

Black Pepper (*Piper nigrum* L.): A Multifaceted Spice With Therapeutic, Industrial, And Synthetic Importance

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ABSTRACT

Black pepper (*Piper nigrum* L.), often referred to as the “King of Spices,” is one of the most economically important spice crops and a valuable medicinal plant with a long history of use in traditional systems of medicine. Besides its culinary significance, black pepper possesses a wide spectrum of pharmacological properties attributed to its rich phytochemical composition, particularly the alkaloid piperine and various volatile constituents. The present review comprehensively summarizes the ethnomedicinal importance, phytochemical profile, nutritional composition, and biological activities of black pepper and its major bioactive constituents. Piperine exhibits diverse pharmacological effects, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, hepatoprotective, neuroprotective, anticancer, antimalarial, and bioavailability-enhancing activities, making it a promising lead compound for drug development. The review further highlights the industrial and pharmaceutical applications of black pepper in functional foods, nutraceuticals, herbal formulations, cosmetics, food preservation, and advanced drug delivery systems. In addition, the synthetic utility of pepper-derived constituents such as piperine, pellitorine, limonene, and related metabolites as valuable synthons in organic synthesis is discussed, emphasizing their role in the preparation of natural products, heterocyclic compounds, pharmaceuticals, fragrances, and biologically active molecules. Collectively, the available evidence underscores the immense therapeutic and synthetic potential of black pepper and supports its continued exploration as a source of novel bioactive compounds and sustainable chemical building blocks.

Keywords: *Piper nigrum*; Black pepper; Piperine; Pellitorine; Phytochemistry; Pharmacological activities; Bioavailability enhancer; Natural products; Chiral synthons; Organic synthesis; Nutraceuticals; Medicinal plants.

INTRODUCTION

Black pepper (*Piper nigrum* L.) belongs to the family Piperaceae is one of the oldest and most widely used spices and occupying a preeminent status in the spice trade, well known for its pungent constituent piperine, an alkaloid that constitutes approximately 2–9% of the dried fruits.¹ Originating in the humid, tropical evergreen forests of the Western Ghats of South India, especially in Kerala, black pepper is now cultivated in most tropical and subtropical regions, with production primarily in Vietnam, Indonesia, Brazil, India, Sri Lanka, China, Malaysia and Cambodia. It has played a significant role in global trade and cultural exchange for more than two millennia¹. Black pepper (*Piper nigrum* L.),

The spice is derived from the dried fruits (peppercorns) of a perennial woody climbing vine.

Depending on the stage of harvest and processing, black, white, and green pepper products are obtained.



Climbing vine of pepper

Apart from its culinary significance, black pepper has occupied a central position in traditional systems of medicine including Ayurveda, Siddha, and Unani. Modern scientific investigations have validated many traditional claims and revealed numerous

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

pharmacological activities associated with pepper-derived compounds.

2. HISTORICAL SIGNIFICANCE OF BLACK PEPPER

The history of black pepper is closely linked with the development of international trade routes and colonial expansion. Ancient Sanskrit texts, Ayurvedic treatises, Biblical records, and Arab literature mention pepper as a valuable commodity.

The spice trade involving pepper contributed substantially to the prosperity of trading centers such as Alexandria, Venice, and Genoa¹. During the colonial period, European powers competed intensely for control over pepper-producing regions, particularly along the Malabar Coast of India. According to the bible, it was during the royal visit of Queen Sheeba to King Solomon (BC 1015–BC 66) that a caravan load of spices, primarily pepper, was presented to the king. Because of its high economic value, black pepper earned the titles “Black Gold” and “King of Spices.”

3. TRADITIONAL AND ETHNOMEDICINAL USES

Black pepper (*Piper nigrum* L.), known as *Maricha* in Ayurveda, is one of the most important medicinal spices used in the traditional systems of medicine, including Ayurveda, Unani, and Siddha. It is a principal component of the classical Ayurvedic formulation *Trikatu*, together with ginger (*Zingiber officinale*) and long pepper (*Piper longum*), which is widely prescribed to stimulate digestion, enhance metabolism, and improve the bioavailability of therapeutic compounds². Ayurvedic texts describe black pepper as a pungent, heating, carminative, expectorant, anthelmintic, and digestive tonic employed in the management of cough, asthma, fever, dyspepsia, intestinal helminthiasis, piles, epilepsy, and various disorders associated with impaired digestion and respiratory function³. Traditional practitioners have also used black pepper to stimulate appetite, promote salivation, improve nutrient assimilation, and restore digestive health. Contemporary pharmacological investigations have validated several of these traditional claims and identified piperine, the major bioactive alkaloid of black pepper, as a potent bioavailability enhancer that

increases the absorption and efficacy of numerous drugs and phytochemicals^{4,5}.

Black pepper is incorporated into numerous traditional formulations and household remedies for the treatment of respiratory, gastrointestinal, and febrile disorders. Preparations containing pepper in combination with honey, ginger, holy basil (*Ocimum tenuiflorum*), milk, butter, or sesame oil are commonly used as expectorants, digestive stimulants, carminatives, and remedies for cough, cold, rhinitis, sinusitis, fever, and indigestion. Externally, pepper-based medicated oils and pastes have been applied to alleviate headaches, neuralgic pain, skin ailments, ear disorders, and nasal congestion. The enduring importance of black pepper in traditional medicine is attributed to its diverse pharmacological properties, including antimicrobial, antioxidant, anti-inflammatory, digestive, immunomodulatory, and bioenhancing activities, many of which have been substantiated by modern scientific studies^{3,4}. Consequently, black pepper continues to serve as an important ingredient in both traditional healthcare systems and contemporary herbal therapeutics.

4. PHYTOCHEMICAL COMPOSITION

Black pepper (*Piper nigrum* L.) possesses a rich and diverse phytochemical profile that contributes to its characteristic aroma, pungency, and wide range of biological activities. The chemical constituents of black pepper include alkaloids, volatile oils, terpenoids, lignans, flavonoids, phenolic compounds, and various nutritional components. Among these, alkaloids and essential oils are primarily responsible for its pharmacological properties and commercial value. Piperine, the principal pungent alkaloid, is considered the most important bioactive constituent and has been extensively studied for its antioxidant, anti-inflammatory, antimicrobial, and bioavailability-enhancing effects⁴.

4.1 Major Alkaloids

The alkaloidal fraction of black pepper is dominated by piperine, accompanied by several structurally related amides, including chavicine, isopiperine, isochavicine, piperittine, pellitorine, pipericide, and guineensine. These compounds contribute to the pungent taste and pharmacological activities of black pepper. Piperine, in particular, has attracted

significant scientific interest due to its ability to enhance the absorption and bioavailability of drugs and nutraceuticals by modulating intestinal permeability and metabolic enzymes^{5,6}.

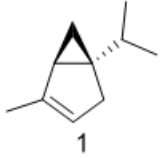
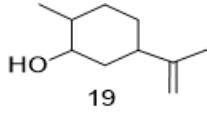
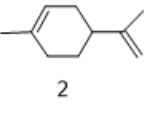
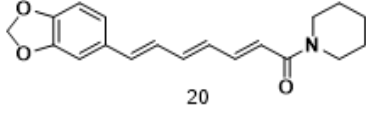
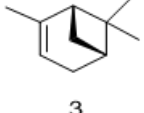
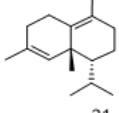
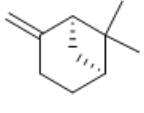
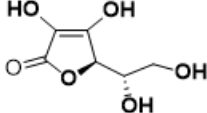
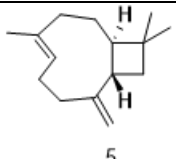
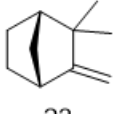
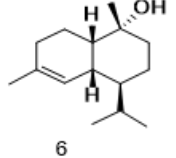
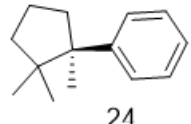
4.2 Essential Oil Constituents

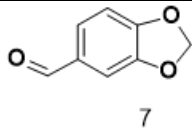
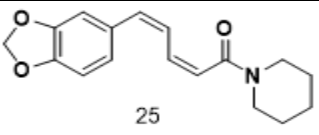
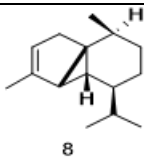
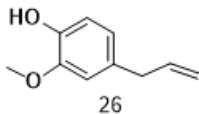
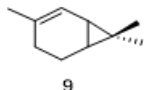
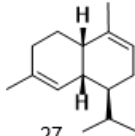
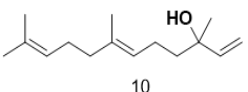
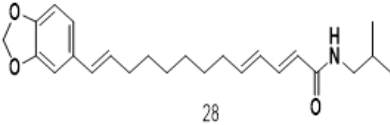
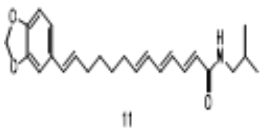
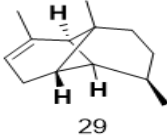
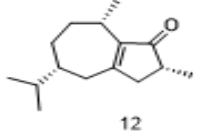
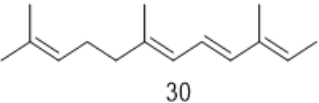

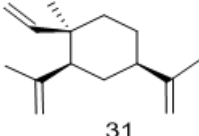
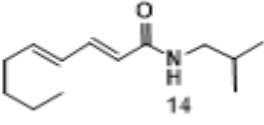
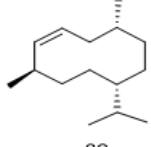
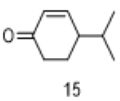
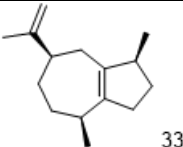
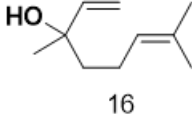
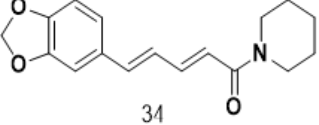
The essential oil of black pepper, typically constituting 1–3% of the dried berries, is composed mainly of monoterpenes and sesquiterpenes that impart its distinctive aroma and flavor. Major constituents include α -pinene, β -pinene, sabinene, limonene, terpinolene, linalool, β -caryophyllene, nerolidol, elemol, cedrol, farnesene, and germacrene. These volatile compounds exhibit diverse biological activities, including antioxidant, antimicrobial, anti-inflammatory, and insecticidal properties, thereby

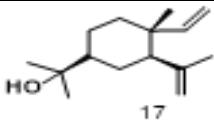
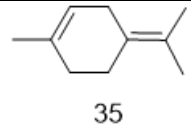
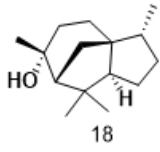
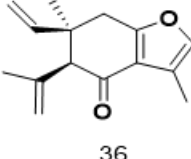
contributing to the medicinal and preservative value of black pepper^{4,7}.

4.3 Nutritional Components

In addition to its secondary metabolites, black pepper is a valuable source of nutrients. The dried berries contain carbohydrates, dietary fiber, proteins, vitamins, and essential minerals such as calcium, potassium, magnesium, phosphorus, and iron. They also provide vitamin C (ascorbic acid) and other micronutrients that contribute to their nutritional and health-promoting properties. The combination of bioactive phytochemicals and nutritional constituents makes black pepper an important functional food as well as a medicinal spice^{4,8}

Compound	Structure	Compound	Structure
Sabinene		Dihydrocarveol	
Limonene		Piperittine	
α -pinene		α -amorphene	
β -pinene		Ascorbic Acid	
Caryophyllane		Camphene	
Torreyol		Cuparene	

Piperonal	 7	Chavicine	 25
Cububen	 8	Eugenol	 26
Carene	 9	α -Murolene	 27
Nerolidol	 10	Guinesine	 28
Pipericide	 11	Copaene	 29
Rotundone	 12	Farnesene	 30
Clovene	 13	Elemene	 31
Pellitorine	 14	Germacrene	 32
Crypton	 15	α -guaiene	 33
Linalool	 16	Piperine	 34

Elemol		Terpinolene	
Cedrol		Curzerenone	

5. BIOLOGICAL ACTIVITY OF COMPOUNDS ISOLATED FROM PEPPER

5.1 Piperine: The Principal Bioactive Constituent

Piperine, the principal bioactive alkaloid of black pepper (*Piper nigrum* L.) and long pepper (*Piper longum* L.), is responsible for their characteristic pungent taste. Chemically, it is a piperidine alkaloid formed from the condensation of piperic acid and piperidine. Since its isolation in 1819, piperine has attracted considerable scientific interest owing to its diverse pharmacological activities and therapeutic potential. Extensive studies have demonstrated that piperine possesses antioxidant, anti-inflammatory, antimicrobial, anticancer, neuroprotective, antidiabetic, and hepatoprotective properties. In addition, piperine is widely recognized as a natural bioavailability enhancer, capable of improving the absorption and efficacy of various drugs, nutrients, and phytochemicals by modulating intestinal permeability and drug-metabolizing enzymes. These multifunctional biological activities have established piperine as one of the most important phytoconstituents of black pepper and a promising candidate for pharmaceutical and nutraceutical applications^{4,5,7}.

5.1.1 Bioavailability enhancement

One of the most significant pharmacological properties of piperine is its ability to enhance the bioavailability of various drugs, nutrients, and phytochemicals. Bioavailability enhancement improves the absorption and systemic availability of therapeutic agents, thereby increasing their efficacy. Piperine acts through multiple mechanisms, including increasing intestinal absorption, modulating membrane dynamics, delaying gastrointestinal transit,

and inhibiting drug-metabolizing enzymes involved in first-pass metabolism, particularly cytochrome P450 enzymes and glucuronidation pathways^{9,10}.

The bio enhancing property of piperine was first demonstrated by Atal and co-workers in 1981, who reported a two-fold increase in the bioavailability of sparteine. Subsequently, numerous studies have confirmed its ability to improve the pharmacokinetic profiles of several therapeutic agents, including propranolol, theophylline, phenytoin, amoxicillin, cefotaxime, and coenzyme Q10¹¹⁻¹⁵. Piperine has also been shown to enhance the bioavailability of the green tea polyphenol epigallocatechin-3-gallate (EGCG) by inhibiting intestinal glucuronidation and delaying gastrointestinal transit. A landmark study by Shoba et al. (1998)¹⁰ demonstrated that co-administration of piperine increased the bioavailability of curcumin by 154% in rats and by as much as 2000% in human volunteers, highlighting its immense potential as a natural bioenhancer. These findings have established piperine as one of the most effective plant-derived bioavailability enhancers and have significantly expanded its applications in pharmaceutical and nutraceutical formulations.

5.1.2 Anti – inflammatory effects and CNS depressant activity of piperine.

Piperine exhibits significant anti-inflammatory activity and has been shown to attenuate both acute and chronic inflammatory responses in experimental models. Studies have demonstrated that oral administration of piperine (50 mg/kg) significantly reduces edema formation in carrageenan-induced paw edema models and suppresses inflammation in cotton pellet-induced granuloma and croton oil-induced granuloma pouch assays, indicating its effectiveness against both exudative and proliferative phases of

inflammation¹⁶. The anti-inflammatory effects of piperine are attributed to its ability to modulate key inflammatory mediators and signaling pathways. Notably, piperine inhibits tumor necrosis factor- α (TNF- α)-induced adhesion of neutrophils to endothelial cells by suppressing the activation of nuclear factor-kappa B (NF- κ B) and I κ B kinase, thereby interfering with early events in the inflammatory cascade. These findings suggest that piperine may serve as a promising natural anti-inflammatory agent for the management of inflammation-associated disorders¹⁷.

5.1.3 Antioxidant effect

Oxidative stress resulting from the excessive production of reactive oxygen species (ROS) and free radicals plays a crucial role in the development of numerous chronic diseases, including atherosclerosis, cancer, diabetes, and age-related disorders. Piperine, the major alkaloid of black pepper, exhibits potent antioxidant activity by scavenging free radicals, quenching reactive oxygen species, and inhibiting lipid peroxidation. Experimental studies have demonstrated that piperine acts as an effective hydroxyl and superoxide radical scavenger and protects biological membranes and lipoproteins from oxidative damage. Piperine has also been shown to inhibit the oxidation of low-density lipoprotein (LDL), a key event in the pathogenesis of atherosclerosis¹⁸.

In addition to its direct free-radical scavenging effects, piperine enhances endogenous antioxidant defense mechanisms. Studies in streptozotocin-induced diabetic rats have revealed that piperine restores reduced glutathione levels and improves the activities of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and glutathione reductase, thereby reducing lipid peroxidation and oxidative tissue damage¹⁹. The antioxidant potential of black pepper and its oleoresins has also been attributed to their polyphenolic constituents, including piperine, which contribute significantly to the preservation of biological systems and food products against oxidative deterioration. These findings highlight the therapeutic potential of piperine in preventing oxidative stress-mediated diseases²⁰⁻²³.

5.1.4 Anti diarrhoeal property

Piperine has demonstrated significant antidiarrheal activity in experimental studies. The inhibition of castor oil-induced diarrhea by piperine suggests its potential role in modulating prostaglandin-mediated intestinal secretion and motility. Capasso et al. reported that piperine, administered at doses ranging from 2.5 to 20 mg/kg, significantly and dose-dependently reduced castor oil-induced fluid accumulation in the small intestine of mice. Mechanistic investigations revealed that the antidiarrheal effect of piperine involves the modulation of capsaicin-sensitive sensory neurons, leading to reduced intestinal fluid secretion. However, this activity appears to be independent of capsazepine-sensitive vanilloid receptors. These findings indicate that piperine may contribute to the traditional use of black pepper in the management of gastrointestinal disorders, including diarrhea, by regulating intestinal secretory responses and fluid balance²⁴.

5.1.5 Antimutagenic and Anticancer Property

Piperine has attracted considerable attention for its anticancer and chemopreventive properties. Studies have demonstrated that piperine can inhibit tumor progression by modulating cell signaling pathways and suppressing the production of pro-inflammatory cytokines involved in cancer development. Experimental investigations in *Drosophila melanogaster* have shown that piperine acts as an effective mutation suppressor against ethyl carbamate-induced mutagenesis, indicating its potential antimutagenic activity²⁵. In animal models of benzo[a]pyrene-induced lung carcinogenesis, piperine exhibited significant chemoprotective effects by regulating mitochondrial tricarboxylic acid (TCA) cycle enzymes, phase I detoxification enzymes, and glutathione-dependent antioxidant systems. These effects were associated with reduced oxidative stress and enhanced cellular defense mechanisms, thereby suppressing tumor development²⁶.

Further evidence of the anticancer potential of piperine has been obtained from both in vitro and in vivo studies. Piperine exhibits cytotoxic effects against various cancer cell lines, including Dalton's lymphoma ascites and Ehrlich ascites carcinoma cells, while black pepper extracts have been reported to

prolong survival in tumor-bearing experimental animals. Notably, piperine significantly inhibited lung metastasis induced by B16F-10 melanoma cells in C57BL/6 mice, reducing tumor nodule formation by approximately 95%²⁷. The anticancer effects of piperine are attributed to its antioxidant, anti-inflammatory, antimutagenic, and immunomodulatory activities, as well as its ability to modulate xenobiotic-metabolizing enzymes and interfere with tumor-promoting signaling pathways. Collectively, these findings highlight the potential of piperine as a promising natural chemopreventive and anticancer agent^{4,23}.

5.1.6 Antibacterial activity

Black pepper and its principal alkaloid, piperine, exhibit notable antibacterial activity against a broad spectrum of pathogenic microorganisms. Several studies have demonstrated that extracts of *Piper nigrum*, particularly ethanolic extracts, possess inhibitory effects against both Gram-positive and Gram-negative bacteria. Piperine has been identified as one of the major bioactive constituents responsible for this antimicrobial activity. Using techniques such as thin-layer chromatography (TLC), melting point analysis, and bioassay-guided fractionation, piperine has been isolated and evaluated against clinically important bacterial pathogens, including *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus* spp., *Aeromonas* spp., *Klebsiella pneumoniae*, and *Acinetobacter* spp.^{28,29} (Gülçin, 2005; Karsha and Lakshmi, 2010).

The antibacterial action of piperine is attributed to its ability to disrupt bacterial cell membranes, interfere with cellular metabolism, and inhibit microbial growth. Experimental studies have reported significant zones of inhibition against several pathogenic bacteria, indicating its potential as a natural antimicrobial agent. The broad-spectrum antibacterial activity of black pepper supports its traditional use in the treatment of infectious diseases and highlights its potential application in pharmaceutical, food preservation, and nutraceutical industries^{4,23,30}.

5.1.7 Antimalarial activity

The emergence of resistance to conventional antimalarial drugs, including artemisinin-based

therapies, has stimulated interest in the search for novel antimalarial agents from natural sources. Piperine, the major alkaloid of black pepper, has shown promising antiplasmodial activity in preliminary studies. Investigations involving *Plasmodium falciparum*, the causative agent of the most severe form of human malaria, have demonstrated that piperine can inhibit parasite growth in vitro. Using a SYBR Green I-based assay, piperine was found to suppress the proliferation of the 3D7 clone of *P. falciparum* in a concentration-dependent manner, with higher concentrations significantly impairing parasite development³¹.

Although piperine-induced growth inhibition was not associated with significant alterations in the expression of major drug-resistance genes such as *pfmdr1*, *pfmrp1*, and *pfprt*, its antiplasmodial effects suggest the involvement of alternative mechanisms of action. Studies on *Piper* species, including *Piper chaba*, have also reported moderate antimalarial activity of ethanolic extracts, further supporting the therapeutic potential of piperine-containing plants. While the exact molecular targets remain to be elucidated, current evidence indicates that piperine may serve as a promising lead compound for the development of new antimalarial agents, particularly in the context of increasing resistance to existing therapies^{32,33}.

5.1.8 Antimycobacterial activity

Piperine and its synthetic derivatives have demonstrated promising antimycobacterial activity against *Mycobacterium tuberculosis*, the causative agent of tuberculosis. To enhance the therapeutic potential of piperine, several amide analogues have been synthesized and evaluated for their antimicrobial efficacy and cytotoxicity. Among these, derivatives containing 3-exo-aminoisoborneol and (+)-isopinocampheylamine exhibited remarkable activity against *M. tuberculosis* H37Rv, with minimum inhibitory concentration (MIC) values of 0.17 and 0.18 μ M, respectively. These compounds showed potent antimycobacterial effects comparable to or exceeding those of conventional antitubercular agents such as ethambutol and isoniazid³⁴.

In addition to their strong antimicrobial activity, piperine-derived amides displayed low cytotoxicity toward human embryonic kidney (HEK-293T) cells

following 72-hour exposure, indicating a favorable safety profile. The combination of high antimycobacterial potency and low toxicity suggests that piperine analogues represent promising lead molecules for the development of novel antitubercular drugs. These findings further support the potential of piperine as a valuable scaffold for designing new antimicrobial agents to combat drug-resistant mycobacterial infections^{23,34,35}.

5.2 Pellitorine

Pellitorine is a naturally occurring alkalamide present in black pepper (*Piper nigrum*), although it occurs in relatively low concentrations (approximately 0.4–1%) compared to other *Piper* species. Despite its limited abundance, pellitorine has attracted considerable scientific interest because of its diverse pharmacological activities. Studies have demonstrated that pellitorine exhibits significant cytotoxic effects against various cancer cell lines, including HL-60 human leukemia and MCF-7 breast cancer cells, suggesting its potential as an anticancer agent. In addition, pellitorine possesses notable antiprotozoal and antimalarial activities. Investigations against multidrug-resistant *Plasmodium falciparum* strains revealed that pellitorine is one of the most active alkalamides, exhibiting an IC₅₀ value of 3.26 µg/mL (14.6 µM), thereby highlighting its potential for the development of new antimalarial therapies³⁶.

Beyond its anticancer and antimalarial properties, pellitorine has shown promising anti-inflammatory and anti-septic effects. Studies have demonstrated that pellitorine suppresses the release of pro-inflammatory mediators such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) through inhibition of the high-mobility group box 1 (HMGB1) signaling pathway and downregulation of NF- κ B and ERK1/2 activation. These findings suggest its potential application in the treatment of severe vascular inflammatory and septic conditions³⁷. Furthermore, pellitorine exhibits potent insecticidal activity against *Aedes aegypti*, the primary vector of dengue and several other arboviral diseases. Histopathological and molecular studies have shown that pellitorine damages anal gill tissues and inhibits the expression of genes encoding V-type H⁺-ATPase and aquaporin-4, resulting in impaired osmoregulation and larval

mortality. Consequently, pellitorine has been proposed as a promising natural larvicidal agent for mosquito control³⁸.

5.3 Pipericide

Pipericide is another biologically active amide constituent identified in *Piper nigrum* and related *Piper* species. Although present in relatively small quantities, it has attracted attention due to its notable insecticidal and pharmacological properties. Studies have demonstrated that pipericide exhibits strong insecticidal activity against the adzuki bean weevil (*Callosobruchus chinensis*), a major storage pest of legumes. Its efficacy has been reported to be comparable to that of pyrethrins, a widely used class of natural insecticides, indicating its potential application as an environmentally friendly biopesticide for pest management³⁹.

In addition to its insecticidal activity, pipericide has shown promising biological effects on mammalian cells. In vitro studies have reported that pipericide stimulates melanocyte proliferation, suggesting a possible role in regulating pigmentation and skin health. This activity has generated interest in the potential therapeutic applications of pipericide for pigmentary disorders and cosmetic formulations, although further investigations are required to elucidate its mechanisms of action and clinical relevance⁴⁰. These findings indicate that pipericide possesses diverse bioactivities and may serve as a valuable lead compound for agricultural, pharmaceutical, and cosmetic applications.

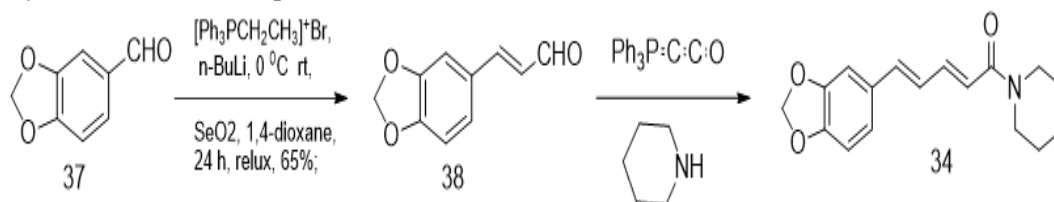
6. SYNTHETIC APPROACHES TO THE CHEMICAL CONSTITUENTS OF PEPPER

6.1 Piperine

Piperine, the principal alkaloid of *Piper nigrum*, has attracted significant synthetic interest owing to its diverse pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, anticancer, and bioavailability-enhancing activities. The growing therapeutic importance of piperine has prompted the development of several synthetic strategies aimed at its efficient preparation and structural modification for medicinal chemistry applications.

Among the reported methods, Rainer Schobert and co-workers described an efficient three-component synthesis of piperine in 2001. This approach utilized 3,4-methylenedioxybenzaldehyde, ketenylidetriphenylphosphorane ($\text{PPh}_3=\text{C}=\text{C}=\text{O}$), and piperidine as the key starting materials. In this synthesis, 3,4-methylenedioxybenzaldehyde was prepared from piperonal through a Wittig olefination followed by oxidation. Subsequent reaction with

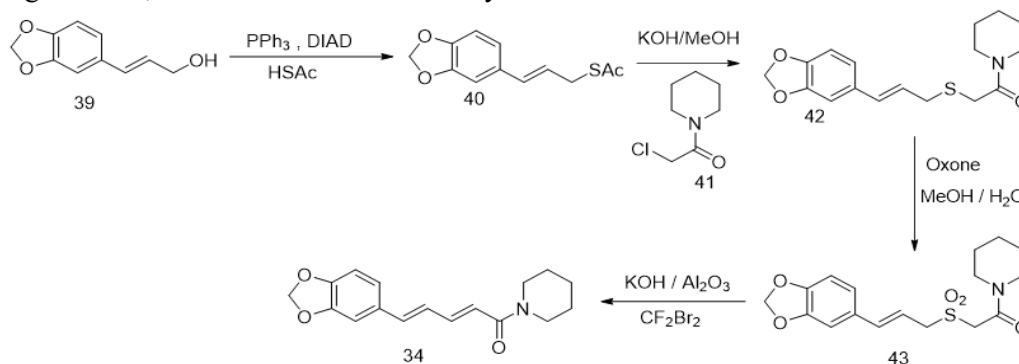
ketenylidetriphenylphosphorane and piperidine afforded piperine in a concise and efficient manner. This methodology demonstrated the utility of multicomponent reactions for the rapid assembly of the piperine framework and provided an attractive route for the synthesis of piperine and related analogues with potential biological activity⁴¹. (Scheme 1)



Scheme 1: Synthesis of piperine

Another elegant synthesis of piperine was reported by Zhang, who employed a modified Ramberg–Bäcklund reaction as the key carbon–carbon double-bond-forming step. In this approach, the starting alcohol was first converted into the corresponding thioacetate through a Mitsunobu reaction. Subsequent in situ deacetylation generated the corresponding thiol, which was alkylated with an appropriate chloroacetamide to afford the sulfide intermediate. Oxidation of the sulphide using Oxone produced the corresponding sulfone, which served as the key

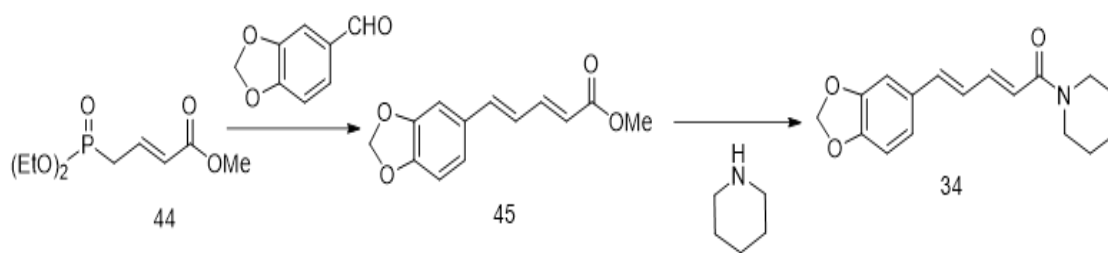
precursor for the final transformation. Treatment of the sulfone with dibromodifluoromethane in the presence of alumina-supported potassium hydroxide in dichloromethane promoted a modified Ramberg–Bäcklund reaction, yielding piperine in an excellent yield of 82%. This methodology provided an efficient and stereoselective route to piperine and demonstrated the utility of the Ramberg–Bäcklund reaction in the synthesis of biologically important alkaloids⁴². (Scheme 2)



Scheme 2: Synthesis of piperine using a modified Ramberg–Bäcklund as the key step

A concise and efficient synthesis of piperine was reported by Gary O. Spessard and co-workers in 1981. The synthetic route involved a Wittig–Horner reaction between piperonal and (E)-4-diethylphosphono-2-butenate, which afforded methyl piperate as the key intermediate. Subsequent aminolysis of the ester with piperidine in the presence

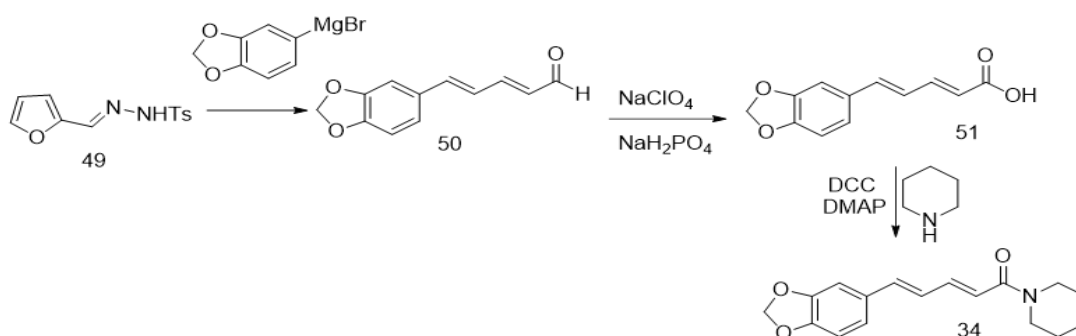
of methoxide catalyst resulted in the formation of the corresponding amide, yielding piperine. This two-step approach provided a straightforward and practical method for the synthesis of piperine, highlighting the utility of phosphonate-based olefination reactions for constructing the conjugated dienamide framework characteristic of the alkaloid⁴³. (Scheme 3)



Scheme 3: Synthesis of piperine by Wittig reaction

Chandrasekhar *et al* reported a synthesis of piperine employing the strategy of addition of carbon nucleophiles to aldehyde tosylhydrazones. Furfural was derivatized as its hydrazone, which was treated with 3,4-methylenedioxyphenylmagnesium bromide

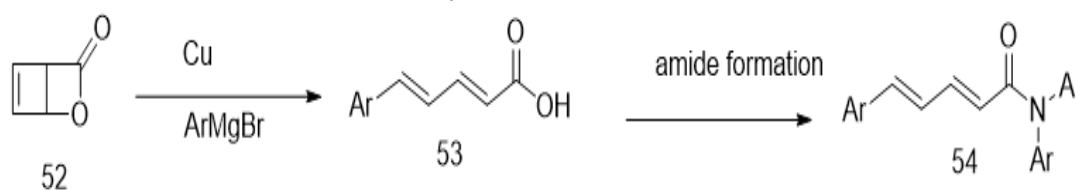
to obtain the aldehyde. The aldehyde was transformed into the corresponding acid (piperic acid) using NaClO_4 . The last step in the synthesis- the amide formation, was achieved by a DCC assisted condensation with piperidine⁴⁴. (Scheme 4)



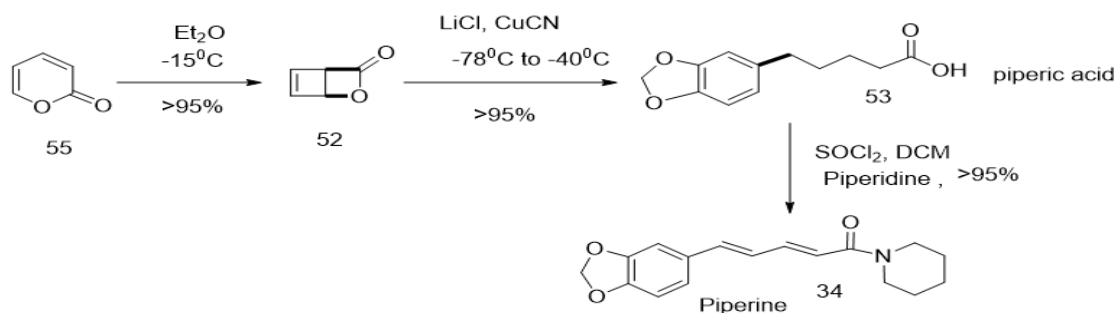
Scheme 4: Synthesis of piperine employing the strategy of addition of carbon nucleophiles to aldehyde tosylhydrazones

A short synthesis by A. Bauer *et al.* in 2019 demonstrated that the bicycle [2.2.0] lactone and its derivatives have been used for the synthesis of piperine and its derivatives. In this reaction they have

shown that copper-mediated nucleophilic addition is very strong method for a trans- selective allylic substitution⁴⁵. (Scheme 5 & 6)



Scheme 5: General Scheme for the synthesis of piperine and its derivatives synthesized from bicycle [2.2.0] lactone



Scheme 6: Representative scheme for the synthesis of piperine from bicycle [2.2.0] lactone

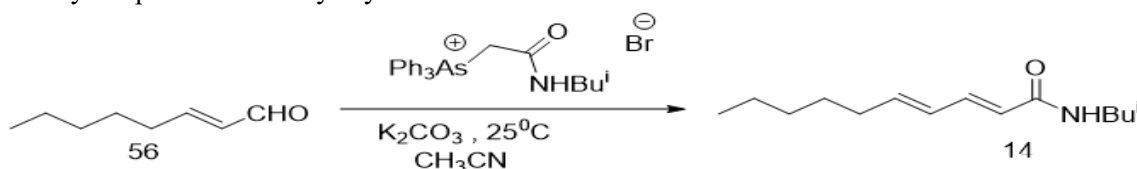
The addition of an electrolytic moiety facilitates 4π -electrocyclic opening. The aryl moiety is a good electron donating group which facilitates electrocyclic ring opening at room temperature or upon mild heating conditions. The trans configured cyclobutene should undergo thermally allowed conrotatory movement

The trans configured cyclobutene was obtained in quantitative yield photochemically. By the addition of

cuprate directly led to the formation of piperic acid in a single form. (scheme 6)

6.2 Pellitorine

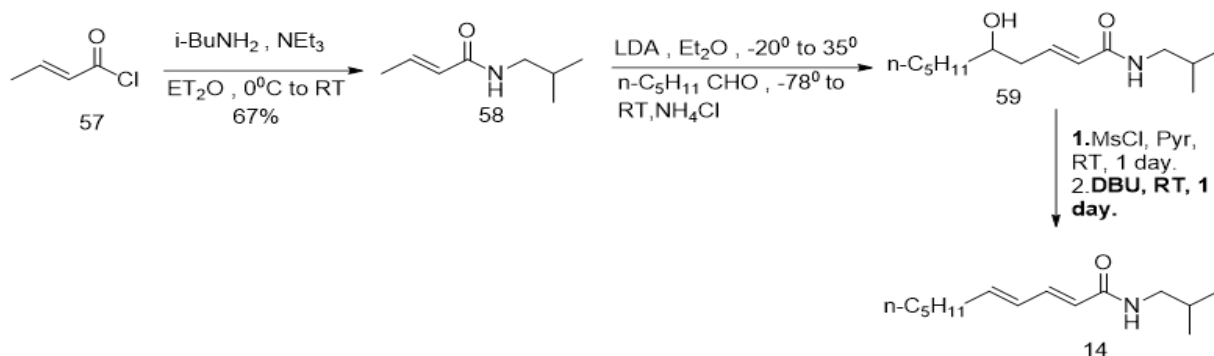
Pellitorine was prepared by a single step reaction of an aldehyde and a corresponding arsonium salt in a yield of 79%^{46,47}. (Scheme 7)



Scheme 7: Synthesis of pellitorine

J. E. Semple reported a simple synthesis of Pellitorine. The addition of isobutylamine to crotonyl chloride in presence of a base like triethylamine yielded the

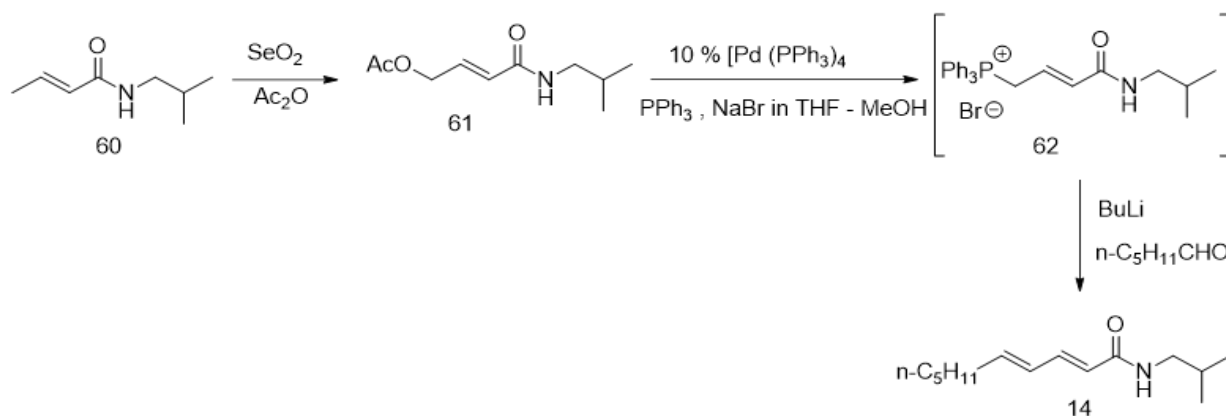
unsaturated amide. A subsequent aldol reaction with pentanal resulted in the formation of the basic alkyl framework of Pellitorine⁴⁸ (Scheme 8)



Scheme 8: Synthesis of Pellitorine

Nokami and co-workers reported a palladium-catalyzed synthesis of pellitorine in 1984 that utilized the in-situ generation of a phosphonium ylide as the key synthetic step. In this approach, an allylic acetate was treated with sodium bromide and triphenylphosphine in the presence of tetrakis(triphenylphosphine)palladium(0) [$\text{Pd}(\text{PPh}_3)_4$], resulting in the formation of a

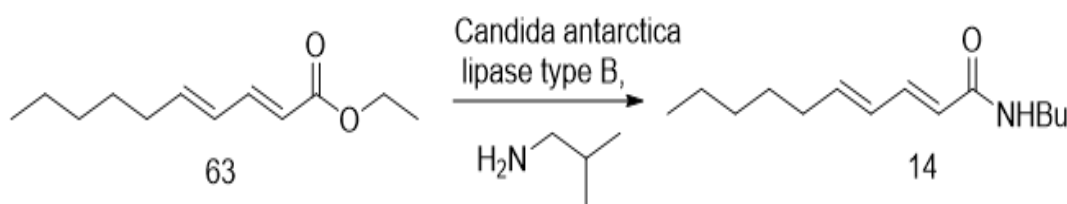
phosphonium salt/ylide intermediate through a palladium-mediated allylic substitution process. The generated phosphonium ylide subsequently underwent a Wittig-type olefination with hexanal, leading to the formation of the characteristic conjugated diene framework of pellitorine⁴⁹. (Scheme 9)



Scheme 9: Pd- catalyzed synthesis of pellitorine

J. P. Ley and co-workers reported an efficient biocatalytic synthesis of pellitorine employing the enzyme *Candida antarctica* lipase B (CAL-B) as a selective catalyst. The synthesis involved the enzymatic aminolysis of ethyl (2E,4Z)-decadienoate with isobutylamine, resulting in the formation of the corresponding amide, pellitorine. The use of CAL-B enabled the reaction to proceed under mild conditions

with high selectivity and efficiency, affording pellitorine in an excellent yield of 80%. This enzymatic approach represents an environmentally friendly and sustainable alternative to conventional chemical methods, highlighting the potential of biocatalysis for the synthesis of naturally occurring alkamides and flavor-active compounds⁵⁰. (Scheme 10)



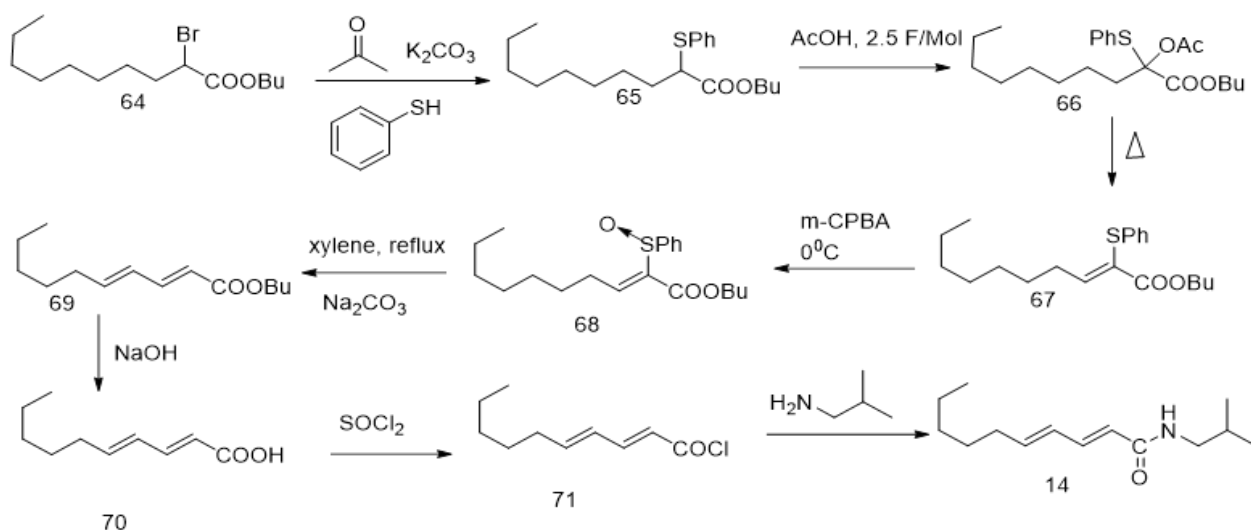
Scheme 10: Synthesis of pellitorine utilizing the selectivity of the enzyme *Candida antarctica* Lipase type B

Nokami and co-workers developed an alternative synthesis of pellitorine utilizing a novel electrochemical methodology based on the acetoxylation of sulfides followed by sulfoxide pyrolysis. In this approach, an appropriate sulfide precursor containing the carbon framework of pellitorine was subjected to anodic oxidation in the presence of acetate ions. The electrochemical reaction generated the corresponding α -acetoxy sulfide through selective acetoxylation at the carbon atom adjacent to sulfur.

Subsequent oxidation of the sulfide afforded the corresponding sulfoxide intermediate. Upon thermal pyrolysis, the sulfoxide underwent a syn-elimination reaction, resulting in the formation of the conjugated

diene system characteristic of pellitorine. This strategy enabled the stereoselective construction of the unsaturated carbon chain without the need for conventional olefination reagents. The electrochemical transformations proceeded in satisfactory yields and provided an efficient route to the naturally occurring alkamide.

The methodology is noteworthy because it combines electroorganic synthesis with sulfoxide elimination chemistry, offering a mild and environmentally attractive alternative for the preparation of conjugated dienes. The work demonstrated the synthetic utility of electrochemically generated intermediates in the synthesis of biologically important natural products such as pellitorine⁵¹. (Scheme 11)

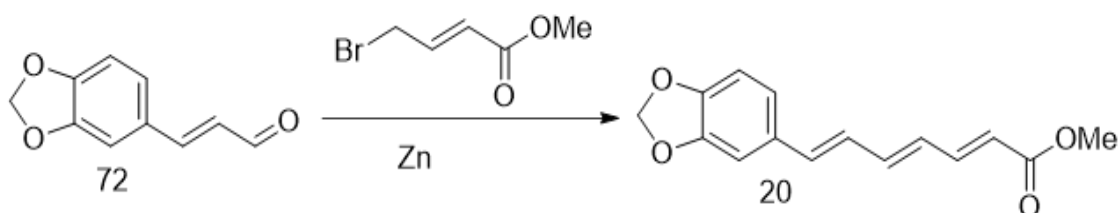


Scheme 11: Synthesis of pelltitorine by employing electro chemical reactions

6.3 Piperittine

Piperittine, one of the naturally occurring amide alkaloids of *Piper nigrum*, can be synthesized through a zinc-mediated carbon-carbon bond-forming reaction involving an aldehyde and a halide of an α , β -unsaturated ester. This methodology is based on a

Reformatsky-type reaction, in which zinc metal promotes the formation of an organozinc intermediate from the unsaturated ester halide. The resulting nucleophilic species subsequently reacts with an aldehyde to generate a β -hydroxy ester intermediate containing the required carbon skeleton of piperittine⁵². (Scheme 12)



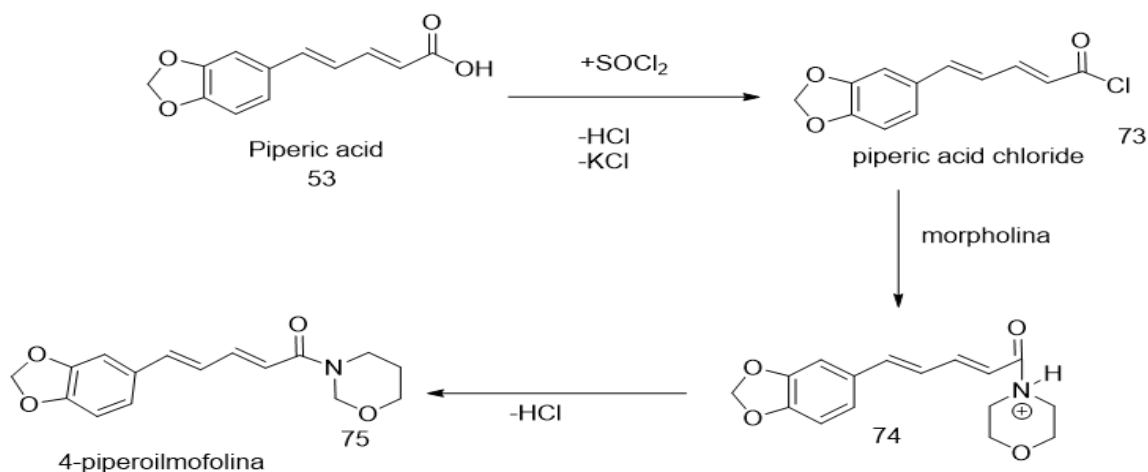
Scheme 12: Synthesis of Piperittine

7. SYNTHETIC APPLICATIONS OF THE CHEMICAL CONSTITUENTS OF PEPPER

7.1 Piperine

Bahri, Ambarwati, Iqbal, and Baihaqy (2019)⁵³ reported a catalyst-free synthesis of 4-piperoilmorpholine starting from naturally derived piperine isolated from *Piper nigrum*. The synthesis was accomplished through a piperoyl chloride intermediate. Initially, piperine was hydrolyzed with ethanolic potassium hydroxide (KOH) for 24 h to yield piperic acid. The resulting piperic acid was then

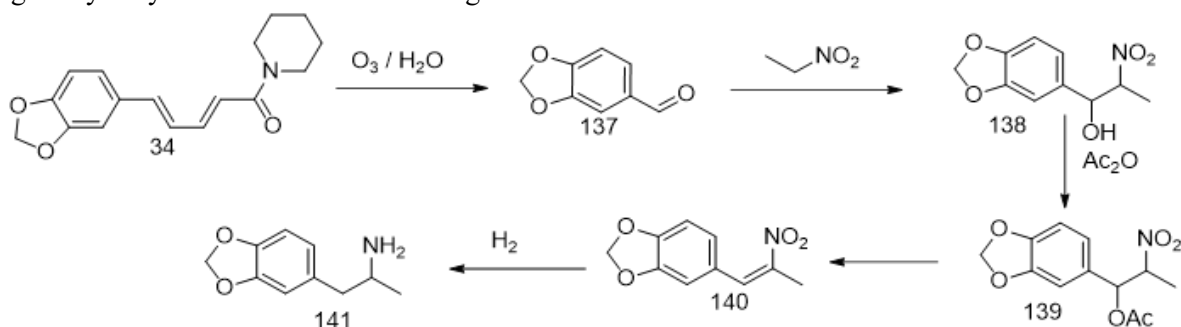
converted into the corresponding acid chloride (piperoyl chloride) by treatment with thionyl chloride (SOCl_2) in the presence of a catalytic amount of dimethylformamide (DMF). The freshly prepared piperoyl chloride was subsequently added dropwise to a chilled solution of morpholine in chloroform at 0–5 °C. The reaction proceeded smoothly via a nucleophilic acyl substitution mechanism without the need for any catalyst, affording 4-piperoilmorpholine after recrystallization from methanol. This reaction follows the nucleophilic chloride addition elimination reaction mechanism. (Scheme 13)



Scheme 13: Synthesis of 4-piperoilmorpholine from piperine

Ando and co-workers demonstrated the utility of piperine as a readily available natural precursor for the synthesis of 3,4-methylenedioxyamphetamine (MDMA). The synthesis exploited the presence of the 3,4-methylenedioxyphenyl moiety already embedded within the piperine structure. Piperine was first converted into suitable aromatic intermediates through hydrolysis and oxidative degradation

reactions, yielding derivatives containing the required methylenedioxybenzene framework. Subsequent functional group transformations enabled the preparation of the key precursor 3,4-methylenedioxyphenyl-2-propanone (MDP2P), which was further converted into MDMA⁵⁴. (Scheme 14)



Scheme 14: Synthesis of MDMA, a very potent psychoactive drug starting from piperine

Krchnák and co-workers exploited the conjugated diene system of piperine in nitroso hetero-Diels–Alder reactions with acyl- and aryl nitroso dienophiles to generate 1,2-oxazine intermediates. These cycloadducts were subsequently transformed into a

variety of heterocyclic derivatives, including pyrroles and quinoxalinones, demonstrating the utility of piperine as a versatile natural scaffold for diversity-oriented synthesis and medicinal chemistry applications⁵⁵ (Figure 1).

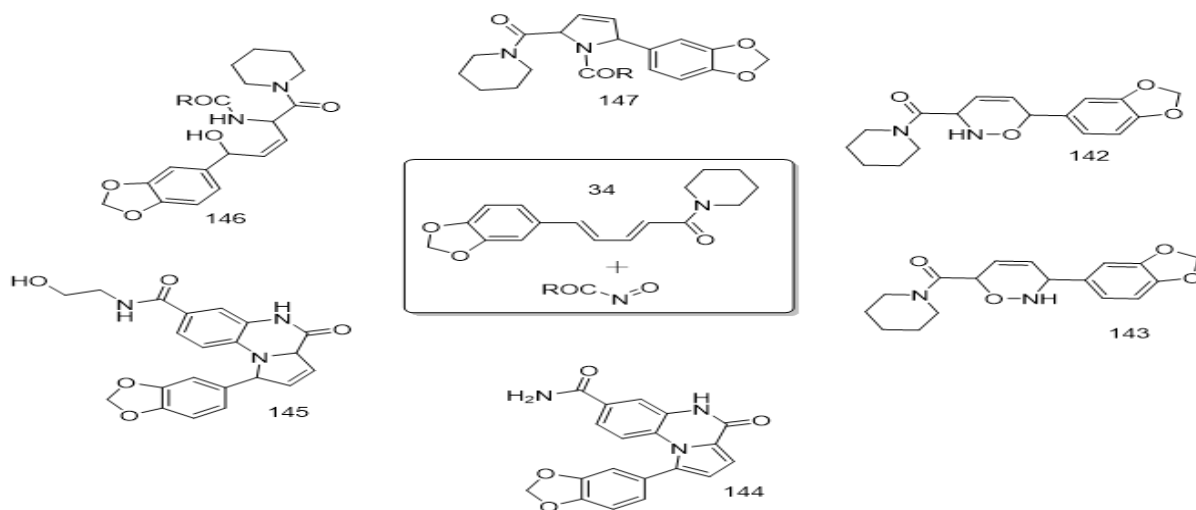


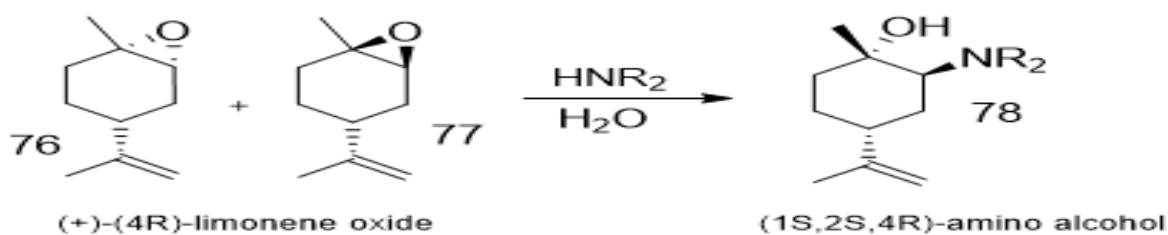
Fig. 1: Heterocyclic derivatives from piperine

7.2 Limonene

Limonene is one of the important monoterpene hydrocarbons present in the essential oil of black pepper (*Piper nigrum* L.). Due to its abundance in nature and well-defined chiral structure, limonene isolated from black pepper and other plant sources has attracted considerable interest as a renewable synthon for organic synthesis.

Steiner and co-workers reported an efficient synthesis of a series of chiral α -amino alcohols from limonene, which were subsequently employed as chiral

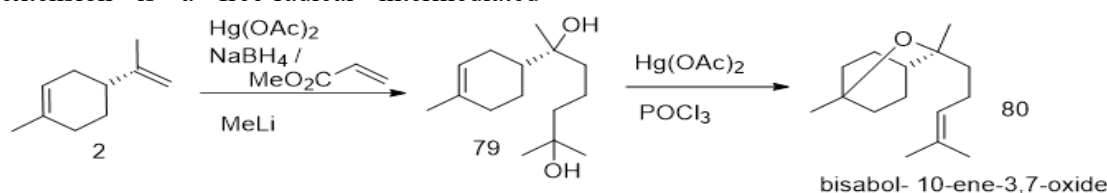
auxiliaries in the enantioselective addition of diethylzinc to benzaldehyde. The synthetic strategy involved the regioselective ring opening of a 1:1 mixture of *cis*- and *trans*-limonene oxide with various secondary amines in the presence of water as a catalyst. The reaction proceeded under mild conditions to afford the corresponding β -amino alcohols in good yields. Owing to the inherent chirality of limonene, the resulting amino alcohols possessed well-defined stereochemical features and were found to be effective chiral ligands for asymmetric carbon-carbon bond-forming reactions⁵⁶. (Scheme 15)



Scheme: 15: Synthesis of chiral α -amino alcohols

Caballero et al. utilized (*R*)-(+)-limonene as the chiral pool starting material for the synthesis of bisabol-10-ene-3,7-Oxide, a close derivative of bisabolol the chain extension is a free-radical intermediated

reaction, and the following oxymercuration furnished the product, bisabol- 10-ene-3,7-Oxide⁵⁷. (Scheme 16)

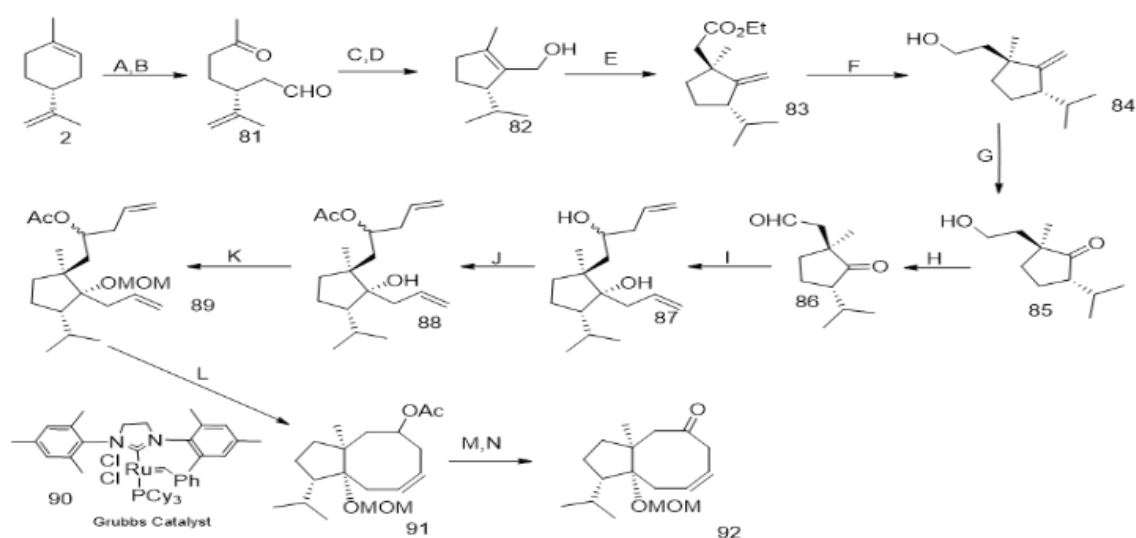


Scheme 16: (*R*)-(+)-limonene as the chiral pool starting material for the synthesis of bisabol-10-ene-3,7-Oxide

While investigating enantiospecific approaches to the construction of the AB ring system of fusicoccane diterpenes, Srikrishna and co-workers employed naturally occurring limonene as a chiral pool synthon. The synthesis commenced with the conversion of limonene into a key allylic alcohol through a four-step sequence involving Wilkinson's catalyst-mediated regioselective hydrogenation of the isopropenyl group, ozonolytic cleavage of the cyclohexene double bond, intramolecular aldol condensation of the resulting keto aldehyde, and reduction of the cyclopentene aldehyde with sodium borohydride in methanol. The allylic alcohol thus obtained was subjected to a Johnson–Claisen rearrangement using

triethyl orthoacetate and catalytic propionic acid to furnish the corresponding unsaturated ester.

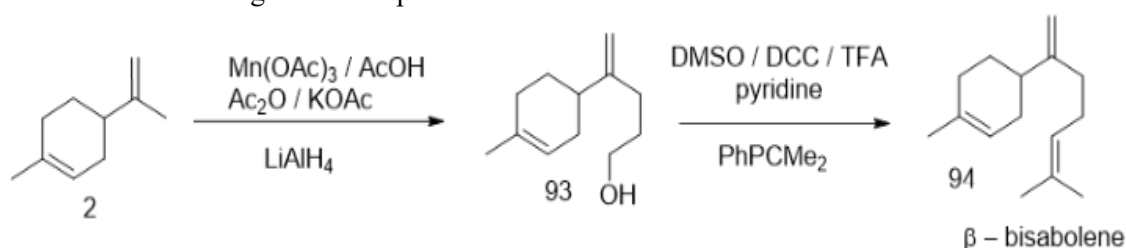
Subsequent functional group manipulations, including selective oxidations and alkylations, transformed the intermediate into a suitable precursor for macrocyclization. The pivotal cyclooctene ring characteristic of the fusicoccane framework was then efficiently constructed through a ring-closing metathesis (RCM) reaction employing the second-generation Grubbs catalyst. This strategy elegantly demonstrated the utility of limonene as a readily available chiral building block for the stereocontrolled synthesis of complex diterpene architectures⁵⁸. (Scheme 17)



Scheme 17: Limonene as a synthon for diterpenes fusicoccanes

The reaction of (+)-limonene with manganic acetate was used by Fukamiya *et al* from Hiroshima University to homologate the monoterpene to β -bisabolene. The homologated compound was

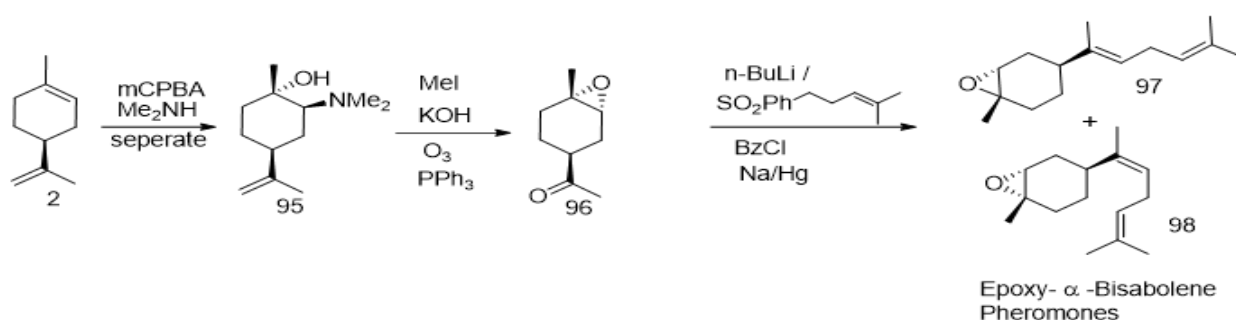
converted into an aldehyde, which was then subjected to a Wittig reaction to obtain β -bisabolene⁵⁹. (Scheme 18)



Scheme 18: Synthesis of β -bisabolene from (+)-limonene

Baker *et al* synthesized epoxy- α -bisabolene Pheromones, which was identified as a component of the sex pheromone of the Southern green stink bug *Nezaraviridula*. starting from S (-) limonene. By forming the dimethylamine adducts, the non-stereo

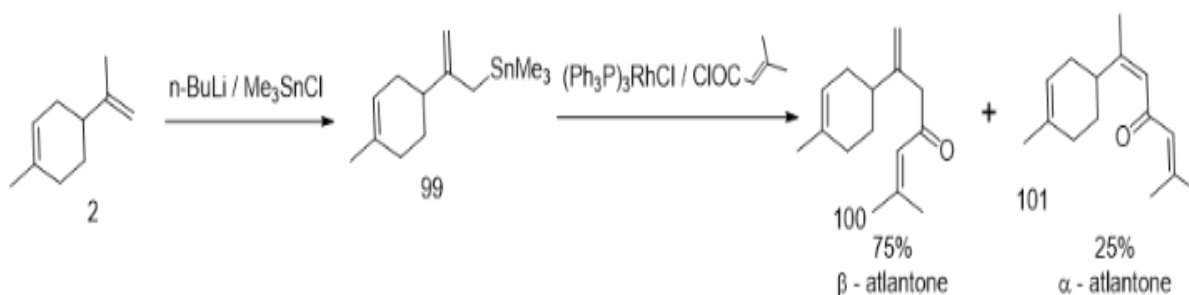
selective route towards limonene oxide was rectified and the following reversion of epoxide and ozonolysis resulted in the formation of a ketone. A Julia reaction with the homoprenyl phenyl sulfone gave the separable epoxy bisabolenes⁶⁰. (Scheme 19)



Scheme 19: Synthesis of epoxy- α -bisabolene Pheromones from *S*-(-) limonene

Andrianome and Delmond demonstrated the utility of limonene as a chiral pool synthon in the synthesis of the naturally occurring sesquiterpenes known as atlantanones. Their strategy exploited the readily available chirality of naturally occurring (*R*)-(+)-limonene to establish the stereochemical framework of the target molecules. Through a sequence of regioselective functional group transformations and carbon skeleton modifications, the limonene

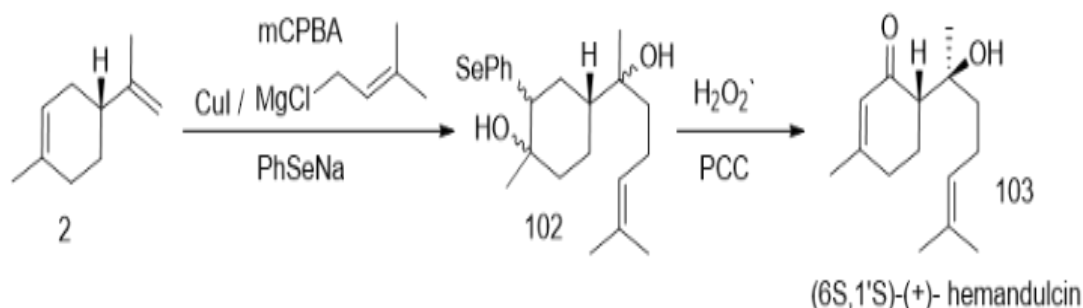
framework was converted into optically active intermediates that were subsequently elaborated into atlantanones. The synthesis highlighted the effectiveness of limonene as an inexpensive and renewable source of chirality for the stereocontrolled preparation of complex sesquiterpenoids and further demonstrated the versatility of monoterpene-derived chiral synthons in natural product synthesis⁶¹. (Scheme 20)



Scheme 20: Synthesis of the atlantanones from limonene

Mori and co-workers reported an elegant synthesis of the naturally occurring sesquiterpene sweetener (+)-

hemandulcin utilizing limonene-derived bis-epoxide as a chiral starting material⁶². (Scheme 21)

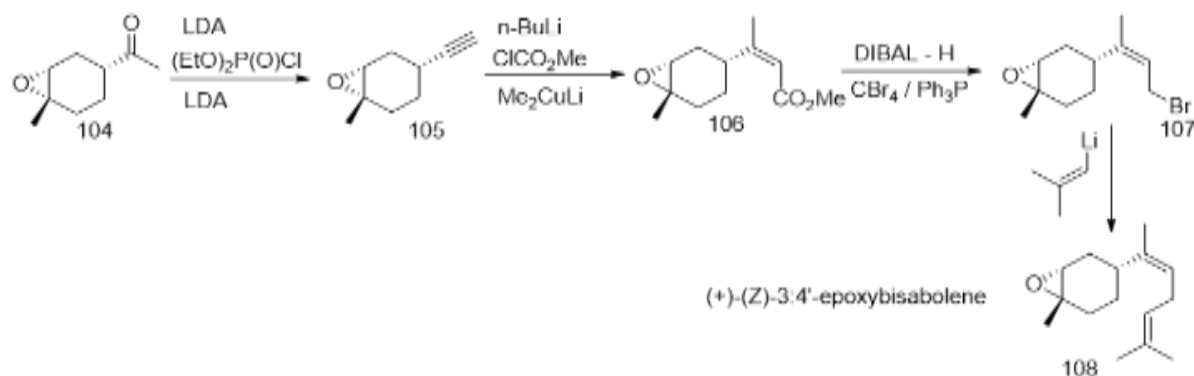


Scheme 21: Synthesis of (+) hemandulcin from limonene bis epoxide

Marron and Nicolaou utilized naturally occurring (*R*)-(+)-limonene as a chiral pool starting material in the stereocontrolled synthesis of the sex pheromone components of the southern green stink bug, *Nezara viridula*. The strategy exploited the inherent chirality

of limonene to establish the stereochemical relationships required for the synthesis of the four diastereomeric 3',4'-epoxides of (*Z*)- α -bisabolene. Through a sequence of regioselective functional group transformations, the limonene framework was

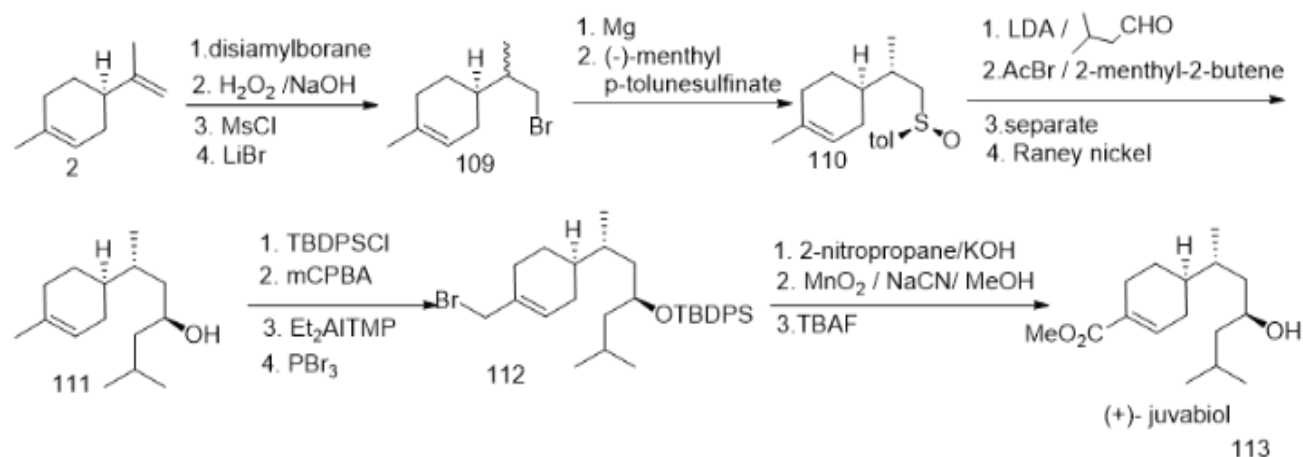
converted into optically active intermediates, which were subsequently elaborated into the target pheromone epoxides⁶³. (Scheme 22)



Scheme 22: Synthesis of (+) - (Z)-3:4'-epoxybisabolene from limonene epoxide

Williams and Phillips reported a stereocontrolled synthesis of the juvabiols utilizing naturally occurring (*R*)-(+)-limonene as a chiral pool precursor. Juvabiols are sesquiterpenoid compounds exhibiting juvenile hormone activity and are structurally related to insect growth regulators. (*R*)-(+)-limonene, which provides the chirality at the cyclohexene stereocenter, is converted to sulfoxide. Sulfoxide is nonstereoselectively alkylated with isovaleraldehyde to complete the carbon skeleton; the sulfoxide is reduced with the novel reagent combination of an acyl

halide and an olefin. Raney nickel reduction of the major isomer gives the alcohol, which requires only oxidation of the vinyl methyl to complete the synthesis. Elimination of the derived epoxide with diethylaluminum tetramethylpiperidide is key in the production of the allylic bromide, which is oxidized to give (+)-juvabiol. The synthesis demonstrated the effectiveness of limonene as an inexpensive and readily available source of chirality and further highlighted its utility in the stereoselective synthesis of biologically active terpenoids⁶⁴. (Scheme 23)



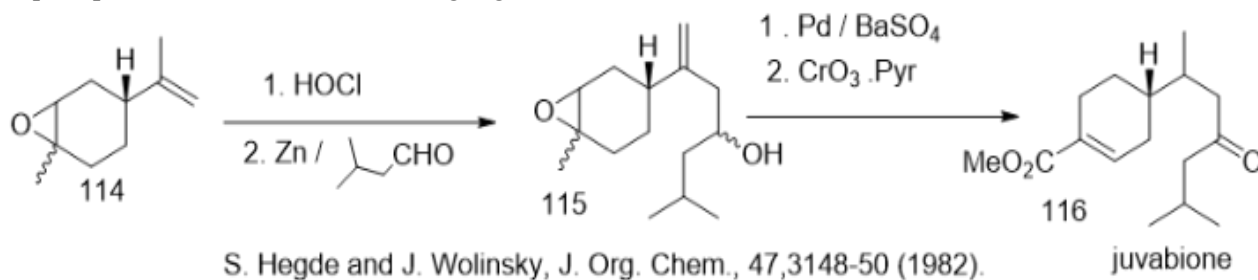
Scheme 23: Synthesis of (+)-juvabiol

Hegde and Wolinsky reported the synthesis of the naturally occurring sesquiterpenoids (+)-bilobanone and the juvabiones from readily available monoterpene precursors, including (+)-limonene monoepoxide. The key transformation involved hypochlorous acid-mediated functionalization of the isopropenyl group to generate 10-chlorolimonene

monoepoxide, providing a versatile intermediate for carbon-carbon bond formation. The corresponding organozinc reagent derived from this chloride was reacted with isovaleraldehyde to furnish a homoallylic alcohol possessing the bisabolane carbon skeleton. Subsequent cyclization and functional group manipulations afforded intermediates that were

converted into the target natural products. The synthesis demonstrated an efficient transfer of chirality from limonene to more complex sesquiterpenoid frameworks and highlighted the

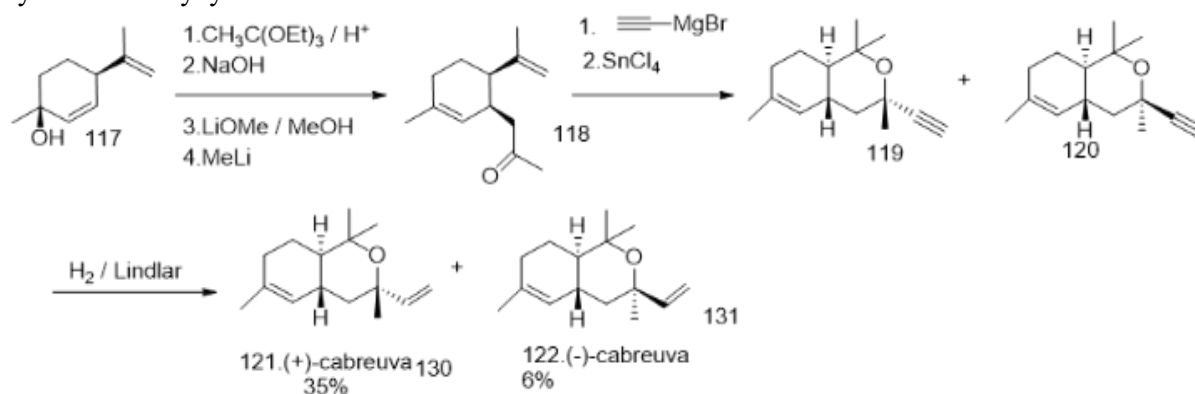
utility of limonene-derived intermediates in stereocontrolled natural product synthesis⁶⁵. (Scheme 24)



Scheme 24: Formal synthesis of juvabione from limonene oxide

Maurer and co-workers at Firmenich utilized a photooxidation product of limonene as a chiral synthon for the synthesis of cabreuva-related fragrance compounds. The key intermediate underwent an orthoester Claisen rearrangement to afford a cis-configured ester, which was subsequently hydrolyzed and transformed into the corresponding methyl ketone. Ethynylation of the ketone furnished a

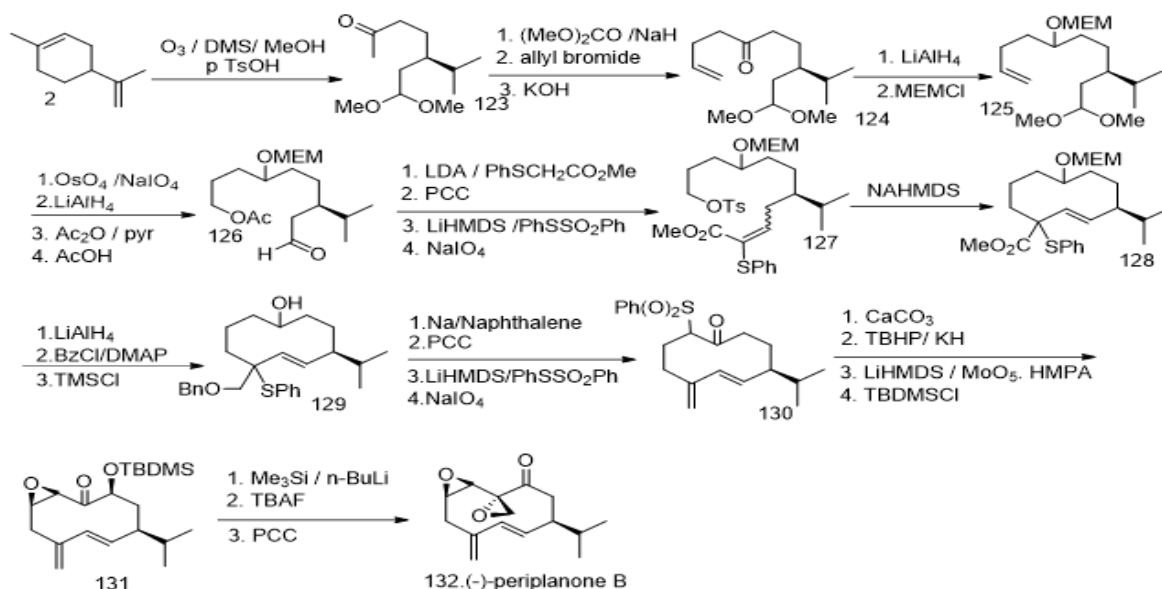
mixture of intermediates that, upon cyclization and reduction, yielded the desired cabreuva diastereomers. This work demonstrated the utility of limonene-derived photooxidation products as versatile chiral building blocks for the stereocontrolled synthesis of valuable aroma compounds⁶⁶. (Scheme 25)



Scheme 25: limonene as synthon for the synthesis of cabreuva

Kitahara, Mori, Koseki, and Mori demonstrated the utility of naturally occurring limonene as a chiral pool precursor for the stereocontrolled synthesis of biologically active terpenoids. Using limonene-derived intermediates, the authors efficiently constructed complex terpenoid frameworks while preserving the inherent stereochemical information of

the monoterpene. The synthetic strategy involved selective functionalization of the limonene skeleton, conversion into oxygenated intermediates, and subsequent regio- and stereoselective carbon-carbon bond-forming reactions to install the required side chains and stereocenters⁶⁷. (Scheme 26)

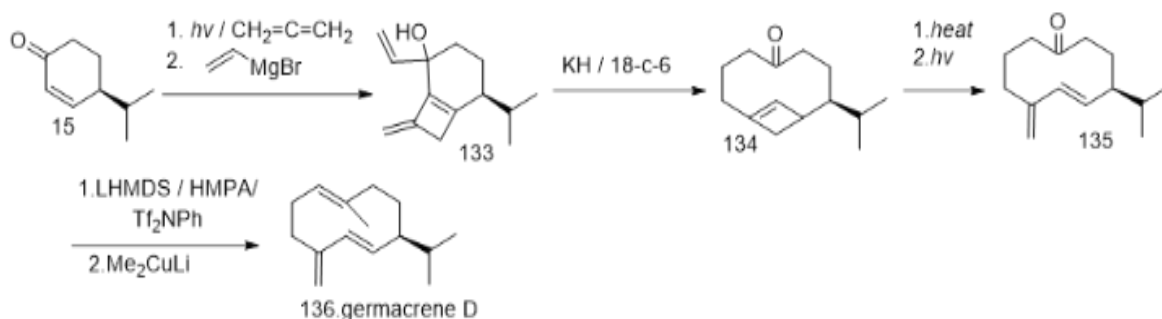


Scheme 26: Synthesis of periplanone from limonene

7.3 Crypton

Crypton was converted into the natural product germacrene D⁶⁸. The photochemical 2+2 cycloaddition results in the exo methylene-cyclobutene ring system and the allyl grignard addition results in the formation of the alcohol. The

oxidation /rearrangement mediated by crown ether fixes the 10 membered ring of germacrene. Ring opening of the cyclobutene ring results in the formation of the diene. Further enol formation and methylcuprate addition completes the synthesis of germacrene D. This synthesis was completed by S. L. Schreiber in 1985. (Scheme 27)



Scheme 27: Conversion of Crypton into the natural product germacrene D

8. FUTURE PERSPECTIVES

Despite extensive research on *Piper nigrum* and its major bioactive constituent piperine, several aspects remain to be explored to fully realize its therapeutic and industrial potential. Future investigations should focus on well-designed preclinical and clinical studies to validate the efficacy, safety, and pharmacokinetic profiles of black pepper-derived compounds in the management of various diseases. Particular attention should be directed toward elucidating the molecular mechanisms underlying the pharmacological activities of piperine and other minor alkaloids, which

may facilitate the identification of novel therapeutic targets.

The bioavailability-enhancing property of piperine offers promising opportunities for the development of advanced drug delivery systems and combination therapies. Structural modification and derivatization of piperine, pellitorine, and related alkaloids may lead to the discovery of new drug candidates with improved potency, selectivity, and pharmacokinetic characteristics. Furthermore, emerging fields such as nanotechnology, nutraceutical development, and functional foods provide attractive avenues for the

incorporation of black pepper-derived bioactives into innovative health-promoting products.

From a synthetic chemistry perspective, the diverse metabolites of black pepper, including piperine, limonene, and other terpenoids, represent valuable renewable synthons for the preparation of pharmaceuticals, fine chemicals, fragrances, and biologically active natural product analogues. Continued exploration of these compounds in diversity-oriented synthesis and green chemistry approaches may contribute to the development of sustainable synthetic methodologies. In addition, conservation of pepper germplasm, characterization of elite cultivars, and application of modern biotechnological tools will be essential for ensuring sustainable production and utilization of this economically and medicinally important spice crop.

Overall, the integration of phytochemical, pharmacological, biotechnological, and synthetic studies is expected to expand the applications of black pepper and establish it as a key resource for future drug discovery, nutraceutical innovation, and sustainable chemical synthesis.

CONCLUSION

Black pepper (*Piper nigrum* L.) represents a unique natural resource that combines significant culinary, medicinal, pharmaceutical, and synthetic value. Its diverse phytochemical composition, particularly the presence of piperine, pellitorine, volatile terpenoids, and other bioactive amides, contributes to a broad range of biological activities including antioxidant, anti-inflammatory, antimicrobial, anticancer, antidiabetic, hepatoprotective, neuroprotective, and bioavailability-enhancing effects. These properties have justified its extensive use in traditional medicine and have attracted increasing scientific interest in modern pharmacological research.

Beyond its therapeutic significance, black pepper serves as an important source of versatile chemical building blocks for organic synthesis. Constituents such as piperine and limonene have been successfully utilized as renewable synthons in the synthesis of natural products, pharmaceuticals, heterocyclic compounds, fragrances, and other value-added molecules, demonstrating the potential of pepper-derived metabolites in sustainable chemical synthesis.

The growing application of piperine in drug delivery and bioavailability enhancement further strengthens the pharmaceutical relevance of black pepper.

Despite substantial progress, many traditional claims and emerging therapeutic applications require rigorous clinical validation. Future studies focusing on mechanistic investigations, structural modification of bioactive constituents, development of novel formulations, and sustainable utilization of pepper-derived metabolites are expected to expand the medicinal and industrial potential of this remarkable spice. Overall, black pepper continues to be an invaluable source of bioactive molecules and synthetic intermediates with promising prospects for future pharmaceutical, nutraceutical, and chemical research.

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HOW TO CITE: Grace Thomas^{1*}, Rani R. Nair², Black Pepper (*Piper nigrum* L.): A Multifaceted Spice With Therapeutic, Industrial, And Synthetic Importance, *Int. J. Sci. R. Tech.*, 2026, 3 (6), 1112-1135. <https://doi.org/10.5281/zenodo.20761610>