam, J. Chen, F. Y. Lau, A. S. M. Wong, G. Y. M. Cheng, P. B. S. Lai, T. W. T. Leung, M. W. Y. Michael, J. C. O. Tang, and A. S. C. Chen, *Bioorg. Med. Chem. Lett*., 2007, **17**, 1155.
45. I. J. Tseng, S. Y. Sheu, P. Y. Lin, J. A. Lee, K. L. Ou, and L.W. Lee, *J. Exp. Clin. Med.*, 2012, **4**, 280.
46. I. J. Tseng, S. Y. Sheu, Y. T. Chen, C. Y. Huang, C. T. Lin, and P. Y. Lin, *Chem. Pharm. Bull.*, 2012, **60**, 1453.

47. H. Guenther, E. Ramstad, and H. G. Floss, *J. Pharm. Sci*., 1969, **58**, 1274; W. D. Woggon, S. A. Hauffe, and H. Schmid, *J. Chem. Soc.*, *Chem. Comm*., 1983, 272; J. P. McCormick, J. E. Carrel, and J. P. Doom, *J. Am. Chem. Soc*., 1986, **108**, 8071; J. P. McCormick and J. E. Carrel, *Environ. Sci. Res.*, 1992, **44** (Secondary-Metabolite Biosynthesis and Metabolism), 261.
48. For a first, unsuccessful attempt, see: F. von Bruchhausen and W. Bersch, *Arch. Pharm. Ber. Deusch. Pharm. Ges.*, 1928, **266**, 697.
49. G. Stork, E. E. van Tamelen, L. I. Friedman, and A. W. Burgstahler, *J. Am. Chem. Soc.,* 1953, **75**, 384.
50. G. Schenck and R. Wirtz, *Naturwissenshaften*, 1953, **40**, 531.
51. W. G. Dauben, C. R. Kessel, and K. H. Takemura*, J. Am. Chem. Soc*., 1980, **102**, 6893 and references therein.
52. P. A. Grieco, J. J. Nunes, and M. S. Gaul, *J. Am. Chem. Soc*., 1990, **112**, 4595.
53. C. E. Puerto Galvis, L. Y. Vargas Mendez, and V. V. Kouznetsov, *Chem. Biol. Drug Des.,* 2013, **82**, 477.
54. A. McCluskey, M. A. Keane, C. C. Walcom, M. C. Bowyer, A. T. R. Sim, D. J. Young, and J. A. Sakoff, *Bioorg. Med. Chem. Lett.,* 2002, **12**, 391.
55. H. Kotsuki, H. Nishizawa, S. Kitagawa, O. Masamitsu, H. Yamasaki, K. Matsuoka, and T. Tokoroyama, *Bull. Chem. Soc. Jpn*., 1979, **52**, 496.
56. Y. Baba, N. Hirukawa, and M. Sodeoka, *Bioorg. Med. Chem*., 2005, **13**, 5164.
57. D. B. Rydberg and J. Meinwald, *Tetrahedron Lett*., 1996, **37**, 1129.
58. W. G. Dauben, J. Y. L. Lam, and Z. R. Guo, *J. Org. Chem*., 1996, **61**, 4816.
59. Selected, recent reviews : A. A. Bekhit, A. Hymete, A. E. A. Bekhit, A. Damtew, and H. Y. Aboul-Enein, *Mini-Rev. Med. Chem*., 2010, **10**, 1014; A. Schmidt and A. Dreger, *Curr. Org. Chem*., 2011, **15**, 1423; G. G. Kumar, K. Vikas, and K. Vinod, *Res. J. Chem. Environ*., 2011, **15**, 90; F. K. Keter and J. Darkwa, *BioMetals*, 2012, **25**, 9; V. Kumar, K. Kaur, G. K. Gupta, G. Girish, and A. K. Sharma, *Eur. J. Med. Chem*., 2013, **69**, 735.
60. K. B. Umesha, R. K. M. Lokanatha, and K. K. Ajay, *Indian J. Chem*., 2002, **41B**, 1450.
61. O. Wallach, *Justus Liebigs Ann. Chem*., 1907, **356**, 197.
62. "Encyclopedia of Food and Color Additives", ed. by G. A. Burdock, Vol. 1, CRC Press, 1997, p. 590.
63. General references: D. E. Metzler and C. Metzler "Biochemistry: The Chemical Reactions of Living Cells", Vol. 2, Academic Press, 2003, Chapter 22, p. 1232; J. Gershenzam and R. B. Croteau, "Lipids Metabolism in Plants", ed. by T. S. Moore Jr., CRC Press, 1993, pp. 339-388; J. Bohlmann,

C. L. Steele, and R. Croteau, *J. Biol. Chem*., 1997, **272**, 21784; J. Bohlmann, G. Meyer-Gauen, and R. Croteau, *Proc. Natl. Acad. Sci. USA*, 1998, **95**, 4126; M. L. Wise, T. J. Sauvage, E. Katahira, and R. Croteau, *J. Biol. Chem*., 1998, **273**, 14891; D. C. Williams, D. J. McGarvey, E. Katahira, and R. Croteau, *Biochemistry*, 1998, **37**, 12213.

64. J. Degenhardt, T. G. Köllner, and J. Gershenzonb, *Phytochemistry*, 2009, **70**, 1621.
65. E. J. L. Lana, K. A. Rocha da Silva, I. V. Kozhevnikov, and E. V. Gusevskaya, *J. Mol. Catalysis*, 2006, **259A**, 99.
66. See reference 64, p. 1050.
67. J. A. Klocke, M. V. Darlington, and M. F. Balandrin, *J. Chem. Ecol*., 1987, **13**, 2131.
68. V. Sfara, E. N. Zerba, and R. A. Alzogaray, *J. Med. Entomol.,* 2009, **46**, 511.
69. F. P. Schiestl and D. W. Roubik, *J. Chem. Ecol.,* 2004*,* **29**, 253.
70. U. R. Juergens, U. Dethlefsen, G. Steinkamp, A. Gillissen, R. Repges, and H. Vetter, *Resp. Med.*, 2003, **97**, 250.
71. J. Lackie, A Dictionary of Biomedicine, Oxford University Press, 2010.
72. U. R. Juergens, M. Stöber, and H. Vetter, *Eur. J. Med. Res*., 1998, **3**, 508; U. Juergens, T. Engelen, K. Racké, M. Stöber, A. Gillissen, and H. Vetter, *Pulmonary Pharmacol. Therapeut*., 2004, **17**, 281.
73. W. Kehrl, U. Sonnemann, and U. Dethlefsen, *Laryngosc*., 2004, **114**, 738.
74. F. A. Santos and V. S. Rao, *Phytotherapy Res*., 2000, **14**, 240.
75. H. Moteki, H. Hibasami, Y. Yamada, H. Katsuzaki, K. Imai, and T. Komiya, *Oncology Reports,* 2002, **9**, 757.
76. W. Jäger, "Metabolism of Terpenoids in Animal Models and Humans", Handbook of Essential Oils: Science, Technology and Applications, ed. by K. Husnucan Baser and G. Buchbauer, CRC Pres, 2009, pp. 214-215.
77. For selected reviews see: S. O. Duke, J. G. Romagni, and A. M. Rimando, *Weed Res*., 2000, **40**, 99; S. O. Duke and A. Oliva, *Allelopathy,* 2004, 201; G. S. Buttar and N. Aggarwal, *Pestology,* 2005, **29**, 27; A. F. M. Barton, B. Dell, and A. R. Knight, *J. Agric. Food Chem.,* 2010, **58**, 10147.
78. S. N. Grag, L. N. Misra, and S. K. Aggarwal, *Phytochemistry,* 1989, **28**, 634.
79. J. P. N. Rosazza, J. J. Steffens, F. S. Sariaslani, A. Goswani, J. M. Beale Jr., S. Reeg, and R. Chapman, *Appl. Environ. Microbiol*., 1987, **53**, 2482.
80. J. P. N. Rosazza, A. Goswani, W. G. Liu, F. S. Sariaslani, J. J. Steffens, R. P. Steffek, J. M. Beale, Jr., R. Chapman, and S. Reeg, *Develop. Industry Microbiol. Series*, 1988, **29**, 181.
81. M. Miyazawa, Y. Nana, K. Yamamoto, and H. Kameoka, *Chem. Express,* 1991, **6**, 771.
82. H. Hamada, K. Ishihara, N. Nakajima, H. Hamada, H. J. Williams, and A. I. Scott, *Lett. Org. Chem.,*

2004, **1**, 171.

83. W. G. Liu, A. Goswami, R. P. Steffek, R. L. Chapman, F. S. Sariaslani, J. J. Steffens, and J. P. N. Rosazza, *J. Org. Chem*., 1988, **53**, 5700.
84. K. Grossmann, J. Hutzler, S. Tresch, N. Christiansen, R. Looser, and T. Ehrhardt, *Pest Manag. Sci*., 2012, **68**, 482.
85. A. Lopukhima, M. Dettenberg, E. W. Weiler, and H. Hollander-Czytko, *Plant Physiol*., 2001, **126**, 1678; E. J. Lee and P. J. Facchini, *Plant. Physiol*., 2011, **157**, 1067; D. Riewe, M. Koochi, J. Lisec, M. Pfeiffer, R. Lippmann, J. Scheimeichel, L. Willmitzer, and T. Altmann, *Plant J*., 2012, **71**, 850 and references cited in these papers.
86. P. Reddy and S. Urban*, Phytochemistry,* 2009*,* **70***,* 250.
87. A. Hausmann and G. Sandmann, *Fungal Genet. Biol.,* 2000, **30**, 147; A. F. Estrada, D. Maier, D. Scherzinger, J. Avalos, and S. Al-Babili, *Fungal Genet. Biol.,* 2008, **45**, 1497.
88. G. Romagni, G. Joanne, S. O. Duke, O. Stephen, and F. E. Dayan, *Plant Physiol.*, 2000, **123**, 725.
89. For a review on the biological function of asparagine synthetase in plants, see: L. Gaufichon, M. Reisdorf-Cren, S. J. Rothstein, F. Chardon, and A. Suzuki, *Plant Sci*., 2010, **179**, 141.
90. P. B. Gomes, M. L. Feitosa, M. I. G. Silva, E. C. Noronha, B. A. Moura, E. T. Venâncio, E. R. V. Rios, D. Pergentino de Sousa, S. M. Mendes de Vasconcelos, M. M. F. Fonteles, and F. C. Florenco de Sousa, *Pharmacol. Biochem. Behav.*, 2010, **96**, 287.
91. S. G. Griffin, S. G. Wyllie, J. L. Markham, and D. N. Leach*, Flavour and Fragrance J*., 1999, **14**, 322.
92. A. Ahad. M. Aqil, K. Kohli, Y. Sultana, M. Mujeeb, and A. Ali, *Curr. Drug Deliver.,* 2011, **8**, 213.
93. K. Endo and H. H. Kino, *Can. J. Chem.,* 1984, **62**, 2011.
94. E. Mousouri, E. Milieu, and P. Magiatis, *J. Agr. Food Chem*., 2014, **62**, 660.
95. P. K. Shashikumar and P. Vijayendra, *J. Essent. Oil Res*., 1993, **5**, 659.
96. L. Caglioti, H. Naef, D. Arigoni, and O. Jeger, *Helv. Chim. Acta,* 1958, **41**, 2278. See also: L. Caglioti, H. Naef, D. Arigoni, and O. Jeger, *Helv. Chim. Acta,* 1959, **42**, 2557; M. I. Nassar, E. A. Abu-Mustafa, and A. A. Ahmed, *Pharmazie,* 1995, **50**, 766; A. Ghosh, A. Banerji, S. Mandal, and J. Banerji, *Nat. Prod. Comm*., 2009, **4**, 1023; M. R. Cha, Y. H. Choi, C. W. Choi, Y. S. Kim, S. H. Ryu, Y. H. Kim, and U. S. Choi, *Planta Med.*, 2011, **77**, 52.
97. M. Iranshahi, P. Arfa, M. Ramezani, M. R. Jaafari, H. Sadeghian, C. Bassarello, S. Piacente, and C. Pizza, *Phytochemistry*, 2007, **68**, 554.
98. L. Teng, G. Z. Ma, L. Li, L. Y. Ma, and X. Q. Su, *Chem. Nat. Compd*., 2013, **49**, 606.
99. J. M. Rollinger, T. M. Steindl, D. Schuster, I. Kirchmair, K. Amain, E. P. Elmerer, T. Langer, H.

Stupper, P. Wutzler, and M. Schmidtke, *J. Med. Chem.,* 2008, **51**, 842; C. L. Lee, L. C. Chiang, L. H. Cheng, C. C. Liaw, M. H. Abd El-Razek, F. R. Chang, and Y. C. Wu, *J. Nat. Prod.,* 2009, **72**, 1568.

100. J. H. Lee, S. Choi, Y. Lee, H. J. Lee, K. H. Kim, K. S. Alin, H. Bae, H. J. Lee, E. O. Lee, K. S. Ahn, S. H. Ryu, J. Lue, and H. S. Kim, *Mol. Cancer Therapeut*., 2010, **9**, 388.
101. E. E. van Tamelen, *Acc. Chem. Res*., 1975, **8**, 152; A. Eschenmoser and D. Arigoni, *Helv. Chim. Acta*, 2005, 3011; R. A. Yoder and J. N. Johnston, *Chem Rev*., 2005, **105**, 4730.
102. E. E. van Tamelen and R. M. Coates, *Chem. Comm*., 1966, 413; E. E. van Tamelen and R. M. Coates, *Bioorg. Chem*., 1982, **11**, 171.
103. E. A. Abu-Mustafa, F. K. El-Bay, and M. B. Fayez, *J. Pharm. Sci.,* 1971, **60**, 788. See also: G. Cravotto, G. Balliano, B. Robaldo, S. Boso-Oliaro, S. Chimichi, and M. Boccalini, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1931.
104. R. P. Hanzlik, *Org. Synth.,* 1977, **56**, 112.
105. C. J. Rhodes, *Ann. Rep. Prog. Chem.,* 2007, **103C**, 287. For a review, see: E. F. Sousa-Aguiar, F. Eduardo, F. E. Triguero, and F. M. Z. Zotin, *Catal. Today,* 2013, 115 and 218.
106. C. Tsangarakis, E. Arkoudis, C. Raptis, and M. Stratakis, *Org. Lett.,* 2007, **9**, 583; C. Tsangarakis, C. Raptis, E. Arkoudis, and M. Stratakis, *Adv. Synt. Catal*., 2008, **350**, 1587.
107. F. W. J. Demmitz, C. Philippini, and R. A. Raphael, *J. Org. Chem*., 1995, **60**, 5114.
108. T. Mukaiyama and N. Iwasawa, *Chem. Lett*., 1981, **10**, 29.
109. O. Hofer and H. Gereger, *Liebigs Ann. Chem*., 1985, 1136.
110. F. O. Bohlmann, C. Zdero, and H. Kaptein, *Liebigs Ann. Chem*., 1968, **17**, 186.
111. M. Aziz and F. Rouessac, *Tetrahedron*, 1988, **44**, 101; X. Zhang, A. Archelas, A. Meou, and R. Furstoss, *Tetrahedron: Asymmetry*, 1991, **2**, 247.
112. M. Leblanc, G. Ferey, F. Rouessac, and M. Aziz, *Acta Cryst*., 1988, **C44**, 1262.
113. R. M. Coates and L. S. Melvin, Jr., *Tetrahedron,* 1970, **26**, 5699.
114. For a short, comprehensive review see : S. Genovese and F. Epifano, *Curr. Drugs Targets*, 2011, **12**, 381.
115. E. E. van Tamelen and T. J. Curphey, *Tetrahedron Lett*., 1962, 121.
116. See reference 113 and: M. Aziz and F. Rouessac, *Tetrahedron Lett*., 1987, **28**, 2579.
117. See reference 113 and: A. Mueller, W. R. Abraham, and K. Kieslich, *Bull. Soc. Chim. Belg.*, 1994, **103**, 405.
118. A. T. Sneden, *Synlett*, 1993, 313.
119. Z. H. Gao, B. Liu, and W. D. Z. Li, *Tetrahedron*, 2005, **61**, 10734.
120. M. P. DiFazio and A.T. Sneden, *J. Nat. Prod*., 1990, **53**, 1357.

121. R. Kaiser and D. Lamparsky, *Helv. Chim. Acta*, 1978, **61**, 373.
122. J. Casadebaig, Y. Pelissier, C. Marion, M. Milhau, and J. M. Bessiere, *J. Essent. Oils*, 2000, 677; A. Boulanger and J. Crouzet, *Food Chem*., 2001, **74**, 209.
123. Y. B. Bose, A. Altintas, O. Tugay, T. Uysal, B. Demirci, K. Ertugrul, and C. H. K. Baser, *Asian J. Chem.*, 2010, **22**, 7159.
124. J. A. Pino and R. Marbot, *J. Agric. Food Chem*., 2001, **49**, 5880.
125. M. LeRoux, J. C. Cronge, B. V. Burger, and J. Elizabeth, *J. Agric. Food Chem*., 2012, **60**, 2657.
126. M. P. DiFazio, W. W. Wallace, and A. T. Sneden, *Heterocycles*, 1989, **29**, 2391.
127. A. B. K. Rao, P. S. N. Murthy, M. K. Chakrabonty, and T. Fujimori, *Tobacco Res*., 1987, **13**, 14.
128. Y. Tagaki, T. Fujimori, T. Hata, K. Tuyoshi, H. Kaneko, and K. Kato, *Agric. Biol. Chem.*, 1980, **44**, 705.
129. X. W. Li, Z. T. Guo, Y. Zhao, Z. Zhao, and J. F. Hu, *Phytochemistry*, 2010, **71**, 682.
130. J. Shitamoto, K. Matsunami, H. Otsuka, T. Shinzato, and Y. Takeda, *Chem. Pharm. Bull.*, 2010, **58**, 1026.
131. T. Kato, H. Kondo, Y. Kitano, G. Hata, and Y. Takagi, *Chem. Lett*., 1980, 757.
132. J. A. Findlay and W. D. MacKay, *Can. J. Chem*., 1971, **49**, 2369; W. Cocker, K. J. Crowley, and K. Srinivason, *J. Chem. Soc., Perkin Trans. 1*, 1973, 2485.
133. I. Brito, M. Cueto, A. Díaz-Marrero, J. Darias, and A. San Martín, *J. Nat. Prod*., 2002, **65**, 946.
134. A. G. González, J. D. Martin, M. Norte, R. Pérez, P. Rivera, J. Z. Ruano, M. L. Rodríguez, J. Fayos, and A. Perales, *Tetrahedron Lett*., 1983, **24**, 4143.
135. M. Suzuki, M. Daitoh, C. S. Variappan, T. Abe, and M. Masuda, *J. Nat. Prod*., 2001, **64**, 597.
136. E. Breitmaier "Terpenes: Flavors, Fragances, Pharmaca, Pheromones", Wiley, 2006 pp. 24-26 and 45; "Total Synthesis of Natural Products: A Sesquidecade of Sesquiterpenes: Total Synthesis, 1980-1994". Part B: Bicyclic and Tricyclic Sesquiterpenes, ed. by D. Goldsmith, M. C. Pirrung, A. T. Morehead, and B. G. Young, Wiley, 2007, Volume 11.
137. K. A. Mohammed, C. F. Hossain, L. Zhang, R. K. Bruick, Y. D. Zhou, and D. G. Nagle, *J. Nat. Prod*., 2004, **67**, 2002.
138. See for instance: M. Quintero, N. Mackenzie, and P. A. Brennan, *Eur. J. Surg. Oncol.*, 2004, **30**, 465 and references therein.
139. M. E. Jung and G. Y. Jamie, *Tetrahedron Lett.,* 2008, **49**, 4962; M. E. Jung and G. Y. Jamie, *J. Org. Chem*., 2009, **74**, 8739.
140. K. F. Podraza and R. L. Basfield, *J. Org. Chem*., 1989, **54**, 5919.
141. Compound **179** was first prepared in 1929. See: O. Diels and K. Alder, *Ber. Deutsch. Chem. Ges*.,

1929, **62B**, 554.

142. B. Bonnlander, B. Baderschneider, M. Messerer, and P. Winterhalter*, J. Agric. Food Chem.,* 1998, **46**, 1474.
143. S. Mukherjee, A. P. Scopton, and E. J. Corey, *Org. Lett.,* 2010, **12**, 1836.
144. M. K. Brown and E. J. Corey, *Org. Lett*., 2010, **12**, 172 and references therein.
145. E. N. Pitsinos, N. Athinaios, and V. P. Vidali, *Org. Lett.*, 2012, **14**, 4666.
146. D. Liu, E. Canales, and E. J. Corey, *J. Am. Chem. Soc*., 2007, **129**, 1498.
147. H. Guth, *Helv.Chim. Acta,* 1996, **79**, 1559.
148. A. G. Chittiboyina, G. M. Kumar, P. B. Carvalho, Y. Liu, Y. D. Zhao, D. G. Nogle, and M. A. Avery, *J. Med. Chem*., 2007, **50**, 6299.
149. D. S. Caine and R. F. Collson, *Synlett,* 1995, 503; D. S. Caine and M. A. Paige, *Synlett,* 1999, 1391.
150. M. N. Paddon-Row, N. G. Rondan, and K. N. Houk, *J. Am. Chem. Soc.,* 1982, **104**, 7162.
151. A. G. Chittiboyina, P. Peddikotla, M. A. Avery, and I. A. Khan, *J. Org. Chem*., 2013, **78**, 9223.
152. H. Buschmann and H. D. Scharf, *Synthesis,* 1988, 827.
153. R. H. Crabtree and M. W. Davis, *J. Org. Chem*., 1986, **51**, 2655; K. H. Hopmann and A. Bayer, *Organometallics*, 2011, **30**, 2483.
154. R. H. Crabtree, *Acc. Chem. Res*., 1979, **12**, 331; J. M. Brown, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 190; T. L. Church and P. G. Anderson, *Coord. Chem. Rev*., 2008, **252**, 513. See also. H. U. Blaser, "Applications of Iridium Catalysts in the Fine Chemical Industry. Iridium Complexes in Organic Synthesis", ed. by L. A. Oro and C. Claver, Wiley, 2009. Chapter 1, pp. 1-14. See in particular pp. 8-12.
155. A. Murai "Biosynthesis of Cyclic Bromoethers from Red Algae. Comprehensive Natural Products Chemistry", ed. by D. Barton, K. Nakanishi, and O. Meth-Cohn, Elsevier, 1999. Vol. 1, p. 303; V. M. Dembiitsky, A. G. Tolstikov, and G. A. Tolstikov, *Chem. Sustainable Develop*., 2003, **11**, 329.
156. S. M. Waraszkiewicz, H. H. Sun, and K. L. Erickson, *Tetrahedron Lett.,* 1976, 3021.
157. S. M. Waraszkiewicz, H. H. Sun, K. L. Erickson, J. Fiver, and J. Clardy, *J. Org. Chem*., 1978, **43**, 3194.
158. H. H. Sun, S. M. Waraszkiewicz, and K. L. Erickson, *Tetrahedron Lett*., 1976, 4227.
159. Z. S. Abou-Elnaga, W. M. Alarif, and S. S. Al-Lihaibi, *Clean. Soil, Air, Water*, 2011, **39**, 787.
160. S. E. N. Ayyad, K. O. Al-Footy, W. M. Alarif, T. R. Sobahi, S. A. Bassaif, M. S. Makki, A. M. Asiri, A. Y. Al Halwani, A. F. Badria, and F. A. A. Badria, *Chem. Pharm. Bull*., 2011, **59**, 1294.
161. C. S. Variappan, M. Daitoh, M. Suzuki, T. Abe, and M. Masuda, *Phytochemistry*, 2001, **58**, 291.
162. C. S. Variappan, M. Suzuki, T. Abe, and M. Masuda, *Phytochemistry*, 2001, **58**, 507.

163. C. L. D. Jennings-White, A. B. Colmes, and P. R. Raithby, *J. Chem. Soc., Chem. Comm*., 1979, 542.
164. A. B. Colmes, C. L. D. Jennings-White, and D. A. Kendrick, *J. Chem. Soc., Chem. Comm*., 1983, 415.
165. E. N. Garbisch, *J. Org. Chem*., 1965, **30**, 2109.
166. A. B. Colmes, R. A. Raphael, and K. N. Wellard, *Tetrahedron Lett*., 1976, 1539.
167. B. Haveaux, A. Dekoker, M. Rens, A. R. Sidote, J. Toye, and L. Ghosez, *Org. Synth*., 1980, **59**, 26.
168. A. B. Colmes, C. L. D. Jennings-White, and D. A. Kendrick, *J. Chem. Soc., Chem. Comm*., 1984, 1594.
169. Compound **285** from *Vetiver* oils: S. P. Weyerstahl, H. Marschall, U. Splittgerber, and D. Wolf, *Liebigs Ann*., 1996, 1195; P. Weyerstahl, H. Marschall, U. Splittgerber, D. Wolf, and H. Surburg, *Flavour Fragrance J*., 2000, **15**, 395; P. Campagnat, G. Figueredo, J. C. Chalchat, A. P. Carnat, and J. M. Bessiere, *J. Essent., Oil Res*., 2006, **18**, 416. Compound **286** from *Ambrosia artemisides* : J. Jakupovic, M. Jaensch, F. Bohlmann, and M. O. Dillon, *Phytochemistry,* 1988, **27**, 3551. Compound **287** from *Varoi nijareiensis* : E. Cabrera, A. García-Granados, and M. A, Quecuty, *Phytochemistry,* 1988, **27**, 183. Compound **288** from *Artemisia barrelieri* : J. A. Marco, J. F. Sanz, A. Yuste, M. Carda, and J. Jakupovic, *Phytochemistry*, 1991, **30**, 3661.
170. J. F. Sanz and J. A. Marco, *Phytochemistry*, 1990, **29**, 2913.
171. J. A. Marco, J. F. Sanz-Cervera, V. García-Lliso, L. R. Domingo, M. Carda, S. Rodríguez, F. López-Ortiz, and J. Lex, *Liebigs Ann.,* 1995, 1837.
172. E. Fattorusso, S. Magno, and L. Mayol, *Gazz. Chim. Ital.,* 1979, **109**, 589.
173. C. Rogers and B. A. Keay, *Tetrahedron Lett*., 1989, **30**, 1349; C. Rogers and B. A. Keay, *Can. J. Chem.*, 1993, **71**, 611.
174. Review: B. A. Keay and I. R. Hunt, "Aspects of the intramolecular Diels-Alder reaction of furan dienes leading to the formation of epoxydecalin systems", *Advances in Cyloaddition*, 1999, **6**, 173, ed. by M. Harmata, Elsevier.
175. J. J. Fernández, M. L. Souto, L. V. Gil, and M. Norte, *Tetrahedron*, 2005, **61**, 8910.
176. D. M. Estrada, J. L. Ravelo, C. Ruiz-Pérez, J. D. Martín, and X. Solans, *Tetrahedron Lett*., 1989, **30**, 6219.
177. J. A. Findlay and G. Li, *Can. J. Chem*., 2002, **80**, 1697.
178. M. Wessels, G. M. Koenig, and A. D. Wright, *J. Nat. Prod*., 2002, **80**, 1697.
179. Review: T. Tokoroyama, *Synthesis*, 2000, 611.
180. Reviews: M. Hiesermann and H. Hemboldt, "Natural products Synthesis: Targets, Methods, Concepts. *Topics in Curr. Chem.*, 2005, **243**, 73, ed. by J. Mulzer, J. D. Connolly, and R. A. Hill,

"Dictionary of Terpenoids", Springer, 991, Vol. 2: Di- and Higher Terpenoids, p. 655.

181. M. C. De la Torre, B. Rodríguez, M. Bruno, G. Savona, F. Piozzi, A. Perales, M. R. Torres, and O. Servettaz, *Phytochemistry*, 1990, **29**, 2229.
182. A. Gallardo, E. Manta, J. D. Martín, C. Pérez, R. Pérez, and M. L. Rodríguez, *Rev. Latinoamericana de Química*, 1988, **19**, 86.
183. E. Ioannou, C. Vagias, and V. Roussis, *Marine Drugs*, 2013, **11**, 1104.
184. Reviews: M. I. Isaev, M. B. Gorovits, and N. K. Abubavikov, *Chem. Nat. Prod*., 1985, **21**, 399; I. Saleem, "Cycloartane Triterpenoids", VDM Verlag, 2010; S. S. Azimova, "Natural Compounds: Cycloartane Triterpenoids and Glycosides", Springer, 2013.
185. J. A. Compton, A. Culham, and S. L. Jury, *Taxon*, 1998, **47**, 593; J. A. Compton, A. Culham, J. G. Gibbings, and S. L. Jury, *Biochem. Syst. Ecol*., 1998, **26**, 185.
186. Z. E. Tian, Y. E. Sun, P. G. Xiao, and E. X. Wu, *Recent Prog. Med. Plants*, 2011, **31**, 49; H. I. C. Lowe, N. J. Toyang, C. T. Watson, and J. Bryant, *Br. J. Med. Med. Res.*, 2014, **4**, 1802; R. Tundis, F. Menichini, and M. R. Loizzo, Recent Insights into the Emerging Role of Triterpenoids in Cancer Therapy. Antitumor Activity of Triterpenoids: The Cycloartene Group. Studies in Natural Products Chemistry, ed. by Atta-ur-Rahman, Elsevier, 2014, Vol. 41, Chap. 1, pp. 2-6.
187. J. X. Lim and Z. Y. Zu, *Curr. Med. Chem*., 2006, **13**, 2927.
188. Pharmacopoeia of Chinese People's Republic; Chemical Industry: Beijing, 2005; Vol. 1, pp. 68-69.
189. First isolation: "Constituents of Cimifuga species. III. Constituents of Cimifuga acerina. 3. Structure of Acerinol". Abstract from Scifinder. T. Takemoto, G. Kusano, and N. Yamamoto, *Yakugaku Zasshi*, 1967, **87**, 1489; "Studies on the constituents of Cimifuga spp. XII. A revised struture of acerinol and the structures of the related compounds". Abstract from Scifinder. G. Kusano, A. Uchida, Y. Murakami, N. Sakurai, and T. Takemoto, *Yakugaku Zasshi*, 1976, **96**, 321; Y. Nian, H. Zhu, W. R. Tang, Y. Luo, J. Du, and M. H. Qiu, *J. Nat. Prod*., 2013, **76**, 896.
190. Y. R. Liu, Z. J. Wu, C. T. Li, F. M. Xi, L. N. Sun, and W. S. Chen, *Planta Med.*, 2013, **79**, 301 and references therein.
191. J. X. Li, S. Kadota, M. Hattori, S. Yosimachi, M. Shiro, N. Oogami, H. Mzuno, and T. Namba, *Chem. Pharm. Bull*., 1993, **41**, 832. Crystal structure: R. Y. Liu, C. T. Li, S. Qin, L. N. Sun, and Z. J. Wu, *Z. Kristallogr.-New Cryst. Struct.,* 2011, **226**, 169.
192. Y. Mian, H. Y. Wang, J. Su, L. Zhou, and G. Feng, *Tetrahedron*, 2012, **68**, 6521.
193. G. Kusano, S. Hojo, Y. Kondo, and T. Takemoto, *Chem. Pharm. Bull*., 1977, **25**, 3182.
194. A Kusano, M. Takahira, M. Shibano, T. Miyase, T. Okuyama, and G. Kusano, *Heterocycles*, 1998, **48**, 1003.

195. G. Kusano, S. Nozoe, Z. Taira, and T. Takemoto, *Heterocycles*, 1983, **20**, 1951.
196. H. Hemmi, F. Kitame, N. Ishida, G. Kusano, Y. Kondo, and S. Nozoe, *J. Pharm. Dyn.,* 1979, **2**, 339.
197. D. L. Liu, Y. J. Li, N. Yao, J. Xu, Z. S. Chen, A. Yiu, C. X. Zhang, W. C. Ye, and D. M. Zhang, *Eur. J. Pharmacol*., 2014, **733**, 34.
198. N. Sakurai, M. Kozuka, H. Tokuda, Y. Nobakuni, J. Takayasu, H. Nishino, A. Kusano, G. Kusano, M. Wagei, Y. Sakurai, and K. H. Lee, *Bioorg. Med. Chem*., 2003, **11**, 1137.
199. A. Kusano, M. Shibano, G. Kusano, and T. Miyase, *Chem. Pharm. Bull*., 1996, **44**, 2078.
200. M. Takahara, A. Kusano, M. Shibano, G. Kusano, K. Koizumi, R. Suzuki, H. S. Kim, and Y. Wataya, *Biol. Pharm. Bull*., 1998, **21**, 823.
201. A. Yawata, Y. Matsuhashi, H. Kato, K. Uemura, G. Kusano, J. Ito, T. Chikuma, and H. Hojo, *Eur. J. Pharm. Sci.,* 2009, **38**, 355.
202. E. Britmaier, "Terpenes: Importance, General Structure and Biosynthesis". Wiley, 2006, p. 96.
203. I. Anthonsen, T. Bruun, E. Hemmer, D. Holme, A. Lamvik, E. Sund, and N. A. Sorensen, *Acta Chem. Scand*., 1970, **24**, 2479. Crystal structure: F. Mo, *Acta Crystallogr*., 1973, **29B**, 796.
204. F. Bohlmann and C. Zdero, *Chem. Ber*., 1976, **109**, 1450; F. Bohlmann, W. Kanupf, R. M. King, and H. Robinson, *Phytochemistry*, 1979, **18**, 1011; F. Bohlmann, C. Zdero, R. M. King, and H. Robinson, *Phytochemistry*, 1979, **18**, 1533; F. Bohlmann, C. Zdero, H. Robinson, and R. M. King, *Phytochemistry*, 1979, **18**, 1993; F. Bohlmann, C. Zdero, M. Grena, A. K. Dhar, H. Robinson, and R. M. King, *Phytochemistry,* 1981, **20**, 281; F. Bohlmann, N. Kramp, M. Grenz, H. Robinson, and R. M. King, *Phytochemistry*, 1981, **20**, 1907; F. Bohlmann, S. Banerjee, J. Jakupovic, M. Grenz, L. N. Misra, G. Schemeda-Hirschmann, R. M. King, and H. Robinson, *Phytochemistry*, 1985, **24**, 511; J. Jakupovic, R. N. Baruali, F. Bohlmann, R. M. King, and H. Robinson, *Tetrahedron*, 1985, **41**, 4537; U. Warning, F. Bohlmann, V. H. Sánchez, S. E. Del Rio, and X. A. Domínguez, *Rev. Latinoamericana de Química*, 1986, **51**, 155; A. P. Rivera, F. Faini, and M. Castillo, *J. Nat. Prod*., 1988, **51**, 155; C. Zdero, F. Bohlmann, J. C. Solomon, R. M. King, and H. Robinson, *Phytochemistry*, 1989, **28**, 531.
205. Review: R. Xu and G. C. Fazio, *Phytochemistry,* 2004, **65**, 261.
206. See T. Kushiro and Y. Ebizuka, "Triterpenes. Comprehensive Natural Products. II. Chemistry and Biology, ed. by C. A. Townsed and Y. Ebizuka, Elsevier, 2010, Vol. 1, Ch., 18, p. 685.
207. M. Shibuya, A. Sagara, A. Sayito, T. Kushiro, and Y. Ebizuka, *Org. Lett*., 2008, **10**, 5071.
208. T. Takahashi, T. Moriyama, Y. Tanahashi, and G. Ourisson, *Tetrahedron Lett*., 1967, **31**, 2991.
209. K. Tachibana, M. Tori, Y. Moriyama, T. Tsuji, and T. Takahashi, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 1552.

210. S. Yamada, S. Yamada, K. Tachibana, Y. Moriyama, Y. Tanahashi, T. Ysuyuki, and T. Takahashi, *Bull. Chem. Soc. Jpn*., 1976, **49**, 1134 and references therein.
211. F. Missima, A. A. da Silva, G. A. Nunes, P. C. P. Bueno, J. P. B. de Sousa, J. K. Bastos, and J. M. Sforcin, *J. Pharm. Pharmacol*., 2007, **59**, 463.
212. A. A. da Silva, P. C. P. Bueno, L. E. Gregório, M. L. A. da Silva, S. Alburquerque, and J. K. Bastos, *J. Pharm. Pharmacol*., 2004, **56**, 1195.
213. M. Herrera-Martínez, M. V. Ramírez-Mares, E. Burgueño-Tapia, E. Cedillo-Portugal, C. Miron-Enriquez, and B. Hernández-Carlos, *Rev. Latinoamericana de Química,* 2012, **40**, 165.
214. S. Rangaswami and P. Venkateswarku, *Proc. Indian Acad. Sci.,* 1965, **62A**, 224. Crystal structure: J. D. White, J. Fayos, and J. Clardy*, J. Chem. Soc., Chem. Comm*., 1973, 357; F. Mo, *Acta Crystallogr.*, 1977, **33B**, 641; F. Mo, *Acta Crystallogr.*, 1982, **38B**, 2166.
215. P. Sengupta and A. K. Dey, *J. Indian Chem. Soc*., 1970, **47**, 713; N. C. Gupta, *Curr. Sci.,* 1978, **47**, 768; I. M. Chung, M. Y. Kim, S. D. Park, W. H. Park, and H. I. Moon, *Phytother. Res*., 2009, **23**, 1634.
216. K. U. Wendt, *Angew. Chem. Int. Ed*., 2005, **44**, 3966.
217. M. Tori , K. Tachibana, S. Yamada, T. Tsuyoki, and T. Takahashi, *Bull. Chem. Soc. Jpn*., 1977, **50**, 469.
218. E. J. Corey and J. J. Ursprung, *J. Am. Chem. Soc*., 1956, **78**, 504; G. Brownley, F. S. Spring, R. Stevenson, and W. S. Strachan, *J. Chem. Soc*., 1956, 2419.
219. M. Tori, M. Takai, Y. Matsumoto, Y. Moriyama, T. Tsuyuki, T. Takahashi, H. Ohnishi, A. Itai, and Y. Iitaka, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 2490 and references therein.
220. Isolated from *Datura innoxia*. See: M. Kocór, J. S. Pyrek, C. K. Atal, K. L. Bedi, and B. R. Sharma, *J. Org. Chem*., 1973, **38**, 3685.
221. M. Takai, M. Tori, T. Tsuyuki, T. Takahashi, A. Itai, and Y. Iitaka, *Chem. Pharm. Bull*., 1984, **32**, 2464.
222. Isolated from different species such as *Cucumis*, *Bryonia*, *Zanthoxylum* and *Pelargonium*. See T. Itoh, T. Shigimoto, N. Shimizu, T. Tamura, and T. Matsumoto, *Phytochemistry*, 1982, **21**, 2414 and references therein.
223. I. M. Chung, M. Y. Kim, S. D. Park, W. H. Park, and H. I. Moon, *Phytother. Res*., 2009, **23**, 1634.
224. H. I. Moon, *Hum. Exp. Toxicol*., 2011, **30**, 870.
225. *In vitro* cultivation of human tumor tissues: A. Billiau, J. J. Cassiman, D. Willems, M. Verhelst, and H. Heremans, *Oncology*, 1975, **31**, 257.
226. J. W. Lee, K. S. Kim, H. K. An, C. H. Kim, H. I. Moon, and Y. C. Lee, *PLoS One*, 2013, **8**,

e83611/1. Note: PLOS ONE (originally PLoS ONE) is an open access peer-reviewed scientific journal published by the Public Library of Science since 2006.

227. T. Masamune, M. Anetai, A. Furuzawa, M. Takasugi, H. Matsue, K. Kobayashi, S. Ueno, and N. Katsui, *Bull. Chem. Soc. Jpn*., 1987, **60**, 981; T. Masamune, A. Furuzawa, A. Furusaki, M. Ikura, H. Matsue, T. Kaneko, A. Abiko, N. Sakamoto, N. Tanimoto, and A. Murai, *Bull. Chem. Soc. Jpn*., 1987, **60**, 1001. Review: T. Masamune, *Nat. Prod. Biol. Act.,* Naito Found. Symp., 1986, pp. 25-32, ed. by H. Imora.
228. A. Furuzawa, H. Matsue, M. Ikura, and T. Masamune, *Tetrahedron Lett*., 1985, **26**, 5539.
229. Review: H. Grisebach, *Comments on Agric. Food Chem.,* 1987, **1**, 27.
230. T. Masamune, M. Anetai, M. Takasugi, and N. Katsui, *Nature,* 1982, **297**, 495; A. Furuzawa, A. Furusaki, M. Ikura, and T. Masamune, *J. Chem. Soc., Chem. Commun.*, 1985, 222.
231. E. J. Corey and B.C. Hong, *J. Am. Chem. Soc.*, 1994, **116**, 3149. This synthetic sequence was described and discussed in reference 1, p. 13544.
232. W. Steglich, M. Klaar, L. Zechlin, and H. J. Hecht, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 698.
233. A. Murai, N. Tanimoto, N. Sakamoto, and T. Masamune, *J. Am. Chem. Soc.,* 1988, **110**, 1985; H. Watanabe and K. Mori, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2919; E. J. Corey and I. N. Houpis, *J. Am. Chem. Soc*., 1990, **112**, 8997.
234. See reference 1, pp. 13540-13544 and: K. Mori and H. Watanabe, *Pure Appl. Chem.*, 1989, **61**, 543; A. Murai, *Pure Appl. Chem.,* 1989, **61**, 393; K. Mori, *Chem. Script.*, 1989, **24**, 395.
235. Y. Shiina, Y. Tomata, M. Miyashita, and K. Tanino, *Chem. Lett*., 2010, **39**, 835.
236. Y. Lu, G. Barth, K. Kieslich, P. D. Strong, W. L. Duax, and C. Djerassi, *J. Org. Chem.,* 1983, **48**, 4549.
237. A. Murai, N. Takimot, N. Sakamoto, and T. Masamune, *J. Am. Chem. Soc*., 1988, **110**, 1985.
238. A. Murai, M. Ohkita, T. Honma, N. Tanimoto, S. Araki, and A. Fukuzawa, *Chem. Lett*., 1992, 2103.
239. S. Giroux and E. J. Corey, *Org. Lett*., 2008, **10**, 5617.
240. G. A. Kraus, L. Yander, S. Leuw, G. Tylk, and D. H. Soh*, J. Agric. Food Chem*., 1996, **44**, 1548; G. A. Kraus and P. K. Choudury, *Eur. J. Org. Chem*., 2004, 2193, and references therein. See also: S. A. Snyder, *Nature Chem*., 2011, **3**, 422.
241. Y. Fukuyama, A. Kaneshi, N. Tani, and M. Kodama, *Phytochemistry*, 1993, **33**, 483.
242. D. Phife, R. W. Patton, R. L. Berrie, R. Yaborough, M. S. Puar, M. Patel, W. R. Bishop, and S. J. Coval, *Tetrahedron Lett*.,1995, **36**, 6995.
243. D. Phife, R. W. Patton, R. L. Berrie, R. Yaborough, M. S. Puar, M. Patel, W. R. Bishop, and S. J. Coval, *Tetrahedron Lett*., 1996, **37**, 5527; D. Wiege, *Aust. J. Chem.*,1996, **49**, 669.

Joaquín Plumet received his Ph. D. in 1973 from the Complutense University of Madrid (UCM). He continued his scientific education, as an Alexander von Humboldt Postdoctoral Fellow, at the Institute of Organic Chemistry, University of Munich with Prof. Rolf Huisgen. In 1986 he joined the Department of Organic Chemistry in the University of Extremadura in Badajoz (Spain) and in 1988 was promoted to Full Professor at the UCM. He has been Visiting Professor at the University of Lausanne (Switzerland), Ecole Nationale Supérieure de Chimie, Toulouse (France), University of California Riverside, Ecole Supérieure de Physique et Chimie Industrielles de la Ville de Paris (France), and Université de Bordeaux-1(France). In January 2010 he was invested Doctor *Honoris Causa* from the Institut National Polytechnique (INP-ENSIACET, Toulouse). From June 2011 to November 2013 he was Vicechancellor (*Vicerrector*) of Research at the UCM.

Silvia Roscales studied chemistry at the Universidad Complutense de Madrid (UCM) where she is carrying out her Ph. D. studies under the supervision of Prof. Aurelio G. Csákÿ in the field of new transition-metal-free reactions with boronic acids. As part of her formation she has carried out a pre-doctoral stay at the ETH (Zürich, Switzerland) with Prof. S. Ametamey.