Chapter 5

Recent Developments in Selected Sesquiterpenes: Molecular Rearrangements, Biosynthesis, and Structural Relationship among Congeners

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Additional information is available at the end of the chapter

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Abstract

Recent developments in selected sesquiterpenoids are reviewed for the past one decade (2005–2017) with special reference to Mechanisms of multistep molecular rearrangements of some sesquiterpenes or derivatives based on isotopic labeling studies and extensive spectroscopic analysis such as molecular rearrangement of acetyl cedrene to cedrene follower, acid catalyzed rearrangement of moreliane-based triketone, synthesis of (−)-isocomene and (−)-triquinane by acid-catalyzed rearrangement of (−)-modhephene, Total synthesis of (+)-cymbodiacetal, BF_3 catalyzed molecular rearrangements of mono epoxides of α- and β-himachalenes, santonic acid: Zn-HCl-ether reduction. Insights into biosynthesis of albaflavenone, caryol-1(11)-ene-10-ol, (+)-koraiol, pogostol, patchouli alcohol and valerenadiene are discussed. Congeners for probing structure-biosynthetic relationship. This approach is discussed with the availability of very interesting results on the isolation of highly oxygenated secondary metabolites from endophytic fungi, *Xylaria* sp.

Keywords: molecular rearrangements, mechanisms, synthetic application, CCR, biosynthesis, labeling experiments, congeners

1. Introduction

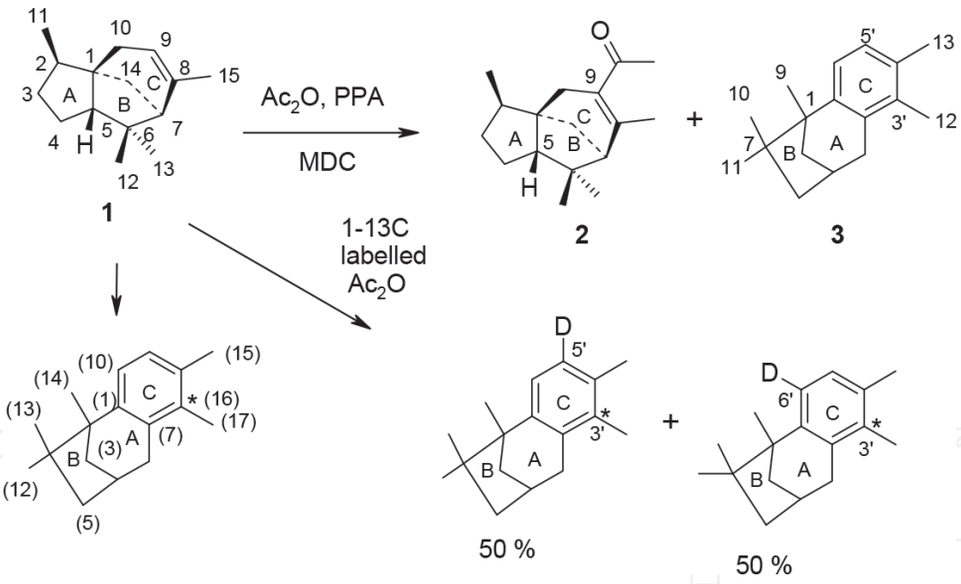
Sesquiterpene carbon frameworks comprise the largest group of terpenoids or sometime referred as isoprenoids. Farnesyl diphosphate (FPP) having three olefinic linkages undergo cyclization to produce very large number major cyclic frameworks which are further modified by oxidative cleavages, molecular rearrangements, loss of carbon atoms. The aim of this chapter is to provide an overview of the recent developments in sesquiterpenes with

particular reference to molecular rearrangements, biosynthesis and structural relationship among congeners. The coverage is not comprehensive but a focused review of the literature (2005–till September 2017) and only the relevant research articles having a link with the above areas are selected for discussion.

2. Mechanisms of multistep molecular rearrangements, insight into biosynthesis and congeners for probing structure-biosynthetic relationship of selected natural products

2.1. Molecular rearrangement of acetyl cedrene to cedrene follower

The acetylation of cedrene **1** can lead to various products depending on the reaction conditions. Paknikar et al. [1] undertook a detailed study on the acetylation of cedar wood oil (Virginia) with acetic anhydride and polyphosphoric acid in dichloromethane which leads, besides acetyl cedrene **2**, also to a minor product, 1,7,7-trimethyl-2,3-(3′4′-dimethylbenzo) bicyclo[3.2.1]-octane **3**, called the follower. Structural analysis of **3** (**Scheme 1**) shows that rings A, B, C of **2** are rearranged as B, A, C in follower **3**.



Scheme 1. Acetyl cedrene **2** and its follower **3**. The numbering in the brackets is the one from acetyl cedrene.

Formation of **3** from **2** can only be explained by a multistep intramolecular rearrangement. This shows that: (i) ring C of 2 has undergone initial ring enlargement and subsequent ring contraction; (ii) cleavage of the C6–C7 bond of 2 and formation of the new C6-C2 bond; (iii) enlargement of ring A of **2** with concomitant loss of water. The mechanism for the formation of **3** from **2** when 1-13C labeled acetic anhydride was used is shown in **Scheme 2**.

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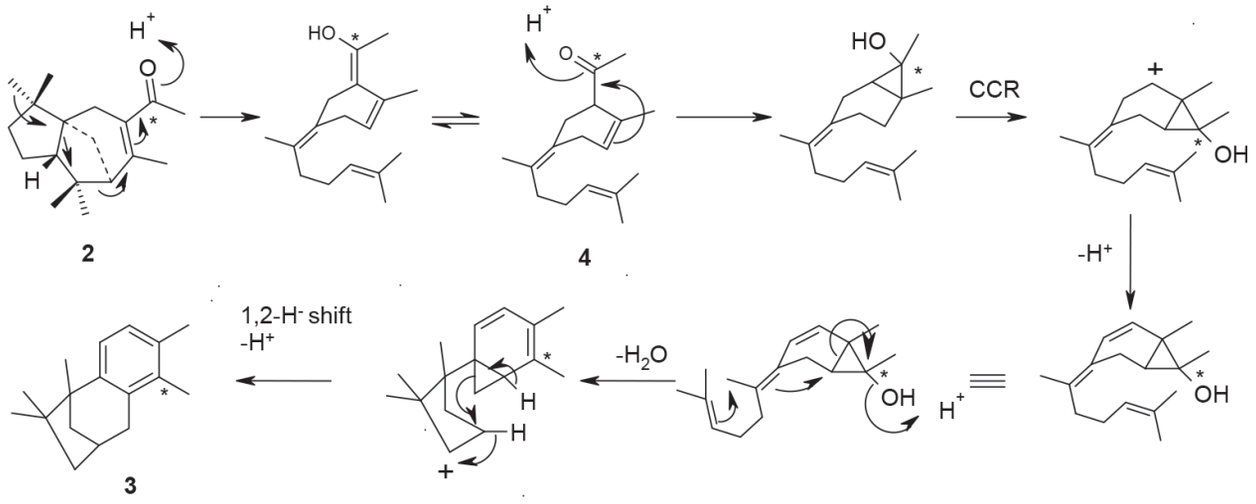


Scheme 2. Mechanism for the formation of follower **3** from acetyl cedrene **2**.

One characteristic feature of the formation of the follower **3** is sluggish reaction rates. Density Functional Theory (DFT) calculation of B3LYP/6-31G* type using the Gaussian version 09 (Gaussian) revealed that the first neutral intermediate **4** (**Scheme 2**) is higher in energy than acetyl cedrene by ~20 kcal. A series of further cascade- like cationic rearrangements is involved with breaking and bond-forming intermediates.

The formation of the neutral intermediate **4** is supported by the observation that this process is the reverse pathway for the biosynthesis of α-cedrene from FPP, which has been established previously [2]. Few other feasible mechanisms for the formation of follower **3** could be devised, and only the one presented fits the observation of 13C enriched label at the C-3′ position of follower **3**. Hence the key rearrangement is cyclopropylcarbinyl cation-cyclopropylcarbinyl cation rearrangement (CCR) [3, 4]. During the deuteriation of commercial acetyl cedrene, the follower was also deuterated, and it was observed that aromatic protons are exchanged. Interestingly, the product was only monodeuterated (**Scheme 1**) and the isotope was shared equally between the C-5′ and C-6′ positions of the follower **3**. This equal distribution of one deuterium atom between C-5′ and C-6′ can be accounted for by the facile 1,2-hydride and 1,2-deuteride shifts and equilibration.

2.2. Acid catalyzed rearrangement of moreliane based triketone. Characterization of keto lactone, a 1-11 seco-moreliane

An interesting molecular rearrangement has been reported by Morales and co-workers [5]. They observed that triketone **5** on treatment with *p*-TSA in benzene resulted in the formation of a keto lactone **6**, a 1–11 seco-moreliane derivative and also the first representative of this group (**Figure 1**).

The rearrangement depicted in **Scheme 3** involves initial cyclobutane ring expansion of the protonated triketone, generation of carbocationic intermediate **7** which rearranges *via* transition state in to protonated seco-moreliane **8**. These steps are supported by DFT calculations.

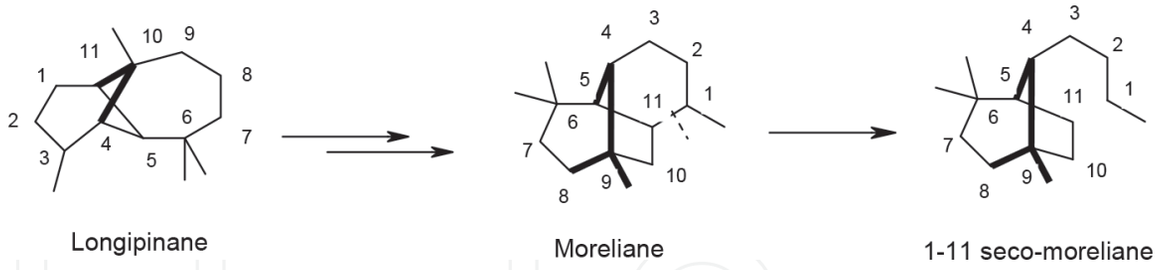
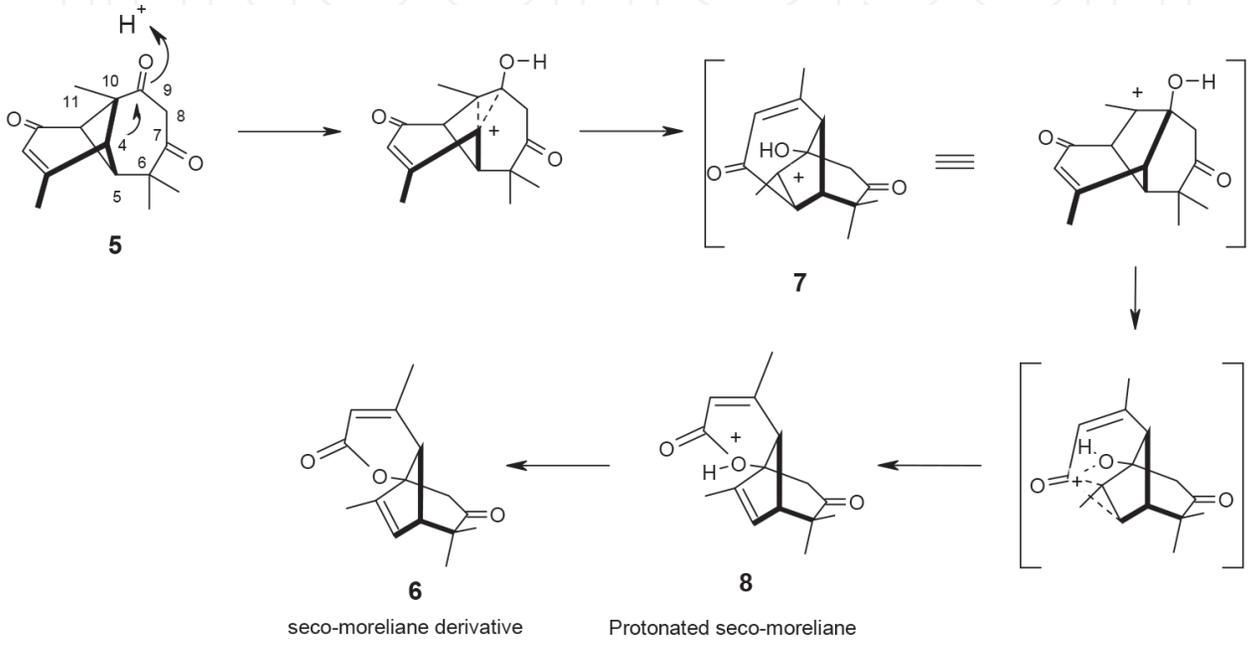


Figure 1. Skeletons of longipinane, moreliane and 1–11 seco-moreliane.



Scheme 3. Acid catalyzed rearrangement of triketone **5** to 1–11 seco-moreliane derivative **6**.

2.3. Synthesis of (−)-isocomene and (−)-triquinane by acid catalyzed rearrangement of (−)-modhephene

Triquinanes have received considerable attention by their unique structure as well as their reported biological activities. (−)-Modhephene **9** of established absolute stereochemistry was subjected to acid catalyzed carbocation rearrangements which led to an interesting synthesis of (−)-isocomene **10** and (−)-triquinane **11**[6]. This study was extended further by preparation of (−)-modhephene **9d** stereospecifically at 14β geminal methyl group. Under same experimental conditions, deuterium labeled (−)-triquinane **11d** a stereospecific 1,2-migration of 7/4β methyl group was observed (**Scheme 4**).

2.4. Total synthesis of (+)-cymbodiacetal

In 2010, Hayes and his co-workers reported [7] a total synthesis of (+)-Cymbodiacetal **12** by a biomimetic route proposed earlier [8, 9] using (R)-(+)-limonene **13**, the key step involves hetero Diels-Alder cycloaddition which proceeds with an *endo* selectivity (2:1) in a quantitative

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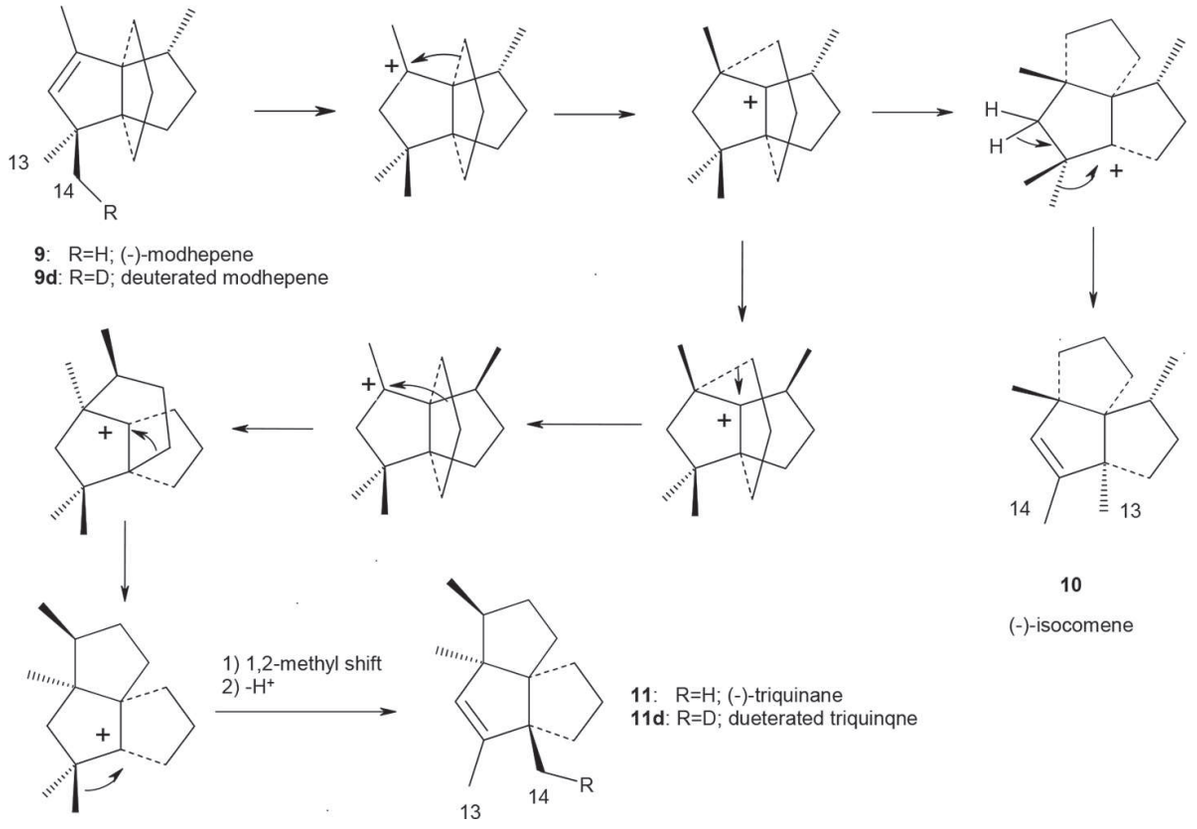
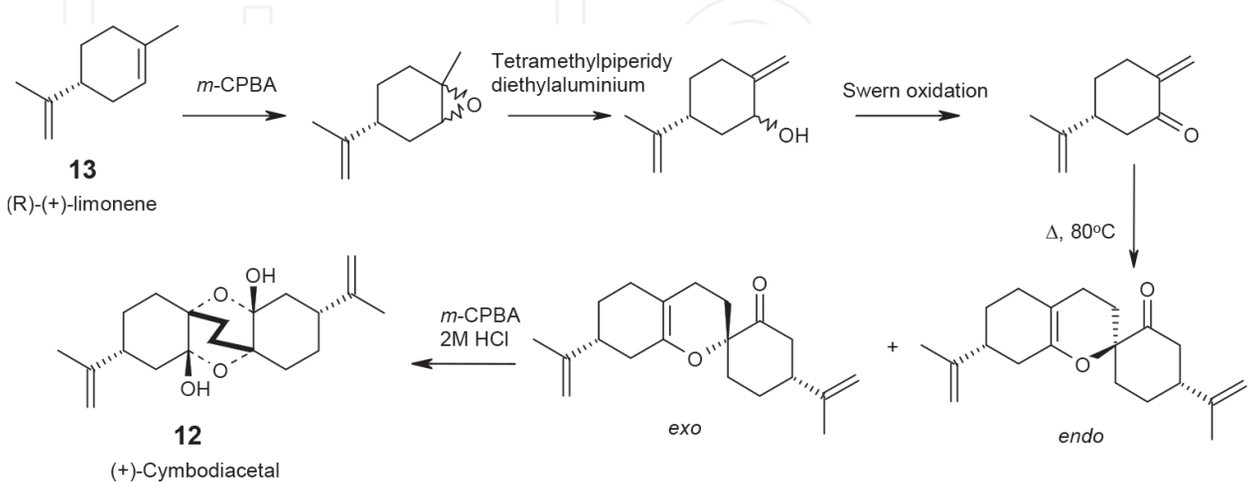


Scheme 4. Molecular rearrangement of (−)-modhephene **9** to (−)-isocomene **10** and (−)-triquinane **11**.

yield. Exploitation of *exo*-isomer with *m*-CPBA followed by acid catalyzed opening afforded (+)-cymbodiacetal **12** (**Scheme 5**). The uncertainty in absolute stereochemistry was independently established by X-ray crystallography. These studies also clarified discrepancies in the previously published work [8, 9].



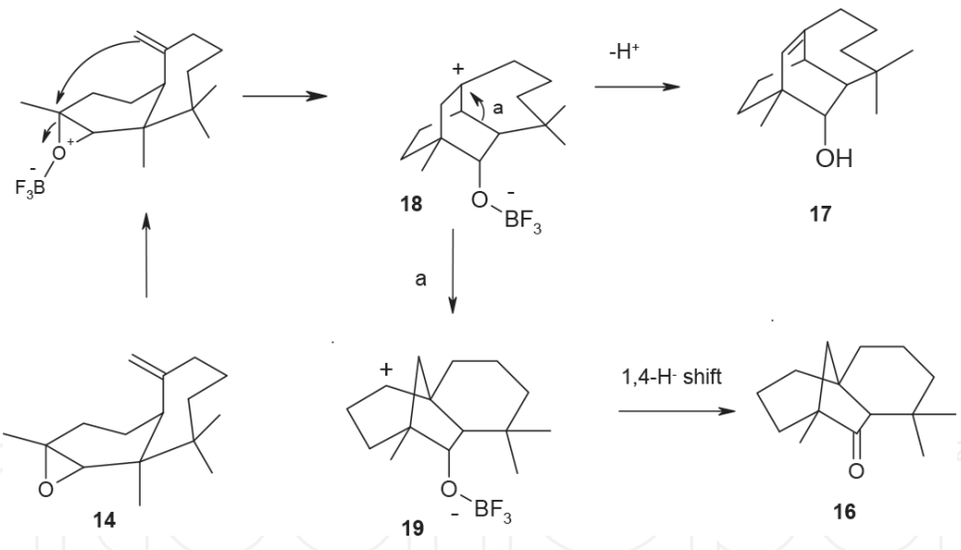
Scheme 5. Total synthesis of (+)-cymbodiacetal **12**.

2.5. BF_3 catalyzed molecular rearrangements of mono epoxides of α- and β-himachalenes

Previous examples of acid catalyzed rearrangements of sesquiterpenes have shown that the opening of the epoxide triggers the reaction and directs the subsequent molecular rearrangements. In practically, among all the cases the aim is to valorize the naturally occurring sesquiterpene hydrocarbons.

Manoury and co-workers [10] observed that on treatment of α-himachalene monoepoxide **14** with BF_3-Et_2O in CH_2Cl_2 at room temperature afforded a tricyclic ketone **16** (71% isolated yield) product along with an unsaturated alcohol **17** (18%). The structure **16** was unambiguously assigned to ketone based on ^1H, ^{13}C, ^1H-2D NMR experiments. The proposed mechanism (**Scheme 6**) involves ring opening of epoxide followed by participation of terminal methylene group to generate a tricyclic bridgehead carbocation **18** by ring contraction of seven membered ring to generate intermediate **19**. A stereospecific 1,4-hydride transfer is proposed in the last step to the formation of **16**.

Inspection of molecular models of intermediate **19** shows that the proposed stereospecific 1,4-hydride shift is unlikely and therefore a different process is responsible for the formation of ketone **16**.



Scheme 6. Proposed mechanism for the formation of unsaturated alcohol **17** and tricyclic ketone **16**.

The structure assignment **17** to the minor product, a tricyclic unsaturated alcohol is based on spectral analysis and confirmed by single crystal X-ray data. The characteristic feature of **17** is the presence of a double bond involving a bridgehead carbon.

β-Himachalene monoepoxide **15** under identical experimental conditions gave two products major product (62%) and aryl-himachalene (10%). The major product was assigned structure **20**. The proposed mechanism explains formation of **20** (**Scheme 7**). The gross structure of this compound an allo-himachalol, a natural product isolated from *Cedrus deodara* [11].

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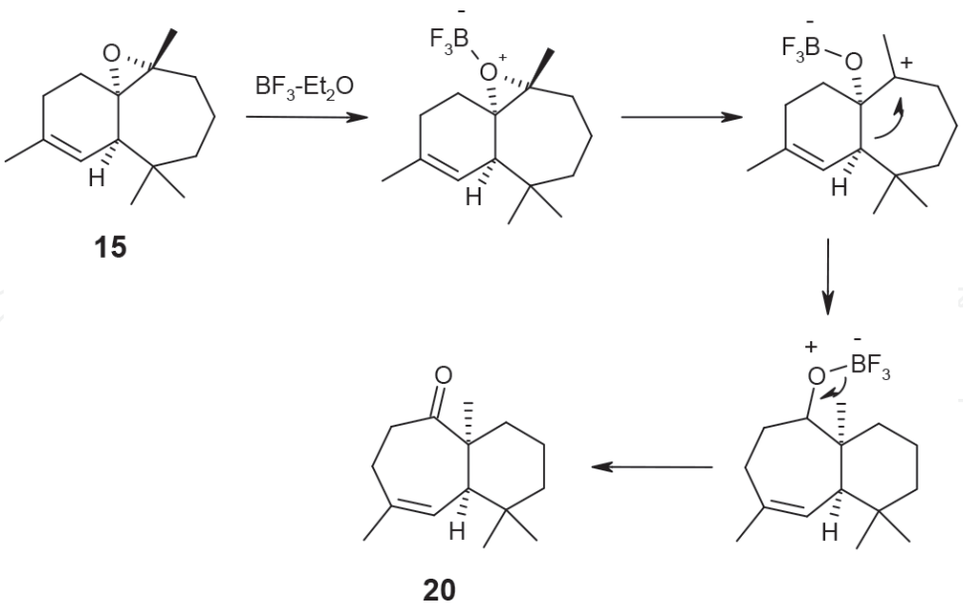


Scheme 7. Mechanism for BF_3 catalyzed transformation of β-himachalenes monoepoxide **15** to ketone **20**.

Compounds **16**, **17** and **20** are all optically active and since the absolute stereochemistry of himachalenes are known, it is observed that C7 α-H of α-himachalenes remains intact throughout the rearrangement. The absolute stereochemistry of **16**, **17** and **20** is shown in **Figure 2**.

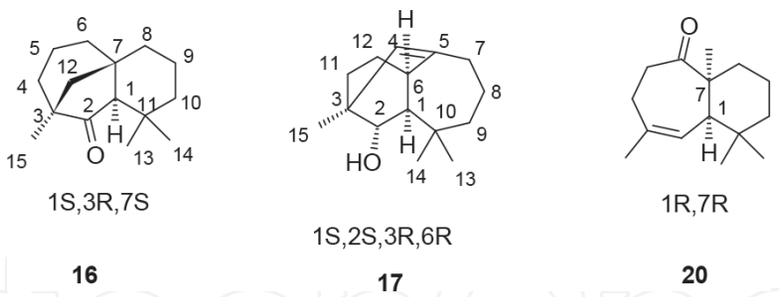
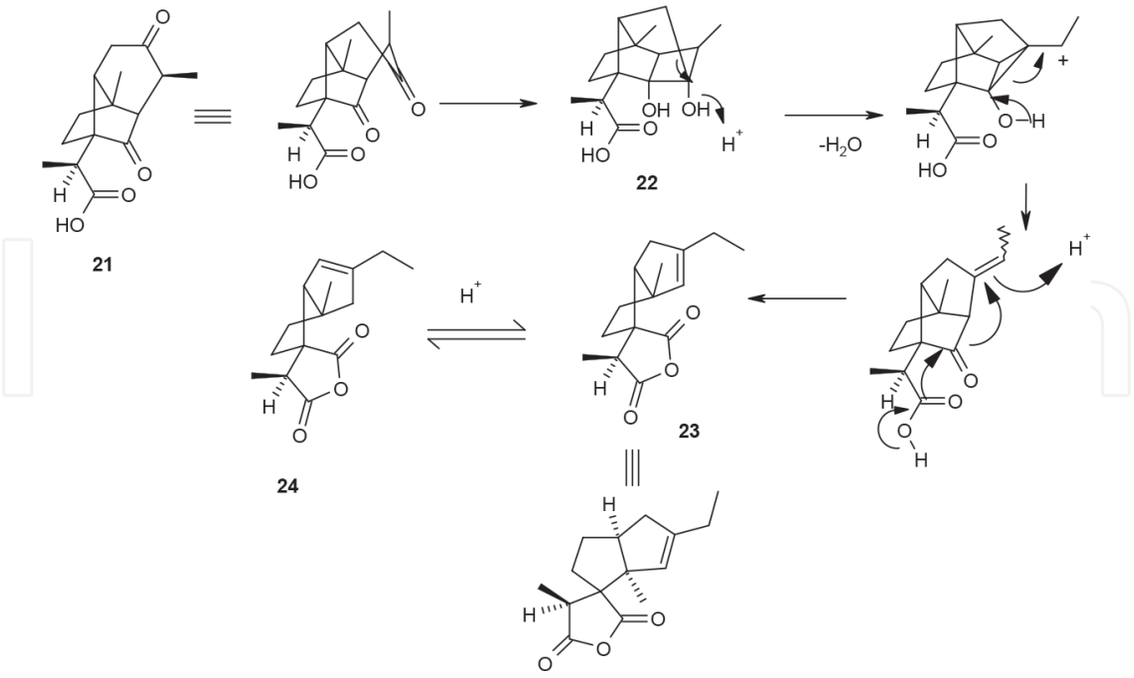


Figure 2. Absolute stereochemistries of ketone **16** alcohol **17** and ketone **20**.

2.6. Santonic acid: Zn-HCl-ether reduction

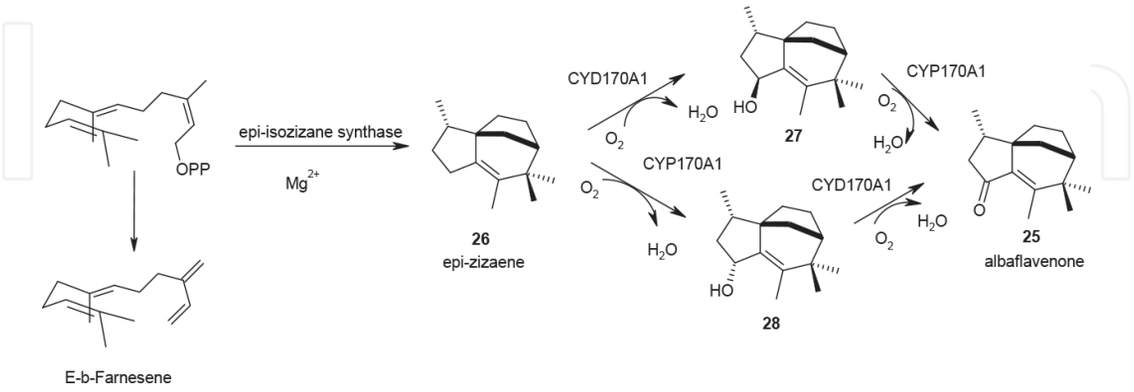
Santonic acid **21** (the diketocarboxylic acid obtained from santonin on digestion with aq. alkali) was subjected to reduction with the Zn-HCl-ether system [12] with an aim to obtain the previously prepared pinacol **22** *via* intramolecular pinacolisation primarily because of conformational structure of santonic acid with close proximity of the 1,4-diketone system. Under these conditions santonic acid **21** did not afford the pinacol **22**, but yielded a 60:40 mixture (GCMS, ^{1}H NMR) of succinic anhydride derivatives **23** and **24**. It is clear that the reaction proceeds *via* pinacol **22**, which, under strong acidic conditions, undergoes further rearrangement to give anhydrides **23** and **24** (**Scheme 8**).



Scheme 8. Mechanistic pathway for the conversion of santonic acid **21** to bicyclo[3.3.0] octanes **23** and **24**.

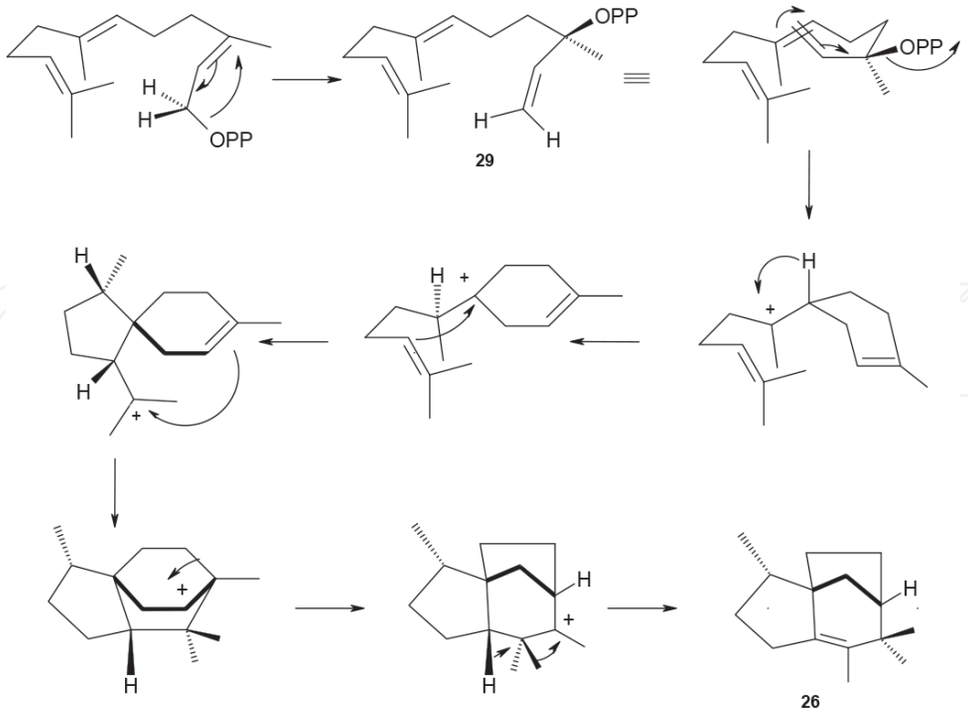
2.7. Biosynthesis of albaflavenone

The tricyclic sesquiterpene antibiotic albaflavenone **25** isolated from the gram positive soil bacteria *Streptomyces coelicolor* A3 and *Streptomyces albidoflavus* is biosynthesized by enzymes encoded in a two-gene operm [13]. Initially, the sesquiterpene epi-isozizaene synthase catalyzes the cyclization of *2E, 6E*-farnesyl diphosphate (FPP) to (+)-epi-isozizaene **26**. A two-step allylic oxidation of **26** catalyzed by a single cytochrome P450170A1 (crP170A1) results in the formation of (+)-albaflavenone **25** *via* an epimeric mixture of (*5S*)-albaflavenol **27** and (*5R*)-albaflavenol **28** intermediates (**Scheme 9**) [14].



Scheme 9. Biosynthetic pathway of albaflavenone **25**.

The mechanism and stereochemistry of FPP to epi-isozizaene **26** *via* (*3R*)-nerolidyl diphosphate **29** has been conclusively established by labeling studies [15]. The entire biosynthetic process from FPP to epi-isozizaene is shown (**Scheme 10**). A two-step chemical synthesis of albaflavenone **25** from epi-isozizaene **26** was reported in this study.



Scheme 10. Mechanism of the cyclization of *E,E*-FPP to epi-isozizaene **26** *via* (*3R*)-nerodilyl diphosphate **29**.

Ito and co-workers [16] reported a concise nine step total synthesis of albaflavenone without use of any protecting groups. Moreover, the absolute configuration of naturally occurring (+)-albaflavenone has been unambiguously established as *1S*, *7S* and *8R*.

2.8. The biosynthesis of caryol-1(11)-ene-10-ol: on the mechanism of the formation of caryolene: a putative biosynthetic precursor to caryol-1(11)-ene-10-ol

In 2013, Nguyen and Tantillo [17] investigated the mechanism of the formation of caryolene **30**, a putative biosynthetic precursor to caryol-1(11)-ene-10-ol **31** by DFT calculations (**Figure 3**).

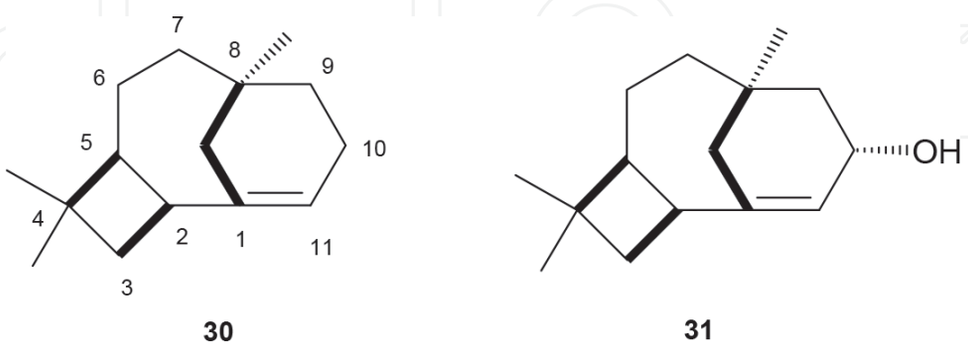
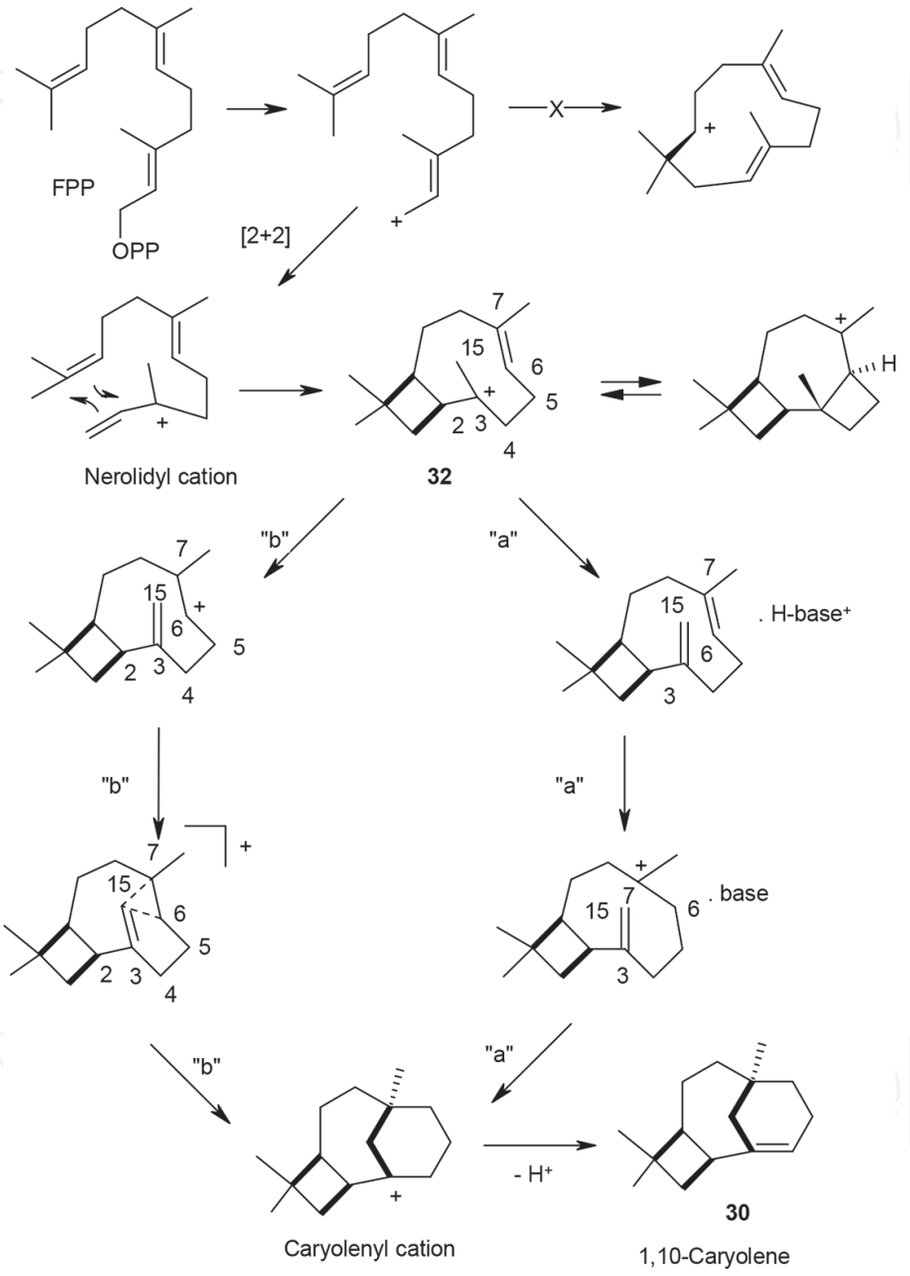


Figure 3. Structures of caryolene **30** and caryol-1(11)-en-10-ol **31**.

Quantum chemical calculations indicated the mechanism involving a secondary carbocation intermediate **32** is not energetically viable. They proposed two mechanisms for caryolene **30** formation (pathway a and b). The pathway involves a base catalyzed deprotonation/reprotonation sequence and a tertiary carbocation minima (more likely) whereas

pathway b involves intramolecular proton transfer and the generation of a secondary carbocation minima. Both mechanisms are predicted to involve concerted suprafacial/suprafacial [2 + 2] cycloaddition, whose asynchomicity allows them to avoid the constrains of orbital symmetry (**Scheme 11**).



Scheme 11. Proposed mechanisms for the formation of 1,10-caryolene **30**.

2.9. Biosynthesis of (+)-koraiol

As an outcome of Tantillo's mechanism for caryolene **30** [17], biosynthetic pathway for koraiol **31** becomes evident (**Scheme 12**).

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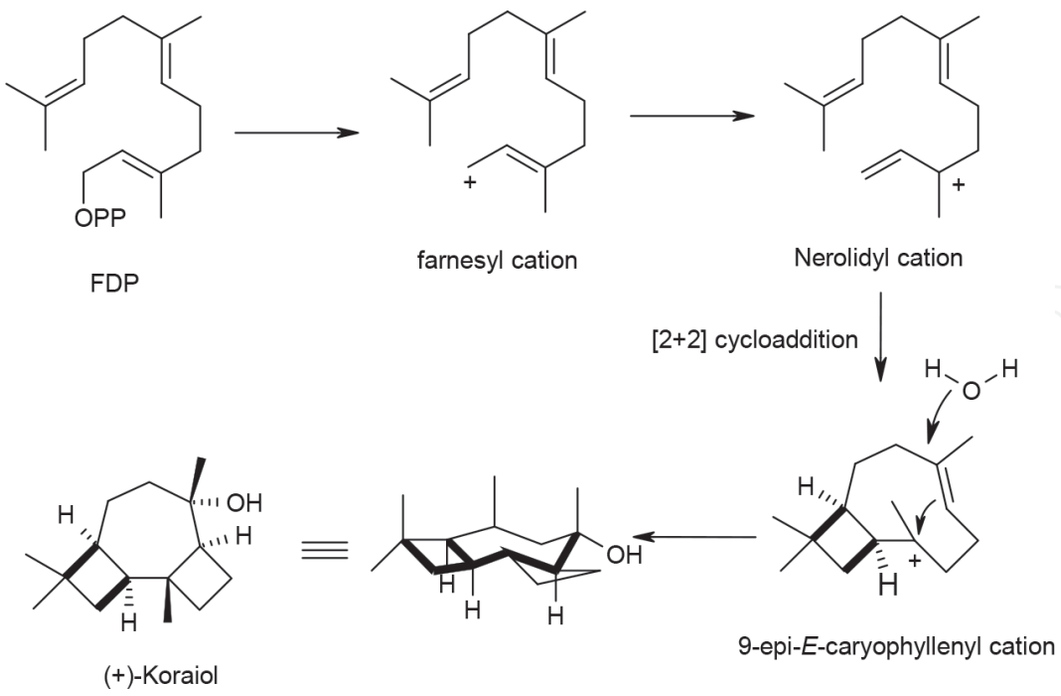

Scheme 12. Biosynthesis of (+)-koraiol **31**.

9-epi-*E*-Caryophyllene **32**, caryophyllene **33** and (+)-koraiol **31** were identified by Dickschat and co-workers [18, 19] who carried out investigation on the volatiles of *Fusarium fujikuroi* by the use of CLSA-GCMS. The sesquiterpenoids were divided in to two groups based on their proposed biosynthetic pathways. Volatile sesquiterpenoids produced by sesquiterpene cyclase Ffsc4 were characterized as β-caryophyllene and an optically active alcohol (+)-koraiol **31**. The structure **31** was assigned by extensive spectral analysis. The relative configuration of (+)-koraiol was elucidated by NOESY experiments. The *cis* fusion of rings A and B was deduced from the NOESY couplings of the bridge head hydrogen atoms 1H and 9H with each other with methyl protons 15-H and the pro-5-methylene protons 3-H. Interestingly, Khan et al. isolated (+)-koraiol, $[\alpha]_D$ + 31.7° from the oleoresin of Korean pine (*Pinus koraiensis* Sieb.). The relative stereochemistry as shown in **31** has been established by X-ray analysis [20]. The absolute stereostructure of the rare sesquiterpene (+)-9-epi-*E*-caryophyllene, an enantiomer of **32** was isolated from *Dacrydium cupressinum* by Weavers and co-workers [21] (**Figure 4**).

It is tempting to speculate (+)-koraiol **31** is biosynthesized from 9-epi-*E*-caryophyllene **32**.

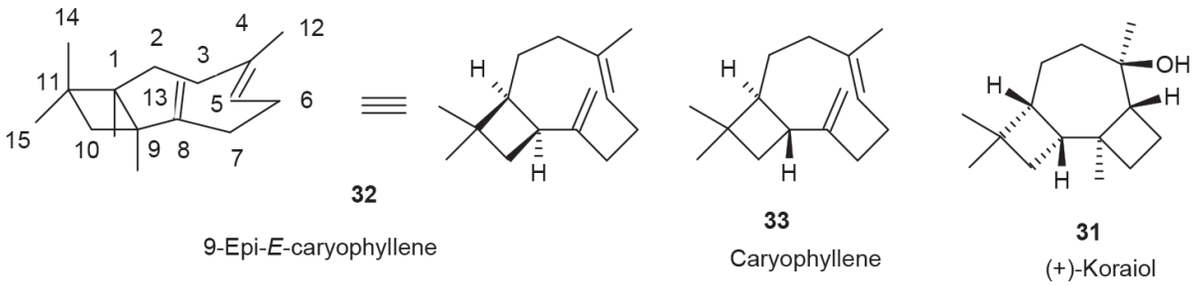

Figure 4. Structures of 9-epi-*E*-Caryophyllene **32**, caryophyllene **33** and (+)-koraiol **31**.

2.10. Biosynthesis of Pogostol

Biosynthesis of pogostol **34** by the endophytic fungus *Geniculosporium* was investigated by Dickschat and co-workers [22]. In this study, six 13C labeled isotopomers of mevalonolactone were synthesized and used in feeding experiments with the endophytic fungus *Geniarlosperium*. Feeding experiments with **35a** and **35b** gave insights into the stereochemical course of the terpene cyclization. The methyl group of the mevalonolactone that is labeled in these two isotopomers is converted into terminal (z)-methyl group of FPP (C-13). Both feeding experiments showed that the deprotonation step leading to germacrene A **36** proceeds with stereospecific deprotonation of C-13 and not C-12 of FPP (**Figure 5**).

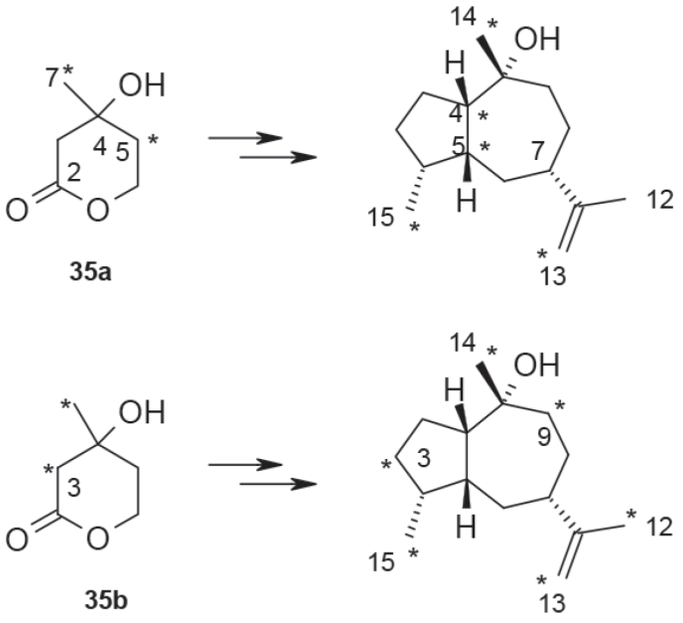

Figure 5. Biosynthesis of Pogostol **34** using isotopomers of mevalonolactone.

The volatile fraction was extracted by closed loop stripping apparatus followed by direct ^{13}CNMR analysis (CLSA-NMR) newly developed by the same group. The biosynthesis of pogostol **34** proceeds through initial formation of germacrene-A **36**. Protonation of 4,5 double bond initiates a second cyclization to cation which gets neutralized with water to give pogostol **34** (**Scheme 13**).

In view of correlation of (−)-pogostol **37** with (+)-bulnesol **38** with known absolute stereochemistry, (−)-pogostol be represented by the stereostructure **37** [23–25]. The stereostructure **34** thus represents (+)-pogostol (**Figure 6**).

2.11. Biosynthesis of patchouli alcohol (patchoulol)

The history of patchouli alcohol **39** from its isolation till date has narrated in a recent exhaustive review article [26]. Biosynthetic pathways were proposed based on experimental work for the conversion of FPP to patchouli alcohol **39** (**Scheme 14**).

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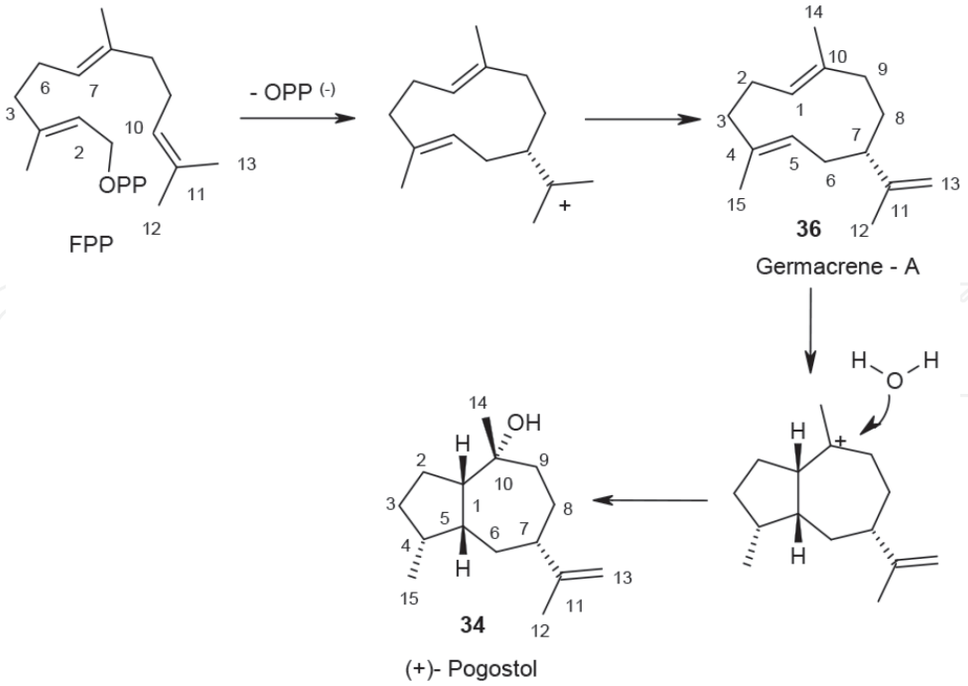


Scheme 13. Mechanism of pogostol **34** formation from FPP.

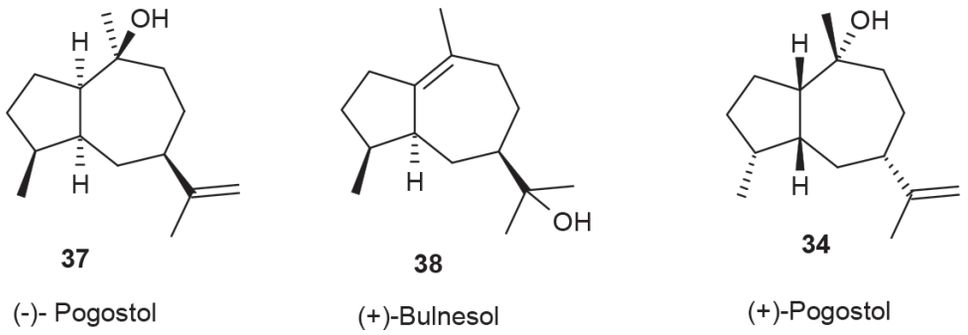
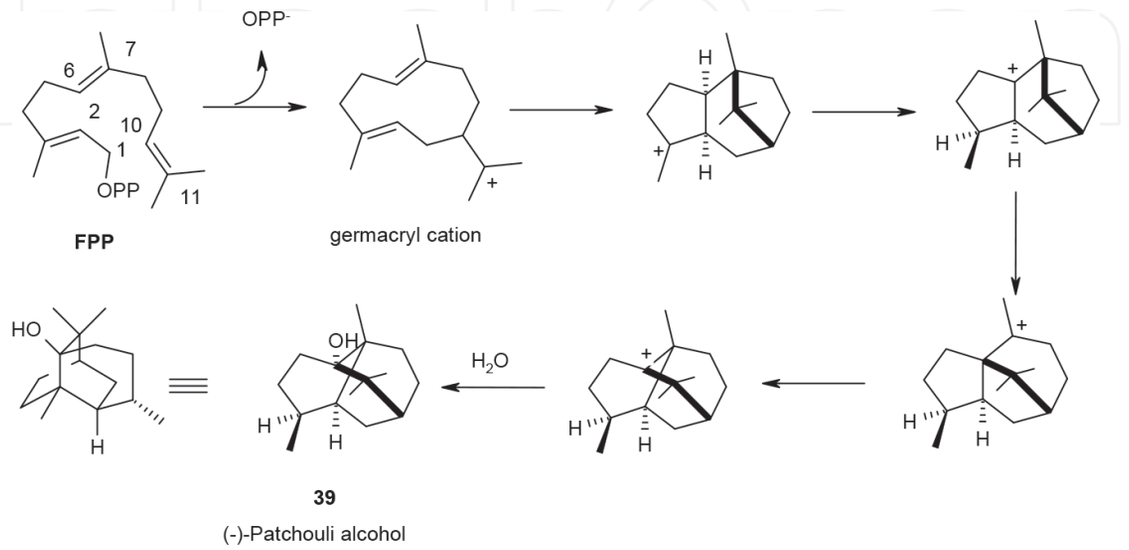
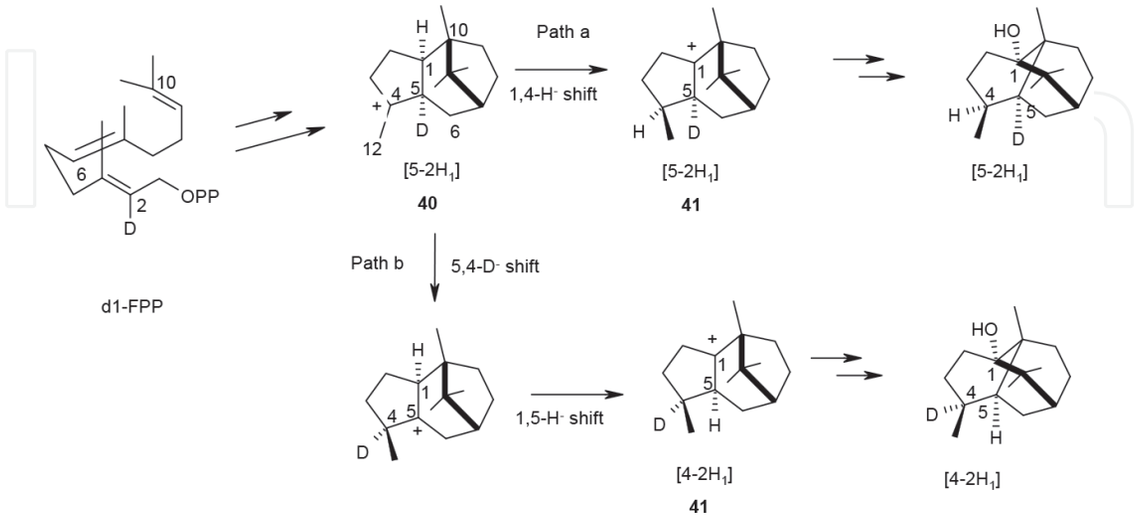


Figure 6. Absolute stereochemistry of (−)-pogostol **37**—correlation of (−)-pogostol **37** and (+)-bulnesol **38**.



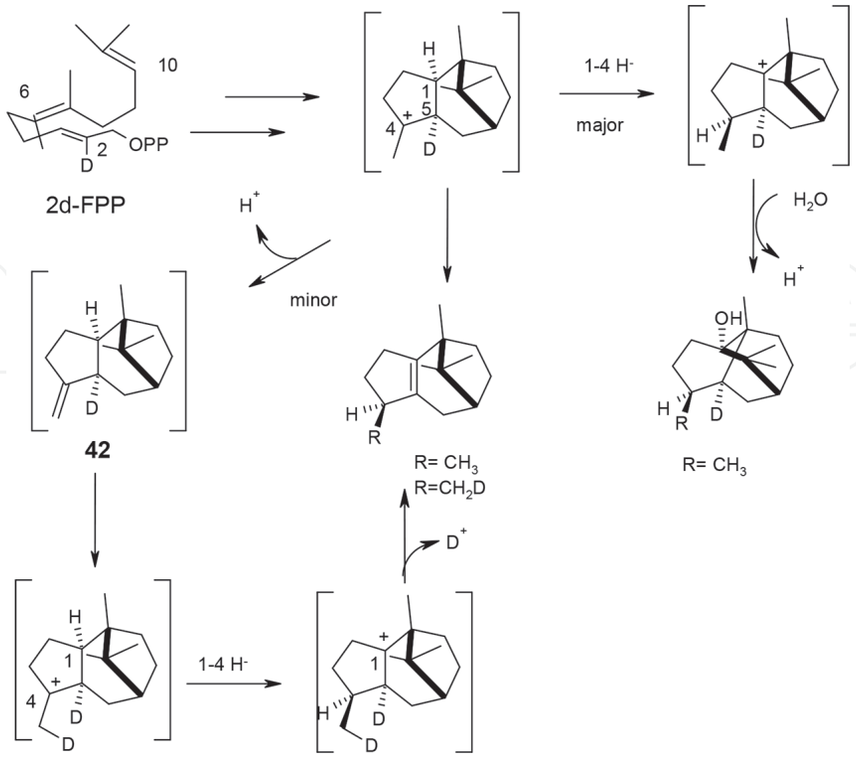
Scheme 14. Mechanism proposed for cyclization and rearrangement of FPP to patchoulol **39**.

Croteau et al. [27] and Akhila et al. [28] proposed biosynthetic pathways for the conversion of FPP to patchouli alcohol **39** based on experimental work. Croteau et al. reported the 1,3-shift for conversion of **40** to **41** while Akhila et al. proposed two consecutive 1,2-hydride shifts for the same conversion (**Scheme 15**).



Scheme 15. Biosynthetic pathways for the conversion of [2-2H_1]-FPP to patchoulol isotopomer.

The recent isotopic labeling studies of Coates and colleagues [29] unrevealed the biosynthetic pathways for **39** which confirmed the 1,3-hydride shift across the five membered ring ruling out two consecutive 1,2-hydride shifts (**Scheme 16**).



Scheme 16. Proposed biosynthesis of patchouliol **39** from deuterated FPP.

Incubation of isotopically pure [2-2H_1] (*E,E*)-farnesyldisulfate with recombinant patchoulol synthase (rPTS) from *Pogostemon cablin* afforded a 65:35 mixture of monodeuterated and di-dueterated patchouliols and several hydrocarbons of which eight have been identified. This is confirmed by extensive NMR analysis on the labeled patchouliol mixture and comparison with those of unlabeled patchouliol. Deuterium label was located at position C5 (both isotopomers ca. 100%) and at C12 (minor isotopomer, 30–35%). The formation of [5,12-2H_2] patchouliol is rationalized through an unknown (so far) hydrocarbon **42** which could incorporate deuterium at C12. This significant observation may have implication on the biosynthesis of nor-patchouliol **43** a congener of patchouliol, the biosynthesis is based on the earlier work [26] (**Figure 7**).

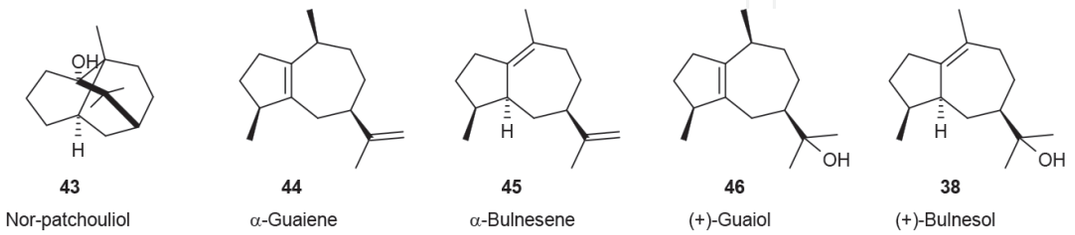


Figure 7. Structures of nor-patchouliol **43**, α-guaiene 44, α-bulnesene **45**, (+)-guaiol **46** and (+)-bulnesol **38**.

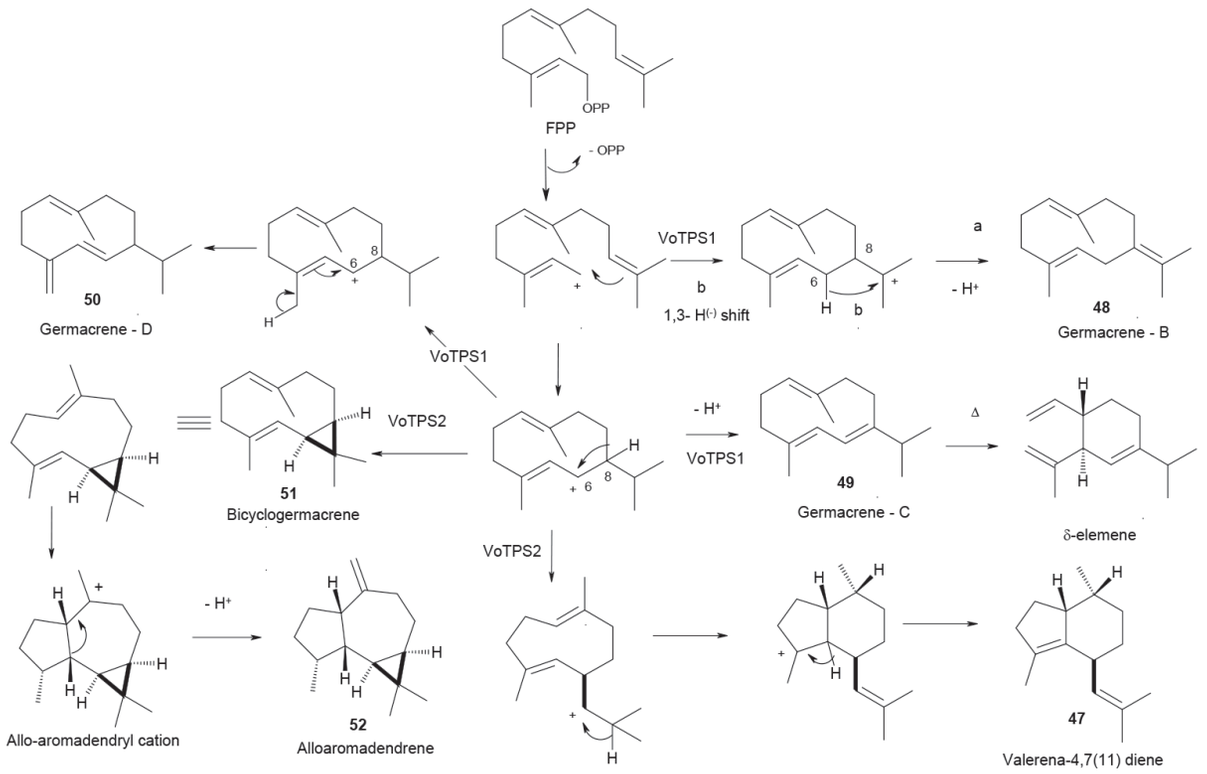
The interesting observation which can be made on the patchouli oil constituents that though α-guaine **44** and α-bulnesene **45** are genuine natural products [26], (+)-guaiol **46** and (+)-bulnesol **38** has never been reported to be present in patchouli oil.

2.12. Biosynthesis of Valerenadiene

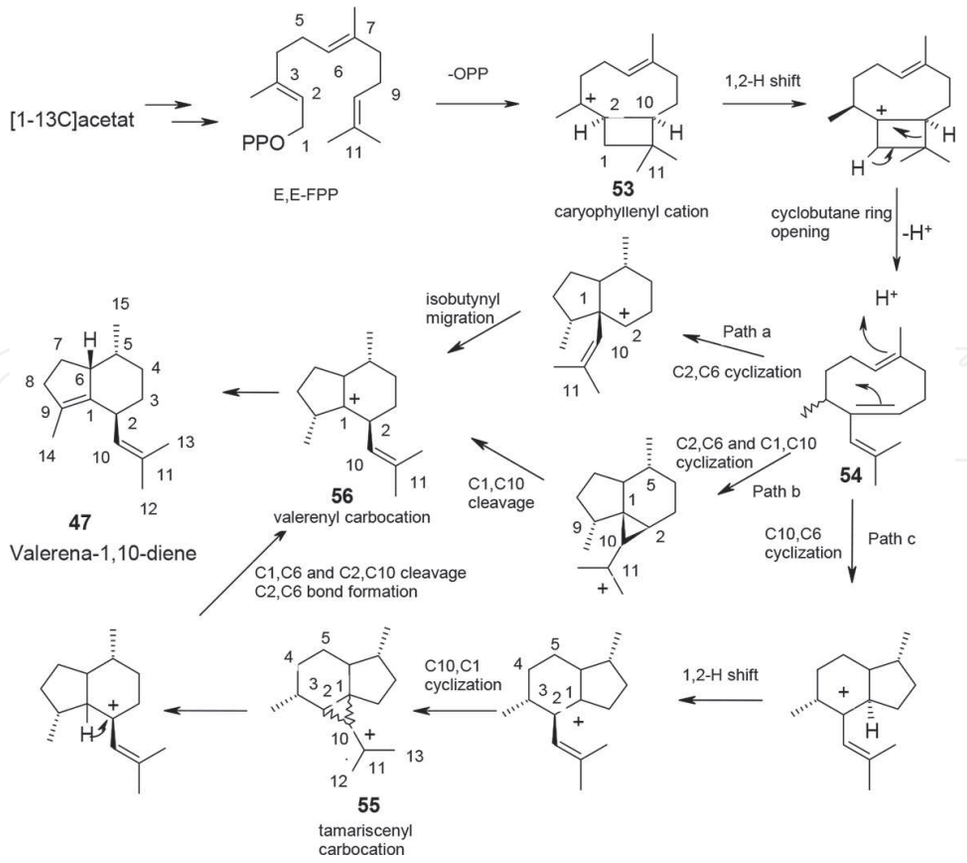
Pyle et al. [30] reported the first enzymatic synthesis of valerena-4,7(11)-diene **47** (numbering used for valarenic acid) by a unique TPS from *Valeriana officinalis*. They identified two TPS's VoTPS1 and VoTPS2. Transgenic yeast expressing VoTPS1 produced germacrene B **48**, germacrene C **49** and germacrene D **50**. On the other hand, VoTPS 2 produced valerena-4,7(11)-diene **47** as a major compound was substantiated by ^{13}CNMR and GC–MS comparison with the synthetic standard. Minor products were identified as bicyclogermacrene **51** and alloaromadendrene **52**. The proposed mechanism involves ring contraction of germacrane ring to a nine-membered intermediate having isobutenyl side chain. Cyclization gives valerena-4,7(11)-diene **47** (**Scheme 17**).

Yeo et al. [31] proposed a mechanism wherein the isobutyl side chain is derived by the intermediacy of a caryophyllenyl carbocation **53**. A 1,2-hydride shift followed by opening of the cyclobutyl ring. In this way the two methylene carbons of the isobutenyl side chain are predicted to arise from C1 and C11 of the originating FPP and therefore should become labeled when [1-13C] acetate is incorporated into FPP by mevalonate pathway operating in yeast (**Scheme 18**).

Valerina-1-10-diene **47** and related sesquiterpenes retain an isobutyl side chain whose origin has been recognized as enigmatic because a chemical rationalization for their biosynthesis has not been obvious. They identified seven *Valeriana officinalis*, terpene synthase genes (VoTPSs) and two were functionally characterized as sesquiterpene synthase VoTPS1 and



Scheme 17. Biosynthesis pathway for valerena-4,7(11) diene **47** and other sesquiterpenes from VoTPS1 and VoTPS2.

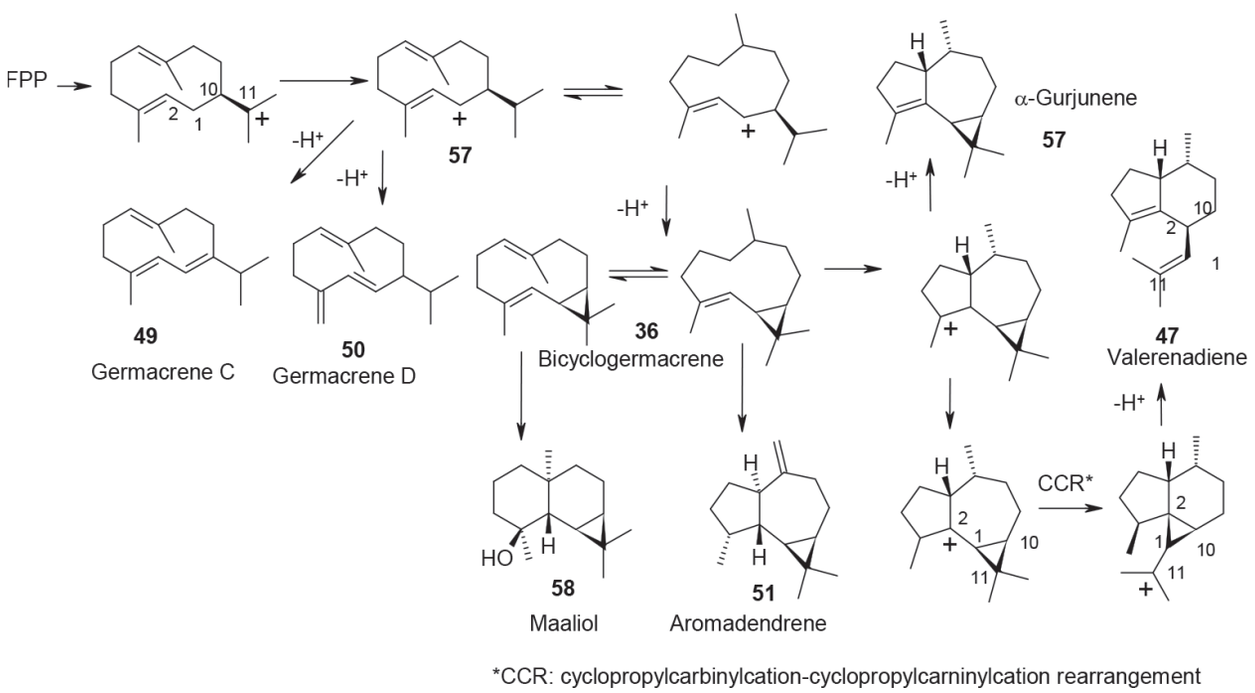


Scheme 18. Three biosynthetic pathways for valerena-4,7(11) diene **47** and other sesquiterpenes from VoTPS1.

VoTPS7. VoTPS7 encodes for a synthase that biosynthesizes germacrene C **49** (90%) whereas VoTPS 1 catalyzes conversion of *E,E*-FPP to valerena-1-10-diene **47**. Overexpression of VoTPS produced valarena-1-10-diene **47** on the basis of one and two dimensional NMR analysis, further confirmed by comparison with published spectral data, GC retention time and EIMS fragmentation pattern. The most characteristic feature of the [1-13C] acetate is the FPP derived from the incorporation of [1-13C] acetate had labels located at C1, C3, C5, C7, C9 and C11 as expected using a yeast expression system, specific labeled [1-13C] acetate. FPP was catalytically cyclized (using VoTPS1) and produce valeriana-1,10-diene **47** whose 13C labels were found at C3, C5, C7, C9, C1 and C11. Of these C1 and C11 were adjacent carbons of the isobutyl side chain. The proposed mechanism involves an intermediate of a caryophyllenyl carbocation **53**, 1,2-hydride shift followed by cleavage of C10-C11 bond generates a neutral monocyclic triene **54**. The proposed scheme also indicates formation of other sesquiterpenes through intermediates tamariscenyl cation **55** and valerenyl cation **56**.

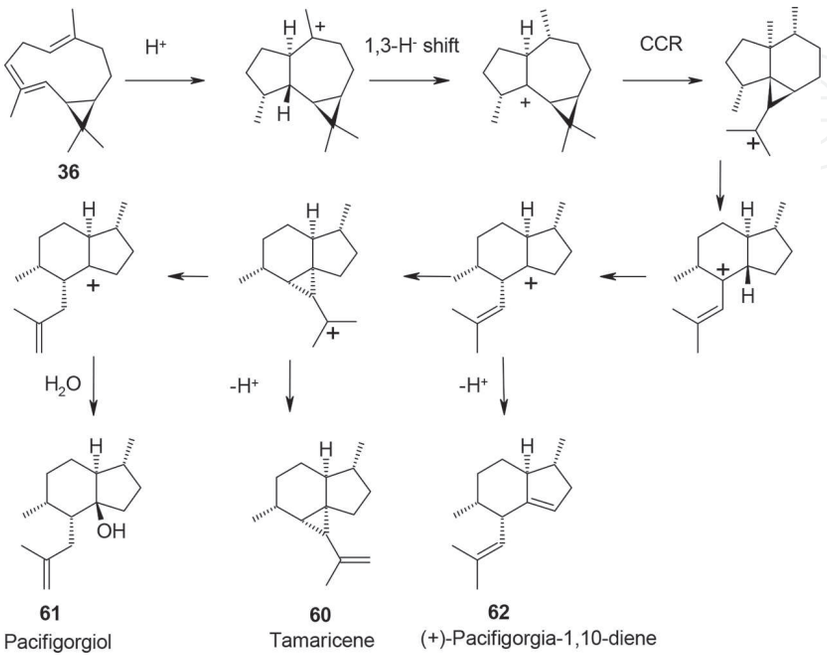
Based on the experimental labeling data of Pyle et al. [30] and Yeo et al. [31], Paknikar et al. [4] proposed a new alternate biosynthetic route (**Scheme 19**) from IPP to valerenadiene **47** which fits the unusual 13C labeling found in valerian and avoids the previously unreported triene **54**.

In **Scheme 19**, the 2-1-10-11 sequence of carbons in the first cyclic intermediate **57** from *E,E*-FPP becomes 2-10-1-11 in valerenadiene **47** which fits the 13C labeling pattern formed from [1-13C] acetate [4]. The biosynthetic pathway involves one neutral intermediate; bicyclogermacrene **36** found in valerian [32]. The key reaction is a cyclopropylcarbinyl cation-cyclopropylcarbinyl cation rearrangement (CCR) analogues to a key reaction in the biosynthesis of squalane from resqualene [3]. Structure interrelationships of the congeners of valerenadiene **47** including bicyclogermacrene **36**, aromadendrene **51**, germacrene C **49**, germacrene D **50**, α-gurjunene **58** and malliol **59** were considered in this alternate pathway.



Scheme 19. A cyclopropropane route to valerenadiene **47** (numbering based on FPP).

Bicyclogermacrene **36** appears also to be an intermediate in the biosynthesis of related set of sesquiterpene with different stereochemistry found in *Valeriana officinalis*, including tamariscene **60**, pacifigorgiol **61** and (+)-pacifigorgia-1,10-diene **62** (**Scheme 20**). In this scheme also the key reaction is again cyclopropylcarbinyl cation-cyclopropylcarbinyl cation rearrangement (CCR) with this time with a different stereoisomer.



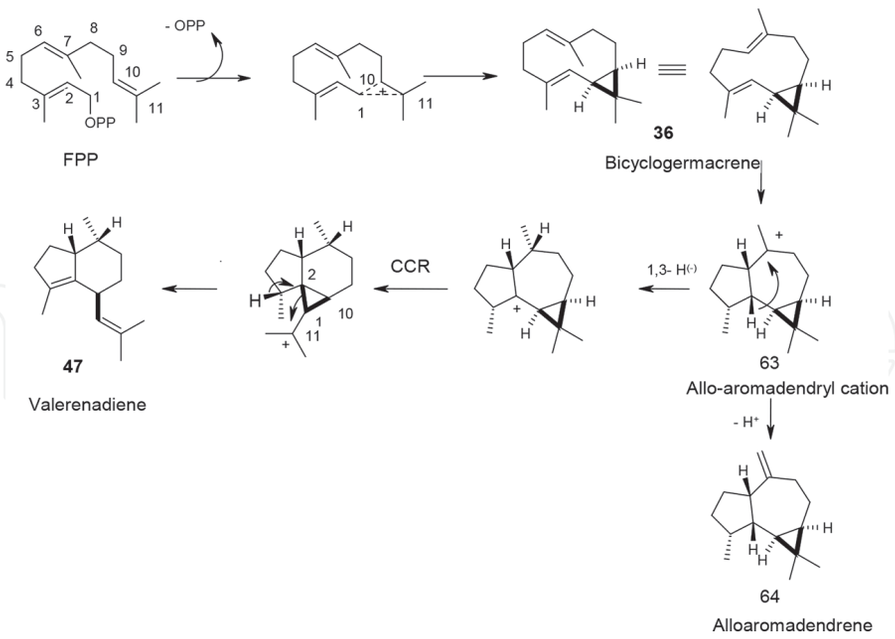
Scheme 20. Biosynthetic pathway of tamariscene **60**, pacifigorgiol **61** and (+)-pacifigorgia-1,10-diene **62** from bicyclogermacrene **36**.

Based on the results of three groups [4, 30, 31] a new consolidated mechanism for the biosynthesis of valerenadiene **47** from FPP *via* bicyclogermacrene **36** through alloaromadendryl cation **63** and CCR is presented which also explains formation of alloaromadendrene **64** (**Scheme 21**) replace alloaromadendryl cation with allo-aromadendryl cation.

2.13. Congeners of *Xylaria* sp.: structural interrelations

Endophytic fungi are reported to produce a number of bioactive metabolites and serve as an excellent source of highly oxygenated compounds which are likely to be potential drugs and also for the applications in crop science. The fungi belonging to genus *Xylaria* produces plethora of biologically related and structurally fascinating cadinenic and eudesmanic sesquiterpenes.

Liu and coworkers [33] reported isolation of highly oxygenated cadinane based compounds, three new xylaric acid A **65**, xylaric acid B **66** and xylaric acid C **67** and nine known compounds xylaric acid D **68**, heptelidic acid (avocetlin) [34] **69** hydroheptelidic acid **70**, gliocladic acid **71**, chlorheptelidic acid **72**, trichoderonic acid A **73**. The structure assignments are based on extensive spectral analysis. All these congeners belong to cadinane or seco-cadinane group of sesquiterpenes (**Figure 8**). The stereochemistry at C6 and C7 is unchanged for all the metabolites where C1 remains same for **66**, **67**, **69**, **70**, **72** and **73** and changes for **65**, **68** and **71**.



Scheme 21. Proposed new consolidated mechanism for the biosynthesis of valerenadiene **47**.

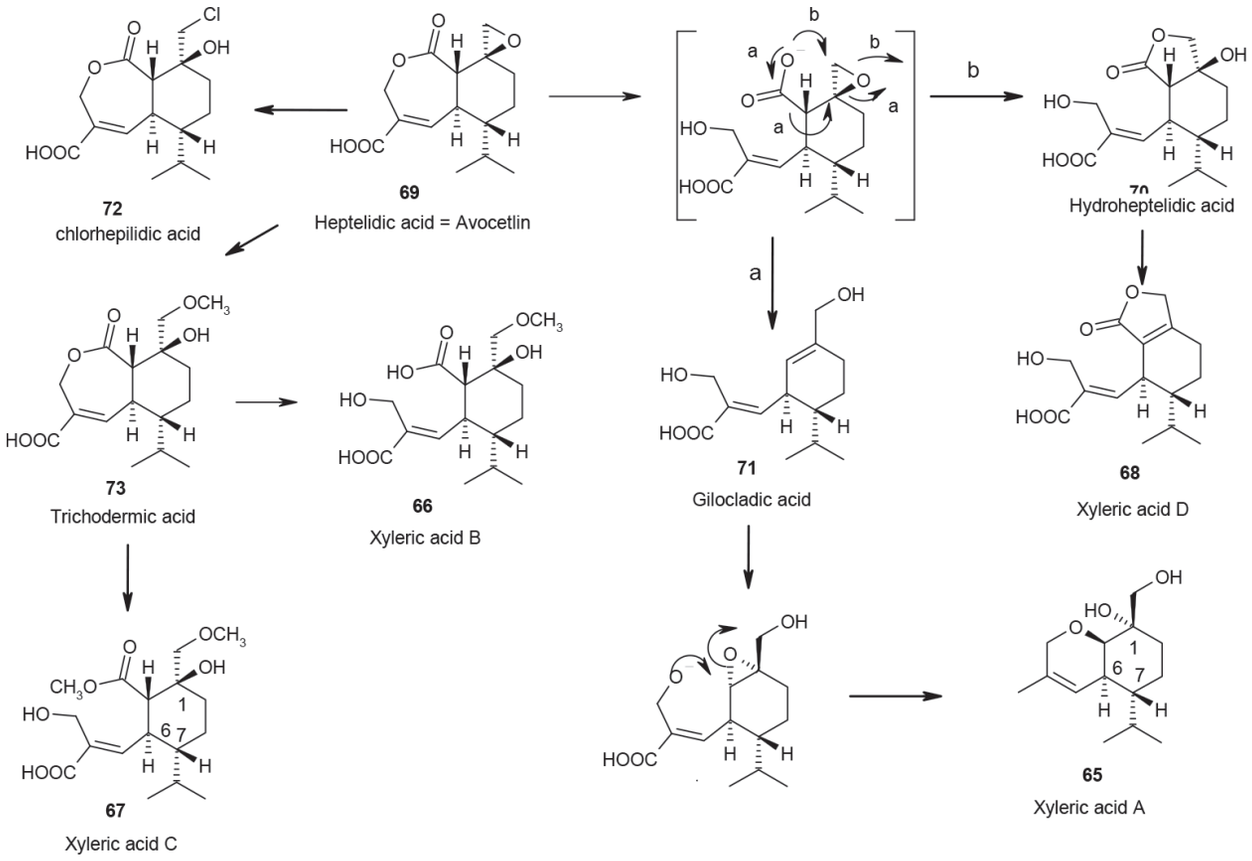
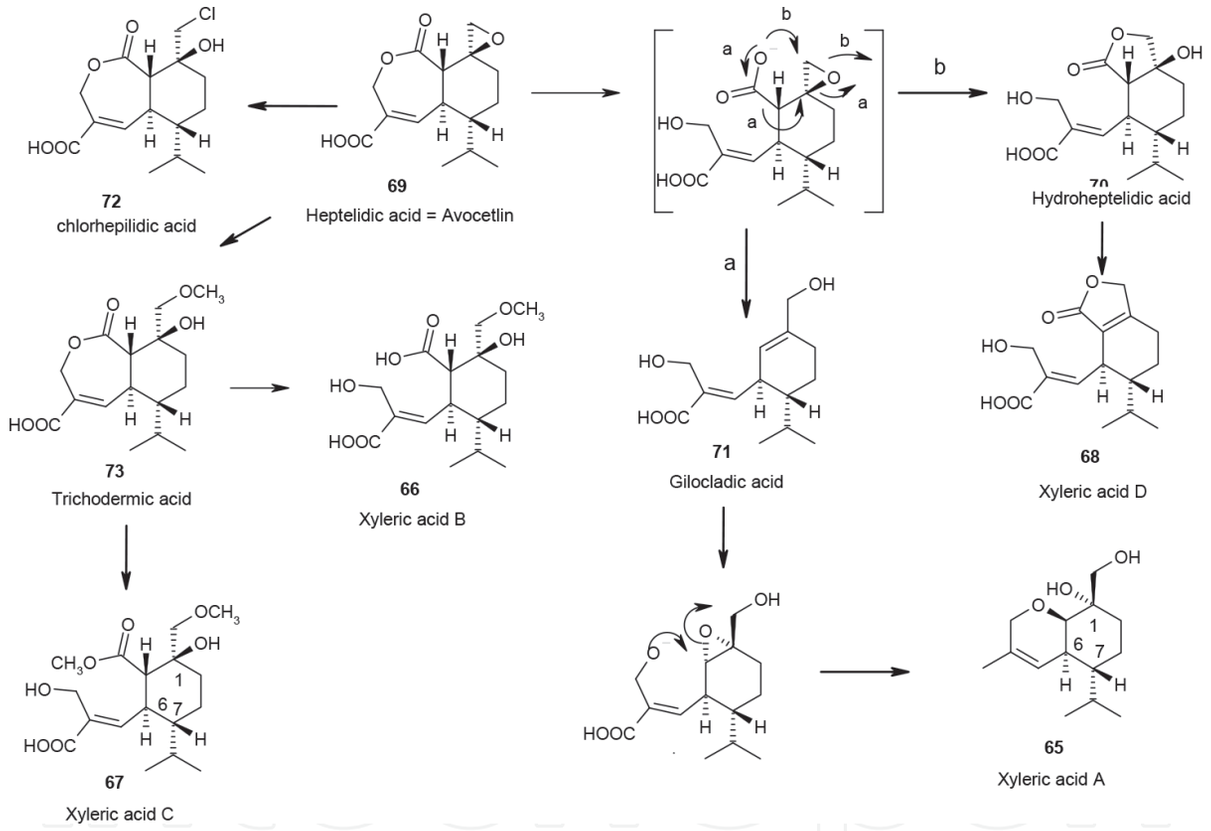


Figure 8. Structural interrelations among the congeners of *Xylaria* sp. and the sequence of formation of isolated metabolites **65–73**.

Knowing the absolute stereochemistry of the congeners and their fungal origin, they belong to the "antipodal" set of compounds and they can be regarded as a result of extensive oxidative reactions of (−)-γ-cadinene **74**. Recently, Rabe *et al.* [35] have reported isolation of several sesquiterpenes including (−)-γ-cadinene, $[\alpha]_D$-32.3° by incubation of FPP with six purified bacterial terpene cyclases. The results were further supported by labeling experiments with 13C labeled isotopomers of FPP. Interestingly, antipodal cadinenic sesquiterpenes with known absolute configurations have been isolated from Indian vetiver oil (*Vetiveria zizanioides*) [36]. Isolation of (−)-γ-cadinene **74**, khusinol **75** and khusinol oxide **76** could be regarded as the precursors for the metabolites of *Xylaria* sp. A very clean sequence indicating a plausible order of formation of *Xylaria sp.* metabolites associated with the termite nest is presented (**Scheme 22**). We believe that this presentation will be useful while investigating the biosynthetic pathways using isotopic labeling studies.



Scheme 22. Proposed plausible order of formation of *Xylaria* sp. metabolites from FPP.

3. Conclusions

This chapter gives overview of some of the interesting molecular rearrangements of sesquiterpenes reported over last decade. Further biosynthesis of albaflavenone, caryol-1(11)-ene-10-ol, (+)-koraiol, pogostol, patchouli alcohol and valerenadiene are also presented. The recent trends in the biosynthesis of natural products is focused on enzymatic synthesis using isotopic labeling, nevertheless discussions on structural interrelationships of various congeners provides insights in to natural occurrence of these molecules and finding their biosynthetic links.

Acknowledgements

We wish to dedicate this review to Professor R. B. Bates on his retirement from Research. We thank Dr. Asha D'Souza, Prof. Shailesh Shah and Rahul Chowgule for their valuable help in providing many research articles required for this review.

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