SYNTHETIC MODIFICATIONS OF ZERUMBONE AND THEIR BIOLOGICAL EVALUATION

Thesis Submitted to AcSIR for the Award of the Degree of
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By
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Dedicated To My Parents

Mr. B. P. Bhaskaran
&
Mrs. Ajitha Bhaskaran

07 th March, 2018

DECLARATION

I hereby declare that the Ph.D.thesis entitled "**Synthetic Modifications of Zerumbone and their Biological Evaluation**" is an independent work carried out by me under the combined supervision of Dr. K. V. Radhakrishnan and Dr. Mangalam S. Nair at the Organic chemistry section, CSTD, CSIR-NIIST, Thiruvananthapuram and it has not been submitted anywhere else for any other degree or diploma.

In keeping the general practice of reporting scientific observations, due acknowledgment has been made wherever the work described is based on the findings of other investigators.

Dhanya B. P.

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CERTIFICATE

*This is to certify that the work incorporated in this Ph.D. thesis entitled "**Synthetic Modifications of Zerumbone and their Biological Evaluation**" submitted by **Ms. Dhanya B. P.** to Academy of Scientific and Innovative Research (AcSIR), New Delhi, in partial fulfilment of the requirements for the award of the **Degree of Doctor of Philosophy in Chemical Sciences**, embodies original research work carried out under our combined supervision and guidance at the Organic Chemistry Section, Chemical Sciences and Technology Division, CSIR-National Institute for Interdisciplinary Science and Technology (CSIR-NIIST), Thiruvananthapuram. We certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma.*

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Dhanya B. P.

CONTENTS

List of Tables

List of Figures

ABBREVIATIONS

AcOH	: Acetic acid
ACE	: Angeotensin converting enzyme
Ar	: Aryl
aq.	: Aqueous
Boc	: Tertiary butyloxycarbonyl
br. s	: Broad singlet
BSA	: Bovine serum albumin
BTMACl	: Benzyl trimethyl ammonium Chloride
Bz	: Benzoyl
calcd	: Calculated
COSY	: Correlation spectroscopy
d	: Doublet
dba	: Dibenzylidene acetone
DCE	: Dichloroethane
DCM	: Dichloromethane
dd	: Doublet of a doublet
DIPE	: Diisopropyl ether
DME	: Dimethyl ether
DMF	: Dimethyl formamide
DMSO	: Dimethyl sufoxide
dppb	: 1,4-Bis(diphenylphosphino)butane
dppf	: 1,1-Bis(diphenylphosphino) ferrocene
ee	: Enantiomeric excess
EDG	: Electron donating group
ESI	: Electron spray ionisation
Et	: Ethyl
EWG	: Electron withdrawing group
equiv.	: Equivalent
h	: Hour
HEPES	: 4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid
HRMS	: High resolution mass spectrometry
Hz	: Hertz
IR	: Infrared
J	: Coupling constant
LA	: Lewis acid
LAH	: Lithium aluminium hydride
LDA	: Lithium diisopropyl amide
m	: Multiplet
MABR	: (Methyl aluminium bis(4-bromo-2,6-di-tert butylphenoxide))
*m*CPBA	: *meta*-Chloroperbenzoic acid
Me	: Methyl
mg	: Milligram
min	: Minute
mL	: Millilitre
Mp	: Melting point
MS	: Mass spectrometry
MTT	: (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) tetrazolium
NBS	: N-bromo succinimide
NMR	: Nuclear magnetic resonance
NOE	: Nuclear Overhauser effect
Nu	: Nucleophile
o	: *ortho*
p	: *para*
PBS	: Phosphate buffered saline
Ph	: Phenyl

PhH : Benzene

^{i}Pr : Isopropyl

q : Quartet

rac : Racemic

R_f : Retention factor

SD : Standard deviation

OD : Optical density

rac-e : Racemic erythro

rac-t : Racemic threo

rt : Room temperature

s : Singlet

t : Triplet

TBHA : *tert*- Butylhydroperoxide

TBHAS : Tetrabutyl ammonium hydrogen sulfate

TCA : Trichloroacetic acid

tert : Tertiary

TFA : Trifluoroacetic acid

THF : Tetrahydrofuran

TLC : Thin layer chromatography

TMS : Tetramethyl silane

TMSCl : Trimethyl silyl chloride

TMSCN : Trimethyl silyl cyanide

p- Ts-OH *: para*-Tolyl sulfonic acid

UV : Ultra violet

Z. : Zingiber

PREFACE

Plants have always played a pivotal role as the prime source of drugs and drug leads for the treatment of a broad spectrum of diseases. Plant based natural products and their semi-synthetic analogues contributed largely to the modern drug discovery process as well. Plants, which find extensive use in various traditional systems of medicine across the world have exclusively provided a considerable number of drug leads and are still an attractive source of novel chemical compounds with lead potential. Zingiberaceae is one of the largest families of the plant kingdom. Plants belonging to Zingiberaceae family have been used around the world as spices and/ or medicines. Numerous compounds having interesting biological activities have been isolated from various Zingiberaceae plants. Among this family, *Zingiber zerumbet* Smith. or *Zingiber aromaticum* popularly referred to as the pinecone, wild ginger, Asian ginger or shampoo ginger is an edible ginger, originating in South-East Asia. The plant has been cultivated for thousands of years as a spice and for medical purposes. Zerumbone is a crystalline achiral 11-membered monocyclic sesquiterpene having a flexible skeleton structure obtained from the rhizome oil of *Z. zerumbet* Smith. and has attained much attention from the scientific community because of its interesting biological properties like anti-cancer, anti- imflammatory, anti HIV etc. Structural manipulation of zerumbone to diverse biologically significant chemical structures has been investigated by various groups.

The thesis is divided into four chapters. An overview of synthetic transformations of zerumbone is presented in the first chapter of the thesis.

Second chapter comprises of two parts *viz.* part A and part B, and explain our efforts toward the synthetic transformation of zerumbone by transition metal/ base catalyzed reactions. An efficient method for the synthesis of zerumbone pendant derivatives *via* the palladium catalyzed Tsuji-Trost coupling using phenols/ arene carboxylic acids with zerumbone is described in part A. The reaction provides a new class of zerumbone pendant derivatives. Preliminary *in vitro* α-glucosidase and α-amylase inhibition assays revealed that the synthesized zerumbone pendant derivatives have potent inhibitory activity than the parent molecule zerumbone. Also, the zerumbone derivatives were evaluated for their ability to

prevent the protein glycation reaction, all the derivatives showed superior anti-glycation property than zerumbone and the standard ascorbic acid. Molecular docking studies were performed to recognize the binding mode of zerumbone derivatives to the enzyme along with activity comparison of derivatives. The zerumbone pendant derivatives were tested for their *in vitro* cytotoxicity against five selected human cancer cells using MTT assay. Among tested compounds, two derivatives showed significant anti-proliferative effect. In addition, we have checked the antihypertensive activity of some selected zerumbone pendant derivatives and most of the derivatives showed better inhibition against angiotensin-converting (ACE) enzyme than zerumbone.

The second part deals with the synthesis of a new class of zerumbone derivatives by incorporating amino acids as well as nucleobases to zerumbone *via* base catalysed reaction. Out of the nine zerumbone pendant amino acid derivatives, two were tested for cytotoxicity against some of the selected human cancer cells using MTT assay. Among them, valine derivative of zerumbone showed significant growth inhibition activity against HeLa cells.

Chapter 3 explains the derivatizations of zerumbone by Lewis acid catalyzed 1,4-conjugate addition/ Heck type reaction, with biologically important heterocycles such as indole/pyrrole. First part describes a synthetic route for the Michael addition product of zerumbone. Second part describes the synthesis of indole functionalized zerumbone derivatives using palladium catalyst. Also we have discussed the preliminary *in vitro* anti-diabetic screening (inhibitory activity against digestive enzymes such as α-glucosidase and α-amylase enzymes, anti-glycation property) as well as inhibitory effect of angiotensin-converting enzyme (anti-hypertensive activity) of the synthesized zerumbone- indole adducts. The synthesized indole functionalized zerumbone derivatives showed improved anti-diabetic activity compared to the parent molecule zerumbone. Molecular docking studies were performed to recognize the binding mode of zerumbone- indole adduct to the enzyme along with activity comparison of derivatives. Compared to zerumbone, some of its indole derivatives showed similar inhibitory activity against angiotensin-converting (ACE) enzyme.

A facile Lewis acid catalysed methodology towards structurally diverse sesquiterpenoid derivatives from zerumbone is presented in chapter 4. The chapter is divided into two parts. First part explains the Lewis acid catalysed transannular cyclisation of indole

functionalised zerumbone derivatives to [5.3.0] decane skeleton. The part B of chapter 4 deals with synthesis of indole functionalized [6.3.0] decane skeleton *via* the interrupted Nazarov cyclisation of zerumbone using Lewis acid catalyst.

CHAPTER 1

Synthetic Transformations of Zerumbone-An Overview

1. Introduction

Natural products have historically been an extremely productive sources or new medicines in all cultures and continue to deliver a great variety of structural templates for drug discovery and development. A natural product is a chemical compound or substance produced by living organism that is, found in nature. The term natural product has also been extended for commercial purposes to refer cosmetics, dietary supplements, and foods produced from natural sources without added artificial ingredients. Natural products have pharmacological or biological activity that can be of therapeutic benefit in treating diseases.

Natural products may be classified according to their biological function, source, biosynthetic pathway and chemical structure.[1]

1.1. Classification of natural product based on biological function

1.1.1 Primary metabolite

Primary metabolites are basic component of the metabolic pathway that required for life. It has intrinsic function that is essential for survival of the organism. Carbohydrates, lipids and amino acids are primary metabolites, which are basic building block of life. Those are associated with essential cellular functions such as nutrient assimilation, energy production and growth or development. They are found universally in the plant kingdom because they are the components or products of fundamental metabolic pathways or cycles such as glycolysis, the Krebs cycle, and the Calvin cycle. The basic structure of cell and organism are also composed of primary metabolite of cell membrane (e.g. phospholipids), cytoskeleton (e.g. protein), cell wall (e.g. peptidoglycan, chitin). Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) which store and transmit genetic information are composed of nucleic acid primary metabolite.

In addition to having fundamental roles in plant growth and development, some primary metabolites are precursors (starting materials) for the synthesis of secondary metabolites.

1.1.2. Secondary metabolite

Secondary metabolites have extrinsic function that mainly affects other organism. They are not essential for the survival but do increase competiveness of the organism within its environment. Because of their ability to modulate biochemical and signal transduction path way, secondary metabolites have a broad range of function. For example, pheromone acts as social signalling molecule with other individuals of the same species and also used against competitor, pray and predators. For many secondary metabolites, the function is unknown. Secondary metabolites are commonly used within the field of medicinal chemistry and pharmacology. These secondary metabolites are classified in to various classes based on their chemical structure, for a better and clear understanding. They include,

- ❖ Flavonoids
- ❖ Glycosides
- ❖ Terpenoids
- ❖ Lignans
- ❖ Steroids
- ❖ Alkaloids

Many of the secondary metabolites have complex molecular structures, with cyclic semi-rigid scaffolds, several chiral centers, more than five H-bond donors, more than ten H-bond acceptors, more than five rotatable C-C bonds, and a large polar surface area. Also, large number of secondary metabolites contains heteroatoms such as nitrogen and oxygen in plenty. Some selected secondary metabolites include alkaloid and terpenoids are shown in figure 1.1.

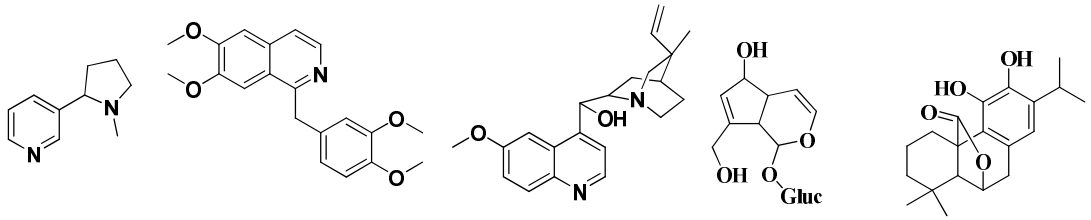

Figure 1.1. Secondary metabolites

1.2. Classification of natural product based on the source

1.2.1. Microbial world derived natural product

Microorganism such as bacteria and fungi has contributed to drug discovery and its development. *Pencillium chrysogenum* is an important example for fungus, which produces the antibiotic penicillin **6**. Most of the drugs derived from microorganism are used as anti-microbial agent. Another example is the asperlicin **7** derived from fungus *Aspergillus alliaceus* which can act as a novel antagonist (Figure 1.2).[2]

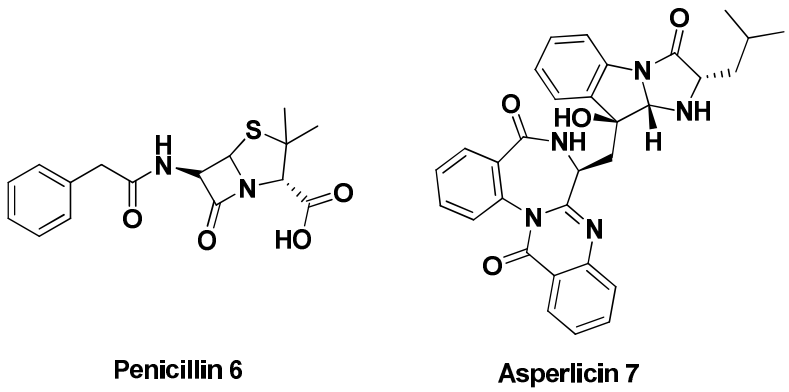

Figure 1.2. Some fungi derived natural products

1.2.2. Animal derived natural product

Animals also represent a source of bioactive natural products. In particular venomous animal such as snakes, scorpions etc. attracted much attention, due to the very specific chemical target interaction of venom constituents with a macromolecular target in the body. Because of the specific chemical-target interaction, venom constituents have proved important tools for studying receptors, ion channels and enzyme.[3] Representative examples of some of the animal derived natural product are shown in figure 1.3.

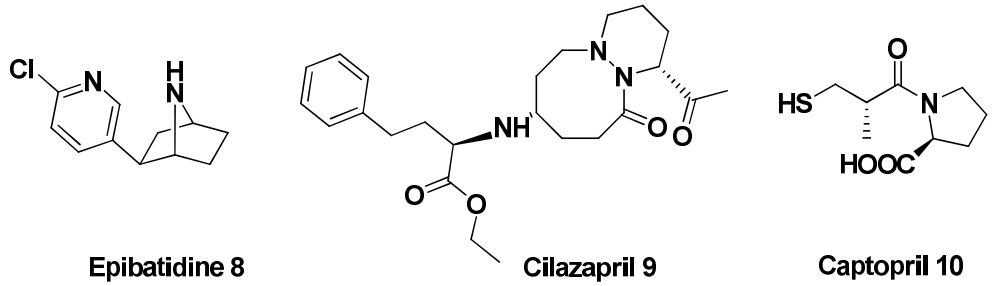

Figure 1.3. Selected examples of animal derived natural product

1.2.3. Marine world derived natural products

The sea contains many untapped sources of drugs with promising activities due to the extensive variety of marine habitats. The census shows that over 6000 potential new species are available in the sea. It points to the fact that the marine environment

represents a largely unexploited reservoir of many unknown natural compounds,[4] which in turn needs to be evaluated for their potential medicinal applications. Various molecules isolated from corals, sponges, fishes and marine microorganisms are reported to have anti-inflammatory, anti-viral, anti-cancer activities. Spongouridine **11** and spongothymidine **12** are the first two compounds isolated from marine source, *Cryptotethya crypta* (Figure1.4).

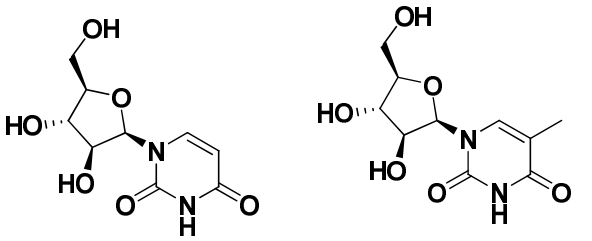

Figure 1.4. Compounds isolated from marine fungi, *Cryptotethya crypta*

1.2.4. Plant derived natural product

Plants are major source of complex and highly structurally diverse chemical compound (Phytochemicals). Major class of phytochemical include phenol, polyphenol, terpene and alkaloid. A number of pharmacologically active natural products have been identified from various plant species. e.g. Paclitaxel **13** (from *Taxus brevifolia*), Artemisinin **14** (from *Artemisia annua*) and Cocaine **15** (from Coca) (Figure 1.5).[5]

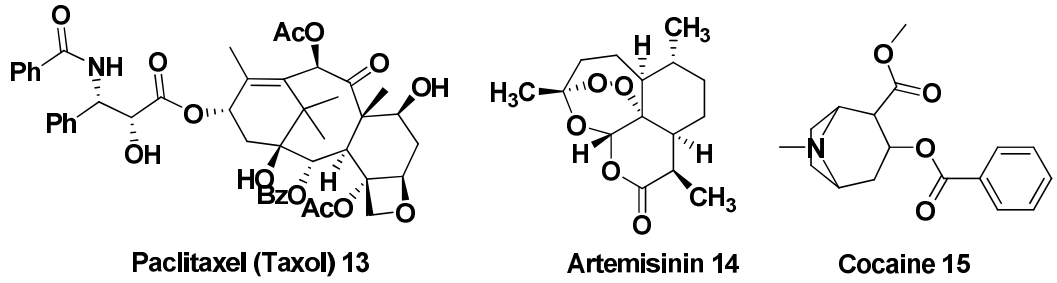

Figure 1.5. Selected examples of plant derived natural product

1.3. Synthetic modification of natural products in modern drug discovery

Phytochemicals and their synthetic derivatives are making a significant contribution in modern drug discovery programs by targeting several human diseases including cancer. Most of these natural compounds are often multi-targeted in nature. Generally they have lower side effects. They are readily available and hence are cost effective. However, its use is limited because of many reasons. One of the most important reasons is the solubility of the natural products. The bioactives, which have potent activity under *in vitro* condition sometime, show poor or no activity under *in vivo*

conditions due to the poor water solubility or lipophilicity. Other reasons include the limited availability from the natural source, poor/moderate activity, lack of chiral centres, adverse side effects, need of high dosage, very high cost of production *etc*.[6] Some of the important therapeutic agents developed from plants are described in the following section.

1.3.1. Camptothecin and its derivatives

Camptothecin **16** is a quinoline alkaloid isolated from the Chinese ornamental tree *Camptotheca acuminata* (Happy tree).[7-9] The molecule became so important and at present the first generation analoques of camptothecin, topotecan **17** and irinotecan **18** are used for the treatment of ovarian and colon cancers (Figure 1.6).

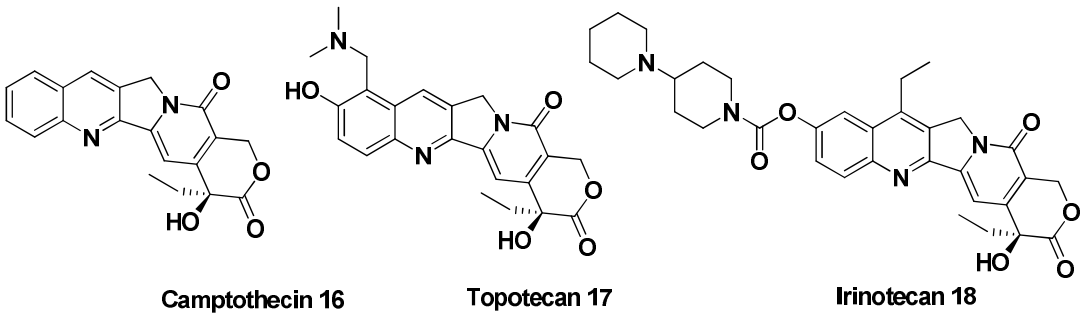

Figure 1.6. Structure of camptothecin and its derivatives

1.3.2. Podophyllotoxin and its derivatives

Podophyllotoxin **19** is a non alkaloid toxin lignin derived from *Podophyllum peltatum*.[10-12] Two of the semisynthetic derivative of podophyllotoxin *viz*. etoposide **20** and tenoposide **21** are currently used in frontline cancer chemotherapy against various cancers (Figure 1.7).

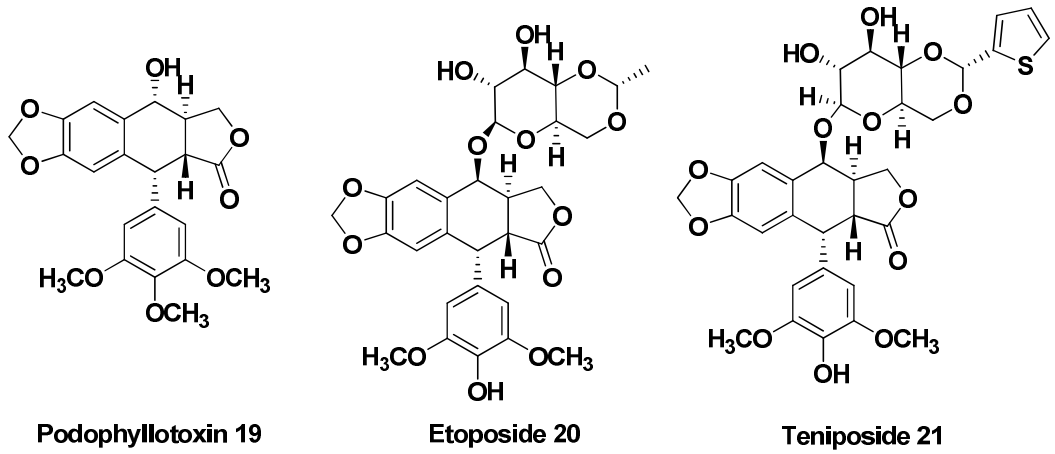

Figure 1.7. Structure of podophyllotoxin and its derivatives

1.3.3. Penicillin and its derivatives

Natural penicillins (eg. Penicillin G **22** and Penicillin V **23**) had a very narrow spectrum of activity, poor pharmacokinetics and chemical stability. These shortcomings were overcome when it was discovered that 6-aminopenicillanic acid (6-APA) **24**, the biosynthetic precursor to the natural penicillins, could be synthetically modified to introduce varying side chains that determined the properties of the modified product. Thus began an era of developing semisynthetic and synthetic analogs of β-lactams with much improved properties, including better stability and pharmacokinetics (especially oral bioavailability), extended antimicrobial spectrum, and resistance to the action of penicillinase. Examples are amoxicillin **25** and ampicillin **26** (Figure 1.8).[13, 14]

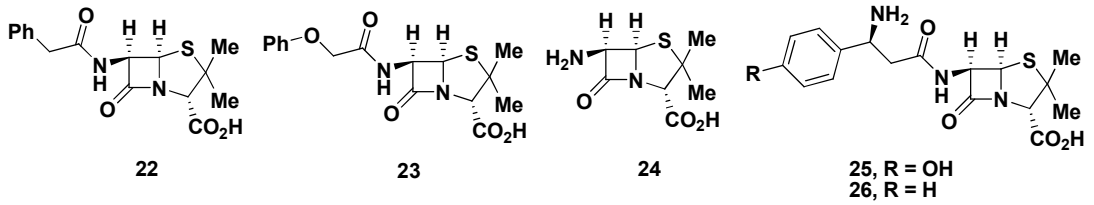

Figure 1.8. Structures of penicillin and its derivatives

1.3.4. Taxol and its derivatives

Paclitaxel **13** is a ditepeniod anti-cancer drug isolated from the bark of Pacific yew tree, *Taxus brevifolia*. The yield of taxol from the bark was very low and the collection of the bark would also lead to the death of the slow growing tree. Supply crisis was solved by developing the semi-synthesis of taxol from readily available natural product, 10-deacetylbaccatin III **27**.[15, 16] Taxol served as lead for the development of other taxane type anticancer compounds such as docetaxel **28**, larotaxel **29** with similar mechanism of action (Figure 1.9).

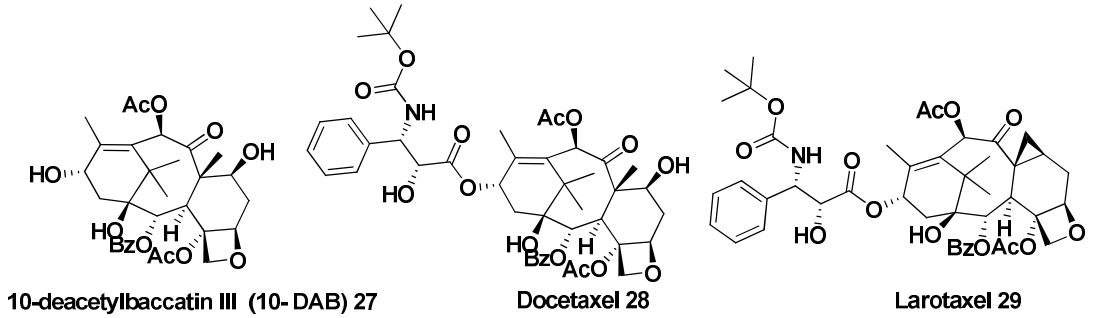

Figure 1.9. Structures of taxol derivatives

1.4. Zingiberaceae family

There is renewed interest in the exploration of medicinal plants used in traditional system of medicines since they have the higher chance of containing novel bio-active molecules in them. One such family of plants which enjoys great reputation in traditional system of medicine all over the world is Zingiberaceae.

Zingiberaceae is one of the largest families of the plant kingdom.[17] Plants belonging to Zingiberaceae family have been used around the world as spices and/ or medicines. It is a large family of rhizomatous herbs originating from Asia and far East and has been cultivated for centuries. Zingiberaceae is comprised of 53 genera and 1400 species. In India, 21 genera and 190 species are found.[18] These include *Curcuma, Kaempferia, Alpinia, Zingiber, Amomum, Globba* etc. Some of the important plants belonging to this family are used extensively either in food preservations or in medicines.[19] Generally, the rhizome and the leaves of these plant species are used for spice, tea, beverage and medical purposes. Numerous compounds having antioxidant activity and other biological activities have been isolated from various Zingiberaceae plants. *Zingiber zerumbet* Smith. or *Zingiber aromaticum* belongs to this family, is an edible ginger, originating in South-East Asia and has been cultivated for thousands of years as a spice and for medical purposes.[20-24] This plant is popularly referred to as the pinecone, wild ginger, Asian ginger or shampoo ginger. It is a tall upright ginger growing up to 3m tall with long, narrow leaves and cone shaped bracts. It is used in cooking for flavor and the clear liquid contents of the cones are used as a shampoo. The rhizome of *Z. zerumbet* has been demonstrated to possess anti-inflammatory, antihyperglycemic, antioxidant, anti-microbial activities at different dose/ concentrations.[25-33]

Jarpia Begam *et al*. reported the phytochemical investigation on leaf and rhizome oils of *Z. zerumbet* Smith. which is obtained by hydro distillation.[34] Humulene, zerumbone, zerumbol, zerumbone epoxide, vanillin, curcumin, zederone, 6-methoxy-2*E*, 9*E*-humuladien-8-one, *p*-hydroxybenzaldehyde, kaempferol-3-*O*-methylether, kaempferol-3,4'-*O*-dimethylether, kaempferol-3,4',7-*O*-trimethylether, 4''-*O*-acetylafzelin, 2'',4''-*O*-diacetylafzelin, 3'',4''-*O*-diacetylafzelin are certain compounds derived from *Z. zerumbet* Smith. It is found that zerumbone is the major component of essential oil of wild ginger. Crystallized zerumbone is obtained quite simply by direct steam distillation. It was first isolated by Sukh Dev in 1960[35] and structure was elucidated in 1965[36] and later characterized by NMR[37] and X-ray[38].

Zerumbone **(30)** is a crystalline achiral 11-membered monocyclic sesquiterpene having a flexible skeleton structure obtained from the rhizome oil of *Z. zerumbet* Smith. (Figure 1.10). It contains three double bonds, an isolated one at C6, and two at C2 and C10 which are part of a cross conjugated dienone system. Of these, C2 double bond appears least hindered, being farthest from the *gem*- dimethyl substituents at C9. The X-ray structure revealed that the dienone system lies in a slightly distorted plane perpendicular to that of the isolated double bond. Zerumbone has attained much attention from the scientific community because of its interesting biological properties.[39-55] Within the last few decades, Kitayama and co-workers established various synthetic modifications of zerumbone, including transannular ring contraction,[56] cyclization,[57-61] regio and diastereoselective conjugate additions,[62-65] various regiospecific ring cleavage reactions,[66-68] ring expansion reaction,[69] asymmetric induction etc.[70- 75]

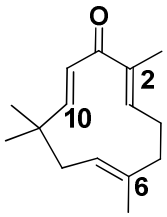

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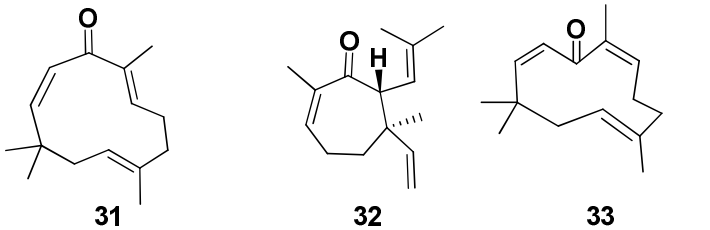
Figure 1. 10. Structure of zerumbone

1.5. Reactions of zerumbone

Zerumbone (**30**), the major component of the essential oil of the leaves and rhizomes of *Z. zerumbet* has been subjected to a number of chemical investigations because of its attractive and diverse reactivity pattern. It undergoes various reactions like cyclization, reduction, ring-expansion, ring-opening, epoxidation, conjugate addition, photochemical reactions *etc*.[76] A brief account of various synthetic transformations performed on zerumbone is presented in the successive sections of this chapter.

1.5.1. Photochemical reaction

In 1967, Sukh Dev *et al*. reported the photochemistry of zerumbone by investigating the photochemical changes involved in zerumbone. The isolated compounds during the reactions are given below (Scheme 1.1).[77]

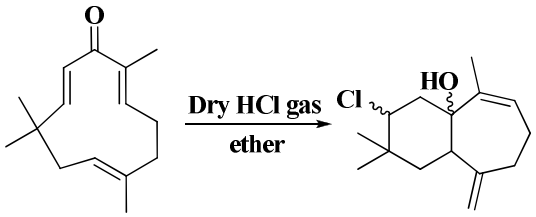


31 ***Trans*-6-*cis*-9-zerumbone** **32** **33** ***ψ*-photozerumbone**

Scheme 1.1

1.5.2. Cyclization reactions

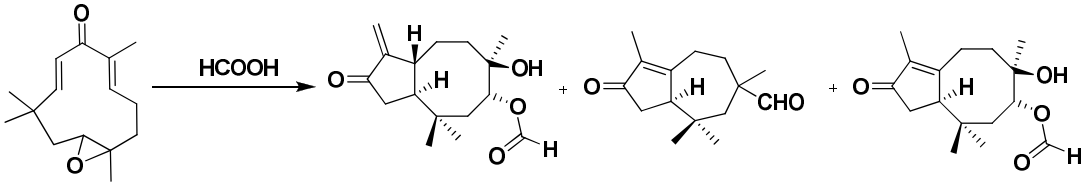
Chhabra and co-workers reported the acid-catalyzed transannular cyclization of zerumbone **30** leading to a bicyclo[5.4.0]-undecane skeleton **34**, a potent pesticide against the stored grain pest *Tribolium castenium*.[61] The reaction is shown in scheme 1.2.



30 **34**

Scheme 1.2

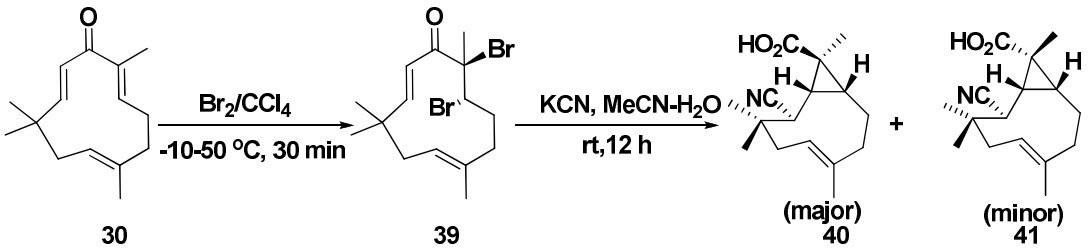
Zerumbone reacts with *m*-chloroperbenzoic acid to yield zerumbone- 6,7-epoxide **35**. Bronsted acid catalyzed Nazarov-type cyclization of zerumbone epoxide **35** afforded mixture of bicyclo[6.3.0]undecane and bicyclo[5.3.0]decane skeletons (Scheme 1.3).[57]



35 **36** **37** **38**

Scheme 1.3

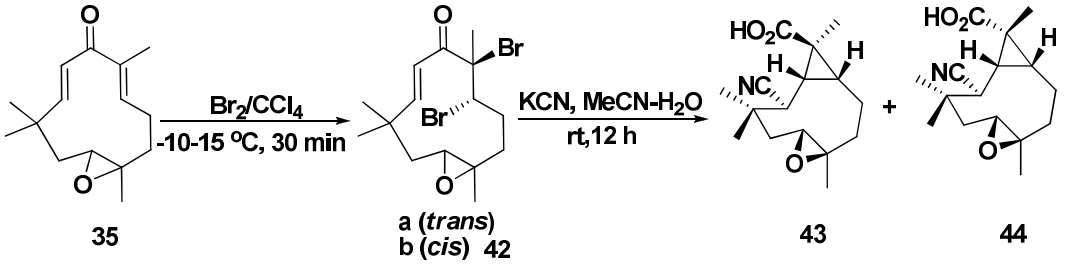
In 1999, Kitayama and co-workers reported the formation of bicyclo[7.1.0]decane skeletons (**40** and **41)** *via* Favorskii- like ring-contractive transannular reaction of 1,2-dibromo zerumbone derivative **39** (Scheme 1.4).[62]



30 39 40 41

Scheme 1.4

Similar type of reaction was carried out in the case of zerumbone epoxide which resulted in the formation of cyclized products (compound **42** and compound **43)** and the reaction is depicted in scheme 1.5.[66]

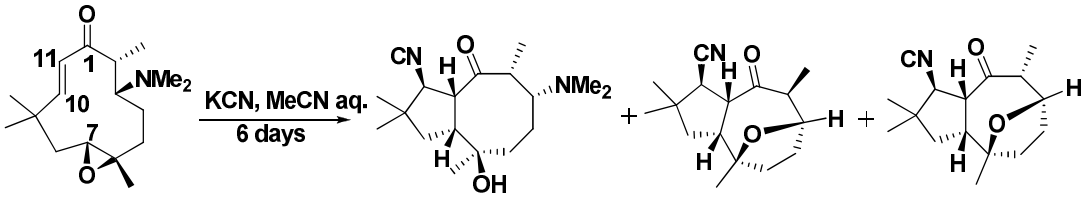


35 a (*trans*) b (*cis*) 42 43 44

Scheme 1.5

1.5.3. Other transannular reaction

Cyanation of the epoxyamine derivative of zerumbone **45** at 0 ^{o}C gave bicyclic aminonitrile as a single diastereomer, while at 30 ^{o}C and at 50 ^{o}C, the product was a mixture of bicyclic **46** and tricyclic nitriles (compounds **47** and **48**).[67] The reaction is shown in scheme 1.6.

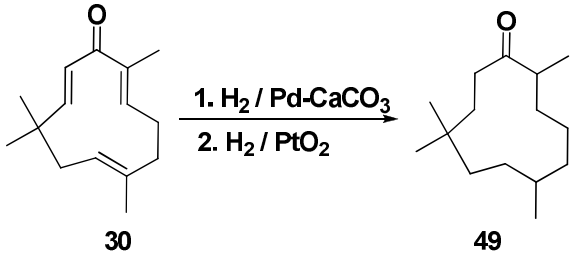


45 46 47 48

Scheme 1.6

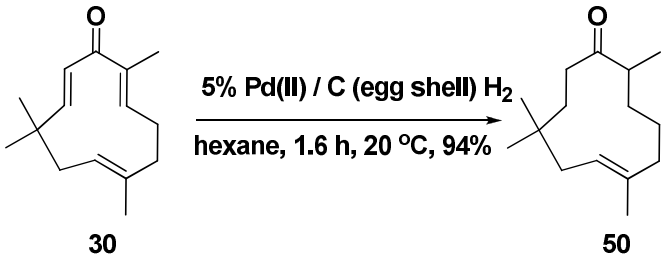
1.5.4. Reduction reactions

The first report on the reduction of zerumbone to hexahydrozerumbone **49** came in 1960. S. Dev and co-workers attempted the reduction in two step pathway using hydrogen gas, Lindlar's catalyst and platinum (IV) oxide (Scheme 1.7).[35]



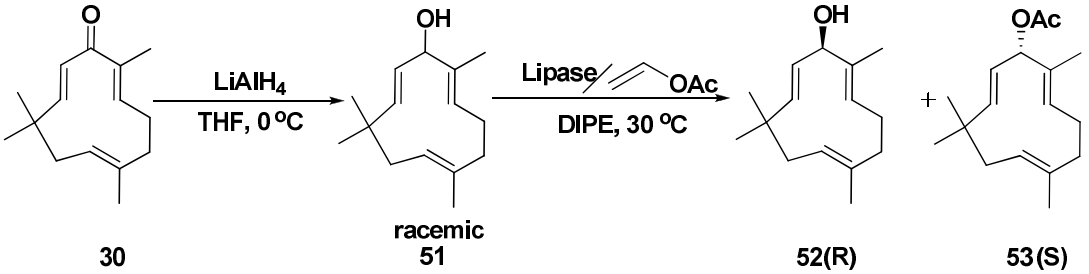
Scheme 1.7

Later in 2010, Kitayama *et al.* presented a regioselective reduction of zerumbone into tetrahydrozerumbone **50**. The unactivated double bond remained as such and selectively reduced the two double bonds of dienone moiety. The reaction afforded the product **50** in 94% yield (Scheme 1.8).[78]



Scheme 1.8

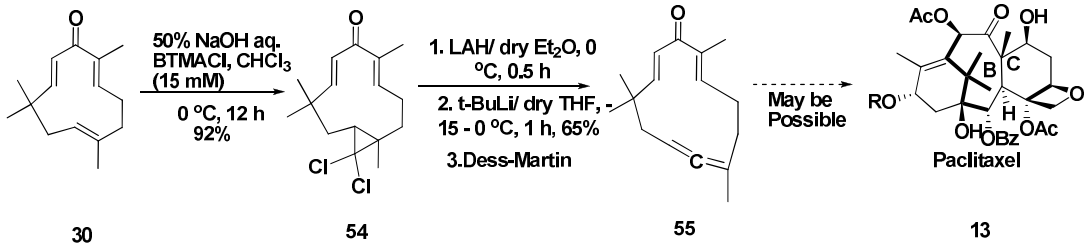
Kitayama *et al.* reported the synthesis of optically active zerumbol **52** and its acetate **53** from zerumbone **30** by reduction followed by lipase-catalyzed stereoselective transesterification (Scheme 1.9).[73]



Scheme 1.9

1.5.5. Ring expansion reaction

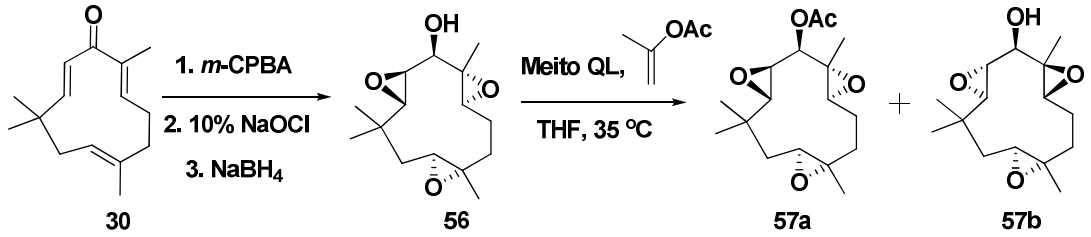
Kitayama *et al.* succeeded in the ring expansion reaction of zerumbone resulting in 12-membered ring, an allene type zerumbone **55**.[69] It was believed that this compound is not only an important building block in synthesizing the BC ring of paclitaxel **13**, but also plays an important role in a novel structure formation and a reaction discovery. Doering–LaFlamme allene synthesis method was adopted for this transformation and the structure of the product was confirmed by single crystal X-ray diffraction analysis. The overall yield of the reaction was 27.7% (Scheme 1.10).



Scheme 1.10

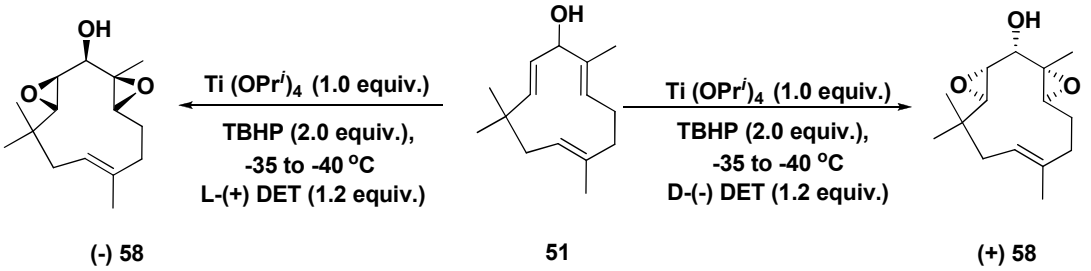
1.5.6. Epoxidation reactions

Optically active substances derived from zerumbone can be used in various industrial fields such as medicine, perfumery, liquid crystal industry and electronics industry. Optically active triepoxyzerumbol (-)-**57b** and its acetate (+)-**57a** were synthesized by lipase-catalyzed enantioselective transesterification of racemic triepoxyzerumbol **56** (Scheme 1.11). [75]



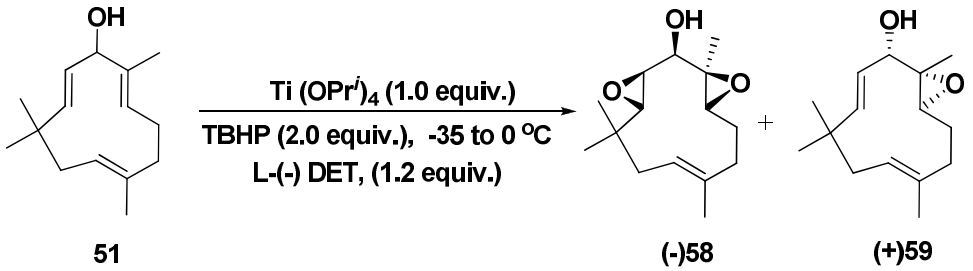
Scheme 1.11

In order to introduce chirality to the readily available achiral sesquiterpene zerumbone **30**, Sharpless asymmetric epoxidation was applied to zerumbol **51**. Single bisepoxides (+) **58** and (−) **58** were obtained in nearly 100% enantiomeric purity (Scheme 1.12).[71]



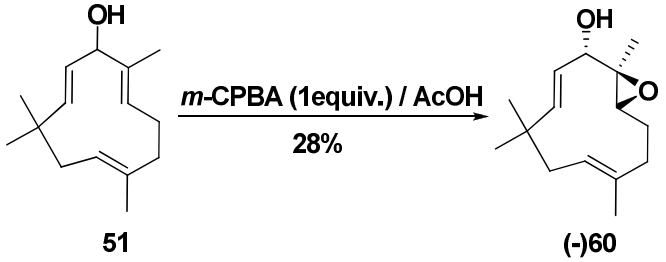
Scheme 1.12

Careful reexamination of the Sharpless asymmetric epoxidation of racemic zerumbol **51** led to the isolation of racemic *erythro* bisepoxide (-)**58** in 40% yield and monoepoxide (+)**59** in 38% yield (Scheme 1.13).[72]



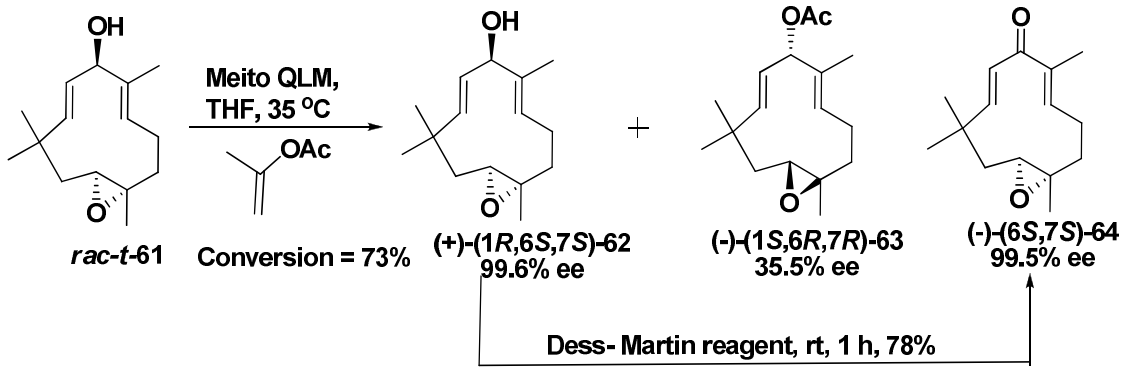
Scheme 1.13

Threo-**60** was prepared by the treatment of (±)-**51** with *m*-chloroperbenzoic acid (Scheme 1.14)

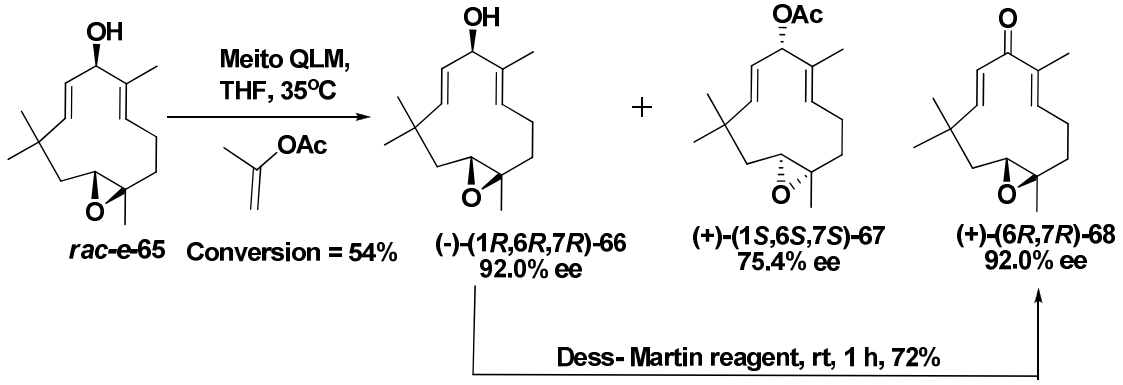


Scheme 1.14

Optically active monoepoxyzerumbones were prepared by the same group in 2008 from monoepoxyzerumbols *via* oxidation. The absolute configurations of the optically active compounds were determined by single crystal X-ray diffraction of their esters with chlorine using anomalous dispersion of heavy atom derivatives.[75] The systematic reactions are depicted in scheme 1.15 and scheme1.16.



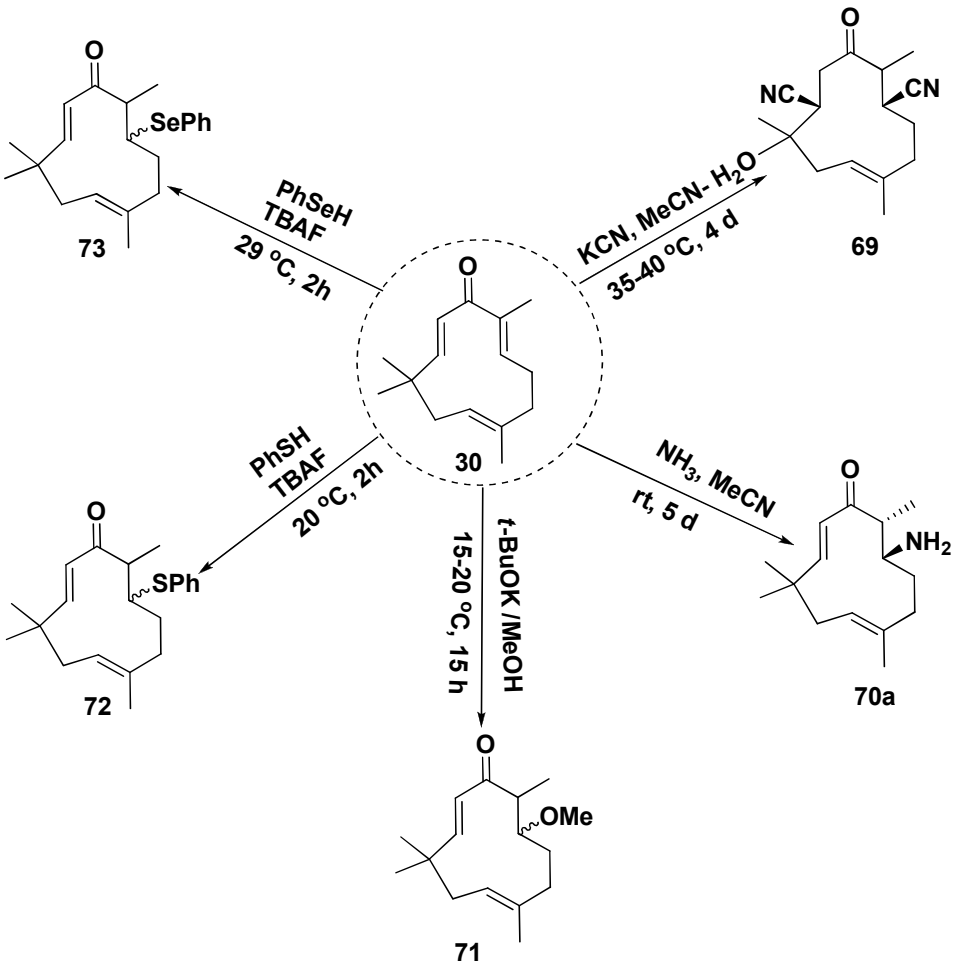
Scheme 1.15



Scheme 1.16

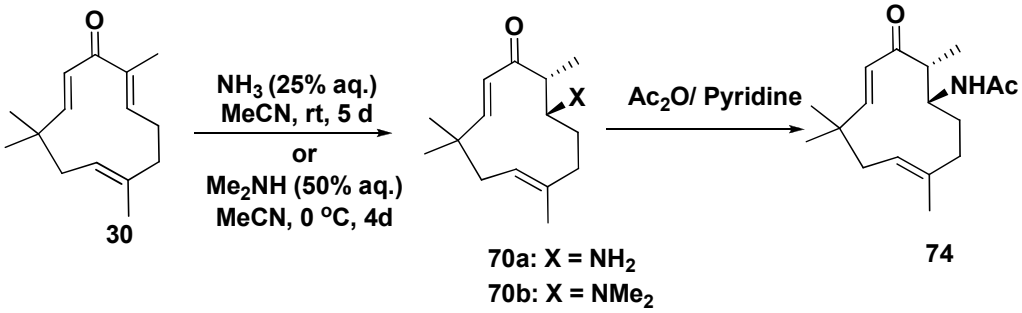
1.5.7. 1, 4- Conjugate addition reactions

Conjugated double bonds of zerumbone permit the introduction of additional functionality and many derivatives of zerumbone were synthesized in moderate to high yield with good regio- and stereoselectivity. 1,4-Conjugate addition reactions of zerumbone with various nucleophiles such as methanol, cyanide, amine, benzene thiol and selenol are illustrated in scheme 1.17. The presence of amine, hydroxylamine, epoxyamine and nitrile groups is believed to play an important role in potent anticancer activities. In 2003, Kitayama *et al.* reported the structural transformation of zerumbone to its dimethylamine derivatives.[56]

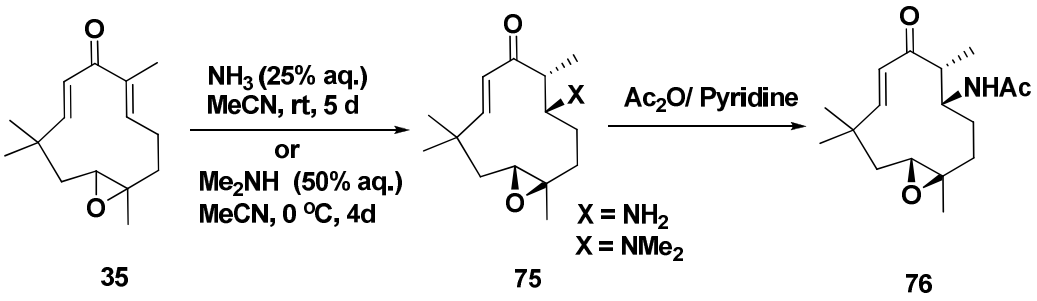


Scheme 1.17

The conjugated addition product reported by Yenjai *et al*. revealed the antimalarial activity of zerumbone derivatives (Scheme 1.18 and Scheme 1.19).[79]

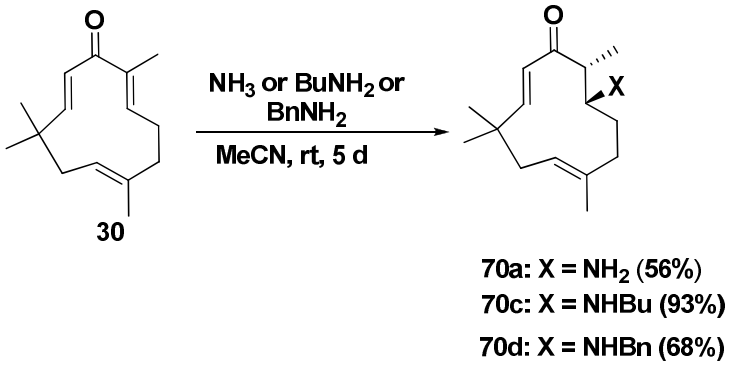


Scheme 1.18



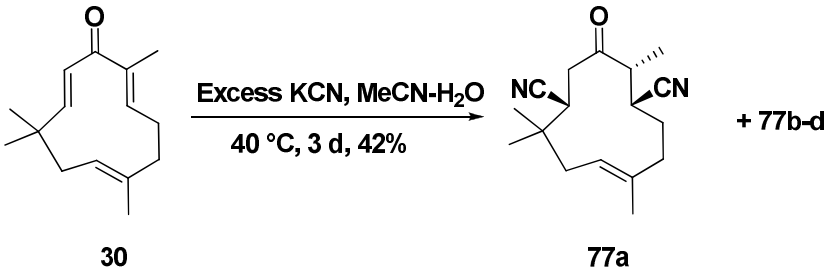
Scheme 1.19

Zerumbone (**30**) was reacted with ammonia, *n*-butylamine, and benzylamine at room temperature to give a single diastereomer of conjugate addition products **70** as shown in scheme 1.20.



Scheme 1.20

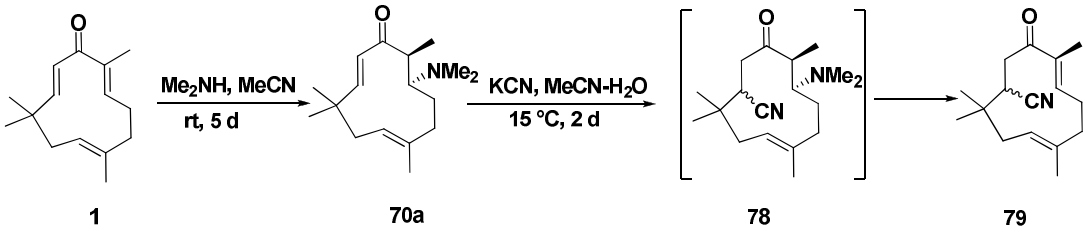
In contrast to the reaction of zerumbone (**30**) with various amines, the excess KCN reacted with zerumbone at 40 °C for 3 days provided conjugate addition of cyanide ion at both C3 and C10 double bonds. A mixture of four diastereoisomeric dicyano derivatives (**77a-77d)** was obtained. It was reported that in the major diastereoisomer (**77a**), two cyano groups were located on the same face of the ring while the two methyl groups at C2 and C6 lie on the opposite face (Scheme 1.21)



Scheme 1.21

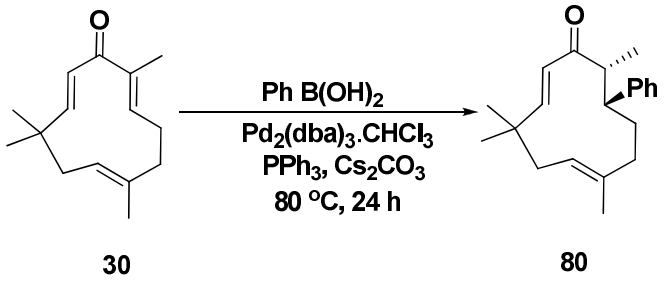
After treatment of zerumbone (**30**) with dimethylamine in the presence of acetonitrile at room temperature, followed by stirring with excess KCN at 15 °C, the

nitrile derivative **79** was detected. The conjugate addition of dimethylamine at C3 gave intermediate **70a**, while conjugate addition of the cyanide ion at C10 yielded intermediate **78**. After the easy elimination of the dimethylamino group, cyano **79** was observed as a sole product (Scheme 1.22).



Scheme 1.22

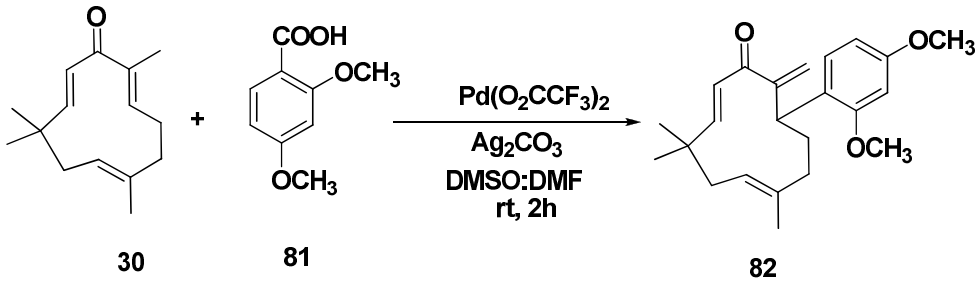
Investigations from our own laboratory has unravelled the transition metal catalyzed regio- and diastereoselective 1,4-conjugate addition reaction of boronic acids of zerumbone (Scheme 1.23).[64]



Scheme 1.23

1.5.8. Decarboxylative coupling reaction

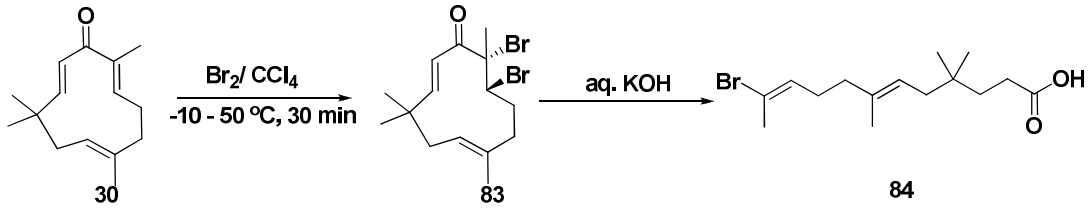
Palladium catalyzed decarboxylative coupling reaction of arene carboxylic acids with zerumbone afforded the arylated zerumbone derivatives having an exocyclic double bond (Scheme 1.24).[65] The derivatives of zerumbone **82** showed superior *α*-glucosidase inhibition activity than the parent molecule zerumbone.



Scheme 1.24

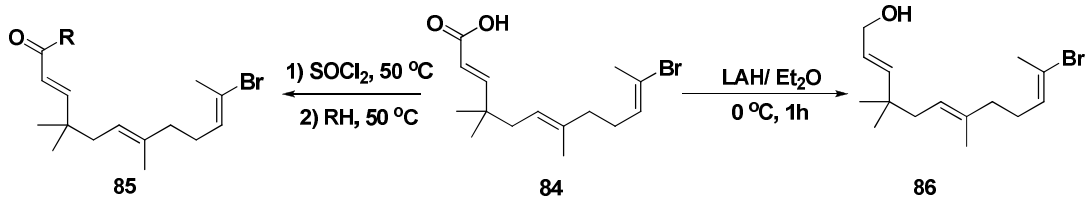
1.5.9. Ring opening reaction

Ring cleavage of zerumbone was investigated by Kitayama and co-workers in 2001. The ring-opened acid (**84)** was obtained by treatment of dibromozerumbone with potassium hydroxide (Scheme 1.25).[66]



Scheme 1.25

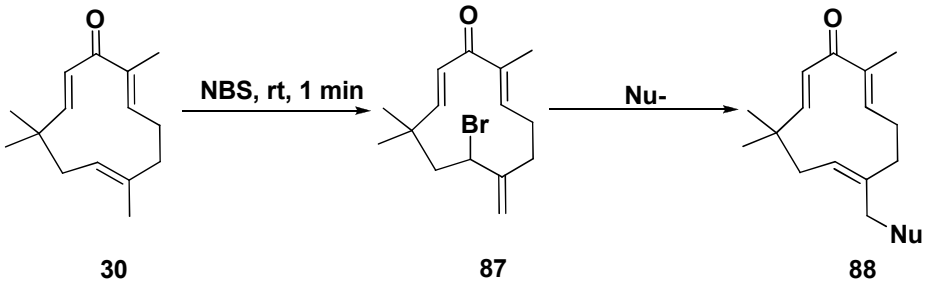
Reduction of **84** using lithium aluminium hydride (LAH) in dry diethyl ether at 0 ^{o}C for 1 h gave corresponding alcohol **86** in 37% yield. Ester and amide derivatives of the ring opened product **85** was achieved by treating **84** with alcohols and amines in presence of thionyl chloride at 50 ^{o}C.[68, 69] Synthetic transformations of the ring opened product **84** are presented in scheme 1.26.



Scheme 1.26

1.5.10. Zerumbone pendant derivatives

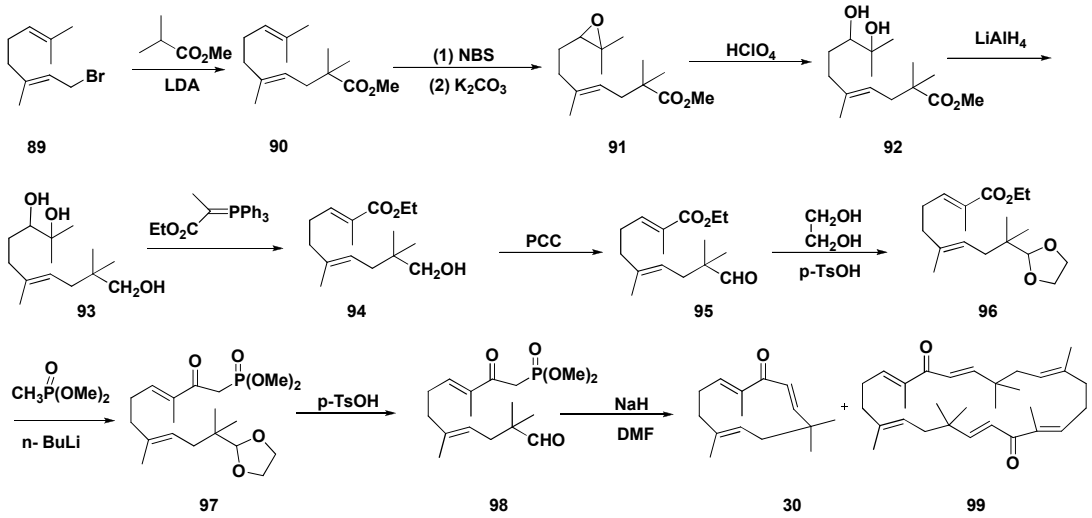
Kitayama *et al*. reported the synthesis of zerumbone derivatives *via* a nucleophilic addition pathway.[80] Zerumbone reacted with *N*-Bromosuccinimide (NBS) at room temperature furnishing a highly reactive intermediate **87** having bromine at C-7 and an exo-methylene group at C-6, after allylic rearrangement. Treatment of **87** with various nucleophiles gave zerumbone-pendant derivatives **88**, maintaining the conjugated system and isolated double bond of the zerumbone (Scheme 1.27). Zerumbone pendant derivatives showed stronger inhibition of NO generation by endothelial cells than zerumbone.



Scheme 1.27

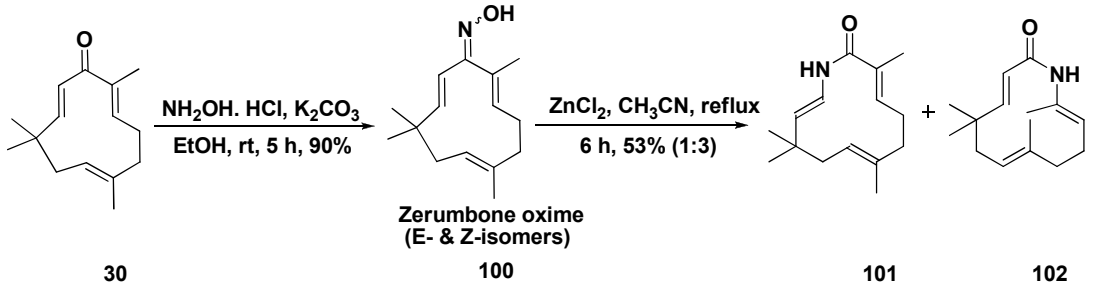
1.5.11. Total Synthesis of Zerumbone

In 1987, Kodama *et al*. reported the total synthesis of this bioactive molecule, zerumbone *via* an intramolecular Wittig-type reaction of the keto-phosphonate (Scheme 1.28). The overall yield of the reaction is 3%. This total synthesis revealed that the method is applicable to the formation of an eleven-membered ring.[81]



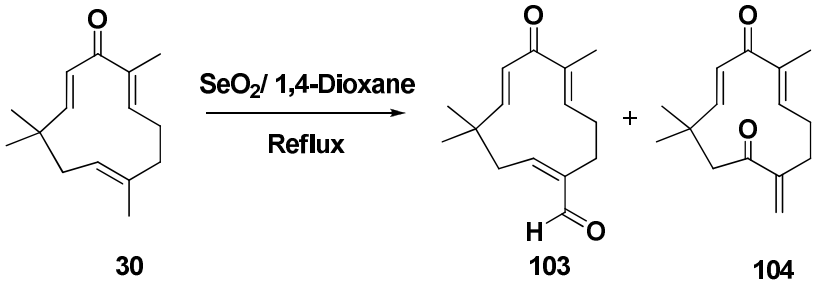
Scheme 1.28

Santosh Kumar and co-workers reported the synthesis of azazerumbone 1 (**101)** and azazerumbone 2 (**102)** *via* Beckmann rearrangement of *E*-zerumbone oxime (**100**). The derivative zerumbone have an amide moiety in the 12-member cyclic ring system and they exhibited better antibacterial and antimutagenic activity than zerumbone. Zerumbone oxime (**100**) and zerumbol (**51**) showed comparable or better bioactive attributes than zerumbone (Scheme 1.29). It was clarified from *in vitro* bioactivity assays that introduction of –NH– group in the zerumbone ring influenced the activity of the molecule.[82]



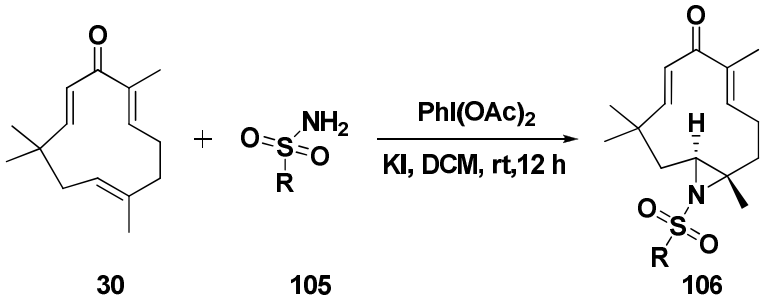
Scheme 1.29

Recently Santosh Kumar *et al*. presented the synthesis of zerumbone-bicarbonyl analogues, zerumbal **103** and zerumbenone **104** by SeO_2 oxidation as shown in scheme 1.30.[83]



Scheme 1.30

Recently our group reported the metal-free *trans*-aziridination of zerumbone and their biological evaluation (Scheme 1.31).[84]



Scheme 1.31

1.6. Conclusion and Present Work

It is obvious from the literature discussions that natural products and its analogues play a pivotal role in modern drug designing and discovery. Even though new approaches like combinatorial chemistry are available, natural sources still play a major role in the development of drugs. A large number of anticancer drugs owes it's origin to natural scaffolds. Drugs, especially in the cancer treatment are coming out from the natural sources. From the literature reports, it is evident that novel and efficient synthetic

methodologies help to make a variety of drugs from a single natural product. Penicillin and its derivatives are classical examples for such group of medicines. The semi-synthesis of taxol from 10-deacetylbaccatin III also portrays the significance of synthetic manipulation in a natural product to make them more useful for the humankind.

Zerumbone, the main component of essential oil of *Z. zerumbet* Smith. showed good chemical reactivity with good, chemo-, regio- and stereo selectivity. It is a natural cyclic sesquiterpene and has been the focus of recent research as it has been found to exhibit selective toxicity towards cancer cells compared to normal cells. This molecule also exhibits anti-tumour, anti HIV, anti-inflammatory activities. The literature studies support the biological significance of zerumbone and zerumbone derivatives. The studies indicate that zerumbone may have potential therapeutic properties and also the derivatization may enhance the biological acivity. The synthetic transformations maily involve cyclization, reduction, ring-expansion, ring-opening, epoxidation, conjugate addition reactions. To improve the biological activities of zerumbone and to build the foundations for the industrial use further functionalization of this molecule is required.

Inspired by the biological profile of zerumbone, we decided to isolate zerumbone from the rhizomes of this plant, with an aim to functionalise this molecule. Hence, we undertook this challenge and invested our time in isolation, characterization and synthetic transformations of phytochemicals from the rhizomes of *Z. zerumbet* with a special focus on zerumbone.

The first part of the second chapter describes the synthesis and evaluation of zerumbone pendant derivatives *via* transition metal catalyzed Tsuji-Trost reaction. Monomer, dimer and trimer of zerumbone pendant derivatives have been synthesized by this method. In addition, we have evaluated the anti diabetic potential, anti-proliferative and anti-hypertensive activities of the synthesized compounds.

Synthesis of zerumbone pendant aminoacids as well as nucleobases by base catalyzed reaction is described in the second part of chapter 2. Some of the derivatives were tested for the growth inhibition activity towards selected cancer cell lines.

Chapter 3 describes a synthetic route for the derivatizations of zerumbone by Lewis acid catalyzed 1,4-conjugate addition, with biologically important heterocycles such as indole/pyrrole. The method provides a straightforward access to conjugate addition

product of zerumbone with indole under mild reaction condition. We have conducted the *in vitro* anti-diabetic screening as well as inhibitory effect of angiotensin-converting enzyme (anti-hypertensive activity) of the synthesized zerumbone-indole adducts. Our effort in this line is discussed in this chapter.

The conjugate double bond of this molecule is the pre-requisite for most of the biological properties. Chapter 3 also describes the synthesis of indole functionalized zerumbone derivatives having an exocyclic double bond using palladium catalyst. In addition the results of the *in vitro* screening for the anti-diabetic potential of the synthesized indole functionalized zerumbone derivatives are also discussed.

The part A of chapter 4 describes the Lewis acid catalyzed annulation reactions of Michael adduct of zerumbone to access structurally diverse polycyclic compounds. The part B of chapter 4 deals with synthesis of indole functionalized [5.8] fused systems using Lewis acid catalyst.

Natural products, especially plant-derived compounds occupy a proficient position in the development of numerous useful drugs. Diversity oriented synthesis has been used widely for the generation of biologically relevant/drug-like molecules *via* simple chemical transformation of readily available natural products. In this line, zerumbone, a humulenoid sesquiterpene which is the major component of essential oils of *Z. zerumbet* Smith., has attracted much attention of the scientific community because of its interesting biological properties as well as chemical reactivity.

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CHAPTER 2

Synthesis of Zerumbone Pendant Derivatives

Part A

Synthesis of Zerumbone Pendant Derivatives *via* Transition Metal Catalyzed Reaction and their Biological Evaluation

2A.1. Introduction

The carbon-carbon bond forming reaction is one of the most powerful tools for making new compounds and for developing creative synthetic methodologies. Such a reaction, in general is most useful and efficient when performed catalytically. Among the complexes of a variety of transition metals for carbon-carbon bond formation employed previously, palladium complexes have been most often used because they display wide reactivity and higher selectivity.[1-3] Palladium has become the most versatile transition metal in metal-catalyzed reactions over the past three decades. Palladium-catalyzed allylic substitution reactions have emerged as a valuable tool for carbon-carbon and carbon-heteroatom (C-O, C-N, C-S) bond forming reactions in contemporary organic synthesis[4-12] and find numerous applications in the preparation of pharmaceuticals, agrochemicals etc.

Among the various palladium catalyzed reactions, Tsuji-Trost reaction is one of the most attractive synthetic approaches to construct the carbon-hetero atom bond.[13-14] Activated form of allylic alcohols such as allylic esters, allylic carbonates are useful precursors of cationic electrophilic "π-allyl palladium" complexes, which allow efficient carbon-carbon bond formation.[15-20] These intermediates have been extensively used in synthesis of many natural products, such as terpenes, alkaloids, cyclopentanoids, steroids, etc.[21-23] A detailed discussion on the Tsuji-Trost reaction of various soft nucleophiles with the highly reactive intermediate of zerumbone is presented in this chapter. In addition, the biological activities of the synthesized zerumbone derivatives are discussed in this chapter. A brief discussion on the palladium catalyzed allylation and amination reactions

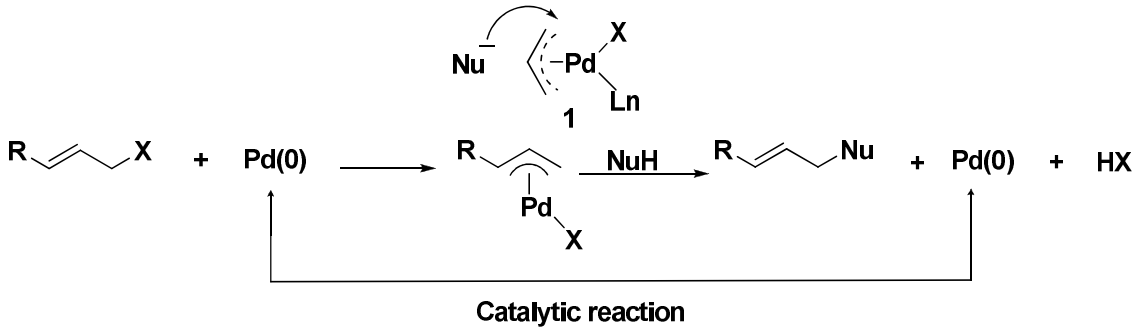
is outlined below.

2A.2. Palladium catalyzed allylation

Beginning with the pioneering work in 1965 by Tsuji,[13] the palladium-catalyzed substitution reaction of allylic substrates has been examined thoroughly during the last four decades. In 1973, Trost published the first asymmetric version of the allylic substitution.[14] Today, excellent yields and enantioselectivities can be achieved through the correct choice of palladium catalyst and ligand system.

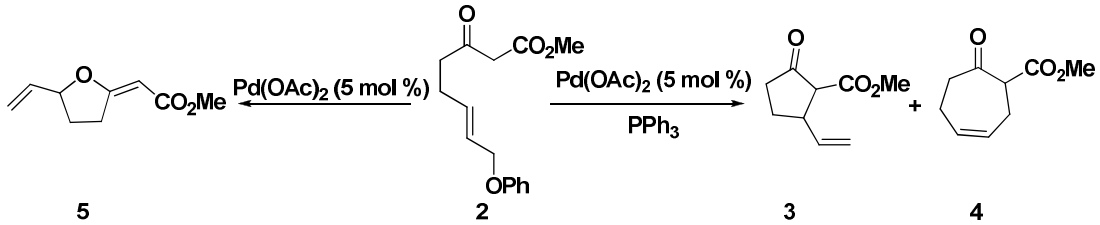
2A.2.1. π-Allylpalladium chemistry

Reactive π-allyl palladium complexes **1** are useful reaction intermediates for the palladium-catalyzed substitution reaction and in general, they are electrophilic in nature. They react with various nucleophiles such as malonates, *β*-keto esters, and amines to form carbon-carbon or carbon-heteroatom bonds under neutral or basic conditions.[24-28] The addition of phosphine or phosphate ligands enhances the allylic alkylation of alkyl substituted *α*-allyl complexes.[20] The mechanism of the proposed reaction is represented in scheme 2A.1.



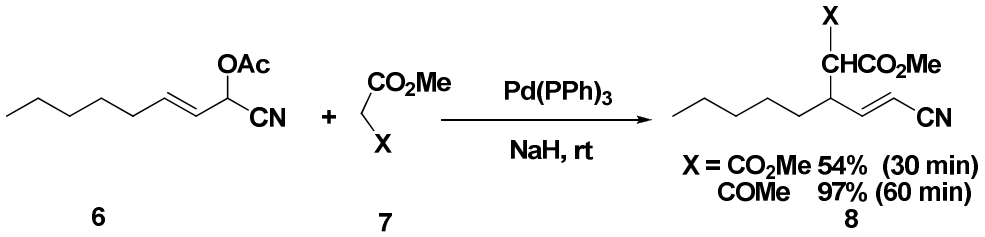
Scheme 2A.1

In 1982, Tsuji reported the synthesis of five and seven-membered cyclic ketones, cyclopentanone **3** and cycloheptanone **4** *via* a palladium-catalyzed intramolecular reaction of active methylene compound with allyl phenyl ether **2**. In the same report, the synthesis of tetrahydrofuran derivative **5** was also presented (Scheme 2A.2).[16]



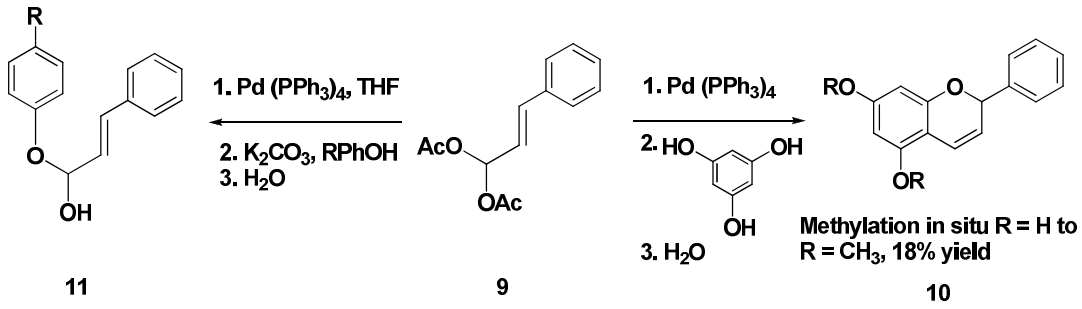
Scheme 2A.2

In 1982, Tsuji described the synthesis of reaction of 4-substituted-2-nonenonitrile **8** by the palladium catalyzed reaction of 2-acetoxy-3-nonenonitrile **6** with the malonate **7** (Scheme 2A.3).[16]



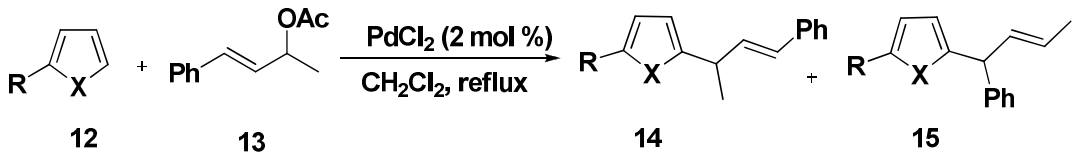
Scheme 2A.3

Bastien Nay and co-workers presented the syntheses of 2-phenyl-2H-chromene (3-flavene) **10** and cinnamaldehyde aryloxy-hemiacetal **11** by the palladium catalyzed nucleophilic substitution of phenols with acylal of cinnamaldehyde **9**.[29]



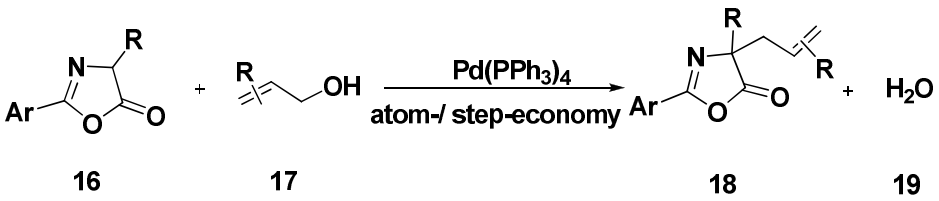
Scheme 2A.4

In 2011, Yuan *et al*. reported the $PdCl_2$-catalyzed protocol for highly efficient allylation and benzylation of a rich variety of N-, O-, and S-containing heteroarenes under base/acid, additive, and ligand-free conditions (Scheme 2A.5).[30]



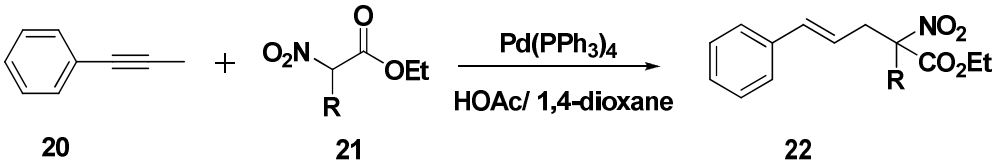
Scheme 2A.5

Recently Zhou *et al*. presented the palladium catalyzed direct allylation of azalactones **16** with simple allylic alcohols **17** in the absence of activators (Scheme 2A.6).[31]



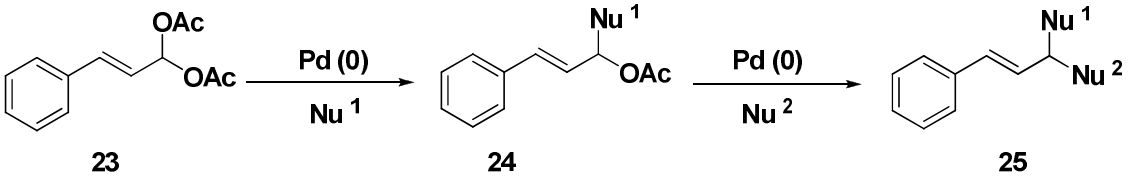
Scheme 2A.6

Yao *et al.* reported the synthesis of allylated *α*-nitroacetates **22** *via* the palladium-catalyzed allylation of *α*-nitroacetates **21** with propynes **20** (Scheme 2A.7).[32]



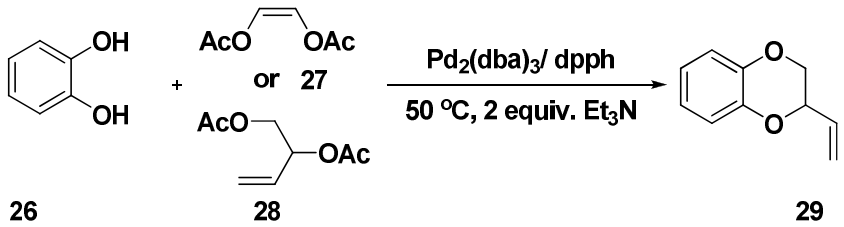
Scheme 2A.7

Heerden *et al.* has demonstrated the palladium catalyzed double substitution of the germinal diacetate **23** by both carbon and oxygen nucleophiles (Scheme 2A.8).[33]



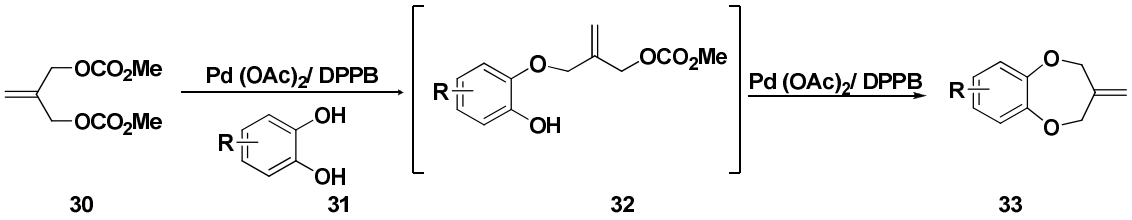
Scheme 2A.8

Vicinal and remote (1,3 and 1,4-*cis*) allylic diacetates have been applied in the synthesis of a 2-vinyl-2,5-dihydrobenzo [1, 4] dioxane **29** while the *trans*-diacetate did not result in the product (Scheme 2A.9).[34]



Scheme 2A.9.

The above methodology was also applied in the synthesis of 3,4-dihydro-2H-1,5-benzo dioxepine **35**.[35] Remote (1,3) allylic dicarboxylates **30** reacted with substituted benzenediols **31** in presence of catalytic amount of $Pd(OAc)_2$ furnished the cyclized product **33** (Scheme 2A.10).



30 31 32 33

Scheme 2A.10

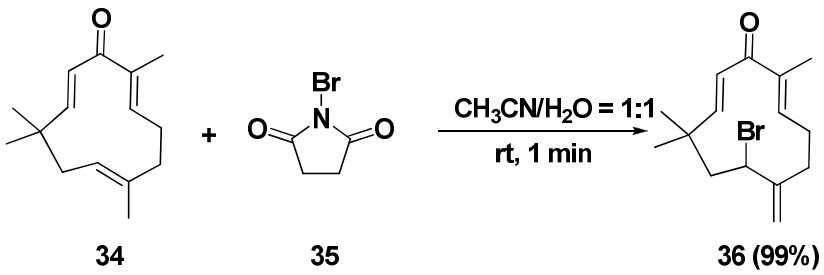
2A.3. Definition of the Problem

Investigation from our laboratory unraveled a viable route for the efficient functionalization of zerumbone by utilizing transition metal catalyst. The *α,β*-unsaturated ketone of zerumbone molecule is considered as the prerequisite for most of the biological activity of this molecule. Kitayama and co-workers described the reactivity of hard nucleophiles with the highly reactive intermediate of zerumbone to furnish zerumbone pendant derivatives.[36] But this transformation requires long reaction time of 2-3 days. The highly reactive intermediate of zerumbone was synthesized *via* an allylic bromination of zerumbone using N-bromo succinimide (NBS). This prompted us to investigate the reactivity of various soft nucleophiles with the highly reactive intermediate. A detailed description of palladium catalyzed Tsuji-Trost reaction of zerumbone derivatives with the soft nucleophiles is presented in the following section. This method offers a straight way to synthesize zerumbone pendant derivatives within a short time. The anti-diabetic activity, cytotoxicity and anti-hypertensive activities of the synthesized zerumbone derivatives are also discussed.

2A.4. Results and Discussion

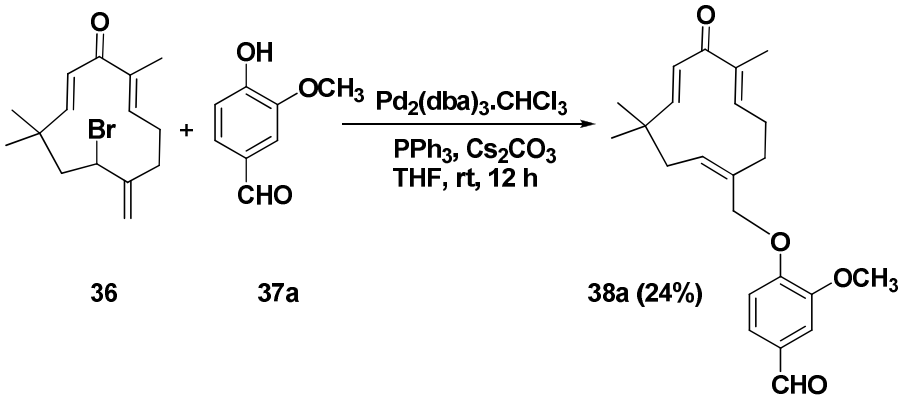
2A.4.1. Palladium catalyzed synthetic transformation of zerumbone: Zerumbone pendant derivatives

In continuation of our interest in the metal catalyzed synthetic modification, we attempted to synthesize a new class of zerumbone pendant derivatives using soft nucleophiles. For this, a highly reactive intermediate **36** was synthesized by treating zerumbone **34** (1 equiv.), N-bromosuccinimide **35** (1 equiv.) in acetonitrile-water solvent system at room temperature for 1 minute (Scheme 2A.11). The reaction afforded **36** in 99% yield.



Scheme 2A.11

We commenced our reaction of the highly reactive intermediate **36** with vanillin **37a** in presence of $Pd_2(dba)_3.CHCl_3$ (10 mol %), PPh_3 (40 mol %) and Cs_2CO_3 (2.0 equiv.) under argon atmosphere in THF at room temperature. The reaction afforded vanillin-appended zerumbone (**38a**) in 24% yield (Scheme 2A.12).



Scheme 2A.12

The structure of the product, **38a** was established using various NMR techniques. The IR spectrum of the compound showed characteristic carbonyl absorption at 1676 cm^{-1}. The ^1H NMR of **38a**, aldehyde proton resonated as singlet at δ 9.85 ppm, the aromatic protons were resonated as multiplet at δ 7.40-7.43 ppm and the aromatic proton *ortho* to the methoxy group appeared as multiplet in the range δ 6.97-6.96 ppm. Three olefinic protons in the bis-enone part resonated in the region δ 5.81-6.02 ppm. The unactivated olefinic proton appeared as doublet of doublet centered at δ 5.5 ppm. The CH_2 protons near oxygen resonated as multiplet in the region δ 4.64-4.51 ppm. The methoxy protons appeared as singlet at δ 3.88 ppm. Three singlets at δ 2.24, 1.27, 1.09 ppm, each accounting for three protons could be readily identified as three methyl groups (Figure 2A.1).

In the ^{13}C spectrum, signal at δ 203.3 ppm indicated the carbonyl group of bisenone part of zerumbone. The carbonyl group of aldehyde appeared at δ 190.5 ppm. The carbons of

the -OCH_2 appeared at δ 66.3 ppm. Methoxy carbon appeared at δ 55.5 ppm (Figure 2A.2). All other spectral values were in agreement with the structure.

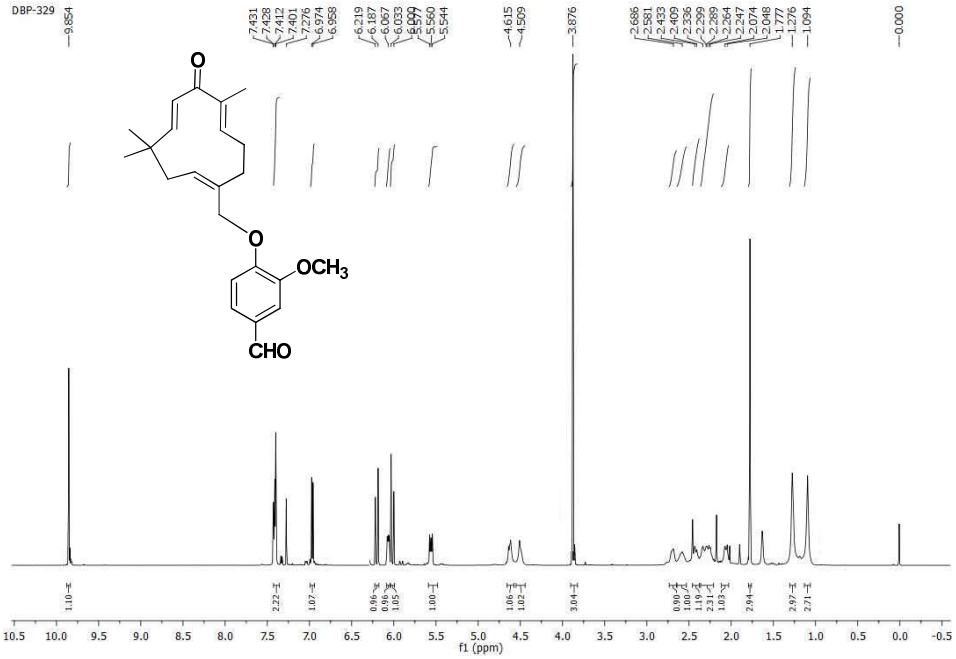


Figure 2A.1. ^{1}H NMR of **38a**

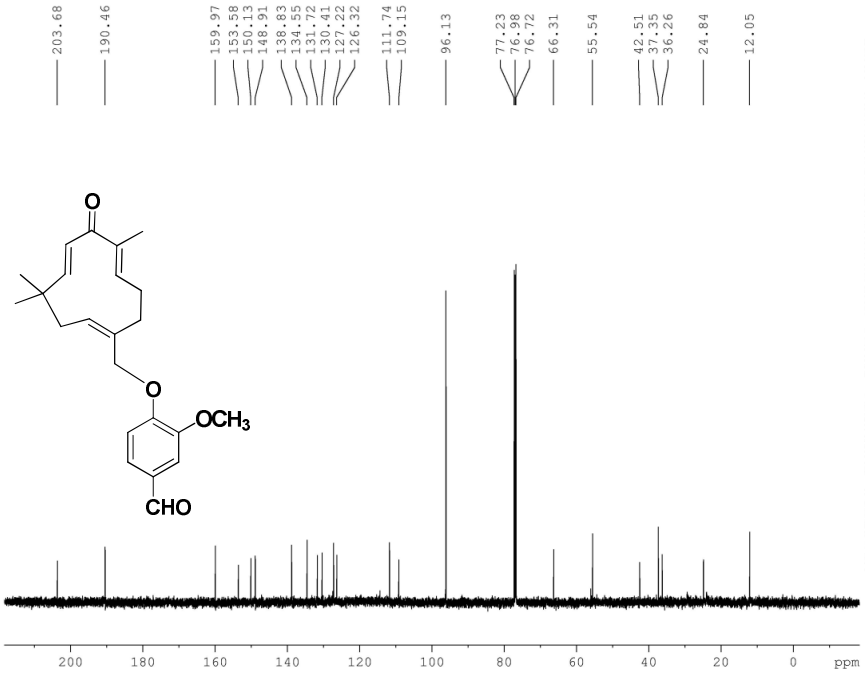


Figure 2A.2. ^{13}C NMR of **38a**

Mass spectrum well supported the structure with $[M+Na]^{+}$ ion peak at *m/z* 391.2085.

2A.4.2. Optimization Studies

Detailed optimization studies were carried out to find out the best condition for the transformation. In order to optimize the reaction condition, we tried different palladium catalyst such as $Pd_2(dba)_3.CHCl_3$, $Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(PPh)_4$ etc. Also, various solvents were screened. Among various palladium catalysts and solvent systems examined, $Pd_2(dba)_3.CHCl_3$ is the best catalyst and THF as the best solvent (Table 2A.1).

Table 2A.1. Optimization studies for suitable catalyst system

Entry	Catalyst	Ligand	Base	Solvent	Yield (%)
1[a]	—	—	Cs_2CO_3	THF	NR
2[a]	$Pd_2(dba)_3.CHCl_3$	PPh_3	K_2CO_3	THF	Trace
3[b]	$Pd_2(dba)_3.CHCl_3$	PPh_3	Cs_2CO_3	THF	43
4[a]	$Pd_2(dba)_3.CHCl_3$	PPh_3	Cs_2CO_3	CH_3CN	44
5[a]	$Pd_2(dba)_3.CHCl_3$	PPh_3	Cs_2CO_3	THF	24
6[a]	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	THF	Trace
7[a]	$Pd(O_2C.CF_3)_2$	PPh_3	Cs_2CO_3	THF	21
8[a]	$Pd(PPh_3)_4$	—	Cs_2CO_3	THF	24
9[a]	$Pd_2(dba)_3$	PPh_3	Cs_2CO_3	THF	43
10[c]	$Pd_2(dba)_3.CHCl_3$	PPh_3	Cs_2CO_3	THF	Trace
11[d]	$Pd_2(dba)_3.CHCl_3$	PPh_3	Cs_2CO_3	THF	46
12	$Pd(OAc)_2$	dppf	NaH	THF	10

Reaction condition:

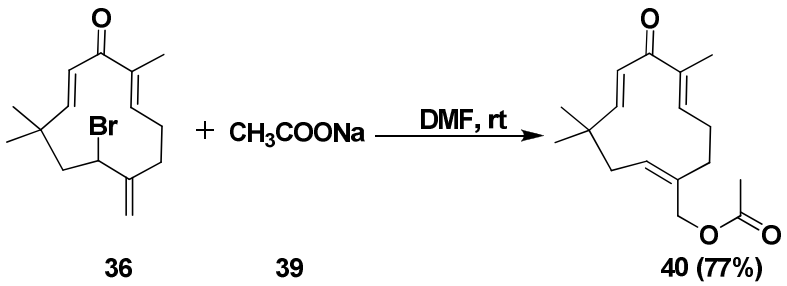
[a] **36**:**37a** = 1:1, Catalyst (10 mol %), Ligand (0.4 equiv.), Base (1 equiv.), Solvent (2 mL)

[b] **36**:**37a** = 1:1, Catalyst (10 mol %), Ligand (0.4 equiv.), Base (2 equiv.), Solvent (2 mL)

[c] **36a**:**37a** = 1:2, Catalyst (10 mol %), Ligand (0.4 equiv.), Base (1 equiv.), Solvent (2 mL)

[d] **36b**:**37a** = 1:1, Catalyst (10 mol %), Ligand (0.4 equiv.), Base (1 equiv.), Solvent (2 mL)

Some undesirable side products were formed during the reaction, hence we reinvestigated the same reaction with 6-acetoxymethyl-2,9,9-trimethylcycloundeca-2,6,10-trienone (**40**) and the reaction afforded the product in 46% yield. The reaction of **36** with sodium acetate **39** in DMF solvent resulted the formation of **40** in 77% yield (Scheme 2A.13). Finally after optimization studies, a 1:1 mixture of **40** and nucleophile **37** in presence of $Pd_2(dba)_3.CHCl_3$ (10 mol %), PPh_3 (40 mol %) and Cs_2CO_3 (1.0 equiv.) in THF at room temperature was the best catalytic condition.



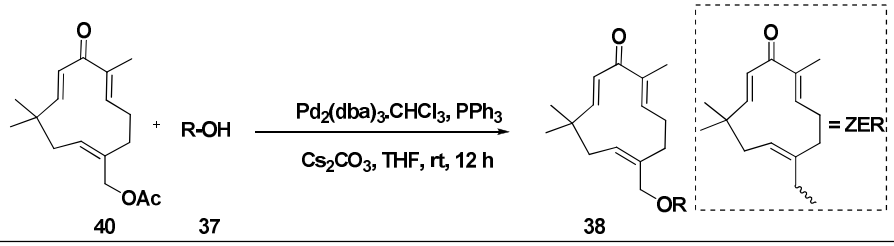
36 **39** **40 (77%)**

Scheme 2A.13

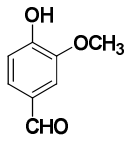
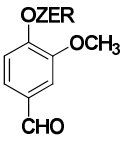
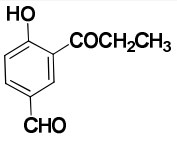
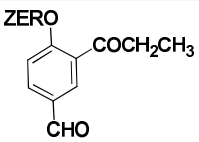
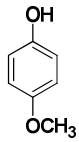
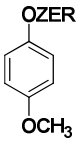
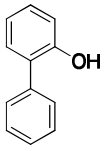
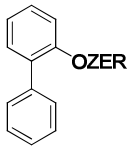
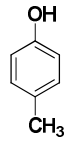
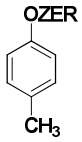
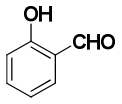
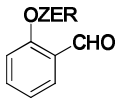
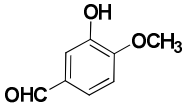
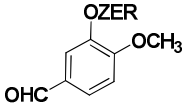
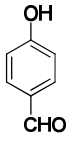
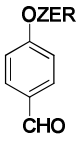
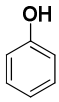
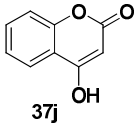
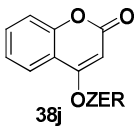
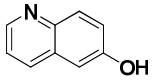
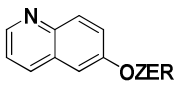
The reaction scope of various nucleophiles was then tested under the optimized reaction conditions. Various soft nucleophiles (**38a-38k**) reacted smoothly with **40** to furnish the corresponding zerumbone pendant derivatives in moderate yields. The results of the substitution reaction of different soft nucleophiles are shown in table 2A.2.

Under the optimised condition, various substituted phenols with both electron withdrawing and electron donating substituents were screened, affording products in moderate to good yields (Table 2A.2). In addition, 4-hydroxycoumarins (**38j**) and 5-hydroxyisoquinoline (**38k**) were also utilised for this transformation, giving the product in 31% and 73% yields respectively.

Table 2A.2. Palladium catalyzed coupling of **40** with various phenols/alcohols **37**



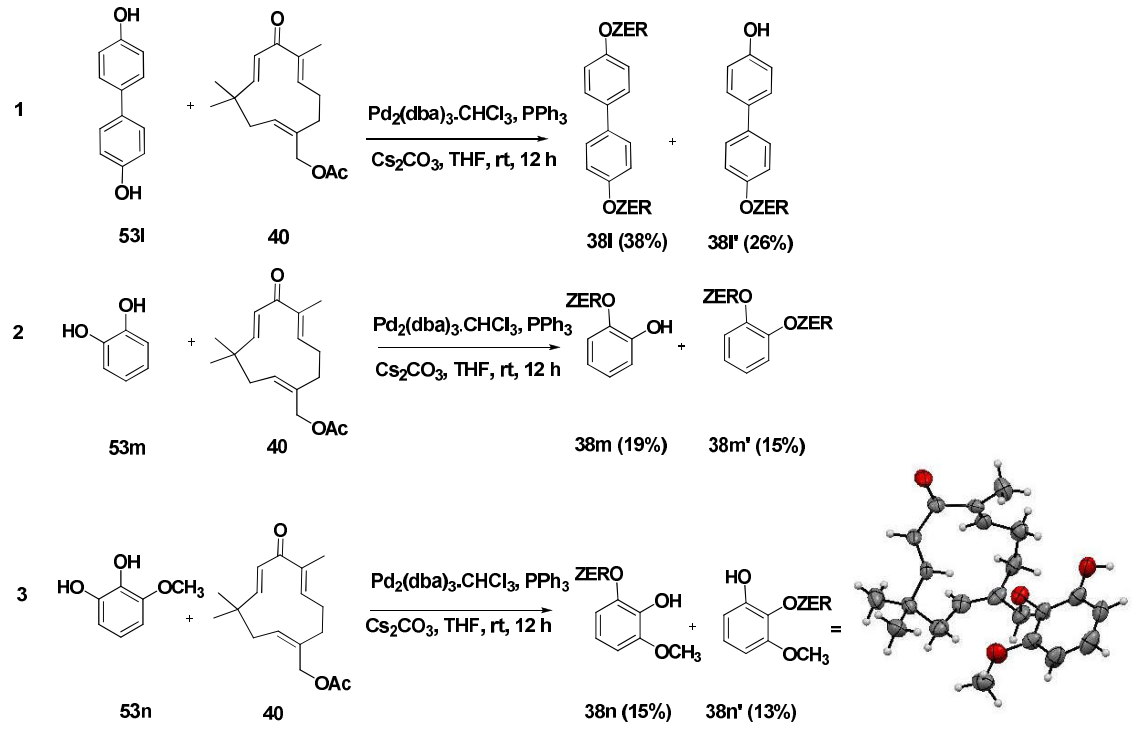
40 37 38

Entry	Nucleophile	Product	Yield (%)	Entry	Nucleophile	Product	Yield (%)
1	 37a	 38a	46	6	 37f	 38f	23
2	 37b	 38b	76	7	 37g	 38g	76
3	 37c	 38c	68	8	 37h	 38h	28
4	 37d	 38d	63	9	 37i	 38i	91
5	 37e	 38e	33	10	 37j	 38j	31
				11	 37k	 38k	73

Reaction conditions: Zerumbone acetate **40** (1.0 equiv.), Alcohol **37** (1.0 equiv.), $Pd_2(dba)_3.CHCl_3$ (10 mol %), PPh_3 (40 mol %), Cs_2CO_3 (1.0 equiv.), THF (2 mL), rt, 12 h.

Next, the scope and generality of the reaction was explored under the optimized reaction conditions with various catechols, carboxylic acids, and hydroxyl acids under the optimized condition. In the case of 4, 4'-dihydroxybiphenyl (**38l**) (Scheme 2A.14, entry 1) with **40**, the corresponding derivatives **38l** and **38l'** were formed in 38% and 26% yields respectively. Encouraged by this observation, we focussed on the synthesis of dimer of zerumbone pendant derivatives by choosing suitable soft nucleophiles such as

catechols (Scheme 2A.14, entry 2 and 3). As mentioned earlier, similar observations were found in the case of unsubstituted catechols (entry 3, **38m**). But in the case of other substituted catechol such as 3-methoxy catechols (**38n**), the isomers **38n** and **38n'** were formed in 15% and 13% respectively (entry 3).The two isomers **38n** and **38n'** were distinguished by various spectroscopic techniques. Finally the single crystal X-ray analysis of **38n'** confirmed the structure.[57]

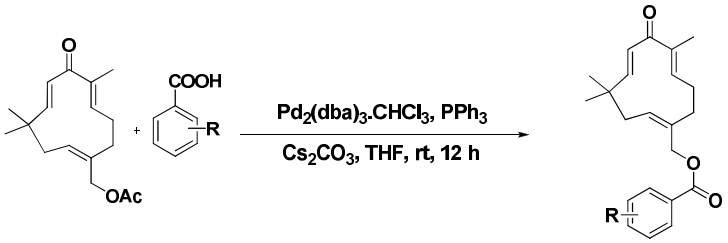


Reaction conditions: Zerumbone acetate **40** (1.0 equiv.), Nucleophile **53** (1.0 equiv.), $Pd_2(dba)_3.CHCl_3$ (10 mol %), PPh_3 (40 mol %), Cs_2CO_3 (1.0 equiv.), THF (2 mL), rt, 12 h.

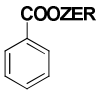
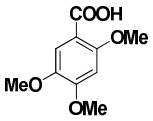
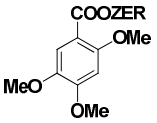
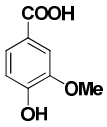
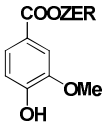
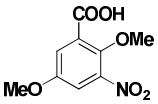
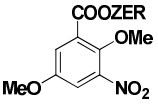
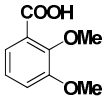
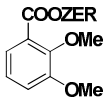
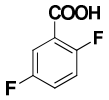
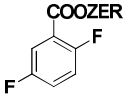
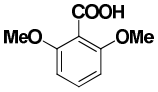
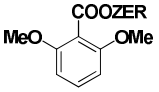
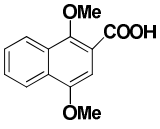
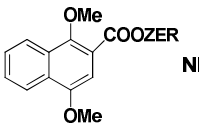
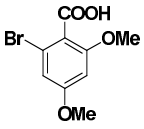
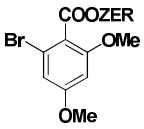
Scheme 2A.14

Then we have elaborated the scope of phenols/alcohols to another class of soft nucleophiles, carboxylic acids. We continued our studies with the reaction **40** and benzoic acid (**41a**) under the optimized condition and no desirable product was formed (Table 2A.3, entry 1). Nevertheless we decided to continue the reaction with other electron rich carboxylic acids such as methoxy-substituted benzoic acids. With the optimized reaction condition, the reaction of **40** and vanillic acid (**41b**) gave the corresponding product **42b** in 28% yield. The structure and stereochemistry of the product (**42b**) was unambiguously confirmed by single crystal X-ray analysis (Figure 2A.3). Therefore, various commercially available carboxylic acids were tested as shown in (Table 2A.3).

Table 2A.3. Substrate Scope of **40** with various aryl carboxylic acids **41**.



40 41 42

Entry	Acid	Product	Yield (%)	Entry	Acid	Product	Yield (%)
1	 41a	 42a	NR	6	 41f	 42f	17
2	 41b	 42b	28	7	 41g	 42g	NR
3	 41c	 42c	19	8	 41h	 42h	NR
4	 41d	 42d	14	9	 41i	 42i	NR
5	 41e	 42e	10				

Reaction conditions: Zerumbone acetate **40** (1.0 equiv.), Acid **41** (1.0 equiv.), $Pd_2(dba)_3.CHCl_3$ (10 mol %), PPh_3 (40 mol %), Cs_2CO_3 (1.0 equiv.), THF (2 mL), rt, 12 h.

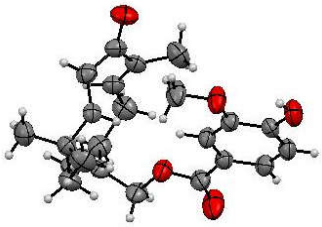
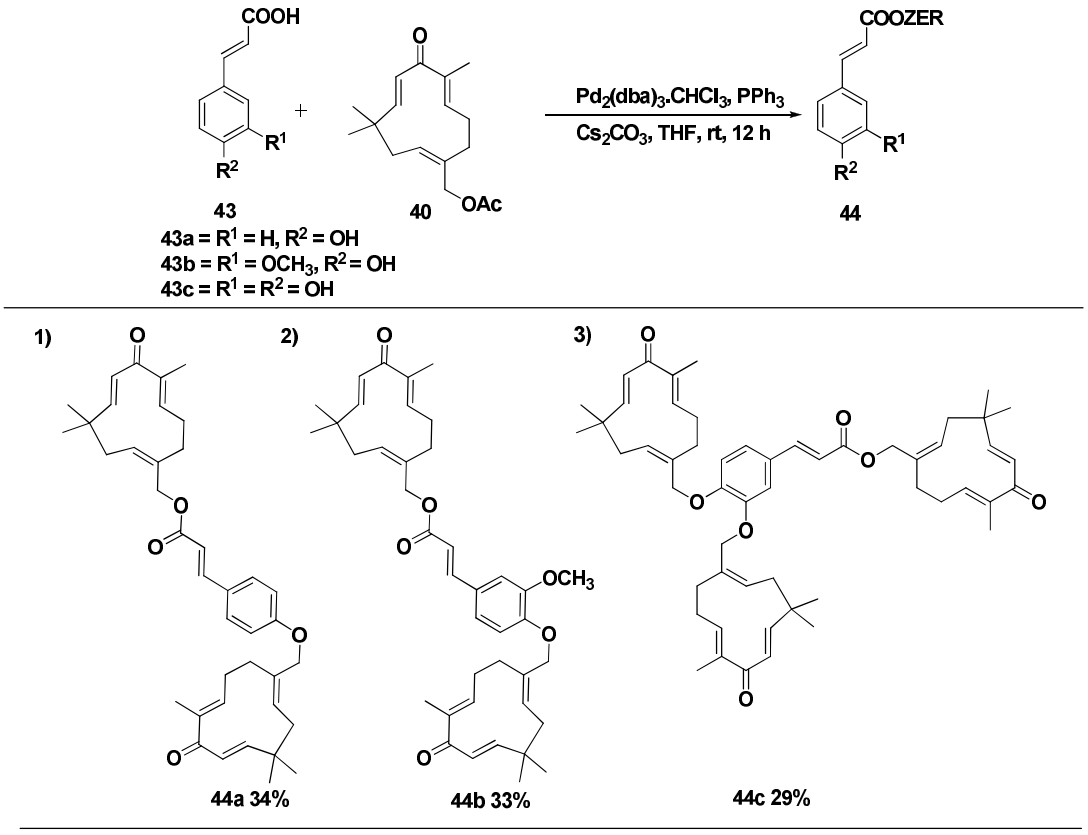


Figure 2A.3. Single crystal X-ray structure of **42b**[57]

When the R group was changed from alcohol to acids, the reaction yield was very low. Carboxylic acids bearing electron donating substituents like methoxy group gave the desirable zerumbone pendant derivatives while no desirable products were formed in the case of electron withdrawing substituents such as NO_2 and F (Table 2A.3, entry 7 and 8).

The reactivity of various cinnamic acid derivatives like *p*-coumaric acid **43a** ferrulic acid **43b**, and caffeicacid **43c** was also tested under the optimal condition and we were pleased to observe the formation of dimer and trimer of zerumbone pendant derivatives **44a**, **44b**, and **44c** (Scheme 2A.15). Hydroxyl and carboxylic functionalities participate in the reaction to provide the corresponding dimer and trimer derivatives. But due to the steric effect of the nucleophiles, the products were obtained in low yield.

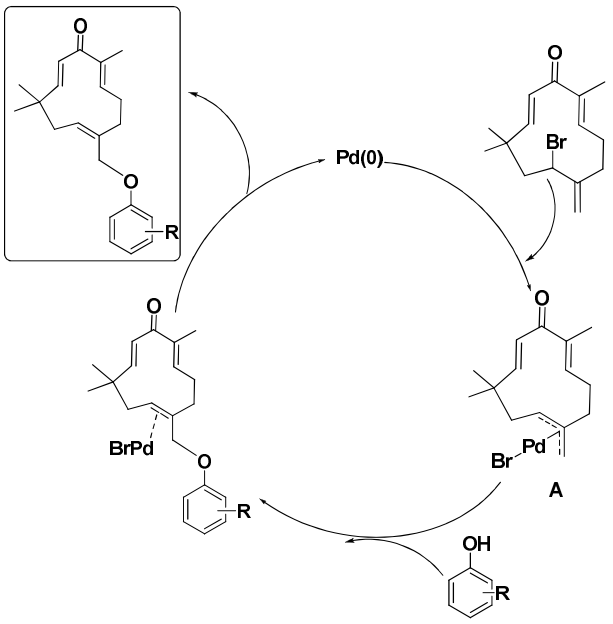


Reaction conditions: Zerumbone acetate **40** (1.0 equiv.), Acid **44** (1.0 equiv.), $Pd_2(dba)_3.CHCl_3$ (10 mol %), PPh_3 (40 mol %), Cs_2CO_3 (1.0 equiv.), THF (2 mL), rt, 12 h.

Scheme 2A.15

2A.5. Mechanism

A plausible mechanistic pathway for the reaction is outlined in scheme 2A.16. The initial event would involve the oxidative addition of the allylbromide **36** to a palladium (0) species to produce the η^3-allylpalladium intermediate A.[20] The subsequent nucleophilic attack on the carbon of allyl group followed by decomplexation form the zerumbone pendant derivatives.



Scheme 2A.16

2A.6. Biological evaluation of zerumbone pendant derivatives

2A.6.1. Anti-diabetic activity

Recently we were involved in biological screening of the phytochemicals and their derivatives from some selected plants.[37-39] Diabetes mellitus is characterized by hyperglycemia in which an elevated amount of glucose circulates in the blood plasma.[40] The enzymes, α-glucosidase and α-amylases, are important therapeutic targets for the modulation of postprandial hyperglycemia which is the initial metabolic abnormality to occur in type 2 diabetes mellitus.[41] We have tested the hyperglycemic activity of the synthesized zerumbone derivatives.

From preliminary *in vitro* α-glucosidase and α-amylase inhibition assays, it can be seen that the synthesized zerumbone pendant derivatives have an improved α-amylase and α-glucosidase inhibition activity. The compound **38h** exhibited potential inhibition of α-amylase with lowest IC_{50} values of 11.933 ± 1.540 μM. It is to be observed that all the derivatives bearing more than one zerumbone moiety (**38m'**, **38l'**, **44a, 44b** and **44c**) exhibit lesser inhibition activities. The derivative **38e** exhibits potent inhibition towards α-glucosidase enzymes with lowest IC_{50} value of 14.06 ± 0.103 μM, much better than the standard acarbose.

Prolonged hyperglycemia increases protein glycation, leading to the gradual build-up of advanced glycation end products (AGEs) in body tissue, which contributes to the

development and progression of various diabetic complications.[42] Hence the compounds were evaluated for its ability to prevent the protein glycation reaction as reported by Matsuura *et al.*[43] The compound **38i** exhibits superior anti-glycation property (15.089 ± 0.187 μM), which is better than the parent compound–zerumbone (104.86 ± 0.183 μM) and the standard ascorbic acid (158.23 ± 0.718 μM).

Table 2A.4. Anti-diabetic assay

Compounds	*α*-amylase	*α*-glucosidase	Antiglycation	Compounds	*α*-amylase	*α*-glucosidase	Antiglycation
	IC_{50} (μM/mL)				IC_{50} (μM/mL)		
38a	22.191±0.262	17.923±1.196	28.874±1.704	**38m**	19.019±1.185	25.374±0.700	21.257±1.504
38b	27.532±1.291	25.723±0.726	27.597±1.895	**38m'**	27.939±1.778	41.852±1.306	34.959±1.705
38c	14.097±1.111	25.573±0.955	24.835±1.275	**38n**	12.504±0.621	26.528±0.585	27.864±0.225
38d	12.975±0.815	27.839±0.594	32.217±0.346	**38n'**	19.466±1.389	19.573±1.977	25.931±1.547
38e	18.599±0.540	14.061±0.103	22.194±0.798	**42b**	28.087±0.164	28.691±0.652	34.281±0.567
38f	18.231±1.230	23.754±0.453	29.254±0.302	**42c**	33.230±0.591	27.090±0.447	30.108±1.293
38g	24.972±0.152	32.952±0.135	28.491±1.149	**42d**	15.900±0.533	29.917±1.306	18.672±2.771
38h	11.933±1.540	29.591±0.922	25.411±0.208	**42e**	26.462±1.469	33.766±0.687	35.247±1.982
38i	29.491±0.142	25.363±0.466	15.089±0.187	**42f**	21.523±0.946	19.912±0.039	34.528±1.754
38j	17.585±1.120	33.215±0.132	29.781±0.222	**44a**	24.739±1.310	52.180±0.750	47.141±0.033
38k	27.086±0.609	25.804±0.845	32.284±0.829	**44b**	32.849±1.005	27.948±0.199	36.962±0.626
38l	43.657±1.610	46.940±0.910	46.433±0.067	**44c**	35.070±1.028	37.563±0.554	62.697±0.080
38l'	19.46±0.098	25.581±0.065	29.281±0.252	**Zerumbone**	**51.070±0.254**	**271.053±0.332**	**104.86±0.183**
Std	**8.5±0.898 (Acarbose)**	**81.3±1.10 (Acarbose)**	**158.23±0.718 (Ascorbic acid)**				

2A.6.2. Molecular docking studies: Docking interaction studies of the compounds with proteins

In order to understand the interaction of zerumbone derivative with the protein, we have carried out the molecular docking studies. The molecular docking studies of **38m** and **38m'** with various proteins 1BVN, 3A4A and 3AJ7 were carried out using MOE 2009.10 (Chemical computing group, Inc.). The MMFF 94x force field with conjugant gradient was used for energy minimisation of the protein molecules.[44] The active site of the proteins was identified using the default 'Site Finder' tool. The molecular docking score of **38m** and **38m'** with the protein 1BVN are -12.8172 and -10.5893 kcal/mol respectively. The binding interactions of the ligands to the target proteins were studied using LigPlot analysis. Binding of **38m** shows a backbone donor bonding interaction with a polar amino acid residue Gly*A*862 (2.18Å, 11%) and **38m'** shows a docking score of -10.5893 kcal/mol. No prominent interactions were observed for **38m'** with this protein. Good molecular docking scores were observed for the compounds with the protein 3A4A.

It shows a docking score of -16.1169 kcal/mol and -15.2893 kcal/mol for **38m** and **38m'** respectively. But **38m** showed an indirect hydrogen bonding interaction with polar, acidic and basic amino acid residue Tyr158, Asp242 and His280 respectively. No prominent interactions were observed for both **38m** and **38m'** with this protein. The molecular docking scores of **38m** and **38m'** with the protein 3AJ7 are -15.3344 and -12.1192 kcal/mol respectively. No prominent interactions were observed for both the compounds with this targeted protein. But **38m** shows two different indirect hydrogen bonding interactions with a polar amino acid residue Gln279 and with an acidic Asp307. Similarly compound **38m'** shows an indirect hydrogen bonding interaction with polar amino acid residues Gly279 and Tyr158, and also with an acidic residue Asp242. The proximity contour near some regions of the ligands indicates the closeness of the groups present in that region to the active site of the protein. The blue smudges that are drawn behind some of groups in certain cases represent the amount of solvent exposure (Figure 2A.4).

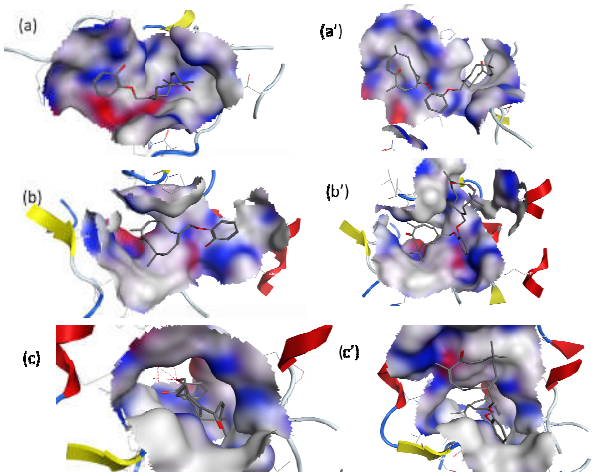


Figure 2A.4. Docking interactions of the compounds with proteins; (**a**) and (**a'**) molecular docking studies of **38m** and **38m'** with the protein 1BVN,; (**b**) and (**b'**) molecular docking studies of **38m** and **38m'** with the protein 3A4A, and (**c**) and (**c'**) molecular docking studies of **38m** and **38m'** with the protein 3AJ7 respectively.

Table 2A.5. The molecular docking studies of **38m** and **38m'** with proteins 1BVN, 3A4A and 3AJ7

	E Score (Kcal/ mol)		
Compounds	**IBVN**	**3A4A**	**3AJ7**
38m	-12.8175	-16.1169	-15.3344
38m'	-10.5893	-15.2893	-12.1192

2A.6.3. Anti-proliferative activity

Cancer, the frightful disease, is a chronic disorder involved in various cell signaling pathways and disorganized cell functions like uncontrolled cell proliferation with disturbed apoptosis.[45-47] Even though we have well developed scientific knowledge in cancer treatments, till today development of anticancer agents without any side effects and with lowest possible cost, is a potential research area for pharmaceutical industry in worldwide. Some of the complications occur during *in vivo* cytotoxic screening but *in vitro* studies provide a species-specific, simpler, convenient, and more detailed analysis of the system.

In the present study, preliminary growth inhibitory activity of zerumbone and some selected zerumbone derivatives (**38b**, **38d**, **38k**, **38e**, **44a**, **44b** and **44c**) against five human cancer cell lines *viz*., A549 (human lung adenocarcinoma), HCT116 (human colon carcinoma), HeLa (Human cervix carcinoma), HT1080 (Human Fibrosarcoma) and MDAMB231 (human breast adenocarcinoma) was carried out using MTT assay and the results were reported in terms of IC_{50} values (Table 4).[48] Results were compared with rat heart myoblast cells (H9c2) which showed non toxicity of cells on treatment with zerumbone and its derivatives. Among the compounds, **44c** showed significant growth inhibition action against A549 (IC_{50} = 8.74 ± 1.95 μM) and HCT116 (IC_{50} = 4.48 ± 0.19 μM). Similarly **44b** showed significant growth inhibition action against HeLa (IC_{50} = 6.35 ± 1.30 μM) and HCT116 (IC_{50} = 4.39 ± 2.01 μM) when compared with other compounds.

Table 2A.6. IC_{50} value of compounds (Entry 1-9)

Entry	Compounds	[a]IC_{50} (μM)				
		HT1080	**A549**	**HeLa**	**HCT116**	**MDAMB231**
1	**38b**	>30	>30	*NA	*NA	29.03 ± 0.52
2	**38d**	24.66±1.57	20.44±2.9	20.15±2.59	4.27±1.51	>30
3	**38k**	>30	28.8±0.72	>30	4.33±0.11	>30
4	**38e**	>30	>30	>30	4.36±0.68	>30
5	**44a**	18.56±1.22	15.39±1.15	>30	4.30±0.100	14.03±0.94
6	**44b**	14.70±1.05	14.10±1.30	**6.35±1.30**	**4.39±2.01**	13.9±1.02
7	**44c**	11.37±1.00	**8.74±1.95**	14.5±0.37	**4.48±0.19**	14.53±0.15
8	**Zerumbone**	>30	>30	16.62±0.48	4.97±0.46	24.4±1.19
9	**Paclitaxel (nM)**	8.64±1.63	31.0±2.50	7.75±0.70	5.5±1.25	9.12±0.15

[a]IC_{50} values of the zerumbone derivatives which showed maximum activity are highlighted using bold letters. *NA- No activity

Further, we will check the effects of these compounds in cell death, including its molecular mechanisms of action. In future, this will provide an approach to develop potent zerumbone derivatives to get new leads for the treatment of diabetes and cancer.

2A.6.4. Anti-hypertensive activity

Hypertension has become one of the most important preventable causes for premature morbidity and mortality worldwide. It is estimated to cause 7.5 million deaths, about 12.8% of all annual deaths.[49, 50] Most of the currently used antihypertensive agents cannot be used as a single drug therapy because of their limited efficacy and side effects.[51] Therefore, the research and development of new drugs with multiple therapeutic effects is most desirable.

In vitro angiotensin converting enzyme inhibition assays of some selected compound were carried out. From the results, it was found that compound **38f** inhibited ACE enzyme completely at 100 µM concentration than other zerumbone pendant derivatives. It is to be noted that the compound, **38f** has two times more potency than the parent molecule zerumbone (% inhibition = 47.25). Also, the compound **38f** showed similar activity in comparison to the standard captopril (% inhibition = 102.20). The results are shown in Table 2A.7.

Table 2A.7. Percentage inhibition of zerumbone derivatives

Compounds	% inhibition				Compounds	% inhibition			
	Concentrations					Concentrations			
	10 µM	**100 µM**	**500 µM**	**1000 µM**		**10 µM**	**100 µM**	**500 µM**	**1000 µM**
38a	34.85	59.85	82.58	93.94	**38k**	11.36	59.85	78.79	92.42
38b	33.33	50.00	71.21	87.88	**38l'**	50.76	68.18	95.45	104.55
38d	31.06	61.36	78.03	96.97	**38m'**	65.15	80.30	86.36	95.45
38e	28.03	37.12	41.67	50.76	**44a**	68.18	78.03	84.09	103.03
38f	70.45	**104.55**	103.03	104.55	**44c**	40.15	46.97	65.91	81.82
38g	66.67	84.09	94.70	104.55	**Zerumbone**	**21.98**	**47.25**	**68.13**	**94.51**
38i	25.76	54.55	59.09	66.67	**Captopril**	**100.55**	**102.20**	**100.55**	**101.10**

2A.7. Conclusion

In conclusion, we have utilised the palladium catalyzed Tsuji-Trost coupling of phenols/arene carboxylic acids with zerumbone to provide a new class of zerumbone pendant derivatives. Preliminary *in vitro* α-glucosidase inhibition assays revealed that the synthesized zerumbone pendant derivatives have potent inhibitory activity than the parent molecule zerumbone (IC_{50}, 271.053 ± 0.332 µM) and the standard acarbose (81.3 ± 1.10 µM). Among them compound **38e** showed better α-glucosidase inhibition activity (IC_{50} = 14.061 ± 0.103 µM) compared to both parent and standard. Also, the zerumbone derivatives showed significantly improved α-amylase inhibitory activity (IC_{50}, 12-43 µM range) as compared to zerumbone (51.070 ± 0.254 µM).

Compounds **38h** and **38i** showed superior α-amylase and glycation inhibition activity (IC_{50} = 11.933 ± 1.540 μM and IC_{50} = 15.089 ± 0.187 μM respectively). Also, all the derivatives showed superior anti-glycation property than zerumbone (104.86 ± 0.183 μM) and the standard ascorbic acid (165.11 ± 0.2306 μM). Molecular docking studies were performed to recognize the binding mode of the active compounds with proteins along with activity comparison of derivatives. The zerumbone pendant derivatives were tested for cytotoxicity against selected human cancer cells *viz*., A549 (human lung adenocarcinoma), HCT116 (human colon carcinoma), HeLa (human cervix carcinoma), HT1080 (human Fibrosarcoma) and MDAMB231 (human breast adenocarcinoma) using MTT assay. Among tested compounds, **44b** showed significant growth inhibition action against HeLa (IC_{50} = 6.35 ± 1.30 μM) and HCT116 (IC_{50} = 4.39 ± 2.01 μM) and **44c** showed significant growth inhibition action against A549 (IC_{50} = 8.74 ± 1.95 μM) and HCT116 (IC_{50} = 4.48 ± 0.19 μM) when compared with other compounds. In addition, some zerumbone derivatives were evaluated for their angiotensin-converting (ACE) enzyme inhibitory activity. Among the screened compounds, compound **38f** showed comparable inhibition activity against angiotensin-converting (ACE) enzyme in comparison to the standard captopril.

2A.8. Experimental Section

General Methods:

All the chemicals were of the best grade commercially available and were used without further purification. All the solvents were purified according to standard procedures; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin layer chromatography was performed on glass plates coated with silica gel containing calcium sulfate binder. Gravity column chromatography was performed using 60-120 or 100-200 mesh silica gel, mixtures of hexane-ethyl acetate were used for elution. Melting point was determined on a Buchi melting point apparatus and is uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a Bruker AMX 500 spectrophotometers ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ, in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.25, singlet). Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); quin (quintet); dd (double doublet); m (multiplet). Coupling constants are reported as *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts

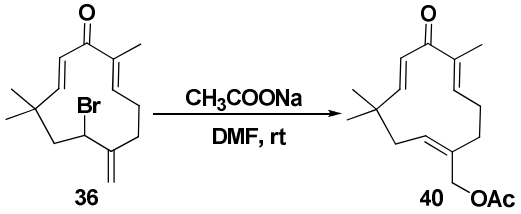
per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.03, triplet). Mass spectra were recorded under ESI/HRMS at 61800 resolution using Thermo Scientific Exactive mass spectrometer. IR spectra were recorded on Bruker Alpha FT-IR spectrometer.

2A.8.1. Synthesis of 7-bromo-2,9,9-trimethyl-6-methyl-6-methylenecycloundeca-2,10-dienone (36)

NBS **35** (0.90 g, 5.0 mmol) was added to a solution of zerumbone **34** (1.0 g, 4.6 mmol) in acetonitrile/H_2O (1:1, 15 mL) mixture, and stirred vigorously at room temperature for 1 min. H_2O (30 mL) was poured into the solution, filtered immediately, and washed with H_2O several times to afford 7-bromo-2,9,9-trimethyl-6-methyl-6-methylenecycloundeca-2,10-dienone, **36** as a colourless solid (99% yield) quantitatively.

2A.8.2. Synthesis of 6-acetoxymethyl- 2,9,9-trimethylcycloundeca-2,6,10-trienone (40)

Sodium acetate **39** (82.8 mg, 1.0 mmol) was added to a solution of **36** (200 mg, 0.67 mmol) in DMF (20 mL) at room temperature and stirred for 16 h. The progress of the reaction was monitored by TLC (hexane/ethyl acetate = 3:2). The DMF solution was extracted with CH_2Cl_2 (3x30 mL) and the combined organic extracts were washed with brine (2x30 mL), dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator. Chromatography on silica gel, eluting with a 2:1 mixture of hexane and ethyl acetate, afforded 6-acetoxymethyl-2,9,9-trimethylcycloundeca-2,6,10-trienone, (**40**) as a colourless oil in 77% yield.



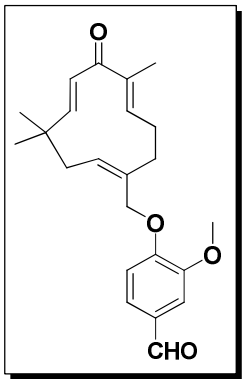
2A.8.3 General Procedure for the Synthesis of zerumbone pendant derivatives

6-Acetoxymethyl-2,9,9-trimethylcycloundeca-2,6,10-trienone **40** (0.1087 mmol) and nucleophile (0.1087 mmol) were taken in a schlenk tube. $Pd_2(dba)_3.CHCI_3$ (10 mol %) as catalyst, PPh_3 (40 mol %) as ligand, Cs_2CO_3 (2.0 equiv.) as base were added followed by THF (2 mL) and stirred the reaction for 12 h at room temperature. After the completion of the reaction as monitored by TLC, the reaction mixture was concentrated and the crude product was purified by column chromatography on silica gel (100-200 mesh) and hexane: ethylacetate as the eluent to afford the product.

2A.9. Spectral details of compounds 34a-44c

3-methoxy-4-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8 trienyl)methoxy)benzaldehyde (38a)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), vanillin **37a** (16.5 mg, 0.1087 mmol), $Pd_2(dba)_3.CHCl_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %), Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **38a** as a white crystalline solid (18 mg, 46%).



R_f: 0.14 (ethylacetate/hexane = 1:3).

Mp: 185-190 ^oC.

IR (neat) υ_{max}: 3268, 3032, 2958, 2953, 2857, 2366, 2336, 1651, 1498, 1467, 1366, 1268, 1232, 1173, 1106, 1038, 823, 736, 703, 631, 570, 528 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.43-7.40 (m, 2H), 6.97 (d, *J* = 8 Hz, 1H), 6.20 (d, *J* = 16 Hz, 1H), 6.07-6.03 (m, 1H), 6.02 (d, *J* = 16.5 Hz, 1H), 5.58-5.54 (m, 1H), 4.64 (brs, 1H), 4.51 (brs, 1H), 3.88(s, 3H),2.69 (brs, 1H), 2.58 (brs, 1H), 2.41-2.34 (m, 1H), 2.30-2.25 (m, 2H), 2.07-2.05 (m, 1H), 1.78 (s, 3H), 1.28 (s, 3H), 1.09 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.7, 190.5, 160.0, 153.6, 150.1, 148.9, 138.8, 134.6, 131.7, 130.4, 127.2, 126.3, 111.7, 109.1, 66.3, 55.5, 42.5, 37.3, 36.3, 24.8, 12.0 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{28}NaO_4$: 391.18853, Found: 391.18878 $[M+Na]^+$.

(2E,6Z,10E)-6-((4-methoxyphenoxy)methyl)-2,9,9-trimethylcycloundeca-2,6,10-trienone (38b)

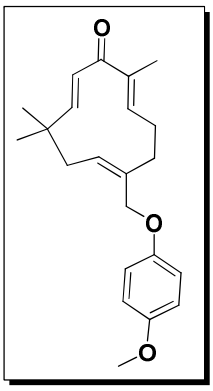
Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **37b** (13.48 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **38b** as a white crystalline solid (28 mg, 76%).

R_f: 0.43 (ethylacetate/hexane = 1:3).

Mp: 110-115 ^oC.

IR (neat) υ_{max}: 2924, 1742, 1652, 1508, 1462, 1365, 1226, 1106, 1038, 827, 625, 578 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.83 (s, 4H), 6.08-6.06 (m, 1H), 6.06 (d, *J* = 16.5 Hz,



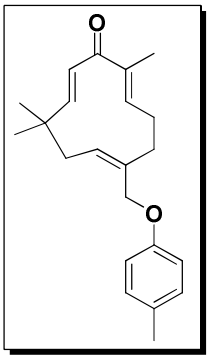
1H),6.02 (d, *J* = 16.5 Hz, 1H), 5.51-5.47 (m, 1H), 4.50 (d, *J* = 9.5 Hz, 1H), 4.31 (d, *J* = 9 Hz, 1H), 3.78 (s, 3H), 2.74-2.72 (m, 1H), 2.60-2.58 (m, 1H), 2.47-2.42(m, 1H), 2.32-2.23 (m, 2H), 2.05-2.03 (m, 1H), 1.83 (s, 3H), 1.27 (s, 3H), 1.10 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.9, 160.2, 154.0, 152.8, 149.3, 138.4, 135.9, 130.3, 127.4, 116.0, 115.5, 114.7, 65.8, 55.6, 42.4, 37.4, 36.2, 25.0, 12.2 ppm.

HRMS (ESI): *m/z* Calcd for $C_{22}H_{28}NaO_3$: 363.19361, Found: 363.23306 $[M+Na]^+$.

(2E,6Z,10E)-2,9,9-trimethyl-6-(p-tolyloxymethyl)cycloundeca-2,6,10-trienone (38c)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **37c** (11.74 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **38c** as colourless liquid (24 mg, 68%)



R_f: 0.571 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 2925, 2852, 2394, 2356, 1714, 1555, 1509, 1430, 1362, 1331, 1232, 1178, 1102, 969, 816, 758, 702, 634, 574, 546 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 6.09-6.07 (m, 1H), 6.07 (d, *J* = 16.5 Hz, 1H), 6.02 (d, *J* = 16 Hz, 1H), 5.52-5.48 (m, 1H), 4.51 (d, *J* = 9.5 Hz, 1H), 4.34 (d, *J* = 9.5 Hz, 1H), 2.74-2.72 (m, 1H), 2.60-2.57 (m, 1H), 2.48-2.43 (m, 1H), 2.31 (s, 3H), 2.28-2.24 (m, 2H), 2.06-2.03 (m, 1H), 1.83 (s, 3H), 1.27 (s, 3H), 1.10 (s, 3H) ppm.

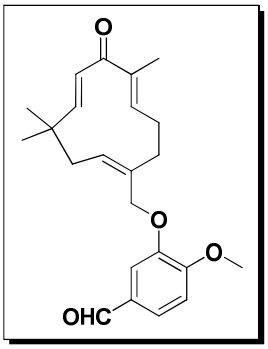
^{13}C NMR (125 MHz, $CDCl_3$): δ 203.5, 159.9, 156.6, 149.0, 138.5, 135.9, 130.3, 130.1, 129.9, 127.4, 114.3, 65.3, 42.4, 37.4, 36.3, 25.0, 20.5, 12.2 ppm.

HRMS (ESI): *m/z* Calcd for $C_{22}H_{28}NaO_2$: 347.19870, Found: 347.19887 $[M+Na]^+$.

4-methoxy-3-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methoxy)benzaldehyde (38d)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **37d** (16.5 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **38d** as colourless

liquid (25 mg, 63%).



R_f: 0.28 (ethylacetate/hexane = 1:3).

Mp: 85-90 ^oC.

IR (neat) υ_{max}: 3351, 2960, 2864, 2724, 1686, 1645, 1588, 1510, 1439, 1395, 1342, 1269, 1161, 1129, 1015, 865, 808, 754, 700, 638, 583 cm^{-1}.

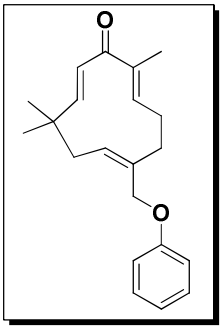
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.46-7.40 (m, 2H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.26 (d, *J* = 16.5 Hz, 1H), 6.06-6.03 (m, 1H), 6.01 (d, *J* = 16.5 Hz, 1H), 5.57-5.54 (m, 1H), 4.57 (brs, 1H), 4.48 (brs, 1H), 3.89 (s, 3H), 2.67 (brs, 1H), 2.57 (brs, 1H), 2.45 (brs, 1H), 2.31-2.25 (m, 2H), 2.07-2.04 (m, 1H), 1.76 (s, 3H), 1.51(s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 202.4, 190.4, 160.3, 158.0, 155.0, 149.1, 138.0, 133.7, 130.2, 127.2, 122.4, 114.7, 66.1, 55.7, 42.7, 37.3, 36.5, 29.7, 24.9, 12.2 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{28}NaO_4$: 391.18853, Found: 391.18878 $[M+Na]^+$.

(2E,6Z,10E)-2,9,9-trimethyl-6-(phenoxymethyl)cycloundeca-2,6,10-trienone (38e)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **37e** (10.21 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **38e** as a white crystalline solid (11 mg, 33%).



R_f: 0.571 (ethylacetate/hexane = 1:3).

Mp: 60-63 ^oC.

IR (neat) υ_{max}: 3390, 2922, 1590, 1462, 1420, 1121, 1040, 856, 540 cm^{-1}.

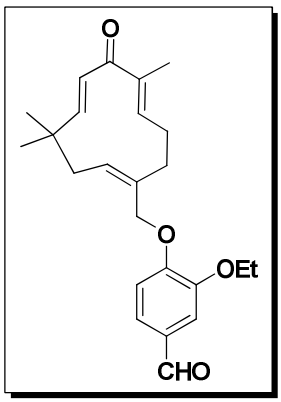
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 6.96-6.93 (m, 1H), 6.88-6.87 (m, 2H), 6.07-5.98 (m, 3H), 5.51-5.48 (m, 1H), 4.51 (brs, 1H), 4.37 (brs, 1H), 2.71 (brs, 1H), 2.56 (brs, 1H), 2.44-2.41 (m, 1H), 2.30-2.23 (m, 2H), 2.05-2.03 (m, 1H), 1.82 (s, 3H), 1.26 (s, 3H), 1.08 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.7, 160.0, 158.7, 149.2, 138.5, 135.7, 130.5, 129.5, 127.4, 121.0, 114.5, 65.1, 42.5, 37.4, 36.3, 25.0, 12.2 ppm.

HRMS (ESI): *m/z* Calcd for $C_{21}H_{26}NaO_2$: 333.18305, Found: 333.18364 $[M+Na]^+$.

3-ethoxy-4-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methoxy)benzaldehyde (38f)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **37f** (18.06 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCl_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **38f** as colourless liquid (19 mg, 23%).



R_f: 0.314 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 3384, 2922, 1586, 1514, 1468, 1425, 1367, 1317, 1266, 1120, 1038, 860, 661, 617, 547 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.84 (s, 1H), 7.42-7.39 (m, 2H), 6.98 (d, *J* = 8 Hz, 1H), 6.30 (d, *J* = 16.5 Hz, 1H), 6.04-6.00 (m, 2H), 5.57-5.53 (m, 1H), 4.60 (brs, 1H), 4.51 (brs, 1H), 4.14-4.10 (q, 2H), 2.69 (s, 1H), 2.56 (brs, 1H), 2.45-2.43 (m, 1H), 2.32-2.26 (m, 2H), 2.06-2.01(m,1H), 1.77 (s, 3H), 1.41 (t, *J* = 7 Hz, 3H), 1.27 (s, 3H), 1.11 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.8, 190.4, 160.5, 153.7, 149.5, 148.5, 138.9, 134.5, 131.7, 130.4, 127.3, 126.0, 112.0, 110.2, 66.6, 64.2, 42.5, 37.4, 36.6, 24.8, 14.6, 12.2 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{30}NaO_4$: 405.20418, Found: 405.20346 $[M+Na]^+$.

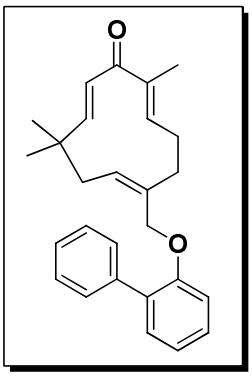
(2E,6Z,10E)-6-((biphenyl-2-yloxy)methyl)-2,9,9-trimethylcycloundeca-2,6,10-trienone (38g)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **37g** (18.5 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCl_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **38g** as a colourless crystalline solid (32 mg, 76%).

R_f: 0.571 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 3372, 3059, 2962, 2929, 2870, 1897, 1709, 1646, 1504, 1479, 1457, 1434, 1388, 1366, 1267, 1223, 1119, 1054, 1007, 973, 912, 834, 754, 735, 700, 614, 566 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.51 (m, 2H), 7.43-7.40 (m, 2H), 7.36-7.31 (m, 3H), 7.10-7.09 (m, 1H), 7.03 (d, *J* = 5.5 Hz, 1H), 6.04-6.02 (m, 1H), 5.99 (d, *J* = 16.5



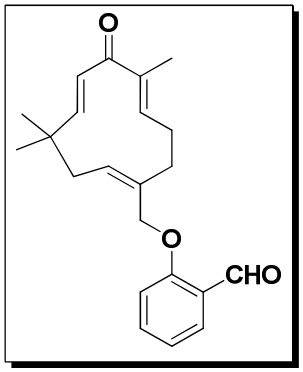
Hz, 1H), 5.75 (d, *J* = 16.5 Hz, 1H), 5.43-5.40 (m, 1H), 4.67 (brs, 1H), 4.16 (brs, 1H), 2.66 (brs, 1H), 2.38-1.99 (m, 5H), 1.69 (s, 3H),1.24 (s, 3H), 1.08 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.2, 159.2, 155.6, 149.3, 138.3, 136.2, 131.0, 129.4, 128.8, 128.5, 127.8, 127.3, 126.9, 127.3, 126.9, 65.9, 42.2, 37.4, 35.2, 24.4, 11.7 ppm.

HRMS (ESI): *m/z* Calcd for $C_{27}H_{30}NaO_2$: 409.21435, Found: 409.21418 $[M+Na]^+$.

2-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methoxy)benzaldehyde (38h)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **37h** (13.26 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **38h** as viscous liquid (10 mg, 28%).



R_f: 0.40 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 3341, 2923, 2855, 1588, 1422, 1366, 1318, 1119, 1040, 858, 669, 618, 524 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.5 (s, 1H), 7.87 (dd, J_1 = 7.5 Hz, J_2 =1.5 Hz, 1H), 7.57-7.54 (m, 1H), 7.09-7.06 (m, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.10-6.08 (m, 1H), 6.04 (d, *J* = 16.5 Hz, 1H), 5.80 (d, *J* = 16.5 Hz, 1H), 5.58-5.55 (m, 1H), 4.83 (brs, 1H), 4.36 (brs, 1H), 2.81 (brs, 1H), 2.48-2.37 (m, 3H), 2.27-2.25 (m, 1H), 2.12-2.09 (m, 1H), 1.82 (s, 3H), 1.27 (s, 3H), 1.14 (s, 3H) ppm.

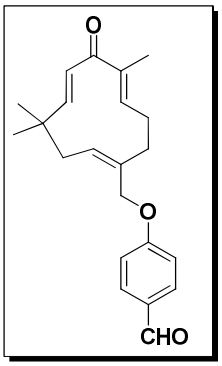
^{13}C NMR (125 MHz, $CDCl_3$): δ 203.0, 189.2, 160.8, 149.0, 135.7, 135.1, 128.9, 128.1, 125.2, 120.9, 112.6, 112.4, 64.9, 42.4, 37.4, 35.1, 29.6, 24.5, 11.7 ppm.

HRMS (ESI): *m/z* Calcd for $C_{22}H_{26}NaO_3$: 361.17796, Found: 361.17822 $[M+Na]^+$.

4-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methoxy)benzaldehyde (38i)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **37i** (13.26 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at

room temperature for 12 h under argon atmosphere gave the product **38i** as a colourless liquid (33 mg, 91%).



R_f: 0.42 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 3341, 2923, 2855, 1588, 1422, 1366, 1318, 1119, 1040, 858, 669, 618, 524 cm^{-1}.

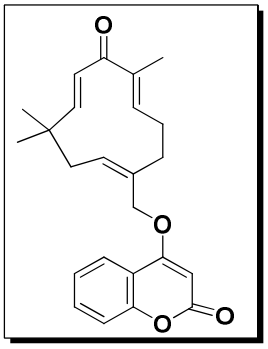
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.83 (d, *J* = 8.5Hz, 2H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.07-6.06 (m, 1H), 6.02 (d, *J* = 16.5 Hz, 1H), 5.97 (d, *J* = 16.5 Hz, 1H), 5.56-5.53 (m, 1H), 4.63 (brs, 1H), 4.45 (brs, 1H), 2.68 (s, 1H), 2.53 (s, 1H), 2.42-2.39 (m, 1H), 2.33-2.26 (m, 2H), 2.09-2.07 (m, 1H), 1.82 (s, 3H) , 1.27 (s, 3H), 1.10 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.6, 190.4, 163.7, 159.7, 149.1, 137.9,135.6, 132.0, 131.2, 130.1, 127.5, 114.9, 67.8, 42.5, 39.8, 37.4, 37.0, 31.8, 24.9, 21.2, 12.2 ppm.

HRMS (ESI): *m/z* Calcd for $C_{22}H_{26}NaO_3$: 361.17796, Found: 361.17822 $[M+Na]^+$.

4-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methoxy)-2H-chromen-2-one (38j)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **37j** (17.6 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **38j** pale yellow solid (13 mg, 31%).



R_f: 0.34 (ethylacetate/hexane = 1:3)

Mp: 165-167 ^oC.

IR (neat) υ_{max}: 3391, 2960, 2924, 2854, 1724, 1649, 1436, 1382, 1283, 1099, 972, 747, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8 Hz, 1H), 7.60-7.57 (m, 1H), 7.36 (d, *J* = 8 Hz, 1H), 7.30-7.28 (m, 1H), 6.12-6.09 (m, 1H), 6.06 (d, *J* = 16.5 Hz, 1H), 5.84 (d, *J* = 16.5 Hz, 1H), 5.71 (s, 1H), 5.66-5.63 (m, 1H), 4.82 (brs, 1H), 4.47 (brs, 1H), 2.75 (brs, 1H), 2.51-2.47 (m, 2H), 2.41-2.31 (m, 3H), 1.84 (s, 3H), 1.27 (s, 3H), 1.16 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 202.8, 165.1, 158.8, 153.3, 148.7, 138.7, 133.3, 132.5, 132.2, 127.5, 123.9, 122.7, 116.9, 115.5, 91.9, 66.0, 42.5, 37.5, 35.2, 29.6, 24.5, 12.1 ppm.

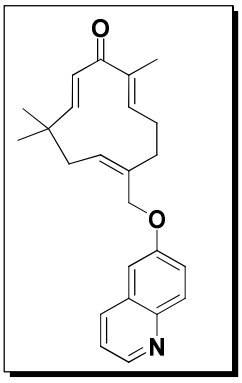
HRMS (ESI): *m/z* Calcd for $C_{24}H_{26}NaO_4$: 401.17288, Found: 401.17199 $[M+Na]^+$.

(2E,6Z,10E)-2,9,9-trimethyl-6-((quinolin-6-yloxy)methyl)cycloundeca-2,6,10-trienone (38k)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **37k** (15.78 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **38k** as a white crystalline solid (27 mg, 73%).

R_f: 0.17 (ethylacetate/hexane = 1:3)

Mp: 125 ^oC.



IR (neat) υ_{max}: 3012, 2918, 2383, 1868, 1829, 1796, 1744, 1652, 1541, 1521, 1422, 1366, 1317, 1272, 1209, 1161, 1119, 1018, 752, 601 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (d, *J* = 3 Hz, 1H), 8.02-7.98 (m, 2H), 7.35-7.31 (m, 2H), 7.05 (d, *J* = 2.5 Hz, 1H), 6.09-6.02 (m, 3H), 5.56-5.53 (m, 1H), 4.65 (brs, 1H), 4.48 (brs, 1H), 2.75 (brs, 1H), 2.57 (brs, 1H), 2.48-2.45 (m, 1H), 2.34-2.27 (m, 2H), 2.24-2.08 (m, 1H), 1.84 (s, 3H), 1.27 (s, 3H), 1.12 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.3, 159.6, 156.7, 149.0, 148.0, 144.4, 138.5, 135.2, 134.7, 131.1, 130.9, 129.2, 127.5, 122.2, 121.4, 106.0, 65.5, 42.5, 37.4, 36.1, 25.0, 12.2 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{28}NO_2$: 362.21200, Found: 362.21200 $[M+Na]^+$.

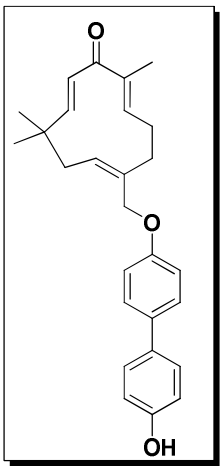
(2E,6Z,10E)-6-((4'-hydroxybiphenyl-4-yloxy)methyl)-2,9,9-trimethylcycloundeca-2,6,10-trienone (38l)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **37l** (10.04 mg, 0.054 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave two product **38l** and **38l'** as viscous liquid and white solid respectively.

38l (11 mg, 26%).

R_f: 0.371 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 3341, 2923, 2854, 2369, 2338, 1742, 1589, 1503, 1461, 1422, 1368, 1316, 1268, 1163, 1118, 1038, 861, 823, 666, 620, 535 cm^{-1}.



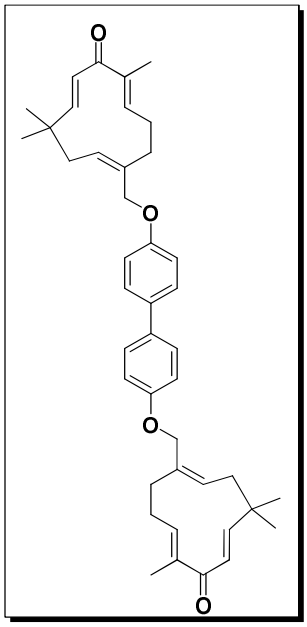
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, *J* = 9 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.11-6.08 (m, 2H), 6.04 (d, *J* = 16.5, Hz, 1H), 5.55-5.52 (m, 1H), 5.08 (s, 1H), 4.56 (brs, 1H), 4.42 (brs, 1H), 2.76-2.75 (m, 1H), 2.62-2.60 (m, 1H), 2.50-2.45 (m, 1H), 2.37-2.27 (m, 2H), 2.09-2.06 (m, 1H), 1.85 (s, 3H), 1.28 (s, 3H), 1.11 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 204.1, 160.2, 157.8, 154.9, 149.4, 138.5, 135.6, 133.8, 133.4, 130.6, 127.9, 127.8, 127.4, 115.6, 114.7, 65.3, 42.5, 37.4, 36.2, 25.0, 22.3, 12.2, 8.5 ppm.

HRMS (ESI): *m/z* Calcd for $C_{27}H_{30}NaO_3$: 425.20926, Found: 425.20904 $[M+Na]^+$.

(2E,2'E,6Z,6'Z,10E,10'E)-6,6'-(biphenyl-4,4'-diylbis(oxy))bis(methylene)bis(2,9,9-trimethylcycloundeca-2,6,10-trienone) (38l')

38l' : A white solid (25 mg, 38%).



R_f: 0.286 (ethylacetate/hexane = 1:3).

Mp: 150-155 ^oC.

IR (neat) υ_{max}: 3268, 3032, 2958, 2953, 2857, 2366, 2336, 1651, 1498, 1467, 1366, 1268, 1232, 1173, 1106, 1038, 823, 736, 703, 631, 570, 528 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.5 Hz, 4H), 6.95 (d, *J* = 9 Hz, 4H), 6.10-6.07 (m, 4H), 6.04 (d, *J* = 16.5 Hz, 2H), 5.55-5.52 (m, 2H), 4.57 (brs, 2H), 4.42 (brs, 2H), 2.76-2.74 (m, 2H), 2.62-2.60 (m, 2H), 2.50-2.45 (m, 2H), 2.37-2.20 (m, 4H), 2.09-2.07 (m, 2H), 1.85 (s, 6H), 1.28 (s, 6H), 1.11 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.7, 160.0, 157.9, 149.2, 138.5, 135.6, 133.8, 130.6, 127.8, 127.5, 114.8, 65.3, 42.5, 37.4, 36.2, 25.0, 12.2 ppm.

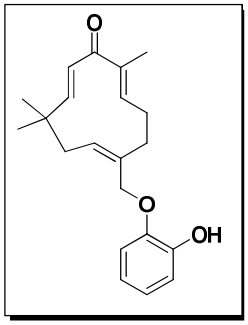
HRMS (ESI): *m/z* Calcd for $C_{42}H_{50}NaO_4$: 641.36068, Found: 641.36.34 $[M+Na]^+$.

(2E,6Z,10E)-6-((2-hydroxyphenoxy)methyl)-2,9,9-trimethylcycloundeca-2,6,10-trienone (38m)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **37m** (5.94 mg, 0.054 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol),

PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave two the products, **38m** and **38m'.**

38m: A white solid (12 mg, 19%).



R_f: 0.4 (ethylacetate/hexane = 1:3).

Mp: 100-105 ^oC.

IR (neat) υ_{max}: 3395, 2923, 2854, 1587, 1463, 1420, 1364, 1121, 1041, 857, 619 cm^{-1}.

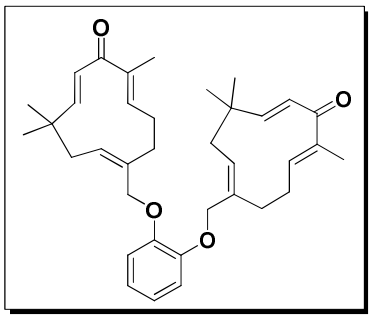
^1H NMR (500 MHz, $CDCl_3$): δ 6.94-6.84 (m, 4H), 6.09-6.08 (m, 1H), 6.03 (d, *J* = 16.5 Hz, 1H), 5.82 (d, *J* = 16.5 Hz, 1H), 5.57-5.59 (m, 1H), 5.51 (s, 1H), 4.71 (brs, 1H), 4.35 (brs, 1H), 2.76 (brs, 1H), 2.51-2.37 (m, 3H), 2.29-2.26 (m, 1H), 2.09 (brs, 1H), 1.83 (s, 3H), 1.28 (s, 3H), 1.13 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.1, 159.2, 149.1, 145.9, 145.6, 138.5, 135.4, 130.8, 127.5, 122.1, 120.1, 114.9, 111.9, 65.5, 42.4, 37.5, 35.3, 24.8, 12.0 ppm.

HRMS (ESI): *m/z* Calcd for $C_{21}H_{26}NaO_3$: 349.17796, Found: 349.17866 $[M+Na]^+$.

(2E,2'E,6Z,6'Z,10E,10'E)-6,6'-(1,2-phenylenebis(oxy))bis(methylene)bis(2,9,9-trimethylcycloundeca-2,6,10-trienone) (38m')

38m': A white solid (2 mg, 15%).



R_f: 0.4 (ethylacetate/hexane = 1:3).

Mp: 165-170 ^oC.

IR (neat) υ_{max}: 3058, 3035, 2960, 2926, 1736, 1652, 1592, 1501, 1454, 1387, 1365, 1246, 1210, 1004, 907, 836, 742, 700, 623, 580 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 6.92 (s, 4H), 6.06-6.05 (m, 2H), 6.02 (d, *J* = 16.5 Hz, 2H), 5.95 (d, *J* = 16.5 Hz, 2H), 5.52-5.48 (m, 2H), 4.65 (brs, 2H), 4.31 (brs, 2H), 2.78 (brs, 2H), 2.57 (brs, 2H), 2.48 (brs, 2H), 2.30 (brs, 2H), 2.19 (brs, 2H), 2.05 (brs, 2H), 1.79 (s, 6H), 1.27 (s, 6H), 1.12 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.4, 159.6, 149.0, 148.9, 138.6, 136.0, 130.0, 127.4, 121.6, 114.3, 65.8, 42.4, 37.4, 35.6, 24.7, 12.1 ppm.

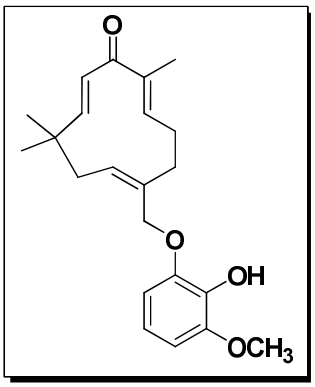
HRMS (ESI): *m/z* Calcd for $C_{36}H_{46}NaO_4$: 565.32938, Found: 565.32991 $[M+Na]^+$.

(2E,6Z,10E)-6-((2-hydroxy-3-methoxyphenoxy)methyl)-2,9,9-trimethylcycloundeca-

2,6,10-trienone (38n)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **37n** (15.3 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave gave two the products, **38n** and **38n'**.

38n: A white solid (6 mg, 15%).



R_f: 0.25 (ethylacetate/hexane = 1:3).

Mp: 133-135 ^oC.

IR (neat) υ_{max}: 3377, 2924, 2032, 1590, 1473, 1421, 1313, 1120, 1090, 1040, 858, 779, 620, 539 cm^{-1}.

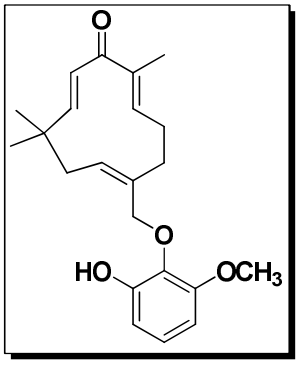
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.78-6.75 (m, 1H), 6.60-6.58 (m, 2H), 6.06-6.05 (m, 1H), 6.00-5.99 (m, 2H), 5.53-5.50 (m, 1H), 5.44 (s, 1H), 4.65 (brs, 1H), 4.40 (brs, 1H), 3.91 (s, 3H), 2.91-2.78 (m, 1H), 2.61 (brs, 1H), 2.48 (brs, 1H), 2.33-2.30 (m, 1H), 2.23 (brs, 1H), 2.06-2.02 (m, 1H), 1.81 (s, 3H), 1.27(s, 3H), 1.11 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.6, 159.7, 153.4, 147.6, 146.1, 138.7, 135.7, 130.4, 127.5, 118.7, 114.2, 105.3, 66.4, 56.0, 42.2, 37.2, 36.0, 25.1, 12.1 ppm.

HRMS (ESI): *m/z* Calcd for $C_{22}H_{28}NaO_4$: 379.18853, Found: 379.18902 $[M+Na]^+$.

(2E,6Z,10E)-6-((2-hydroxy-6-methoxyphenoxy)methyl)-2,9,9-trimethylcycloundeca-2,6,10-trienone (38n')

38n': A white solid (5 mg, 15%).



R_f: 0.28 (ethylacetate/hexane = 1:3).

Mp: 132-135 ^oC.

IR (neat) υ_{max}: 3377, 2924, 1590, 1473, 1421, 1313, 1120, 1090, 1040, 858, 779, 620, 539 cm^{-1}.

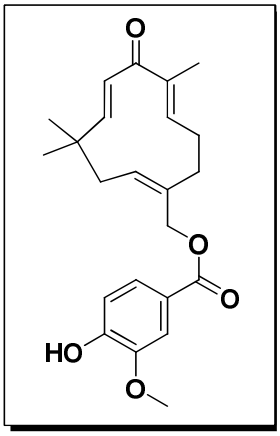
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.94 (t, J = 8.5 Hz, 1H), 6.60 (dd, J_1 = 8.5 Hz, J_2 = 1 Hz, 1H), 6.48 (dd, J_1 = 8.5 Hz, J_2 = 1 Hz, 1H), 6.04- 6.02 (m, 1H), 6.00 (d, J = 16.5 Hz, 1H),5.82 (d, J = 16.5 Hz, 1H), 5.69 (s, 1H), 5.52- 5.48 (m, 1H), 4.58 (brs, 1H), 4.38 (brs, 1H), 3.89 (s, 3H), 2.89-2.88 (m, 1H), 2.69- 2.68 (m, 1H), 2.57-2.46 (m, 1H), 2.37-2.35 (m, 1H), 2.26 (brs, 1H), 2.00-1.97 (m, 1H), 1.81 (s, 3H), 1.25 (s, 3H), 1.09 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.4, 159.6, 152.5, 149.8, 149.0, 138.4, 136.3, 134.2, 130.8, 127.3, 124.3, 108.3, 103.9,. 68.9, 55.7, 42.2, 37.3, 35.7, 24.8, 12.0 ppm

HRMS (ESI): *m/z* Calcd for $C_{22}H_{28}NaO_4$: 379.18853, Found: 379.18902 $[M+Na]^+$.

2-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methoxy)benzaldehyde (42b)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **41b** (18.26 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **42b** white solid (11.7 mg, 28 %).



R_f: 0.17 (ethylacetate/hexane = 1:3).

Mp: 110-112 ^oC.

IR (neat) υ_{max}: 2922, 2856, 2404, 2300, 1707, 1641, 1600, 1514, 1458, 1366, 1282, 1215 1102, 1029, 970, 766 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (dd, J_1 = 8.5 Hz, J_2 = 2 Hz, 1H), 7.52 (d, J = 1.5 Hz, 1H), 6.93 (d, J = 8.5 Hz, 1H), 6.05-6.04 (m, 2H), 6.01 (d, J = 16.5 Hz, 1H), 5.94 (d, J = 16.5 Hz, 1H), 5.52-5.48 (m, 1H), 4.89 (d, J = 12 Hz, 1H), 4.68 (d, J = 12 Hz, 1H), 3.94 (s, 3H), 2.70-2.69 (m, 1H), 2.59-2.45 (m, 2H), 2.31-2.25 (m, 2H), 2.08-2.04 (m, 1H), 1.70 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 206.1, 161.1, 150.3, 146.1, 138.4, 134.6, 131.2, 127.2, 124.1, 122.0, 120.1, 114.0, 111.5, 61.3, 55.9, 42.4, 37.5, 35.7, 29.8, 24.7, 11.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{28}NaO_5$: 407.18344, Found: 407.18428 $[M+Na]^+$.

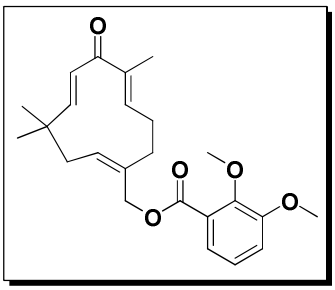
((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl 2,3-dimethoxybenzoate (42c)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **41c** (19.8 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **42c** white solid (8 mg, 19%).

R_f: 0.17 (ethylacetate/hexane = 1:3).

Mp: 65-67 ^oC.

IR (neat) υ_{max}: 2919, 2850, 2370, 2341, 1974, 1798, 1741, 1649, 1582, 1373, 1160,



1119, 662, 619 cm^{-1}.

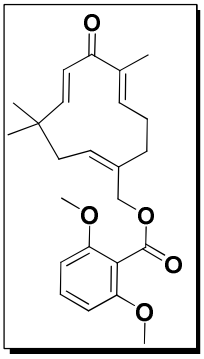
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.28 (m, 1H), 7.10-7.06 (m, 2H), 6.07-6.04 (m, 1H), 6.00 (d, *J* = 16.5 Hz, 1H), 5.88 (d, *J* =16.5 Hz, 1H), 5.53-5.49 (m, 1H), 4.92 (brs, 1H), 4.68 (brs, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.77-2.76 (m, 1H), 2.58-2.54 (m, 2H), 2.32-2.28 (m, 2H), 2.09-2.06 (m, 1H), 1.71 (s, 3H), 1.27 (s, 3H), 1.14 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.3, 159.9, 153.7, 148.7, 138.4, 134.8, 127.1, 125.7, 123.6, 121.9, 117.7, 115.9, 61.3, 55.9, 37.4, 35.4, 29.8, 24.7, 22.7, 12.1 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{30}NaO_5$: 421.19909, Found: 421.19976 $[M+Na]^+$.

((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl2,6-dimethoxybenzoate (42d)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **41d** (19.8 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **42d** white solid (6 mg, 14%).



R_f: 0.28 (ethylacetate/hexane = 1:3).

Mp: 103-105 ^oC.

IR (neat) υ_{max}: 3363, 2924, 2852, 2038, 1739, 1648, 1423, 1370, 1230, 1122, 1040, 856, 780, 567, 527 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8 Hz, 1H), 6.56 (d, *J* = 8.5 Hz, 2H), 6.03-6.01 (m, 1H), 5.99-5.93 (m, 2H), 5.52-5.48 (m, 1H), 4.88 (d, *J* = 11.5 Hz, 1H), 4.73 (d, *J* = 12 Hz, 1H), 3.79 (s, 6H), 2.71-2.69 (m, 1H), 2.54-2.49 (m, 2H), 2.26 (brs, 2H), 2.05-2.03 (m, 1H), 1.52 (s, 3H), 1.24 (s, 3H), 1.10 (s, 3H) ppm.

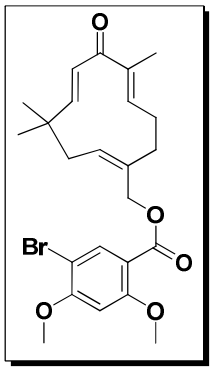
^{13}C NMR (125 MHz, $CDCl_3$): δ 204.2, 166.5, 159.9, 157.2, 149.1, 138.4, 134.3, 131.6, 131.3, 127.2, 113.4, 103.8, 62.3, 55.8, 42.5, 37.3, 36.9, 36.6, 24.8, 11.5 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{30}NaO_5$: 421.19909, Found: 421.19976 $[M+Na]^+$.

((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl 5-bromo-2,4-dimethoxybenzoate (42e)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **41e** (28.3 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCI_3$ (11.25 mg, 0.1 mmol),

PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **42e** as pale yellow liquid (5 mg, 10%).



R_f: 0.171 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 2924, 2370, 2118, 1705, 1650, 1597, 1463, 1402, 1319, 1279, 1238, 1181, 1111, 1024, 823, 624, 534 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (s, 1H), 6.46 (s, 1H), 6.01-5.97 (m, 1H), 5.90 (d, *J* = 16.5 Hz,1H), 5.91 (d, *J* = 16 Hz, 1H), 5.50-5.47 (m, 1H), 4.89 (d, *J* = 11.5 Hz, 1H), 4.63 (d, *J* = 12 Hz, 1H), 3.96 (s, 3H), 3.91(s, 3H), 2.71 (brs, 1 H), 2.55-2.49 (m, 2H), 2.30-2.27 (m, 2H), 2.06- 2.04 (m, 1H), 1.69 (s, 3H), 1.25 (s, 3H), 1.13 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.7, 164.1, 159.7, 148.8, 138.4, 136.1, 134.6, 131.3, 127.2, 115.7, 115.1, 114.5, 102.1, 61.1, 56.0, 42.2, 37.2, 35.7, 31.0, 24.5, 11.8 ppm.

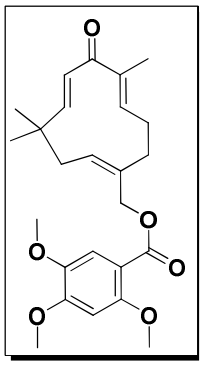
HRMS (ESI): *m/z* Calcd for $C_{24}H_{29}BrNaO_5$: 499.10961, Found: 499.10787 $[M+Na]^+$.

((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl-2,4,5-trimethoxybenzoate (42f)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **41f** (23.0 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCl_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **42f** as a white solid (8 mg, 17%).

R_f: 0.412 (ethylacetate/hexane = 1:3).

Mp: 117-120 ^oC.



IR (neat) υ_{max}: 3402, 2959, 1716, 1691, 1648, 1611, 1516, 1462, 1405, 1360, 1244, 1212, 1161, 1072, 1030, 779, 700, 531 cm^{-1}.

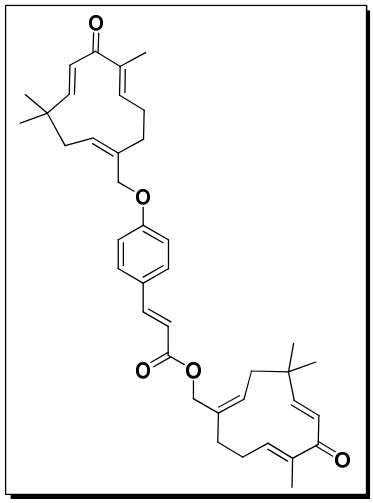
^{1}H NMR (500 MHz, $CDCl_3$): 7.39 (s, 1H), 6.54 (s, 1H), 6.08-6.05 (m, 1H), 6.02 (d, *J* = 16.5 Hz, 1H), 5.95 (d, *J* = 16.5 Hz, 1H),5.52-5.49 (m, 1H), 4.96 (d, *J* = 11.5 Hz, 1H), 4.62 (d, *J* = 12.Hz, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 2.79-2.77 (m, 1H), 2.60-2.55 (m, 2H), 2.82-2.25 (m, 2H), 1.80-1.78 (m, 1H), 1.70 (s, 3H), 1.27 (s, 3H), 1.13 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): 203.5, 165.5, 159.7, 155.1, 153.7, 148.9, 142.5, 138.5, 134.9, 130.8, 127.2, 114.6, 110.4, 61.0, 56.6, 56.4, 55.9, 42.3, 37.3, 35.7, 24.7, 11.8 ppm.

HRMS (ESI): *m/z* Calcd for $C_{25}H_{32}NaO_6$: 451.20966, Found: 451.21035 $[M+Na]^+$.

(E)-((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl 3-(4-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methoxy)phenyl)acrylate (44a)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **43a** (17.84 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCl_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **44a** as a colourless liquid (22 mg, 34%).



R_f: 0.34 (ethylacetate/hexane = 1:3)

Mp: 103-105 ^oC.

IR (neat) υ_{max}: 3403, 3037, 2960, 2926, 2866, 1708, 1652, 1601, 1510, 1453, 1388, 1362, 1305, 1244, 1159, 1105, 1064, 1001, 906, 831, 780, 736, 699, 632 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 7.64 (d, *J* = 16 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.28 (d, *J* = 16 Hz, 1H), 6.06-6.05 (m, 2H), 6.02-5.98 (m, 4H), 5.55-5.48 (m, 2H), 4.73 (brs, 1H), 4.65-4.62 (m, 1H), 4.57 (brs, 1H), 4.40-4.38 (m, 1H), 2.69-2.66 (m, 2H), 2.53-2.36 (m, 4H), 2.32-2.17 (m, 4H), 2.06-2.05 (m, 2H), 1.83 (s, 3H), 1.79 (s, 3H), 1.27 (s, 6H), 1.12 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): 203.5, 203.4, 166.9, 160.6, 159.9, 149.0, 144.9, 138.5, 135.1, 134.6, 131.5, 131.0, 129.8, 127.3, 127.2, 115.2, 114.9, 65.3, 61.0, 42.5, 42.3, 37.4, 37.3, 36.0, 35.9, 24.8, 24.9, 12.7 ppm.

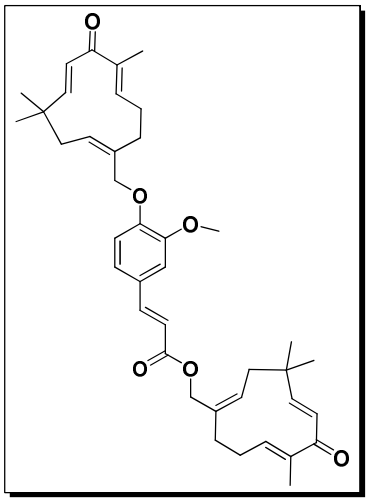
HRMS (ESI): *m/z* Calcd for $C_{39}H_{48}NaO_5$: 619.33994, Found: 619.33987 $[M+Na]^+$.

(E)-((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl 3-(3-methoxy-4-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methoxy)phenyl)acrylate (44b)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **43b** (21.11 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCl_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **44b** as a colourless liquid (16 mg, 33%).

R_f: 0.28 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 3398, 3057, 2963, 2922, 2412, 2356, 1710, 1640, 1512, 1464, 1424, 1363, 1266, 1161, 1033, 738, 704 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8 Hz, 1H), 7.01 (d, *J* = 1 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 6.27 (d, *J* = 16 Hz, 1H), 6.20 (d, *J* = 16.5 Hz, 1H), 6.07-6.04 (m, 2H), 5.99-5.92 (m, 4H), 5.55-5.48 (m, 2H), 4.72 (brs, 1H), 4.65-4.63 (m, 1H), 4.56-4.53 (m, 1H), 4.44 (brs, 1H), 3.84 (s, 3H), 2.69-2.66 (m, 2H), 2.55-2.52 (m, 4H), 2.46-2.42 (m, 2H), 2.32-2.24 (m, 4H), 1.80 (s, 3H), 1.77 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H), 1.12(s, 3H), 1.09 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.7, 203.4, 166.8, 160.1, 159.7, 150.4, 149.9, 149.0, 145.2, 145.2, 138.8, 138.4, 135.0, 134.6, 131.3, 127.6, 127.2,122.1, 115.4, 112.9, 109.9, 66.3, 61.1, 55.4, 42.5, 42.4, 37.3, 36.3, 35.9, 29.7, 29.4, 24.9, 24.1, 14.2, 12.2, 12.1 ppm.

HRMS (ESI): *m/z* Calcd for $C_{40}H_{50}NaO_6$: 649.35051, Found: 649.35112 $[M+Na]^+$.

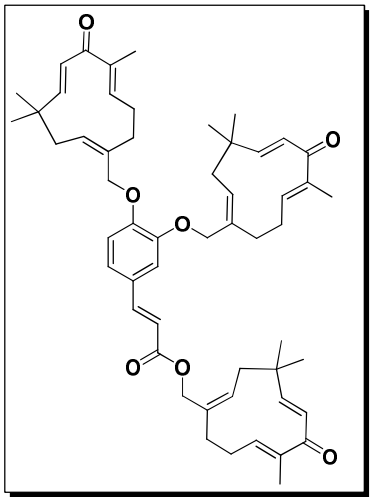
(E)-((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl 3-(3,4-bis(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methoxy)phenyl)acrylate (44c)

Following the general experimental procedure, the zerumbone acetate **40** (30 mg, 0.1087 mmol), **43c** (19.57 mg, 0.1087 mmol), catalyst $Pd_2(dba)_3.CHCl_3$ (11.25 mg, 0.1 mmol), PPh_3 (28.47 mg, 40 mol %) as ligand, Cs_2CO_3 (35.4 mg, 2.0 equiv.) in THF (2 mL) at room temperature for 12 h under argon atmosphere gave the product **44c** as a colourless liquid (17 mg, 29%).

R_f: 0.17 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 3436, 2962, 2921, 2852, 2075, 1705, 1646, 1511, 1460, 1431, 1364, 1260, 1161, 1134, 1006, 738, 702, 530 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 16 Hz, 1H), 7.09 (d, *J* = 8 Hz, 1H), 7.02 (s, 1H), 6.88 (d, *J* = 8 Hz, 1H), 6.24 (d, *J* = 16 Hz, 1H), 6.09-5.91 (m, 9H), 5.54-5.49 (m, 3H), 4.70-4.67 (m, 4H), 4.35-4.34 (m, 2H), 2.72-2.65 (m, 3H), 2.52-2.49 (m, 7H), 2.36-2.27 (m, 8H), 1.79 (s, 9H), 1.26 (s, 9H), 1.12 (s, 9H) ppm.



^{13}C NMR (125 MHz, $CDCl_3$): δ 203.4, 203.3, 166.7, 159.6, 149.2, 148.9, 138.6, 138.6, 135.3, 135.2, 134.4, 131.8, 130.6, 127.4, 127.1, 122.4, 115.6, 11.33, 112.5, 65.7, 29.3, 24.8, 24.6, 24.0, 12.1, 12.0 ppm.

HRMS (ESI): *m/z* Calcd for $C_{54}H_{68}NaO_7$: 851.48627, Found: 851.48746 $[M+Na]^+$.

2A.10. Procedure for various biological assays

2A.10.1. Anti-diabetic assay

2A.10.1.1. *α*-Amylase inhibition assay

α-Amylase inhibition assay was carried out according to Xiao *et al*.[52] based on the starch-iodine test. The total assay mixture composed of 40 µL 0.02 M sodium phosphate buffer (pH 6.9 containing 6 mM NaCl), 0.02 units of porcine pancreatic amylase solution and compounds / standard at different concentrations were incubated at 37 °C for 10 min. Then 40 µL soluble starch (1%, w/v) was added to each reaction well and incubated at 37 °C for 15 min. The reaction was stopped by addition of 1 M HCl (20 µL), followed by the addition of 100 µL of iodine reagent (5 mM I_2 and 5 mM KI), which will react with remaining starch. The absorbance was read at 600 nm on a microplate reader. The known *α*-amylase inhibitor, acarbose, was used a positive control.

2A.10.1.2. *α*-Glucosidase enzyme inhibition assay

The *α*-glucosidase enzyme inhibition assay was carried out according to the method described by Apostolidis.[53] The enzyme inhibition assay mixture contained 50 µL *p*-nitrophenyl-*α*-D-glucopyranoside, different concentrations of compound/standard and the reaction mixture was made up to 2.8 mL with sodium phosphate buffer (pH 6.8; 50 mM). The reaction was initiated by adding 20 µL of *α*-glucosidase enzyme. The reaction was monitored by increase in absorbance at 405 nm.

2A.10.1.3. Antiglycation assay

It was performed according to the methods reported by Matsuura *et al*. with slight modifications.[54] About 500 µL of albumin (1 mg/mL final concentration) was incubated with 400 µL of glucose (500 mM) in the presence of 100 µL of compound at different

concentrations. The reaction was allowed to proceed at 60 °C for 24 h and thereafter reaction was stopped by adding 10 µL of 100% TCA. Then the mixture was kept at 4 °C for 10 min. before subjected to centrifugation at 10000g. The precipitate was redissolved in 500 µL alkaline PBS (pH10) and immediately quantified for relative amount of glycated BSA based on fluorescence intensity at 370 nm (excitation) and 440 nm (emission).

2A.10.2. MTT assay

The MTT (3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide) assay developed by Mosmann was used with slight modifications. In brief, the trypsinized cells from T-25 flask were seeded in each well of 96-well flat-bottomed tissue culture plate at a density of $1x10^4$ cells/well in growth medium and cultured at 37 °C in 5% CO_2 to adhere. After 48h. incubation, the supernatant was discarded and the cells were pretreated with growth medium and were subsequently mixed with both standard (Paclitaxel) and (compound **38b, 38d, 38k, 38e, 44a, 448b** and **44c** to achieve a final volume of 100 µL and then cultured for 24 h. The compound was prepared as 1.0 mg/mL concentration stock solutions in DMSO. Each well then received 20 µL of fresh MTT (5mg/mL in PBS) followed by incubation for 4h. at 37 °C. The supernatant growth medium was removed from the wells and replaced with 100 µL of DMSO to solubilize the coloured formazan product. After 30 min. incubation, the absorbance (OD) of the culture plate was read at a wavelength of 570 nm on a microplate reader (Biotek Synergy 4, VT, USA). The percent cell viability was determined with respect to control, is calculated using formula. % Viability = corrected OD of sample /Control OD * 100 and percentage of inhibition was determined by using formula, % Inhibition = 100-% viability.

2A.10.3. Anti-hypertensive activity

Concentrations tested: 10, 100, 500 and 1000 µM

Materials: Hippuryl-His-Leu-Acetate Salt, Plasma Membranes from Kidney Cortex, Captopril – Standard ACE Inhibitor

Method:

The compound of interest is tested at four concentrations as mentioned above. The samples were dissolved in respective solvents and mixed with assay buffer (10 mM HEPES buffer containing 0.3 M NaCl and 10 µM Zinc Sulphate) containing 20 µL kidney cortex plasma membranes (ACE enzyme source) and 1 mM Hippuryl-His-Leu as substrate.[55-56]. The compounds were incubated with the enzyme for 10 minutes at 37 ^oC. Then 10 µL of substrate (1 mM) was added which makes a final reaction volume of 50

μL and incubated for 45 min. at 37 ^{o}C. The reaction is terminated by the addition of 1M HCl (0.1 mL). The yellow colour is developed by the addition of 100 μL of pyridine and 50 μL of Benzene Sulphonyl Chloride. The yellow colour that formed is measured at 410 nm in an ELISA Plate Reader (iMARK, BIORAD). Compounds with an inhibitory potential block the substrate availability to the enzyme and thereby cause enzyme inhibition leading to no formation of yellow colour. The inhibition is represented in the form of percentage over control. Captopril, a known ACE inhibitor is tested in this assay as a standard compound.

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57. CCDC numbers for compounds **42b** and **38n'** are 1530675 and 1530676, respectively.

CHAPTER 2

Synthesis of Zerumbone Pendant Derivatives

Part B

Synthesis of Zerumbone-Pendant Amino acids/ Nucleobases: A Base Catalyzed Reaction

2B.1. Introduction

Amino acids have received much interest as building blocks in organic synthesis[1] and are found throughout the natural world, occurring in biologically active natural products such as paclitaxol[2-5] and docetaxel[6] (Figure 2B.1). They are the fundamental components of living organisms playing a crucial role both as building blocks of proteins and as intermediates in metabolism. Conjugating amino acid residues with small bioactive heterocyclic motifs have emerged as a new diagnosing method in biomedical research.[6] The literature survey revealed that the amino acid derivatives have promising biological profile.[7-13]

Nucleoside analogues and nucleobases are a pharmacologically diverse family, which includes cytotoxic compounds, antiviral agents and immunosuppressive molecules.[14] Several analogues of pyrimidine and purine nucleosides and nucleobases are well-known for their anticancer property. Cladribine and fludarabine (Figure 2B.1) are the two primary purine analogues and these are the effective drugs for treatments of lymphoproliferative disorders.[15-16] Among the currently available pyrimidine analogues, cytarabine is extensively used in the treatment of acute leukaemia[17]; gemcitabine has activity in various solid tumours and some hematological malignant diseases[18]; and the fluoropyrimidines, fluorouracil[19] and capecitabine[20] have shown activity in colorectal and breast cancers.

The growing importance of nucleoside analogues as cytotoxic agents has stemmed both from the development of newer compounds with broad applicability to common cancers and from an understanding of their mechanisms of action, enabling pharmacological intervention to potentiate the antitumor effects of these compounds.

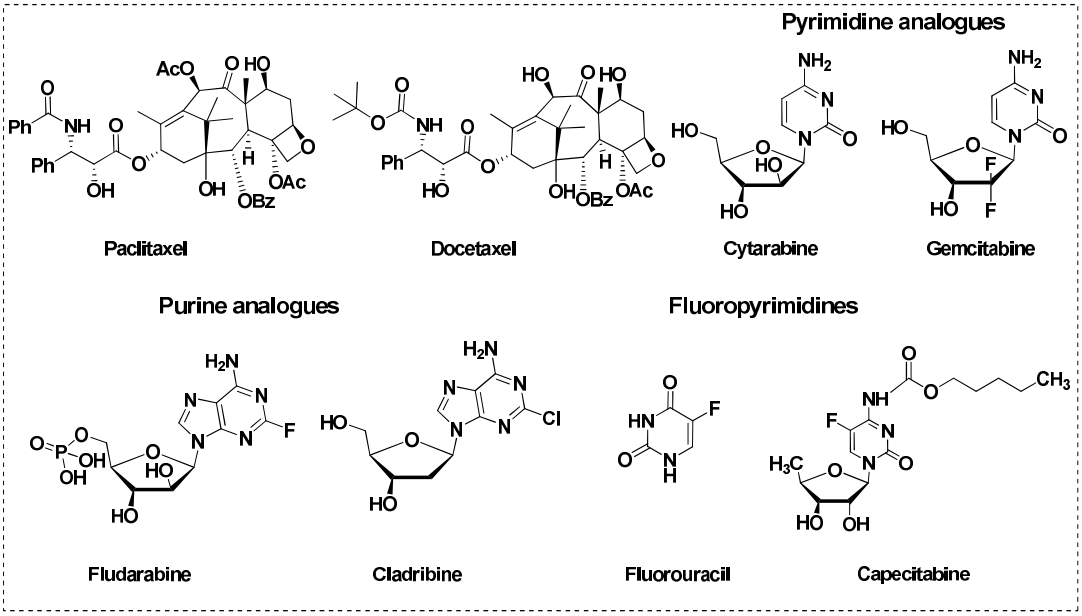


Figure 2B.1. Anti-cancer compounds

The biological profile of zerumbone is highly remarkable. The biological activity of the zerumbone pendant derivatives was studied by Kitayama *et al*. in 2013.[21] This inspired us in search for the new aspects as well as potency of the zerumbone derivatives. We focused on the incorporation of biologically important cores such as amino acids and nucleobases to zerumbone *via* simple reactions. This may enhance the biological activity of the newly derived zerumbone derivatives. A detailed discussion on the substitution reaction of zerumbone derivatives and the incorporation of amino acids as well as nucleobases is described in this chapter.

The highly reactive intermediate of zerumbone, formed *via* allylic bromination of zerumbone is a valuable synthetic intermediate toward the synthesis of zerumbone pendant derivatives.[21]

2B.2. Definition of the Problem

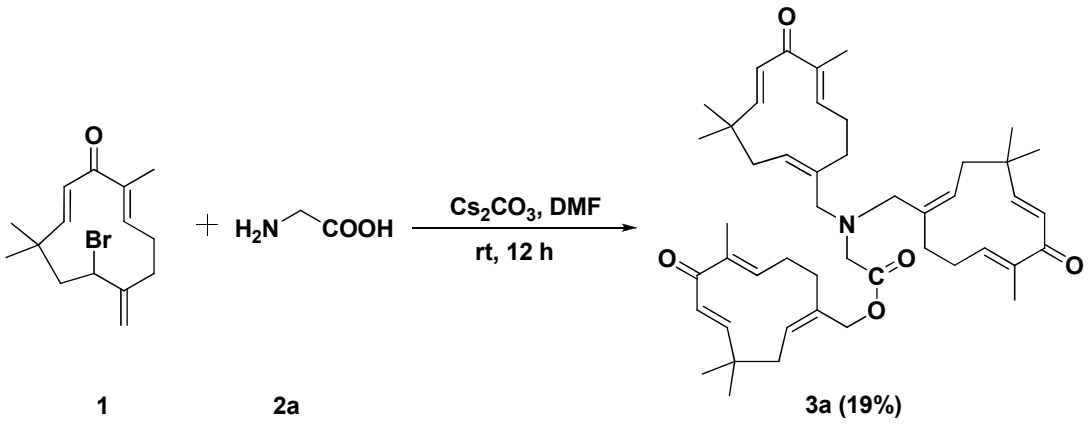
The zerumbone pendant derivatives discussed in chapter 2A showed remarkable biological activity, we decided to focus on the synthesis of new zerumbone appended derivatives by incorporating biologically important cores on zerumbone. As continuation of our investigation on the synthesis of new zerumbone pendant derivatives, we were interested in the construction of a new series of amino acids/ nucleobases derivatives of zerumbone to improve biological activity through a facile reaction strategy. Till to date, there are no reports available in the literature on amino acids/ nucleobases appended zeumbone *via* base catalyzed nucleophilic substitution reaction. In this chapter, we describe our efforts on the synthesis of zerumbone pendant amino acids as well as

zerumbone pendant nucleobases. Some of the amino acid appended zerumbone derivatives were tested for their growth inhibitory against cancer cell lines.

2B.3. Results and Discussion

2B.3.1. Base Catalyzed Nucleophilic Substitution of Amino acids with Bromosubstituted Zerumbone 1

The highly reactive intermediate, bromosubstituted zerumbone (**1**)[21] required for the studies are easily accessible through allylic bromination. We commenced our experiment with the reaction of the simplest amino acid, glycine (**2a**) with bromosubstituted zerumbone (**1**) in presence of 3 equivalent Cs_2CO_3 as base in DMF at room temperature and the reaction afforded the tri-substituted product **3a** in 19% yield (Scheme 2B.1).



Scheme 2B.1

The structure of the product **3a** was elucidated by various spectroscopic analyses. The IR spectrum showed the characteristic carbonyl absorption at 1663 cm^{-1}. In the ^1H NMR spectrum (Figure 2B.2), the six protons on α- and β- carbons of the enone part were resonated as multiplet in the region δ 6.00-5.96 ppm. The other six olefinic protons were resonated as multiplet in the region δ 5.81-5.45 ppm. The two CH_2 protons adjacent to oxygen appeared at δ 4.68-4.45 ppm. The ^1H NMR spectrum of compound is shown in the figure 2B.2. All other signals were in agreement with the proposed structure of **3a**.

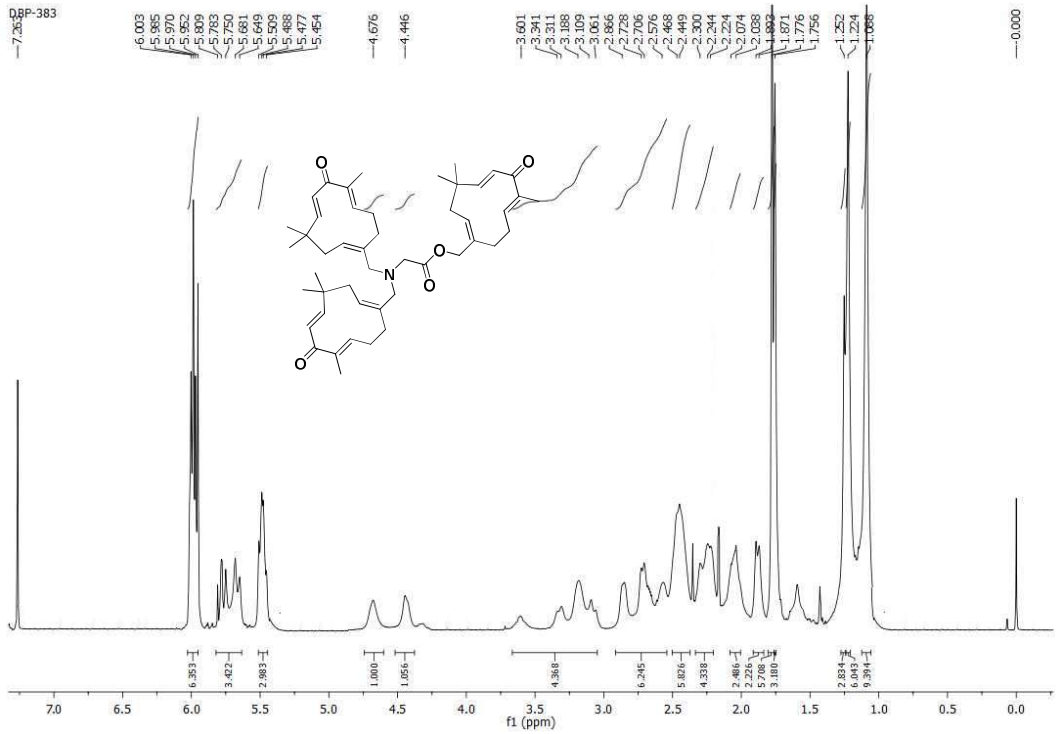


Figure 2B.2. ^{1}H NMR of compound **3a**

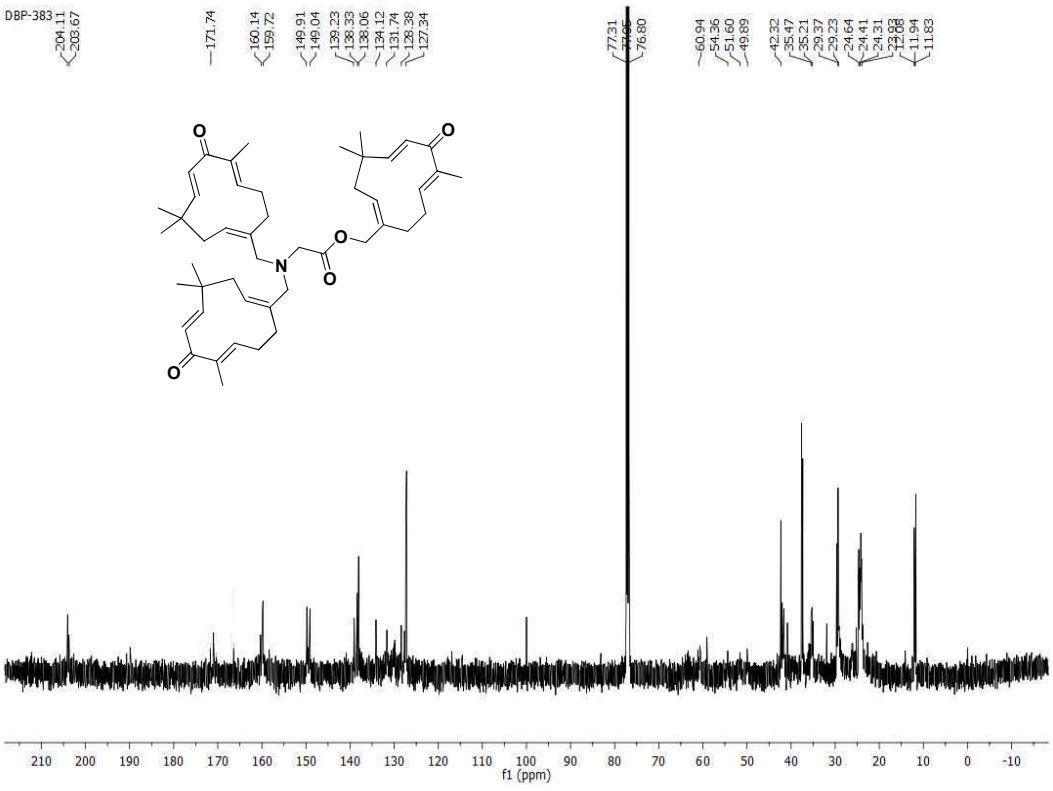


Figure 2B.3. ^{13}C NMR of compound **3a**

In the ^{13}C NMR spectrum, the characteristic carbonyl peaks appeared at δ 203 ppm. The ^{13}C NMR spectrum of compound **3a** is shown in the figure 2B.3. Finally mass spectrum well supported the structure of the product **3a** with $[M+H]^+$ ion peak at *m/z* 724.49457.

Detailed optimization studies were performed to find the best reaction condition for the transformation as in table 2B.1. In the initial stage, the reaction was carried out with 1 equivalent of brominated zerumbone **1** and 1 equivalent of glycine **2a** in presence of base (1 equiv. Cs_2CO_3), in DMF solvent at room temperature. The reaction resulting the desired product in 19% yield (Table 2B.1, Entry 1). Only trace amount of the product was formed in the absence of base (Table 2B.1, Entry 6). In order to find, whether there is a formation of mono-, di- and tri substituted products, we have screened the equivalence of amino acid from one to five (Table 2B.1, Entry 1-5). One equivalent of brominated zerumbone **3a** and 3 equivalent of glycine **2a** in presence of 1 equivalent of Cs_2CO_3 as base in DMF solvent at room temperature is the best reaction condition for this transformation. The tri substituted product **3a** was formed in 70% yield (Table 2B.1, Entry 2).

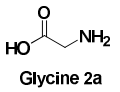
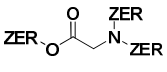
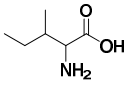
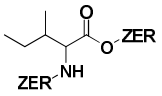
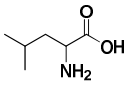
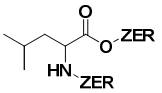
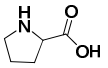
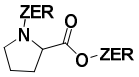
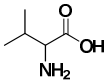
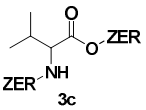
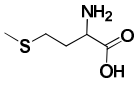
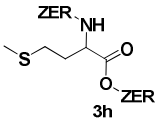
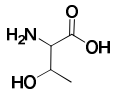
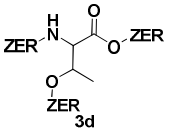
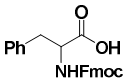
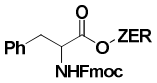
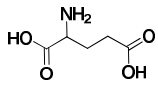
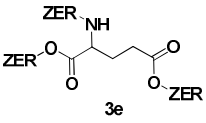
Table 2B.1. Optimization studies for the formation of amino acid derivative of zerumbone

Entry	Equiv. of aa	Base	Equiv. of base	Solvent	[b] Yield (%)
1	1	Cs_2CO_3	3	DMF	19
2	3	Cs_2CO_3	3	DMF	70
3	3	Cs_2CO_3	20 mol%	DMF	44
4	3.5	Cs_2CO_3	3	DMF	67
5	5	Cs_2CO_3	3	DMF	66
6	3	-	-	DMF	Trace

[a] Reaction condition: Bromosubstituted zerumbone **1** (1 equiv.), Solvent (2 mL), rt, [b] Isolated yield.

With the optimal conditions in hand, the scope of the reaction was tested with various amino acids (**2a**-**2i**) (Table 2B.2). Leucine (**2b**), valine (**2c**), iso-leucine (**2f**), proline (**2g**) and methionine (**2h**) led to the formation of di- substituted products in moderate yield. Threonine (**2d**) and glutamic acid (**2e**) gave the tri-substituted products **3d** and **3e** in 24% and 63% respectively. In addition Fmoc protected amino acid **2i** furnished the produced **2i** in 56% yield.

Table 2B.2. Reaction of various amino acids (**2a**-**2i**) with **1**

Entry	Aminoacid	Product	[b]Yield (%)	Entry	Aminoacid	Product	Yield (%)
1	 Glycine 2a	 3a	70	6	 Isoleucine 2f	 3f	60
2	 Leucine 2b	 3b	60	7	 Proline 2g	 3g	16
3	 Valine 2c	 3c	72	8	 Methionine 2h	 3h	37
4	 Threonine 2d	 3d	24	9	 2i	 3i	56
5	 Glutamic acid 2e	 3e	63				

Reaction conditions: Bromosubstituted zerumbone **1** (1.0 equiv.), Aminoacid **2** (3.0 equiv.), Cs_2CO_3 (3.0 equiv.), DMF (2 mL), rt, 12h.

During the reaction, a side product (**4**) was formed in 24% yield. The structure of the product **4** was elucidated by various spectroscopic analyses. The IR spectrum showed characteristic carbonyl absorption at 1666 cm^{-1}. In the ^1H NMR spectrum (Figure 2B.4), the olefinic proton at C-3 resonated between 6.02-5.99 ppm as multiplet. The olefinic proton at C-10 resonated as doublet at δ 5.97 with coupling constant J = 16.5 Hz and the proton at C-11 visible at 5.70 ppm as doublet having coupling constant J = 16 Hz. The unactivated olefinic proton at C-7 appeared as multiplet in the range 5.37-5.34 ppm. The CH_2 protons attached to –OH, appeared as doublets and it resonated at 4.33 as doublet with J value 10.5 Hz and at δ 3.87 ppm as doublet with J value 9.5 Hz. The OH proton appeared as broad singlet at 2.78 ppm. The other CH_2 protons are appeared as broad multiplet in the range of 2.52-1.78 ppm. The three CH_3 protons are appeared as singlet at 1.08, 1.22 and 1.57 ppm.

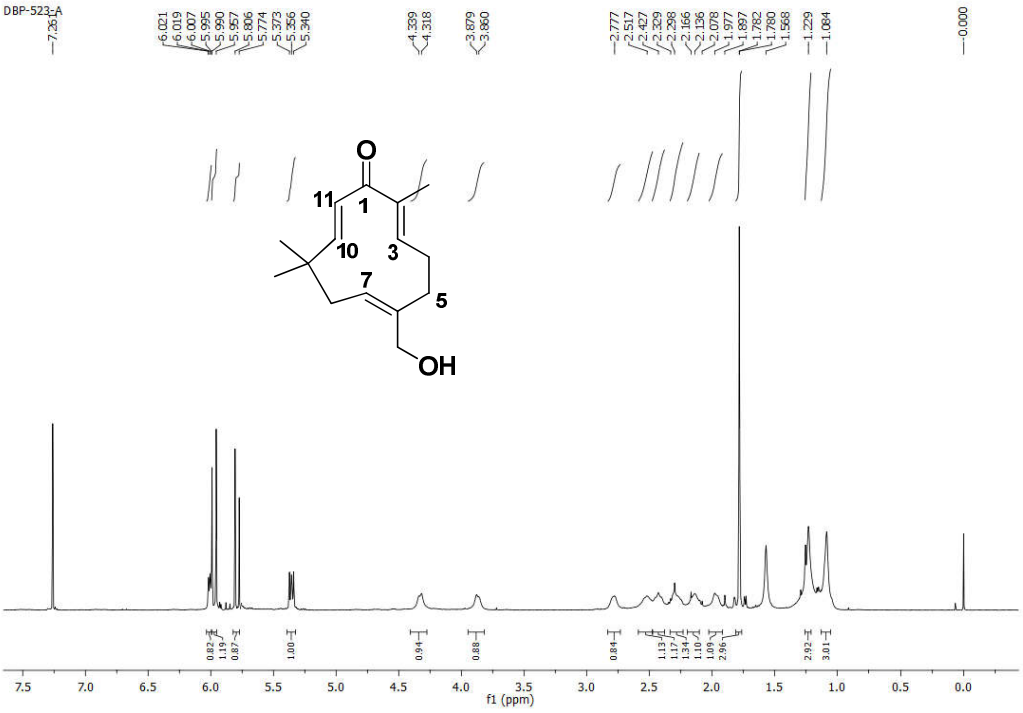


Figure 2B.4. ^{1}H NMR of compound **4**

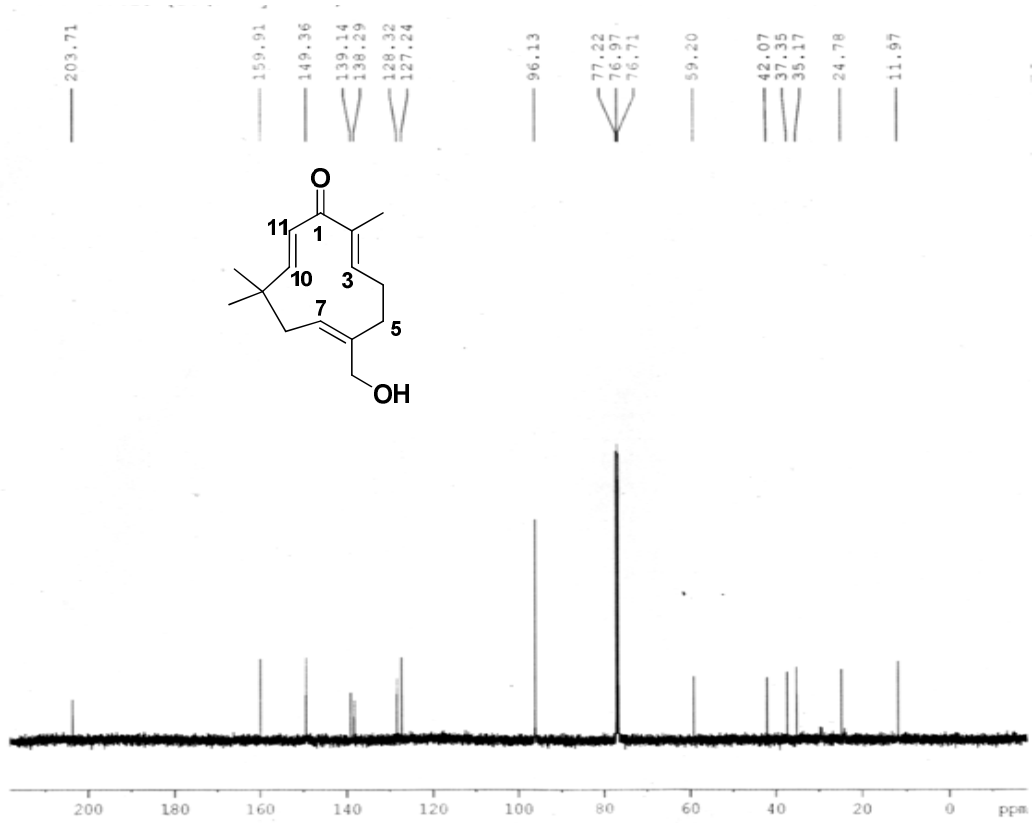


Figure 2B.5. ^{13}C NMR of compound **4**

In ^{13}C NMR spectrum (Figure 2B.5), the carbonyl carbon was resonated at δ 203.7 ppm. The carbon (C10) and carbon (C11) resonated at δ 159.9 and 127.2 respectively. The olefinic carbon at C3 resonated at 149.4 ppm. The olefinic carbon (C2) appeared at δ 138.3 ppm. The C6 and C7 carbons are appeared at δ 139.1 and 127.2 ppm respectively. The CH_2 carbon attached to –OH resonated at δ 59.2 ppm respectively. And all other signals in ^{13}C NMR spectra were in good agreement with the proposed structure. The mass spectral analysis showed a peak at *m/z* 257.15186 $[M+Na]^+$, which also supported the proposed structure.

After the successful synthesis of distinctive derivatives of zerumbone, we tried to expand the scope of the reaction by incorporating another class of biologically significant heterocycles. With this aim, we initiated the reaction of **1** with adenine (**5a**), a nucleobases under the optimal reaction condition, and the reaction afforded adenine substituted zerumbone derivative (**6a**) in 54% yield. The reaction also worked well with other nucleobases such as 2-amino purine (**5b**), uracil (**5c**) and thymine (**5d**) and the corresponding derivatives were formed in moderate yields.

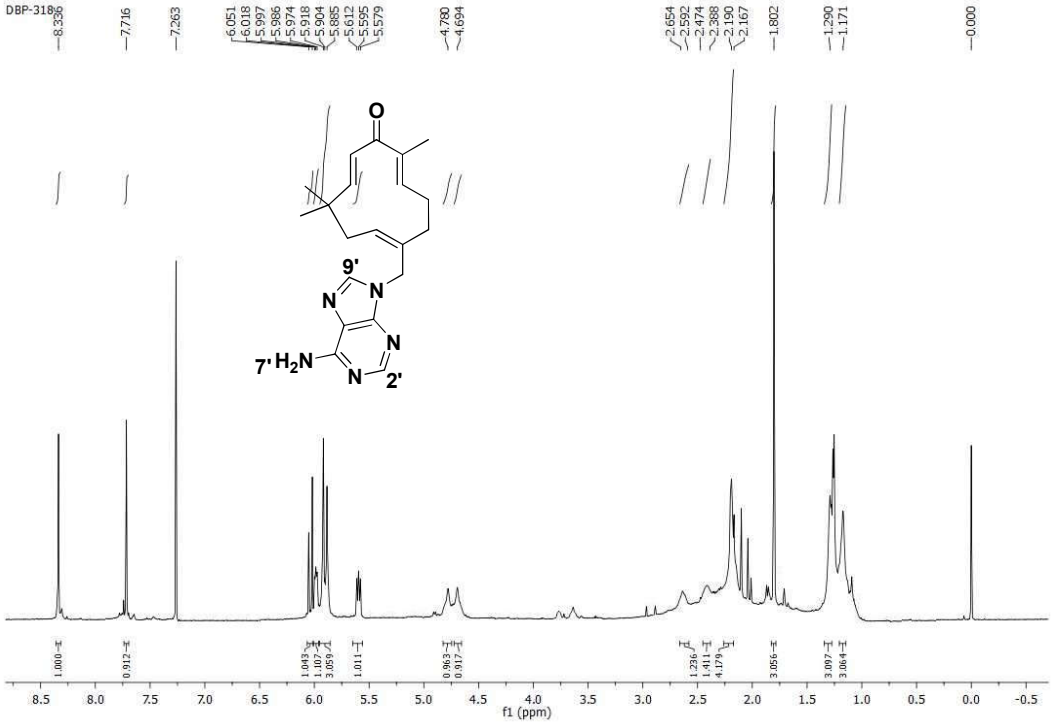


Figure 2B.6. ^1H NMR of compound **6a**

The structure of the product **6a** was elucidated by various spectroscopic analyses. The IR spectrum showed the characteristic carbonyl absorption at 1645 cm^{-1}. In the ^1H NMR spectrum (Figure 2B.6), the olefinic proton at C-2' resonated as singlet at δ 8.34

ppm and the olefinic proton at C-9' resonated as singlet at δ 7.72 ppm. The olefinic proton at C-10 resonated as doublet at δ 6.03 with coupling constant J = 16.5 Hz and the olefinic proton at C-3 resonated between δ 6.00-5.97 as multiplet. The proton at C-11 and $-NH_2$ protons appeared as multiplet in the range δ 5.92-5.89 ppm. The unactivated olefinic proton at C-7 appeared as multiplet in the range δ 5.61-5.58 ppm. The CH_2 protons attached to nitrogen, appeared as broad multiplet in the range of δ 4.78-4.69 ppm. The other CH_2 protons are appeared as broad multiplet in the range of δ 2.65-2.17 ppm. The three CH_3 protons are appeared as singlet at 1.80, 1.29 and 1.17 ppm.

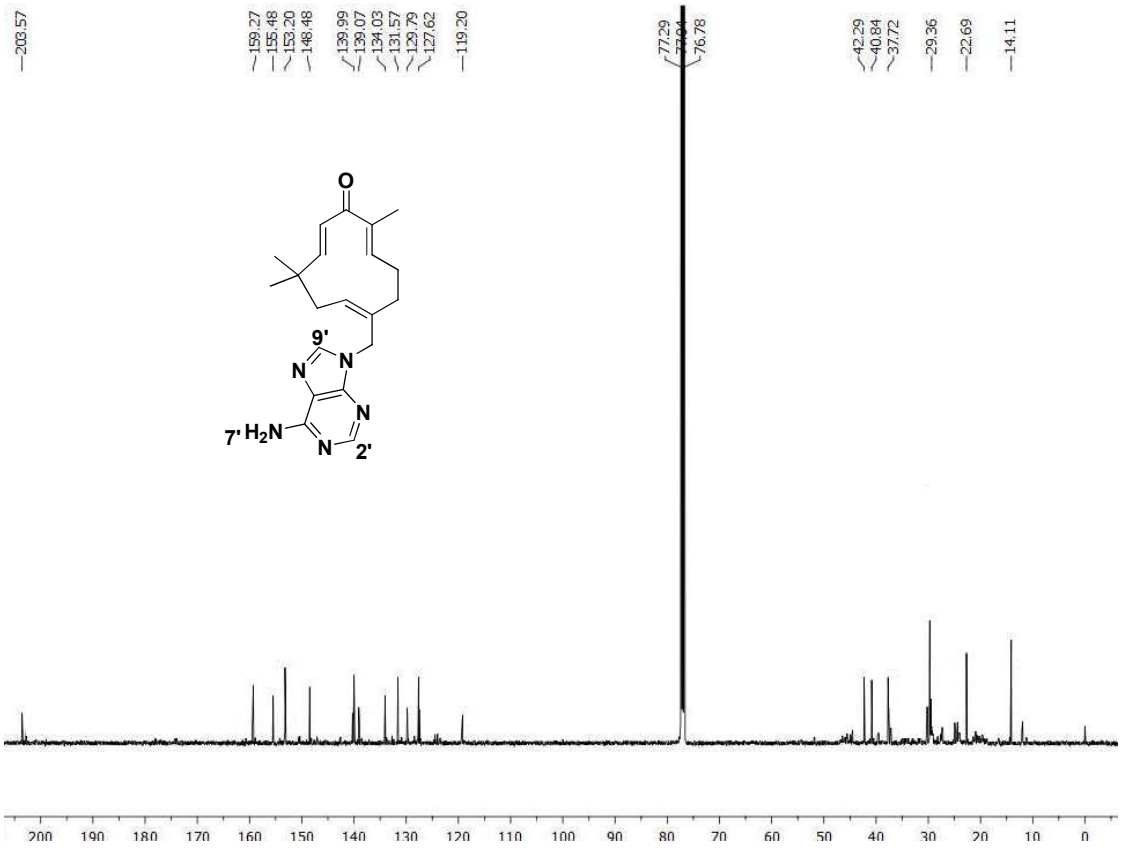
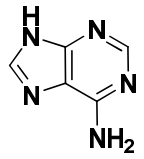
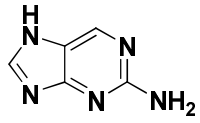
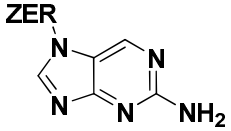
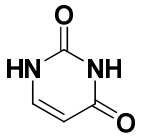
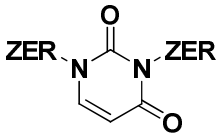
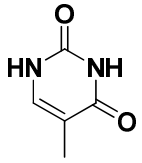
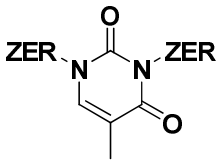


Figure 2B.7. ^{13}C NMR of compound **6a**

In ^{13}C NMR spectrum (Figure 2B.7), the carbonyl carbon was resonated at δ 203.6 ppm. The carbon (C10) and carbon (C11) resonated at δ 159.3 and 127.6 respectively. The olefinic carbon at C3 resonated at 148.5 ppm. The olefinic carbon (C2) appeared at δ 139.1ppm. The C6 and C7 carbons are appeared at δ 140.0 and 119.2 ppm respectively. And all other signals in ^{13}C NMR spectra were in good agreement with the proposed structure. The mass spectral analysis showed a peak at *m/z* 352.2137 $[M+ H]^+$, which also supported the proposed structure.

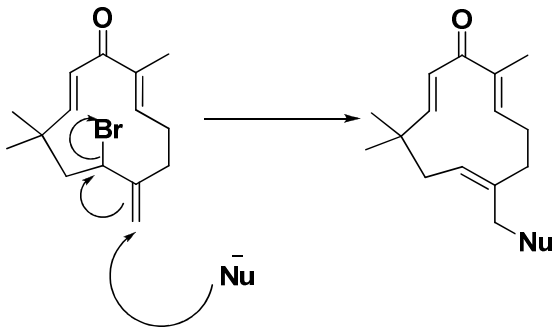
Table 2B.3. Reaction of various nucleobases (**5a**-**5e**) with **1**

Entry	Nucleobases	Product	Yield (%)
1	 5a	 6a	54
2	 5b	 6b	68
3	 5c	 6c	31
4	 5d	 6d	25

Reaction conditions: Bromosubstituted zerumbone **1** (1.0 equiv.), Nucleobase **5**

2B.4. Mechanistic consideration

The mechanism involves a S_N2' type pathway in which the nucleophile attacks on the exocyclic olefinic carbon followed by allylic rearrangement with the elimination of bromide ion yielded the desired zerumbone pendant derivatives (Scheme 2B.2).



Scheme 2B.2. Proposed mechanism

2B.5. Biological Evaluation of Compounds 3c and 3f

2B.5.1. Anti-Proliferative Activity

The notable anti-proliferative activity of zerumbone pendant derivatives, led us to carry out the *in vitro* cytotoxic screening of some of the amino acid derivatives against five human cancer cell lines viz., A549, HCT116, HeLa, HT1080 and MDAMB231. The results obtained from the MTT assay are shown in terms of IC_{50} values (Table 2B.4). Results were compared with rat heart myoblast cells (H9c2) which showed non toxicity of cells on treatment with zerumbone and its derivatives. The results showed that the two derivatives (**3c** and **3f**) have negligible cytotoxicity against most of the cell lines except HCT116. And the compound **3f** (Entry 2) showed better growth inhibitory activity against the HeLa cells.

Table 2B.4. IC_{50} value of compounds (Entry 1-4)

		IC_{50} (mM)					
Entry	Compounds	HT 1080	A549	HeLa	HCT116	MDAMB231	H9c2
1	3c	> 30	> 30	11.0	4.36	> 30	> 30
2	3f	> 30	NA	NA	4.39	NA	> 30
3	Zerumbone	> 30	> 30	16.62	4.97	24.4	> 30
4	Paclitaxel (nM)	8.64	7.31	7.75	5.5	9.12	> 25

2B.6. Conclusion

In summary, we have synthesized a new class of zerumbone derivatives by incorporating amino acids as well as nucleobases. The two zerumbone-pendant amino acids (**3c** and **3f**) derivatives were screened for their anti-proliferative activity and among them, compound **3c** showed good cytotoxicity against HeLa cells.

2B.7. Experimental Section

General information about the experiment is given in section 2A.8 of chapter **2A**.

2B.7.1. Synthesis of 7-Bromo-2,9,9-trimethyl-6-methyl-6-methylenecycloundeca-2,10-dienone (1)

The synthesis of compound **1** is given in Section 2A.8.1 of chapter 2A

2B.7.2. General experimental procedure for the base catalyzed substitution reaction of brominated zerumbone (1) with amino acids (2)/ nucleobases (4)

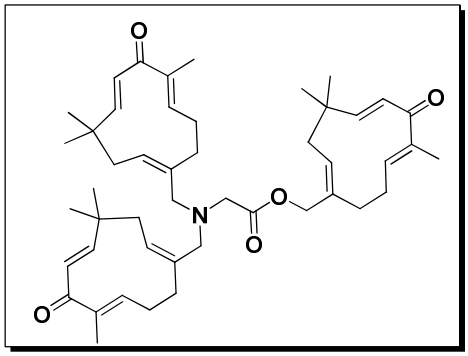
2B.7.2.1. General Procedure for the Synthesis of zerumbone pendant derivatives

To a solution 7-bromo-2,9,9-trimethyl-6-methyl-6-methylenecycloundeca-2,10-dienone (**1**) in DMF, nucleophile (**2**/**4**) (amino acids/ nucleobases) was added followed by base and stirred the reaction for 12 h at room temperature. After the completion of the reaction as monitored by TLC, the reaction mixture was concentrated and the crude product was purified by column chromatography on silica gel (100-200 mesh) and hexane: ethylacetate as the eluent to afford the product.

2B.8. Spectral details of compounds 3a-6d

((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl2-(bis(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl)amino)acetate (3a)

Following the general procedure, the brominated zerumbone **21** (30 mg, 0.10135 mmol), glycene (**2a)** (22.8 mg, 0.304 mmol) and Cs_2CO_3 (98.8 mg, 0.304 mmol) in DMF (2 mL) at rt for 12 hours gave the substituted product **3a** as a colourless liquid (51.29 mg, 70%).



R_f: 0.91 (ethylacetate/hexane = 1:2.3).

IR (neat) υ_{max}: 3432, 2968, 2082, 1641, 1458, 1366, 1269, 1184, 1104, 971, 911, 838, 741, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 6.00-5.95 (m, 6H), 5.81-5.65 (m, 3H), 5.51-5.45 (m, 3H), 4.68 (brs, 1H), 4.45 (brs, 1H), 3.60-3.06 (m, 4H), 2.87-2.58 (m, 6H), 2.47-2.45 (m, 6H), 2.30-2.22 (m, 4H), 2.07-2.04 (m, 2H), 1.89-1.87 (m, 2H), 1.78 (s, 6H), 1.76 (s, 3H), 1.25 (s, 3H), 1.22 (s, 6H), 1.09 (s, 9H) ppm.

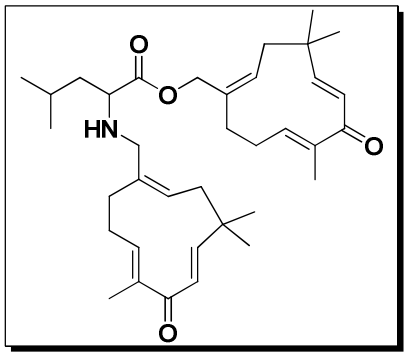
^{13}C NMR (125 MHz, $CDCl_3$): 204.1, 203.7, 171.7, 160.1, 159.7, 149.9, 149.0, 139.2, 138.3, 138.1, 134.1, 131.7, 128.4, 127.3, 60.9, 54.4, 51.6, 49.9, 42.3, 42.1, 41.7, 37.5, 37.4, 35.5, 35.2, 35.0, 29.8, 29.4, 29.2, 24.6, 24.4, 24.3, 23.9, 23.7, 12.1, 11.9, 11.8 ppm.

HRMS (ESI): *m/z* Calcd for $C_{47}H_{66}NO_5$: 724.49410, Found: 724.49457 $[M+H]^+$.

((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl 4-methyl-2-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methylamino)pentanoate (3b)

Following the general procedure, the brominated zerumbone **1** (30 mg, 0.10135 mmol), Leucine **2b** (39.82 mg, 0.304 mmol) and Cs_2CO_3 (98.8 mg, 0.304 mmol) in DMF (2

mL) at rt for 12 hours gave the substituted product **3b** as a colourless liquid (34.23 mg, 60%).



R_f: 0.86 (ethylacetate/hexane = 1:2.3).

IR (neat) υ_{max}: 3431, 2108, 1639, 1412, 1254, 1148, 752, 567 cm^{-1}.

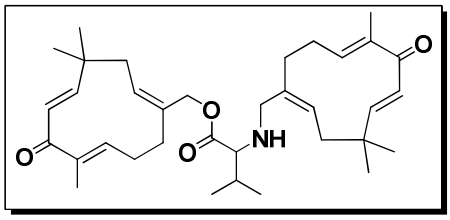
^{1}H NMR (500 MHz, $CDCl_3$): 6.01-5.94 (m, 4H), 5.78-5.69 (m, 2H), 5.50-5.46 (m, 1H), 5.39-5.32 (m, 1H), 4.79-4.74 (m, 1H), 4.43-4.34 (m, 1H), 3.32-3.24 (m, 1H), 3.19 (t, 1H, J = 7 Hz), 2.87-2.59 (m, 4H), 2.45-2.22 (m, 9H), 2.10-2.02 (m, 3H), 1.92-1.88 (m, 1H), 1.80 (s, 3H), 1.77 (s, 3H), 1.44-1.41 (m, 2H), 1.25 (s, 3H), 1.22 (s, 3H), 1.11 (s, 3H), 1.08-1.07 (m, 3H), 0.94-0.92 (m, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): 203.6, 202.6, 178.0, 159.8, 158.1, 149.3, 148.7, 139.0, 138.3, 128.5, 127.7, 127.6, 127.3, 127.1, 59.3, 42.5, 42.1, 37.6, 37.4, 35.2, 31.9, 29.7, 29.4, 29.3, 29.1, 24.8, 24.2, 24.1, 23.9, 22.7, 22.2, 14.1, 13.8, 12.0 ppm.

HRMS (ESI): *m/z* Calcd for $C_{36}H_{54}NO_4$: 564.40528, Found: 564.40522 $[M+H]^+$.

((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl 3-methyl-2-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methylamino)butanoate (3c)

Following the general procedure, the brominated zerumbone **1** (30 mg, 0.10135 mmol), valine **2c** (35.61 mg, 0.304mmol) and Cs_2CO_3 (98.8 mg, 0.304 mmol) in DMF (2 mL) at rt for 12 hours gave the substituted product **3c** as a colourless liquid (40.13 mg, 72%).



R_f: 0.93 (ethylacetate/hexane = 1:2.3).

IR (neat) υ_{max}: 3436, 2973, 2082, 1641, 1454, 1366, 1272, 1184, 1129, 971, 916, 838, 735, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 6.05-5.95 (m, 5H), 5.81-5.74 (m, 2H),5.50-5.46 (m, 1H), 5.39-5.32 (m, 1H), 4.77-4.69 (m, 1H), 4.42-4.28 (m, 1H), 3.29-3.21 (m, 1H), 2.90 (s, 1H), 2.74-2.71 (m, 1H), 2.62-2.61 (m, 1H), 2.52-2.46 (m, 4H), 2.31-2.21 (m, 4H), 2.06-2.04 (m, 2H), 1.91-1.87 (m, 2H), 1.80 (s, 3H), 1.77 (s, 3H), 1.25 (s, 3H), 1.21 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): 203.5, 203.0, 175.2, 159.1, 149.5, 148.5, 138.6, 138.5,

138.0, 134.4, 133.7, 132.0, 131.3, 128.9, 127.4, 127.1, 64.5, 42.3, 41.9, 37.4, 37.3, 35.5, 31.6, 30.8, 29.6, 29.3, 29.7, 24.4, 24.1, 19.6, 18.4, 12.0, 11.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{35}H_{52}NO_4$: 550.38963, Found: 550.38922 $[M+H]^+$.

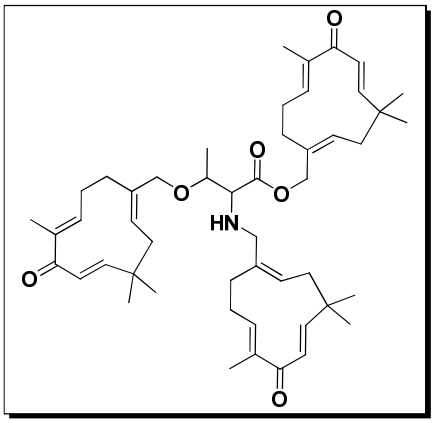
((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl 3-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methoxy)-2-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methylamino)butanoate (3d)

Following the general procedure, the brominated zerumbone **1** (30 mg, 0.10135 mmol), threonine **2d** (36.21 mg, 0.304mmol) and Cs_2CO_3 (98.8 mg, 0.304 mmol) in DMF (2 mL) at rt for 12 hours gave the substituted product **3d** as a colourless liquid (18.68 mg, 24%).

R_f: 0.88 (ethylacetate/hexane = 1:2.3).

IR (neat) υ_{max}: 3437, 2962, 2114, 1647, 1459, 1266, 1178, 1124, 969, 754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 6.02-5.98 (m, 6H), 5.69-5.60 (m, 4H), 5.50-5.47 (m, 2H), 4.98-4.81 (m, 1H), 4.72-4.71 (m, 1H), 4.42-4.28 (m, 2H), 4.99-3.97 (m, 1H), 3.35-3.31 (m, 1H), 3.18-3.08 (m, 1H), 2.83-2.82 (m, 1H), 2.71-2.61 (m, 4H), 2.46-2.42 (m, 6H), 2.31-2.29 (m, 5H), 2.21-2.19 (m, 4H), 2.05-2.02 (m, 2H), 1.94-1.90(m, 1H), 1.80 (s, 3H), 1.77 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.08 (s, 9H) ppm.

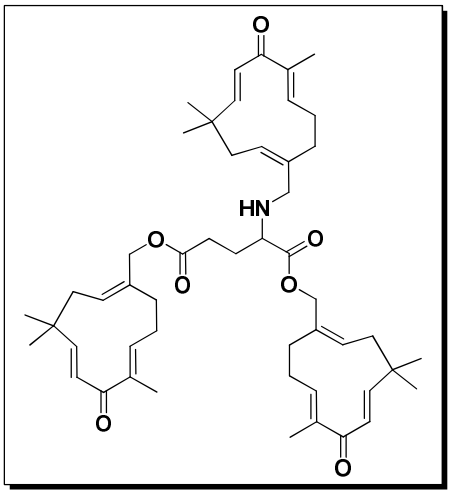


^{13}C NMR (125 MHz, $CDCl_3$): 203.6, 173.3, 159.1, 148.1, 145.5, 139.0, 138.2, 137.9, 127.3, 118.4, 110.4, 108.3, 68.4, 47.8, 42.5, 41.6, 37.5, 30.1, 29.5, 24.2, 22.7, 14.2, 12.1, 11.2 ppm.

HRMS (ESI): *m/z* Calcd for $C_{49}H_{70}NO_6$: 768.52031, Found: 768.52222 $[M+H]^+$.

bis(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl) 2-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methylamino)pentanedioate (3e)

Following the general procedure, the brominated zerumbone **1** (30 mg, 0.10135 mmol), glutamic acid **2e** (44.72 mg, 0.304mmol) and Cs_2CO_3 (98.8 mg, 0.304 mmol) in DMF (2 mL) at rt for 12 hours gave the substituted product **3e** as a colourless liquid (50.76 mg, 63%).



R_f: 0.75 (ethylacetate/hexane = 1:2.3).

IR (neat) υ_{max}: 3784, 2961, 1733, 1648, 1448, 1367, 1268, 1216, 1103, 971, 910, 839, 738, 701, 630, 545 cm^{-1}.

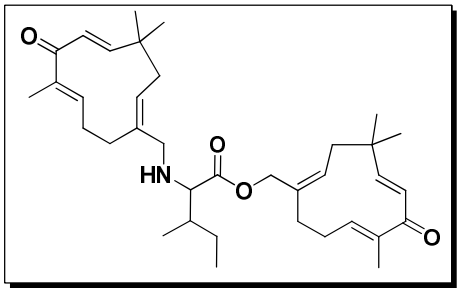
^{1}H NMR (500 MHz, $CDCl_3$): 6.01-5.96 (m, 6H), 5.81-5.78 (m, 1H), 5.72-5.64 (m, 2H), 5.52-5.48 (m, 2H), 5.37-5.34 (m, 1H), 4.87-4.70 (m, 1H), 4.47-4.33 (m, 2H), 4.06-3.89 (m, 1H), 3.39-3.24 (m, 1H), 2.76-1.86 (m, 25H), 1.78-1.76 (m, 6H), 1.25 (s, 6H), 1.23 (s, 3H), 1.11-1.08 (m, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): 203.8, 203.7, 203.5, 177.0, 172.9, 160.1, 159.9, 159.7, 159.4, 149.6, 149.1, 148.9, 138.6, 138.4, 134.3, 134.2, 131.6, 131.4, 127.4, 127.3, 127.2, 61.0, 59.2, 42.3, 42.1, 42.0, 41.9, 37.5, 37.4, 35.4, 29.7, 29.4, 28.2, 24.8, 24.7, 24.5, 24.0, 12.1, 12.0, 11.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{50}H_{70}NO_7$: 796.51523, Found: 796.5159 $[M+H]^+$.

((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl 3-methyl-2-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methylamino)pentanoate (3f)

Following the general procedure, the brominated zerumbone **1** (30 mg, 0.10135 mmol), leucine **2f** (39.82 mg, 0.304mmol) and Cs_2CO_3 (98.8 mg, 0.304 mmol) in DMF (2 mL) at rt for 12 hours gave the substituted product **3f** as a colourless liquid (34.23 mg, 60%).



R_f: 0.85 (ethylacetate/hexane = 1:2.3).

IR (neat) υ_{max}: 3426, 2098, 1642, 1420, 1262, 1093, 1022, 789, 654 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.04-6.01 (m, 1H), 5.97-5.94 (m, 3H), 5.78-5.73 (m, 1H), 5.50-5.46 (m, 1H), 5.39-5.32 (m, 1H), 4.78-4.73 (m, 1H), 4.50- 4.36 (m, 1H), 3.31-3.22 (m, 1H), 3.07-3.06 (m, 1H), 2.98-2.91(m, 1H), 2.73-2.61 (m, 2H), 2.45-2.36 (m, 4H), 2.31-2.16 (m, 3H), 2.07-2.04 (m, 2H), 1.92-1.88 (m, 1H),1.80 (s, 3H), 1.77 (s, 3H), 1.25 (s, 3H), 1.21 (s, 3H), 1.10 (S, 3H), 1.06 (s, 3H), 0.90 (s, 3H), 0.89 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.6, 203.0, 175.4, 159.3, 155.7, 148.6, 138.6, 137.9, 145.5, 131.3, 127.3, 64.6, 42.4, 41.9, 38.4, 37.4, 37.3, 29.7, 29.4, 26.7, 25.5, 24.7, 24.4, 24.1, 18.1, 16.0, 14.8, 13.9, 13.6, 12.0, 11.9, 11.8 ppm.

HRMS (ESI): *m/z* Calcd for $C_{36}H_{54}NO_4$: 564.40528, Found: 564.40564 $[M+H]^+$.

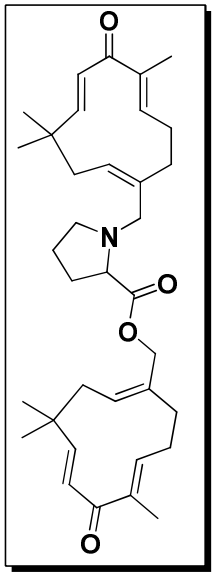
((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl 1-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl)pyrrolidine-2-carboxylate (3g)

Following the general procedure, the brominated zerumbone **1** (30 mg, 0.10135 mmol), proline **2g** (34.99mg, 0.304mmol) and Cs_2CO_3 (98.8 mg, 0.304 mmol) in DMF (2 mL) at rt for 12 hours gave the substituted product **3f** as a colourless liquid (8.87 mg, 16%).

R_f: 0.9 (ethylacetate/hexane = 1:2.3).

IR (neat) υ_{max}: 3424, 2097, 1642, 1418, 1262, 1095, 1022, 797, 653 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 5.97-5.88 (m, 4H), 5.75-5.71 (m, 1H), 5.64-5.61 (m, 1H), 5.42-5.39 (m, 1H), 5.31-5.27 (m, 1H), 4.64-4.62 (m, 1H), 4.40-4.28 (m, 1H), 3.24-2.90 (m, 3H), 2.80-2.78 (m, 1H), 2.59-2.53 (m, 2H), 2.45-2.36 (m, 4H), 2.01-1.96 (m, 2H), 1.86-1.81 (m, 3H), 1.73 (s, 3H), 1.71 (s, 3H), 1.18 (s, 3H), 1.15 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H) ppm.

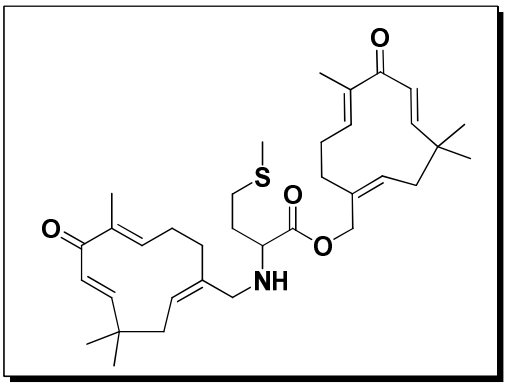


^{13}C NMR (125 MHz, $CDCl_3$): 205.1, 202.1, 175.2, 158.7, 158.7, 158.3, 148.9, 148.2, 147.6, 137.7, 137.5, 137.0, 133.4, 130.3, 127.2, 126.3, 126.2, 98.9, 64.6, 59.7, 58.2, 52.2, 50.3, 41.3, 41.0, 40.8, 36.6, 36.3, 34.6, 34.4, 34.1, 29.8, 28.6, 28.3, 23.7, 23.5, 23.0, 21.9, 13.1, 11.0, 10.8 ppm.

HRMS (ESI): *m/z* Calcd for $C_{35}H_{50}NO_4$: 548.37398, Found: 548.37463 $[M+H]^+$.

((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl 4-(methylthio)-2-(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methylamino)butanoate (3h)

Following the general procedure, the brominated zerumbone **1** (30 mg, 0.10135 mmol), methionine **2h** (45.36mg, 0.304mmol) and Cs_2CO_3 (98.8 mg, 0.304 mmol) in DMF (2 mL) at rt for 12 hours gave the substituted product **3h** as a colourless liquid (21.78 mg, 37%).



R_f: 0.82 (ethylacetate/hexane = 2:2.3).

IR (neat) υ_{max}: 3746, 3431, 2968, 2397, 2333, 2091, 1728, 1648, 1588, 1459, 1419, 1268, 1123, 1041, 857, 754, 669, 557, 540, 519 cm^{-1}.

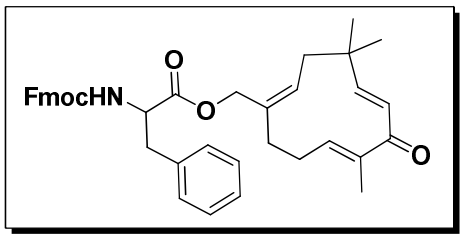
^{1}H NMR (500 MHz, $CDCl_3$): 6.01-5.95 (m, 5H), 5.81-5.72 (m, 2H), 5.50-5.47 (m, 1H), 5.37-5.34 (m, 1H), 4.80-4.68 (m, 1H), 4.45-4.33 (m, 1H), 3.38-3.27 (m, 1H), 2.89-2.88 (m, 2H), 2.78-2.71 (m, 3H), 2.61-2.45 (m, 5H), 2.30- 2.20 (m, 5H), 2.09 (s, 3H),1.93-1.91 (m, 4H), 1.80 (s, 3H), 1.78 (s, 3H), 1.25 (s, 3H), 1.22 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): 203.3, 202.8, 175.2, 159.6, 158.9, 148.0, 148.3, 129.0, 138.6, 138.3, 138.1, 134.2, 131.3, 128.3, 127.4, 127.2, 59.2, 53.2, 42.3, 42.0, 41.9, 37.4, 37.3, 35.1, 29.7, 24.4, 15.3, 12.0, 11.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{35}H_{52}NO_4S$: 582.36170, Found: 582.3607 $[M+H]^+$.

((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-phenylpropanoate (3i)

Following the general procedure, the brominated zerumbone **1** (30 mg, 0.10135 mmol), methionine **2i** (117.69mg, 0.304mmol) and Cs_2CO_3 (98.8 mg, 0.304 mmol) in DMF (2 mL) at rt for 12 hours gave the substituted product **3i** as a colourless liquid (34.22 mg, 72%).



R_f: 0.22 (ethylacetate/hexane = 2:3).

IR (neat) υ_{max}: 3429, 2097, 1642, 1262, 1021, 796, 743 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): 7.75 (d, 2H, *J* = 7.5 Hz), 7.54 (t, 2H, *J* = 6 Hz), 7.38 (t, 2H, *J* = 7.5 Hz), 7.29 (t, 5H, *J* = 7.5 Hz), 7.10 (s, 2H), 5.99-5.94 (m, 2H), 5.70 (d, 1H, *J* = 16 Hz), 5.45 (t, 1H, *J* = 8 Hz), 5.22 (d, 1H, *J* = 8 Hz), 4.91-4.72 (m, 1H), 4.67-4.63 (m, 1H), 4.44-4.41 (m, 1H), 4.34-4.31 (m, 1H), 4.19 (t, 1H, *J* = 7 Hz), 3.15-3.07 (m, 2H), 2.52-2.24 (m, 5H), 2.11-2.01 (m, 1H), 1.77 (s, 3H), 1.22 (s, 3H), 1.09 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): 202.7, 178.9, 159.1, 155.6, 143.7, 141.4, 139.0, 135.5, 129.3, 129.0, 127.8, 127.3, 125.1, 120.1, 67.0, 56.7, 46.9, 42.2, 37.2, 35.1, 30.7, 28.9,

24.8, 21.3, 13.9, 12.1, 8.9 ppm.

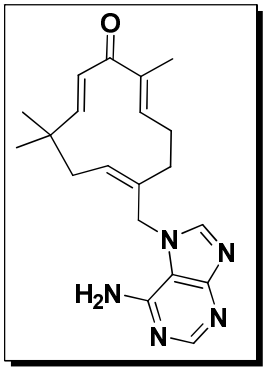
HRMS (ESI): *m/z* Calcd for $C_{39}H_{42}NO_5$: 604.30630, Found: 604.30599 $[M+H]^+$.

(2E,6Z,10E)-6-((6-amino-7H-purin-7-yl)methyl)-2,9,9-trimethylcycloundeca-2,6,10-trienone (6a)

Following the general procedure, the brominated zerumbone **1** (30 mg, 0.101 mmol), adenine **5a** (3 mg, 0.025 mmol) and Cs_2CO_3 (197.44 mg, 0.606 mmol) in DMF (2 mL) at rt for 12 hours gave the substituted product **6a** as a colourless liquid (7 mg, 54%).

R_f: 0.22 (ethylacetate/hexane = 1:2.3).

IR (neat) υ_{max}: 3103, 2957, 2921, 2853, 2340, 1732, 1645, 1599, 1464, 1368, 1329, 1302, 1243, 1190, 1106, 1071, 969, 901, 795, 744, 652, 528 cm^{-1}.



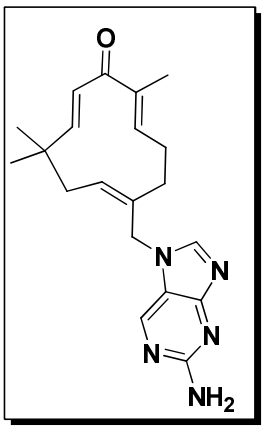
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.72 (s, 1H), 6.03 (d, J = 16.5 Hz, 1H), 6.00-5.97 (m, 1H), 5.92-5.89 (m, 3H), 5.61-5.58 (m, 1H), 4.78 (brs, 1H), 4.69 (brs, 1H), 2.65-2.59 (m, 1H), 2.47-2.39 (m, 1H), 2.19- 2.17 (m, 4H), 1.80 (s, 3H), 1.29 (s, 3H), 1.17 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.6, 159.3, 155.5, 153.2, 148.5, 140.0, 139.1, 134.0, 131.6, 129.8, 127.6, 119.2, 42.3, 40.8, 37.7, 29.4, 22.7, 14.1 ppm.

HRMS (ESI): *m/z* Calcd for $C_{20}H_{26}N_5O$ $[M+H]^+$: 352.21374: , Found: 352.2137.

(2E,6Z,10E)-6-((2-amino-7H-purin-7-yl)methyl)-2,9,9-trimethylcycloundeca-2,6,10-trienone (6b)

Following the general procedure, the brominated zerumbone **1** (30 mg, 0.1013 mmol), 2-aminopurine **5b** (3.4 mg, 0.025 mmol) and Cs_2CO_3 (49.46 mg, 0.41 mmol) in DMF (2 mL) at rt for 12 hours gave the substituted product **6b** as a colourless liquid (6 mg, 68%).



R_f: 0.22 (ethylacetate/hexane = 1:2.3).

IR (neat) υ_{max}: 3430, 2925, 2855, 2138, 1640, 1579, 1464, 1426, 1362, 1267, 1184, 1102, 966, 908, 860, 794, 754, 699, 628 cm^{-1}.

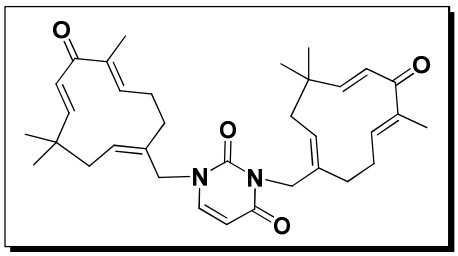
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (s, 1H), 7.69 (s, 1H), 6.05 (d, *J* = 16.5 Hz, 1H), 6.01-6.00 (m, 1H), 5.95 (d, *J* = 16.5 Hz, 1H), 5.61-5.58 (m, 1H), 5.13 (s, 2H), 4.66 (brs, 1H), 4.61 (brs, 1H), 2.62-2.60 (m, 1H), 2.37-2.30 (m, 1H), 2.22-2.17 (m, 4H), 1.29-1.28 (m, 3H), 1.26-1.25 (m, 3H), 1.17 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.5, 159.9, 159.2, 149.8, 148.6, 139.3, 138.9, 134.0, 131.4, 127.6, 114.1, 42.2, 37.7, 31.9, 29.4, 24.5, 22.7, 14.1, 11.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{20}H_{25}N_5NaO$: 374.19568, Found: 374.19556 $[M+H]^+$.

1,3-bis(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl)pyrimidine-2,4(1H,3H)-dione, **(6c)**

Following the general procedure, the brominated zerumbone **1** (30 mg, 0.1013 mmol), uracil **5c** (2.08 mg, 0.025 mmol) and Cs_2CO_3 (197.44mg, 0.606 mmol) in DMF (2 mL) at rt for 12 hours gave the substituted product **6c** as a colourless liquid (3 mg, 31%).



R_f: 0.91 (ethylacetate/hexane = 1:2.3).

IR (neat) υ_{max}: 3430, 2961, 2926, 2858, 2108, 1652, 1453, 1390, 1266, 1105, 970, 755 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03 (d, *J* = 8 Hz, 1H), 6.04-5.94 (m, 5H), 5.76-5.73 (m, 2H), 5.64- 5.61 (m,1H), 5.44-5.42 (m, 1H), 4.55-4.52 (m, 3H), 4.19 (brs,1H), 2.84-2.72 (m, 1H), 2.65-2.47 (m, 4H), 2.36-2.27 (m, 3H), 2.20-2.08 (m, 4H), 1.85 (s, 3H), 1.82 (s, 3H), 1.25 (s, 6H), 1.15 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 204.2, 203.4, 177.1, 162.9, 158.9, 152.0, 149.5, 148.5, 140.9, 139.0, 138.5, 134.2, 132.6, 130.8, 127.6, 127.0, 114.1, 102.1, 42.1, 37.7, 37.6, 33.8, 33.2, 31.9, 29.4, 28.2, 26.7, 24.3, 22.7, 14.1, 12.0, 12.0 ppm.

HRMS (ESI): *m/z* Calcd for $C_{34}H_{44}N_2NaO_4$: 567.31988, Found: 567.32028 $[M+H]^+$.

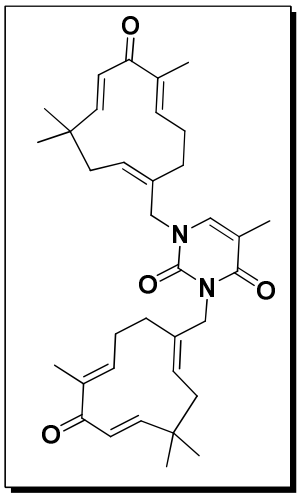
5-methyl-1,3-bis(((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8 trienyl)methyl)pyrimidine-2,4(1H,3H)-dione (6d)

Following the general procedure, the brominated zerumbone **1** (30 mg, 0.1013 mmol), thymine **5d** (3.15 mg, 0.025 mmol) and Cs_2CO_3 (197.44 mg, 0.606 mmol) in DMF (2 mL) at rt for 12 hours gave the substituted product **6d** as a colourless liquid (3.3 mg, 25%).

R_f: 0.91 (ethylacetate/hexane = 1:2.3).

IR (neat) υ_{max}: 3445, 2962, 2313, 1699, 1639, 1522, 1460, 1367, 1266, 974, 908, 861, 757, 700, 544 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84 (s, 1H), 6.05-5.95 (m, 5H), 5.74 (d, *J* = 16.5 Hz, 1H), 5.64-5.60 (m, 1H), 5.45-5.42 (m, 1H), 4.58-4.51 (m, 3H), 4.14 (brs, 1H), 2.82-2.47 (m, 4H), 2.26-2.04 (m, 8H), 1.93 (d, *J* = 1.5 Hz, 3H), 1.86 (s, 3H), 1.84 (s, 3H), 1.25 (s,



6H), 1.15 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.8, 203.0, 163.5, 158.6, 152.0, 149.2, 148.1, 139.2, 138.5, 136.7, 134.3, 132.0, 130.8,127.7, 127.1, 110.4, 44.4, 42.2, 42.1, 39.4, 37.7, 37.3, 35.2, 34.6, 29.7, 29.4, 24.3, 21.2, 13.2, 12.0, 11.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{35}H_{46}N_2NaO_4$: 581.33553, Found: 581.33647 $[M+H]^+$.

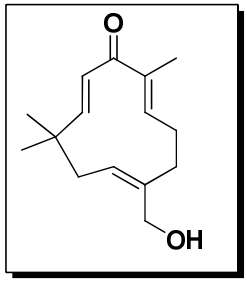
(2E,6Z,10E)-6-(hydroxymethyl)-2,9,9-trimethylcycloundeca-2,6,10-trienone (4)

Yield: 25%, Colourless liquid

R_f: 0.91 (ethylacetate/hexane = 1:2.3)

IR (neat) υ_{max}: 3445, 2962, 2313, 1699, 1639, 1522, 1460, 1367, 1266, 974, 908, 861, 757, 700, 544 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.02-5.99 (m, 1H), 5.97 (d, *J* = 16.5 Hz, 1H), 5.79 (d, *J* = 16.5 Hz, 1H), 5.37-5.34 (m, 1H), 4.33 (d, *J* = 10.5 Hz, 1H), 3.87 (d, *J* = 9.5 Hz, 1H), 2.78 (brs, 1H), 2.52 (brs, 1H), 2.43 (brs, 1H), 2.33-2.30 (m, 1H), 2.17-2.08 (m, 1H),



1.98-1.90 (m, 1H), 1.78 (d, *J* = 1 Hz, 3H), 1.23 (s, 3H), 1.08 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.7, 159.9, 149.4, 138.1, 138.3, 128.3, 127.2, 59.2, 42.1, 37.4, 35.2, 24.8, 12.0 ppm.

HRMS (ESI): *m/z* Calcd for $C_{15}H_{22}NaO_2$: 257.15175, Found: 257.15186 $[M+Na]^+$.

2A.9. Procedure for boilogical assays

2A.9.1. MTT assay

Refer: Chapter 2A, Procedure for various biological assays, 2A.10.2.

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CHAPTER 3

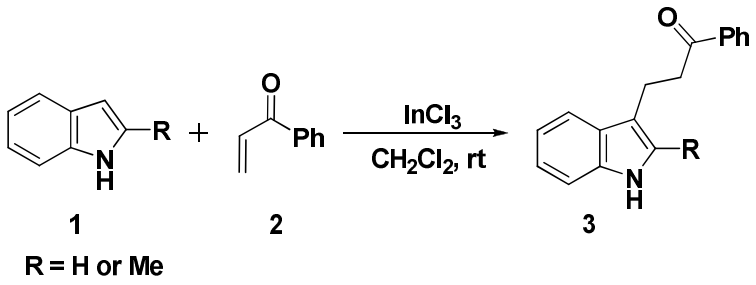
Synthesis and Biological Evaluation of Indole/Pyrrole Functionalized Zerumbone Derivatives

3.1. Introduction

Structural manipulation of zerumbone to diverse biologically significant chemical structures has been investigated by Kitayama and co-workers. Zerumbone has gained much attention to the scientific community because of its interesting chemical reactivity and biological profile. The proper utilization and functionalization of this molecule may lead to new compounds or drug like molecules with interesting biological activity. Substrates bearing bio-active cores by simple chemical transformation provided the complex structures with broad spectrum of biological activity. The present chapter deals with a facile synthesis of indole/pyrrole functionalized zerumbone derivatives. The anti-hyperglycemic and anti-hypertensive activities of the zerumbone derivatives are also discussed.

3.2. Conjugate Addition Reactions of Indoles

Yadav *et al.* reported a superior catalytic Lewis acid activity of $InCl_3$ in the conjugative addition of indoles in 2001 (Scheme 3.1).[1]

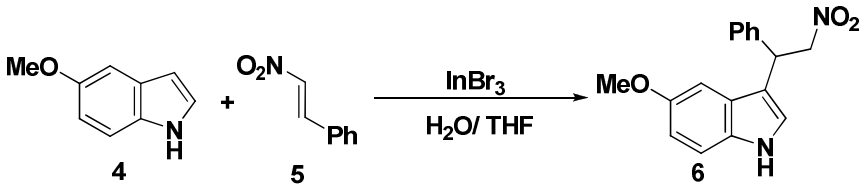


1 2 3

R = H or Me

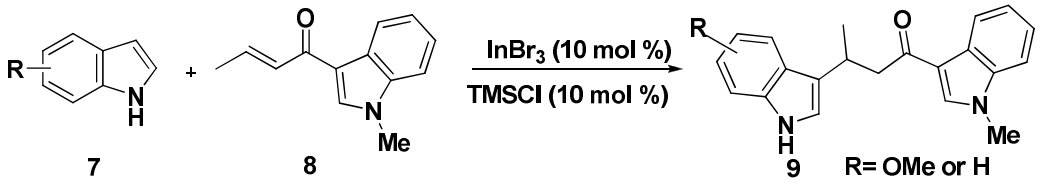
Scheme 3.1

A general and mild $InBr_3$-catalyzed protocol for the conjugate addition of indoles (**4**) to nitroalkenes (**5**) to give 2-indolyl-1-nitroalkanes (**6**) was described by Bandini, and Umani-Ronchi.[2] The process performed in aqueous media, provides the functionalized indoles in excellent yields (99–65%) and allows catalyst to be reused several times without loss of effectiveness (Scheme 3.2)



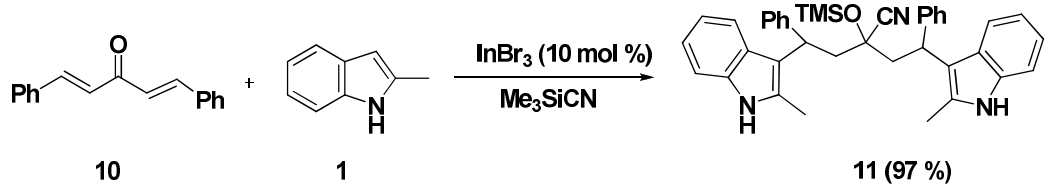
Scheme 3.2

A general procedure for the synthesis of 1,3-bis(indol-3-yl)butane-1-ones (**9**) was developed by Bandini and co-workers *via* Michael addition reaction catalyzed by $InBr_3$/ TMSCl (chlorotrimethylsilane) (Scheme 3.3). [3]



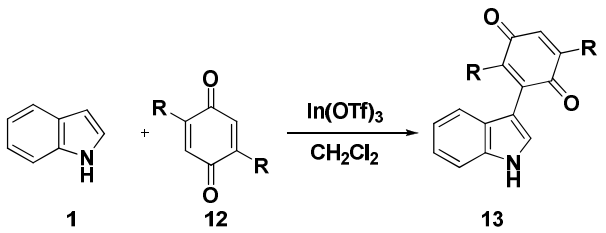
Scheme 3.3

Cozzi *et al.* described a sequential, one-pot $InBr_3$-catalyzed 1,4-addition of indoles, followed by 1,2-addition to enones. When $InBr_3$ (10 mol %) catalyst is used together with trimethylsilylcyanide (TMSCN), then the reaction is initiated by the 1,4-conjugate addition of indoles to *α,β*-unsaturated ketone and then finished by the 1,2-addition of TMSCN to the *β*-substituted ketones in one pot (Scheme 3.4).[4]



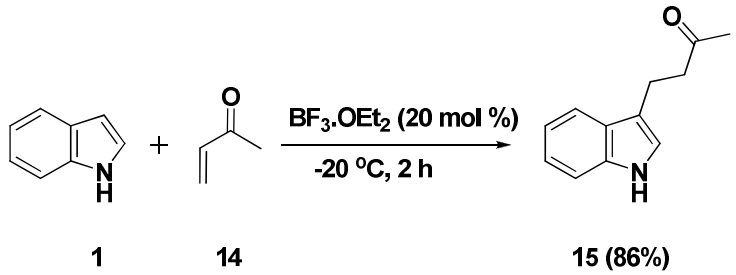
Scheme 3.4

$InBr_3$ catalyzes efficiently the Michael addition of indole (**1**) to 1,4-benzoquinone and 1,4-naphthoquinone under mild conditions, resulting in the formation of 3-indolylquinones (**20**). The reactions proceeded rapidly at room temperature in dichloromethane. Hydroquinone produced from the first addition to quinone is oxidized with another equivalent of *p*-quinone in the formation of 3-indolylquinones (Scheme 3.5).[5]



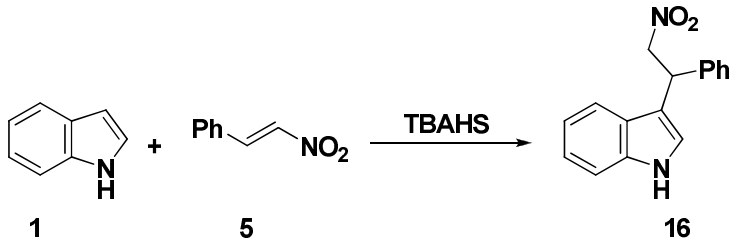
Scheme 3.5

Igbal and Djardin *et al*. independently reported the catalytic conjugate addition of indoles to enones (**4**) (Scheme 3.6).[6-7] The reaction afforded the addition product **15** in 86% yield.



Scheme 3.6

Damodiran *et al.* reported the simple and direct method for the synthesis of 3-alkylated indoles *via* the conjugate addition reaction of indoles to *α,β*-unsaturated compounds in the presence of either protic or Lewis acids.[8] Recently, studies have been carried out to explore tetrabutylammonium hydrogen sulfate (TBAHS) for its catalytic activity in organic synthesis. The treatment of indoles with electron deficient olefins in the presence of catalytic amount of TBAHS, resulting in the formation of 3-alkylated indoles **26** in good to excellent yield. The rate of the reaction was accelerated by electron donating groups present on the indole nucleus. Indole substrate bearing an electron-withdrawing group afforded adduct in less yield compared to other indoles (Scheme 3.7).

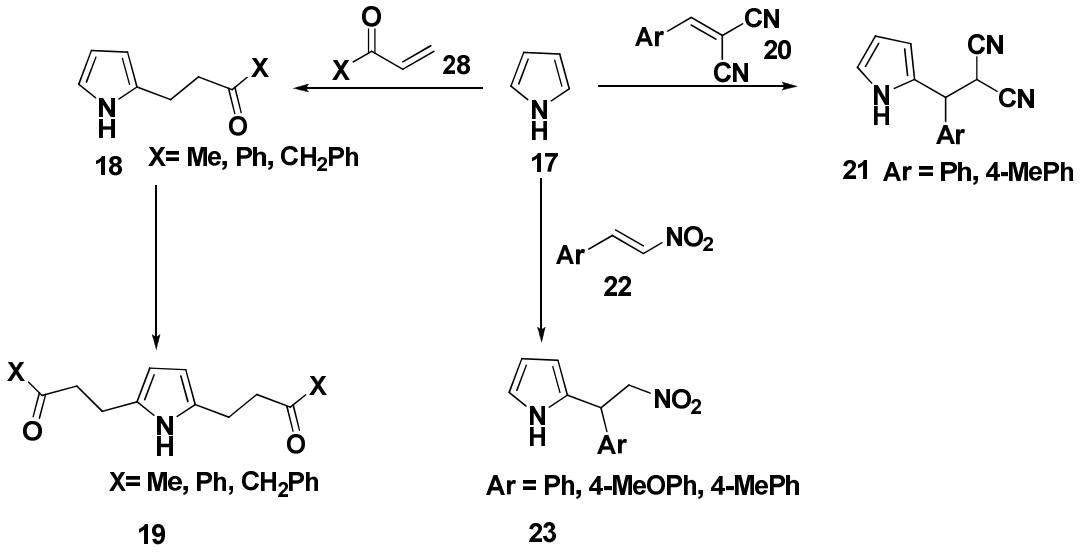


Scheme 3.7

3.2.1. Michael Addition Reactions of Pyrroles

A number of simple and direct methods were reported for the synthesis of 2-alkyl pyrroles *via* Michael additions catalyzed by various Lewis acids. $InCl_3$ is the first Lewis acid used for the synthesis of 2-alkylated pyrroles *via* the conjugate addition with electron-deficient olefins of pyrrole without polymerization.[9] The reactions proceeded smoothly at ambient temperature in excellent yields with high selectivity. The electron-deficient olefins, such as alkyl-, aryl- and benzyl vinyl ketone, 2-benzylidenemalononitrile, bis(benzylidene) ketone and *β*-nitrostyrenes afforded the

corresponding 2-alkylated pyrroles in moderate to good yields (Scheme 3.8). By increasing the reaction time and changing the molar ratio of substrates, the reaction of unsaturated ketones with pyrroles afforded 2,5-dialkylated products in good yields.



Scheme 3.8

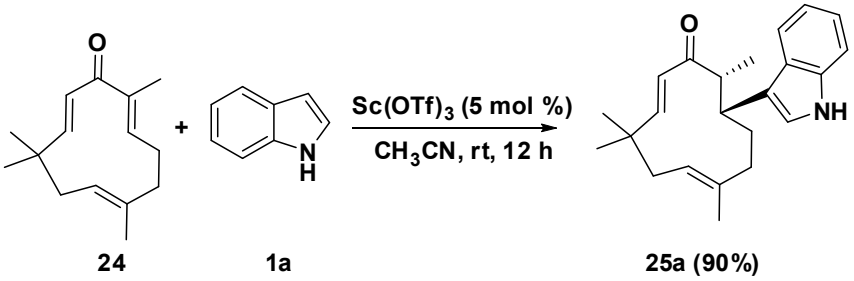
3.4. Definition of the Problem

Due to the presence of conjugate double bonds, zerumbone underogoes 1,4-conjugate addition reaction by various nucleophiles such as KCN, NH_3, CH_3OH and PhSH etc.[10] Investigation from our own laboratory revealed the anti-diabetic potential of the zerumbone derivatives.[11-12] Thus, with the aim of constructing new zerumbone derivatives, we were interested in incorporating biologically active heterocyclic systems which are important structural units in pharmaceuticals. Among them indoles[13-18] and pyrroles have been identified as a privileged motif for the development of pharmaceuticals. We have initiated Lewis acid catalyzed conjugated addition reactions of zerumbone with indoles and pyrroles. A detailed description of the Lewis acid catalyzed conjugated addition reactions of zerumbone with indoles and pyrroles is presented in the following section.

3.5. Results and Discussion

Our initial studies began with the reaction of zerumbone **24** with unsubstituted indole **1a** in the presence of $Sc(OTf)_3$ in acetonitrile at room temperature for 12 h. The reaction afforded regioselective 1,4-conjugate addition product **25a** in 90% yield (Scheme 3.12). The structure of the product **25a** was established based on various spectroscopic

techniques. Regioselective 1,4-conjugate addition was unambiguously confirmed by single crystal analysis of compound **25b** (Figure 3.3).



Scheme 3.9 1,4-conjugate addition of indole **1a** with zerumbone **24**

In the IR spectrum, the signal at 1663 cm^{-1} was diagnostic of the enone moiety of the product **25a**. The ^1H NMR spectrum showed that the proton at δ 8.07 ppm as singlet corresponding to NH proton of indole, the aromatic protons resonated at δ 7.50, 7.39 ppm as doublets, and between δ 7.23-7.12 ppm as multiplet. The *α*- and *β*- protons of the enone part resonated at δ 6.48 and 6.26 ppm respectively as doublets. The isolated olefinic proton was observed at δ 5.23 ppm a doublet of doublet. The ^1H NMR spectrum of compound **25a** is shown in the figure 3.1.

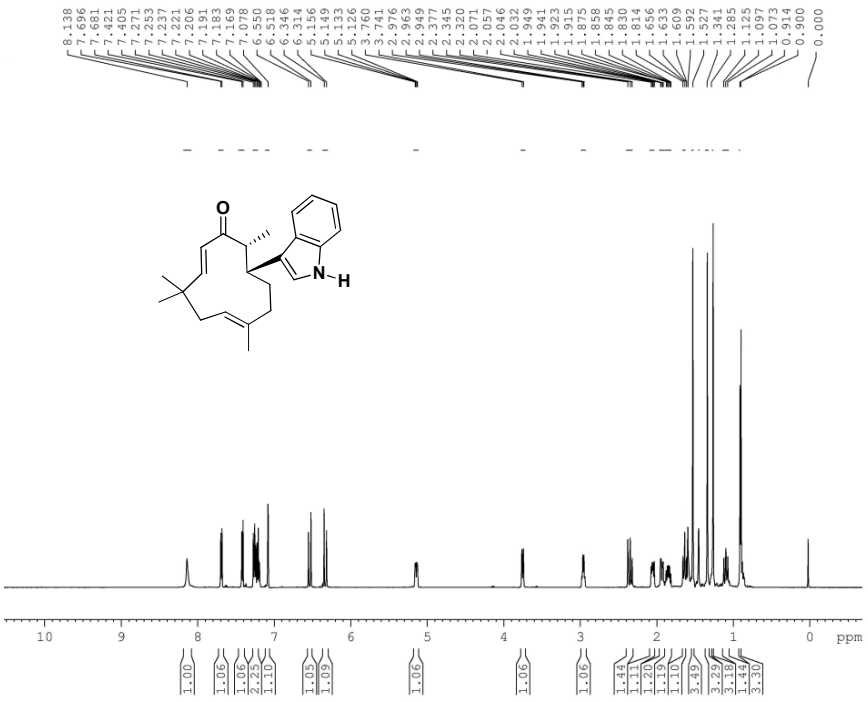


Figure 3.1. ^1H NMR of compound **25a**

The ^{13}C NMR spectrum showed the characteristic carbonyl peak at δ 203 ppm. The ^{13}C NMR spectrum of compound **25a** is shown in the figure 3.2. Finally mass spectrum well supported the structure with $[M+Na]^+$ ion peak at *m/z* 434.24539.

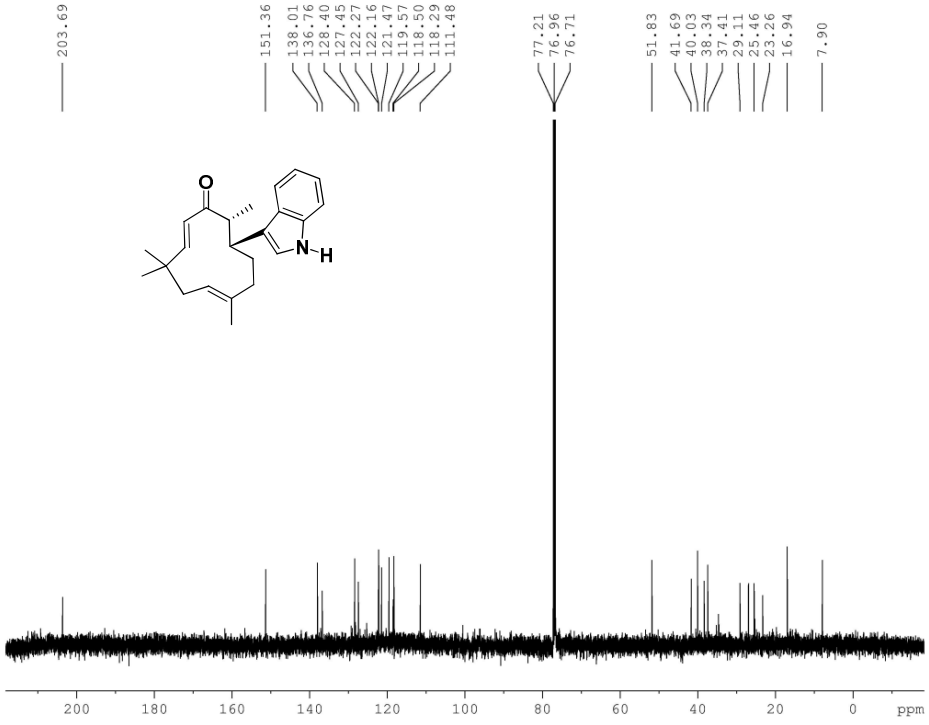


Figure 3.2. ^{13}C NMR of compound **25a**

Table 3.1. Optimization studies for suitable catalyst system

Entry	Lewis acid	Solvent	Yield (%)
1	$Sc(OTf)_3$	CH_3CN	90
2	$Fe(OTf)_3$	CH_3CN	63
3	$Cu(OTf)_2$	CH_3CN	76
4	$La(OTf)_3$	CH_3CN	NR
5	$Yb(OTf)_3$	CH_3CN	Trace
6	AgOTf	CH_3CN	NR
7	$Zn(OTf)_2$	CH_3CN	NR
8	$BF_3{\cdot}(OEt_2)$	CH_3CN	72

Reaction condition: Zerumbone (1 equiv.), Indole (1 equiv.), Lewis acid (5 mol %), Solvent (2 mL), rt, 12 h

In an attempt to improve the yield of the reaction, we investigated the influence of different Lewis acids on the outcome of the reaction. Among various Lewis acids screened, initially employed $Sc(OTf)_3$ exhibited superior catalytic activity (Table 3.1, Entry 1). Lewis acids $La(OTf)_3$, $Zn(OTf)_2$ and AgOTf did not furnish any 1,4-addition product even after providing a prolonged reaction time.

The substrate scope was investigated by utilizing various substituted indoles. A variety of indole substituted zerumbone were synthesized. The results obtained are summarised in Table 3.2. To broaden the scope of the 1,4-conjugate addition reaction, various N-substituted and C-2, C-4, C-5 and C-7 substituted indoles were employed as reaction partners with zerumbone under the optimal reaction conditions and the results obtained are summarized in Table 3.2. Conjugate addition of N-methyl substituted indoles (**1b** and **1c**) with zerumbone **24** provided products (**25b** and **25c**) in good yields whereas indole bearing electron withdrawing group on nitrogen atom, for *eg*. N-benzoyl indole, did not furnish 1,4-addition product(Table 3. 2, entry 16). Also the 2-phenyl indole (**1e**) readily reacted with zerumbone resulting in the formation of the product **25e** in 80% yield.

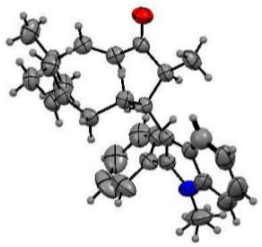
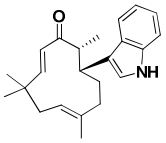
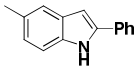
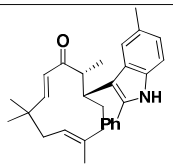
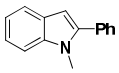
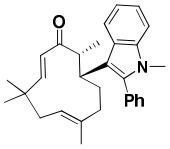
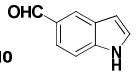
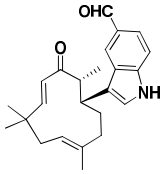
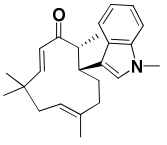
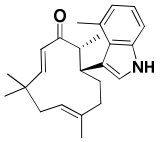
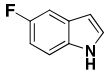
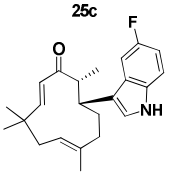
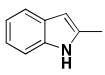
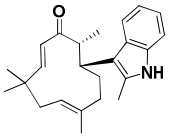
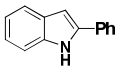
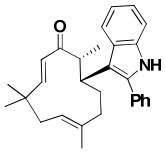
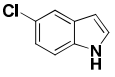
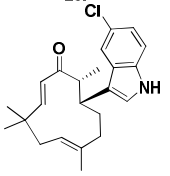
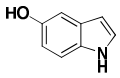
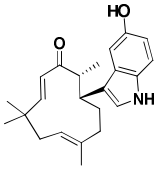
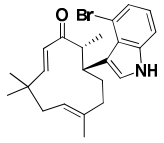
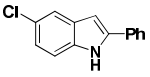
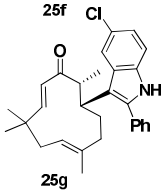
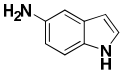
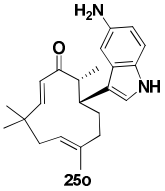
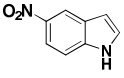
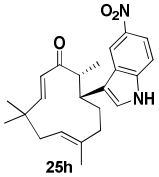
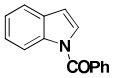
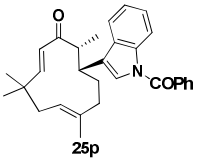


Figure 3.3. Single crystal X-ray structure of compound **25b** (CCDC number-1430677**)**

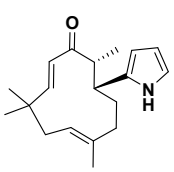
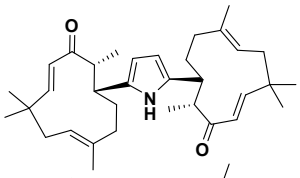
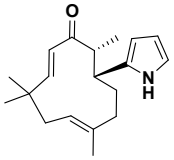
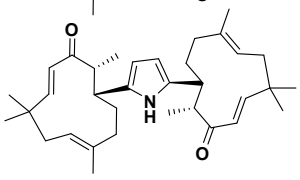
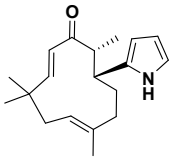
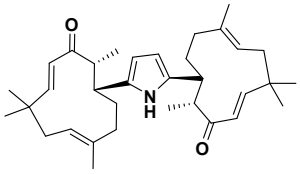
Various 5-substituted indoles such as 5-fluoroindole, 5-hydroxyindole and 5-chloroindole afforded Michael addition products **25d**, **25f** and **25m** in good yields (Table 3.2, entries 4, 6, 13) while the indoles bearing nitro and formyl substitution at C-5 showed diminished reactivity providing the addition products in low yields (Table 3.2, entries 8, 10) and the reaction of 5-aminoindole with zerumbone did not provide the product. In the case of C-4 substituted indole such as 4-bromo indole (**1n**), the reaction delivered the corresponding product (**25n**) in low yield of 16% (Table 3.2, entry 14). A methyl group at the C-2 and C-7 position of indole remarkably increased the yield of the reaction upto 95% (Table 3.2, entries 12, 11).

Table 3.2. 1, 4-Conjugate addition of indoles **1** with zerumbone **24**

Entry	Indole	Product	Yield (%)	Entry	Indole	Product	Yield (%)
1	 1a	 25a	90	9	 1i	 25i	28
2	 1b	 25b	72	10	 1j	 25j	12
3	 1c	 25c	86	11	 1k	 25k	95
4	 1d	 25d	74	12	 1l	 25l	94
5	 1e	 25e	80	13	 1m	 25m	83
6	 1f	 25f	69	14	 1n	 25n	16
7	 1g	 25g	8	15	 1o	 25o	NR
8	 1h	 25h	20	16	 1p	 25p	NR

Reaction condition: Zerumbone (1 equiv.), Indole (1 equiv.), $Sc(OTf)_3$ (5 mol %), CH_3CN (2 mL), rt, 12 h

Further, we focused to expand the scope of the reaction to other heterocyclic cores such as pyrrole. We commenced our reaction with 1 equiv. of zerumbone (**24**) and 1 equiv. of pyrrole (**26a**) in presence of Lewis acid at room temperature. The reaction furnished two products **27a** and **28a** in 31% and 13% respectively. In order to tune the reaction, we optimized the corresponding equivalents of zerumbone so that we could selectively synthesize compound **27a** in 76% yield. The double Michael addition product (**28a**) was obtained by altering the corresponding ratio of the substrates and the desired product was formed in 59% yield (Scheme 3.10).

Entry	Ratio Zerumbone (24)	pyrrole (26a)	Product 27a	Product 28a	Yield 27a:28a
1	1	1			31: 13
2	1	10			76:0
3	2	1			0:59

Reaction condition: $Sc(OTf)_3$ (5 mol %), CH_3CN (2 mL), rt, 12 h

Scheme 3.10.

With the optimized reaction condition in hand, we next investigated the viability of the reaction with different substituted pyrroles and the products were obtained in moderate to good yields (Table 3.3, Entry 1-4). Regioselective 1,4-conjugate addition was unambiguously confirmed by single crystal analysis of compound **27b** (Figure 3.4).

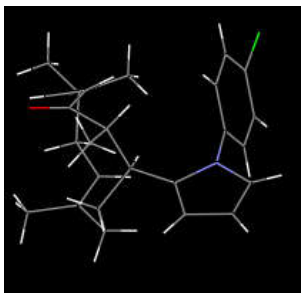
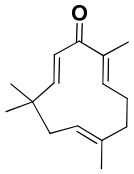
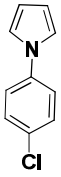
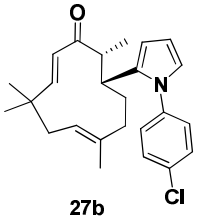
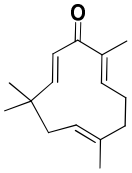
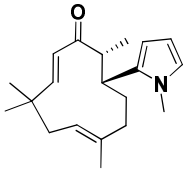
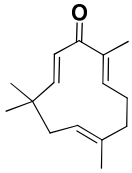
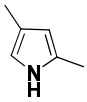
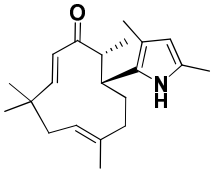
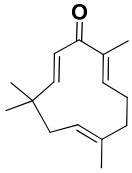
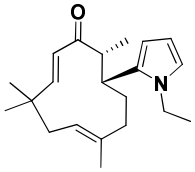
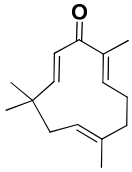
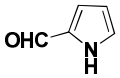
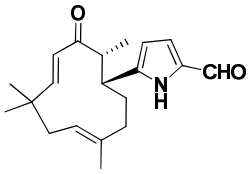


Figure 3.4. Single crystal X-ray structure of compound **27b** (CCDC number-1530682)

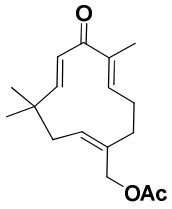
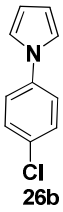
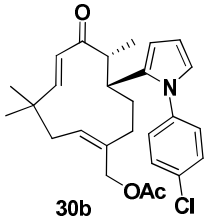
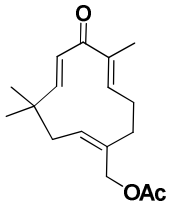
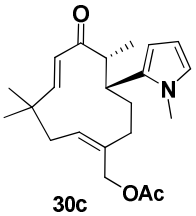
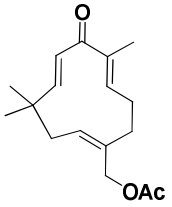
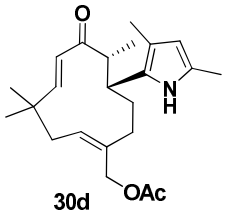
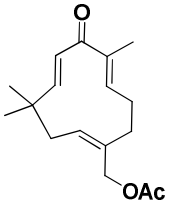
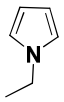
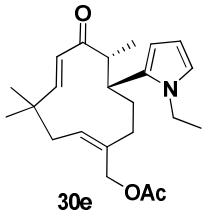
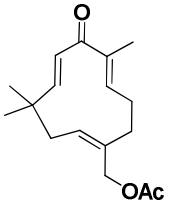
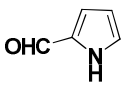
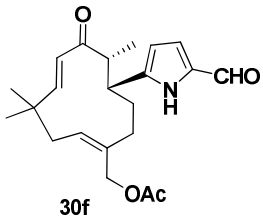
Table 3.3. Lewis acid catalyzed 1,4-conjugate addition of substituted pyrrole **26** with zerumbone **24**.

Entry	Zerumbone (24)	Pyrrole (26)	Product (27)	Yield (%)
1		 **26b**	 **27b**	81
2		 **26c**	 **27c**	47
3		 **26d**	 **27d**	79
4		 **26e**	 **27e**	55
5		 **26f**	 **27f**	NR

Reaction condition: Zerumbone **24** (1.0 equiv.), Pyrrole **26** (1.0 equiv.), $Sc(OTf)_3$ (5 mol %), CH_3CN (2 mL), rt, 12 h

Next we extended the generality of the reaction with ((1Z,5E,8E)-4,4,8-trimethyl-7-oxocycloundeca-1,5,8-trienyl)methyl acetate (**29)** and the corresponding zerumbone-substituted pyrrole derivatives were formed in moderate yields in the presence of a catalytic amount of Lewis acids (Table 3.4, Entry 1-4). Substituted pyrroles gave only the monosubstituted products (Table 3.4, **30b-30e**). The electron withdrawing substituent such as CHO group at the C2 position of the pyrrole did not furnish the desired product (Table 3.4, Entry 5).

Table 3.4. Lewis acid catalyzed 1,4-conjugate addition of substituted pyrrole **26** with **29**

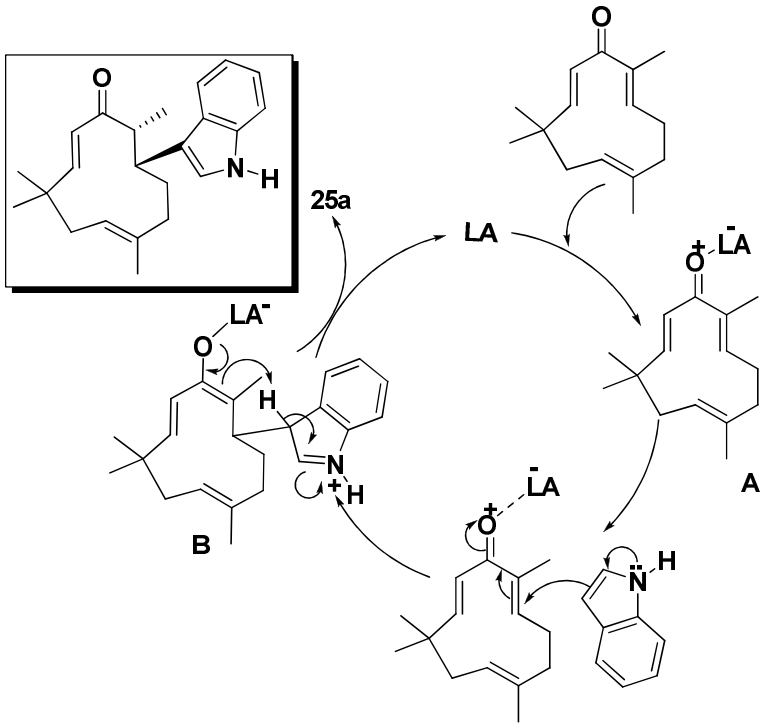
Entry	Zerumbone acetate (29)	Pyrrole (26)	Product 30	Yield (%)
1		 **26b**	 **30b**	34
2		 **26c**	 **30c**	29
3		 **26d**	 **30d**	33
4		 **26e**	 **30e**	29
5		 **26f**	 **30f**	NR

Reaction condition: Zerumbone acetate **29** (1.0 equiv.), Pyrrole **26** (1.0 equiv.), $Sc(OTf)_3$ (5 mol %), CH_3CN (2 mL), rt, 12 h

3.6. Mechanistic considerations

A plausible mechanism for the conjugate addition of indole to electron deficient dienone moiety of zerumbone is outlined in scheme 3.11. Coordination of Lewis acid to the oxygen atom of carbonyl group of zerumbone followed by the nucleophilic addition of electron rich β-carbon of indole at C-3 position of zerumbone results in the formation

of intermediate B.[19] The intermediate would then undergo hydrogen transfer to afford the conjugate addition product.

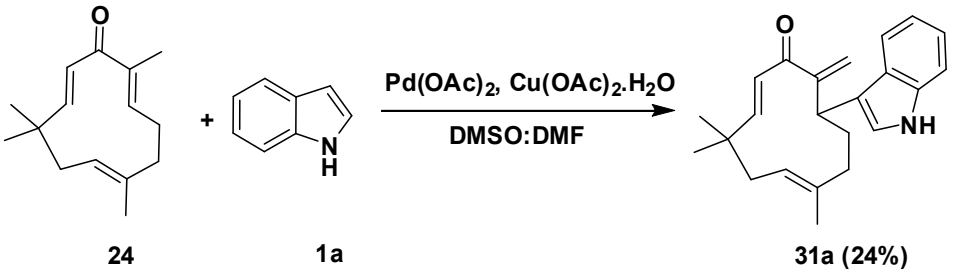


Scheme 3.11

In the light of successful synthesis of zerumbone derivatives, we envisioned the synthesis of new class of indole-zerumbone hybrids. With our interest in transition metal catalyzed reactions prompted us to devote our time on developing a new synthetic methodology for further derivatization with an aim to improve its biological properties. Palladium catalyzed decarboxylative coupling reaction of arene carboxylic acids with zerumbone afforded the arylated zerumbone derivatives having an exocyclic double bond and these derivatives showed superior α-glucosidase inhibition activity than the parent molecule zerumbone. With this perspective, we chose palladium catalyzed Heck type reaction for the synthesis of new zerumbone derivatives.[20-23]

3.7. Palladium Catalyzed Heck-Type Reaction of Zerumbone with Indoles

Our experiments started with the reaction of zerumbone **24** (1equiv.) with indole **1a** (1equiv.), palladium acetate (20 mol %), hydrated copper acetate (1.8 equiv.) in DMSO: DMF (1:20) solvent system at 80 ^{o}C for 12 h (Scheme 3.12). The reaction afforded indole-zerumbone hybrid **31a** having an exocyclic double bond in 24% yield.



Scheme 3.12

The structure of the compound **31a** was established by spectral analysis. In the IR spectrum, the signal at 1663 cm^{-1} was characteristic of the enone moiety. The ^1H NMR showed that the proton at δ 8.07 ppm as singlet corresponding to NH proton of indole, aromatic protons resonated at δ 7.50, 7.39 ppm as a doublets, δ 7.23-7.12 ppm as multiplet. The protons on *α,β*-unsaturated carbon of the enone part resonated at δ 6.48 and 6.26 ppm respectively as doublets. Two protons on the exocyclic double bond appeared at δ 5.65 and 4.92 ppm. The proton at the isolated olefin was observed as doublet of doublet at δ 5.23 ppm. All the other spectral values are in good agreement with the desired structure of the product **31a**. The ^1H NMR spectrum of compound **31a** is shown in the figure 3.5.

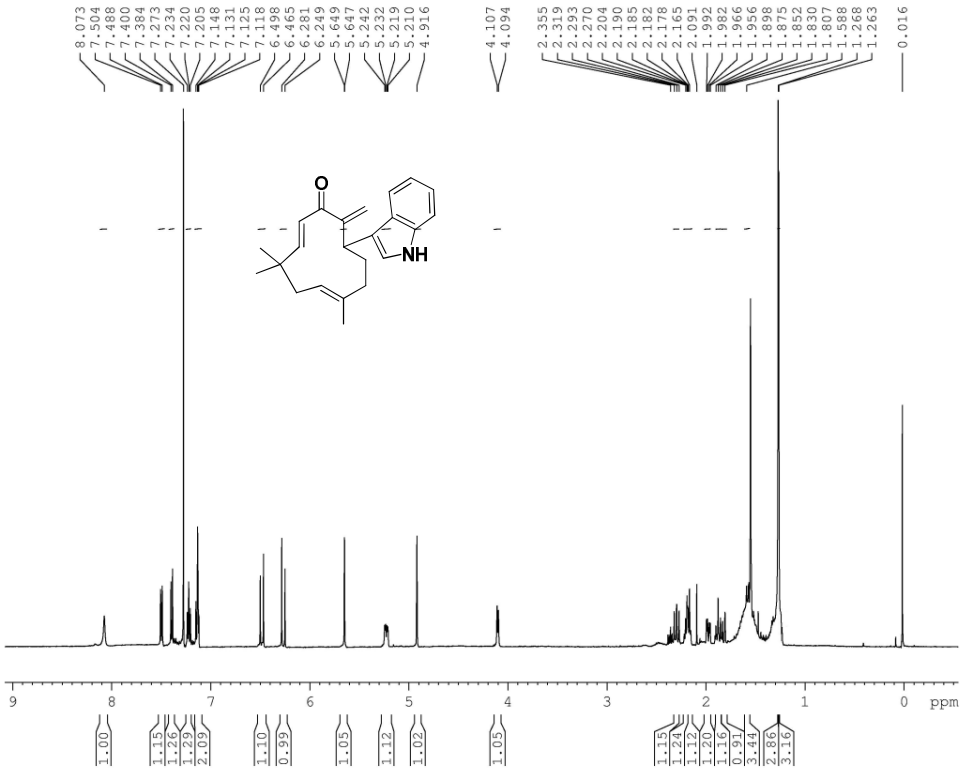


Figure 3.5. ^1H NMR of compound **31a**

The ^{13}C NMR showed the characteristic carbonyl peak at δ 197.7 ppm. The methylenic carbon of exocyclic double bond resonated at δ 117.4 ppm. The ^{13}C NMR spectrum of compound **31a** is shown in the figure 3.6. Finally the mass spectrum well supported the structure with $[M+Na]^+$ ion peak at *m/z* 356.19913.

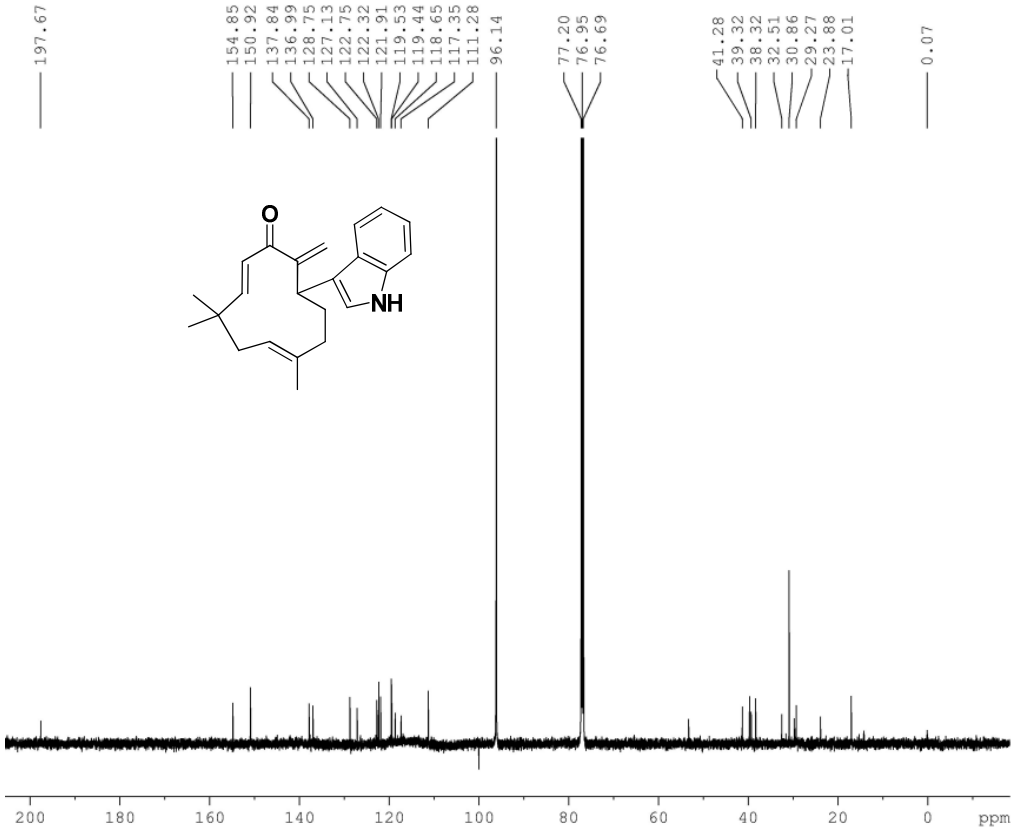


Figure 3.6. ^{13}C NMR of compound **31a**

We carried out detailed optimization studies in order to find the best catalyst system for the reaction. Various palladium catalyst, oxidants, ligands, solvent systems and temperature were screened. Among the various palladium catalyst employed, $Pd(OAc)_2$ is found to the best catalyst and the best oxidant found to be $Cu(OAc)_2.H_2O$. Among the various solvents such as THF, CH_3CN, DMF, DMSO and DMF:DMSO mixture, DMF:DMSO mixture found to the good solvent system. But the presence of ligand has not enhanced the reaction yield and the reaction requires 80 ^oC.

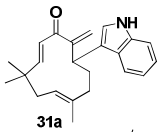
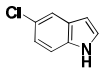
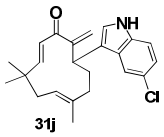
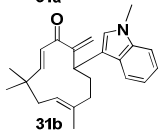
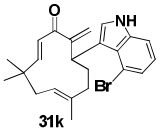
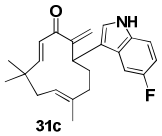
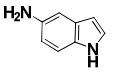
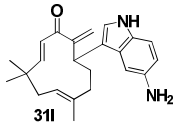
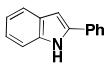
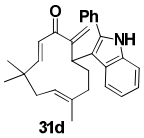
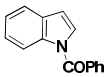
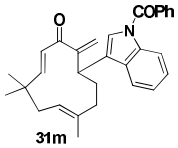
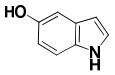
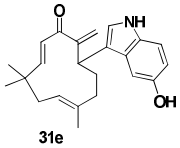
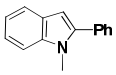
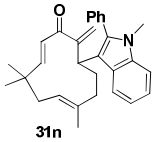
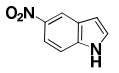
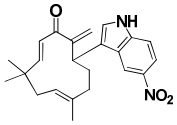
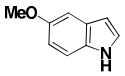
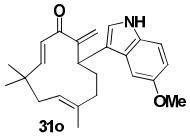
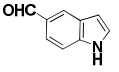
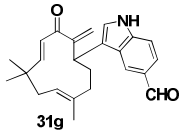
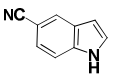
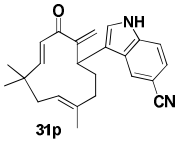
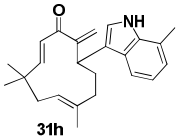
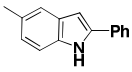
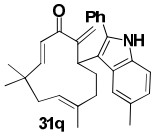
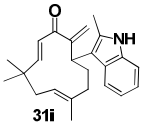
Table 3.5. Optimization of reaction condition: Palladium catalyzed coupling of indole (**1a**) with zerumbone (**24**).

Entry	Catalyst	Oxidant	Ligand	Solvent	Temperature (°C)	Yield (%)
1	$Pd(OAc)_2$	$Cu(OAc)_2.H_2O$	-	DMSO:DMF	70	4
2	$Pd(OAc)_2$	$Cu(OAc)_2.H_2O$	-	CH_3CN	70	NR
3	$Pd(O_2C.CF_3)_2$	$Cu(OAc)_2.H_2O$	-	DMSO:DMF	70	24
4	$Pd(OAc)_2$	$Cu(OAc)_2.H_2O$	-	DMSO:DMF	80	28
5	$PdCl_2$	$Cu(OAc)_2.H_2O$	-	DMSO:DMF	80	11
6	$Pd(O_2C.CF_3)_2$	$Cu(OAc)_2.H_2O$	-	DMSO:DMF	80	6.5
7	$Pd(O_2C.CF_3)_2$	Ag_2CO_3	-	DMSO:DMF	80	26
8	$Pd(O_2C.CF_3)_2$	$Cu(OAc)_2.H_2O$	-	DMF	100	6.5
9	$Pd(O_2C.CF_3)_2$	$Cu(OAc)_2.H_2O$	-	DMSO	100	9
10	-	-	-	-	100	NR
11	$Pd(OAc)_2$	$Cu(OAc)_2$	-	DMSO:DMF	80	24
12	$Pd(OAc)_2$	$Cu(OAc)_2$	-	DMSO:DMF	120	Trace
13	$Pd(OAc)_2$	Ag_2CO_3	-	DMSO:DMF	120	NR
14	$Pd(OAc)_2$	-	-	DMF	120	8.7
15	$Pd(OAc)_2$	$Cu(OAc)_2$	-	DMF	rt	25
16	$Pd(OAc)_2$	$Cu(OAc)_2$	PPh_3	DMSO:DMF	rt	19.7
17	$Pd(OAc)_2$	$Cu(OAc)_2$	PPh_3	DCM	rt	13.1
18	$Pd(OAc)_2$	Ag_2CO_3	-	THF	60	24
19	$Pd(OAc)_2$	$Cu(OAc)_2.H_2O$	PPh_3	DMSO:DMF	60	NR
20	$Pd(OAc)_2$	Ag_2CO_3	PPh_3	DMSO:DMF	60	NR

Reaction condition: Zerumbone **24** (1.0 equiv.), Indole **1a** (2.0 equiv.), Oxidant (1.8 equiv.), Ligand (40 mol %), Solvent (2 mL), 12 h

So from the optimization studies the reaction between zerumbone (1equiv.), indole (2 equiv.), $Cu(OAc)_2.H_2O$ (1.8 equiv.) in DMSO:DMF (1:20) at 80 °C for 12 hours gave the coupled product 28% yield. The results are summarized in table 3.5. With the optimal condition in hand, the generality of the reaction was checked with various substituted indoles.

Table 3.6. Reaction of various indoles **1** with zerumbone **24**

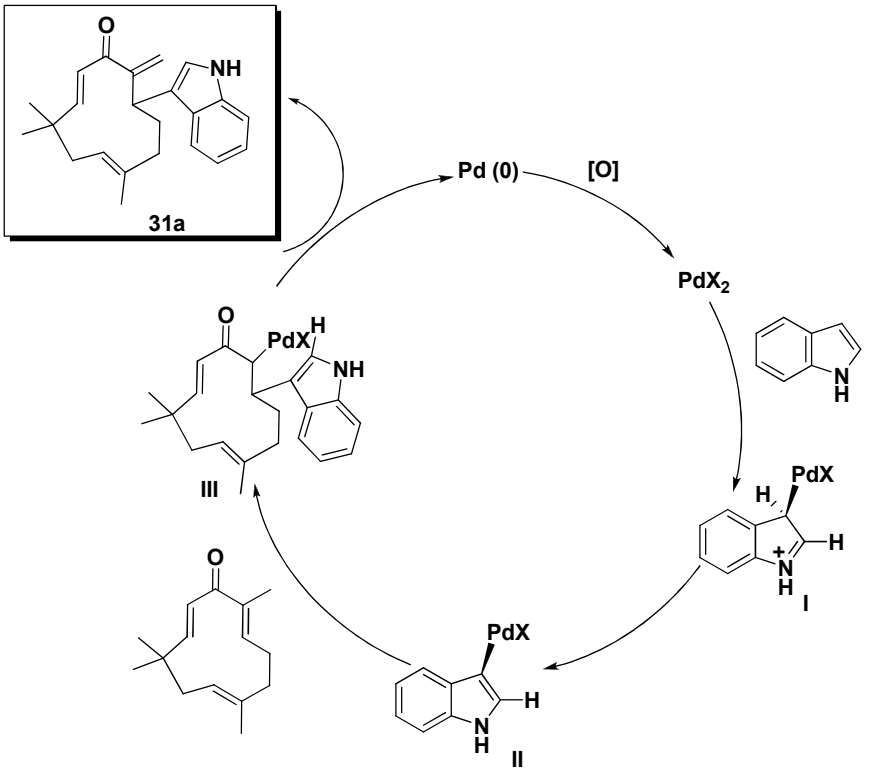
Entry	Indole	Product	Yield (%)	Entry	Indole	Product	Yield (%)
1	 1a	 31a	28	10	 6j	 31j	20
2	 1b	 31b	NR	11	 1k	 31k	21
3	 1c	 31c	34	12	 1l	 31l	NR
4	 1d	 31d	5	13	 1m	 31m	4
5	 1e	 31e	NR	14	 1n	 31n	NR
6	 1f	 31f	33	15	 1o	 31o	10
7	 1g	 31g	5	16	 1p	 31p	6
8	 1h	 31h	NR	17	 1q	 31q	NR
9	 1i	 31i	NR				

Reaction condition: Zerumbone **24** (1.0 equiv.), Indole **1** (2.0 equiv.), $Cu(OAc)_2.H_2O$(1.8 equiv.), DMSO:DMF (1:20, 2 mL), 80 °C 12 h

Electron rich indoles such as N-methyl indole, 7-methyl indole and 2-methyl indole did not furnish the product (Table 3.6., Entry 2, 8 and 9). But the indole bearing electron withdrawing group provided the desired product in moderate to low yield and the results are summarised in table 3.6. It is to be noted that indoles bearing electron donating

group such as methyl, hydroxyl and amino group did not furnish the desired product. All the reaction gave the coupled product in low yield.

3.8. Mechanistic pathway



Scheme 3.13

Indole initially undergoes electrophilic palladation at the more nucleophilic C3 position *via* intermediate **I**, and following **II**. Heck- type reaction forms the C3-functionalization of indole. Under neutral conditions, the acetate ion formed from the attack of indole on $Pd(OAc)_2$ will readily remove a proton from **I** to form the C3-palladated species **II**. This C3-palladated indole attacks on the enone part of zerumbone to form **III** and finally on *β*-hydride elimination of the proton from the adjacent methyl proton yielded the desired product **31** (Scheme 3.13).

3.9. Biological Screening of the Synthesized Zerumbone Derivatives/Indole Functionalized Zerumbone Derivatives

3.9.1. Anti-diabetic assay of compounds:

The synthesized zerumbone derivatives were tested for their activity against digestive enzymes such as *α*-glucosidase and *α*-amylase enzyme and anti-glycation properties as per the procedure mentioned in in section 2A.8.4 of chapter 2A.

3.9.1.1. Inhibition of digestive enzymes

The *α*-amylase and *α*-glucosidase inhibition of various derivatives and the zerumbone is given in table 3.5. As can be seen, all the derivatives, except **25e, 25f, 27b, 30c** and **31h,** exhibited better *α*-amylase inhibition than the parent compound zerumbone. The compound **25a** exhibited potential *α*-amylase inhibitory activity with lowest IC_{50} values, better than the standard acarbose, followed by **30e.** The derivatization of zerumbone improved the *α*-glucosidase inhibitory activity as compared to zerumbone, except for the compounds **25e, 25f** and **30e**. The inhibition of *α*-glucosidase by the compound **25a** was significantly higher than the standard acarbose. The results indicate the significant binding of indole-zerumbone hybrid, **25a** towards the digestive enzymes suggesting that it can be a promising candidate for reduction of postprandial hyperglycemia.

3.9.1.2. Anti-glycation properties

As in the case of previous assays, it was noted that the derivatization has improved the antiglycations properties significantly as compared to the parent compound except for **25d**, **25f**, **25g**, **27c**, **27d** and **30c** (Table 3.7). The compounds **25a**, **25e** and **25h** demonstrated excellent anti-glycation activity compared to the standard ascorbic acid.

Table 3.7. IC_{50}-μM of the compounds

Sr. No	Compounds	(IC_{50}-μM)			Sr. No	Compounds	(IC_{50}-μM)		
		α-Amylase	**α-Glucosidase**	**Antiglycation**			**α-Amylase**	**α-Glucosidase**	**Antiglycation**
1	**25a**	**11.06±0.811**	**10.57±1.14**	**29.2±1.719**	12	**28a**	15.055±0.245	185.84±1.81	35.65±0.35
2	**25c**	17.24±0.381	15.52±1.21	44.84±1.268	13	**30c**	88.72±0.38	189.45±0.81	590.55±0.55
3	**25d**	16.12±0.363	19.05±1.524	-	14	**30d**	17.25±0.05	169.225±1.155	617.5±0.5
4	**25e**	-	-	29.27±0.594	15	**30e**	13.1±0.3	403.845±1.155	87.8±0.6
5	**25f**	-	-	-	16	**31a**	44.50±0.219	48.73±0.353	67.95±0.06
6	**25g**	15.57±0.128	22.10±1.168	-	17	**31d**	39.64±0.438	41.99±0.304	68.26±0.346
7	**25h**	14.71±0.246	18.36±2.014	23.85±0.625	18	**31h**	51.68±0.636	149.45±0.304	74.59±0.169
8	**27a**	24.445±0.555	75.13±0.83	94.45±0.25	19	**31j**	46.69±1.004	56.65±0.417	62.88±0.537
9	**27b**	97.72±0.715	30.34±1.96	71.75±0.25	20	**31p**	35.74±0.233	135.04±0.360	56.58±0.940
10	**27c**	15.84±0.06	216.84±1.81	221.05±0.85	21	**Zerumbone**	**51.19±0.254**	**271.053±0.332**	**104.86±0.183**
11	**27d**	19.45±0.25	512.07±1.31	243.55±0.45	22	**Standard**	**8.965±0.135**	**81.855±1.355**	**154.6±1.4**

From the above studies it can be seen that the synthesized "zerumbone-indole hybrids" significantly improved anti-diabetic properties than the "zerumbone-pyrrole hybrids" as compared to the parent zerumbone. The results of the antidiabetic activities of the synthesized compounds are summarized in table 3.7.

3.10. Molecular docking studies

Molecular docking studies were carried out to understand the binding interaction of zerumbone and compound **25a** with *α*- glucosidase and *α*- amylase using Autodock 4.2 and IGEMDOCK v2.[24-26] The 3D model of *α*- amylase (PDB id: 4W93) and *α*-glucosidase(PDB id:4J5T) were retrieved from the Brookhaven Protein Data Bank (PDB) (http:// www.rcsb.org/pdb/). Zerumbone (ChemSpider ID: 4580581) structures were downloaded from Chemspider (http://www.chemspider.com/) and converted to PDB file using Chem3D Pro 10. The free energy of binding was determined for compound **25a** and zerumbone, are shown in table 3.8. The predicted interactions with residues SER177, ARG176, ASP173, GLU171, ASP135, VAL175, LYS178 of *α*- amylase by zerumbone and on residues SER177, ASP173, TYR174, TYR131, PRO130, LYS178, LYS172, ASP135, SER132, ARG176, VAL175 by the compound **25a**. Zerumbone was bound to residues GLU351, ASN366, LYS368, ALA367 and GLU369 of *α*- glucosidase. The compound **25a** was bound to ASN366, LYS368, ALA367, LEU365 and GLU351 of *α*-glucosidase. The best conformation of the ligand binding to the receptor and also the residues on receptor to which the ligand can bind in, are shown in figure 3.7 and the visualization was done using PYMOL.[27]

Table 3.8. The free binding energy(kcal mol^{-1}) of compound **25a** and zerumbone to *α*-amylase and *α*-glucosidase using Autodock 4.2.

	Compound 25a	**Zerumbone**
α-amylase	-8.1	-6.6
α-glucosidase	-9.28	-7.4

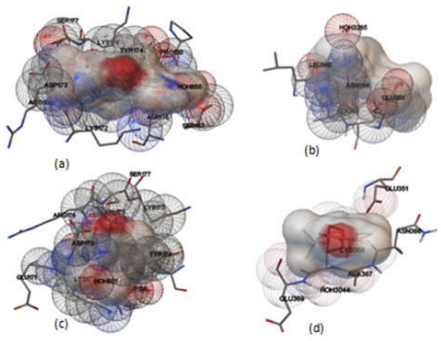
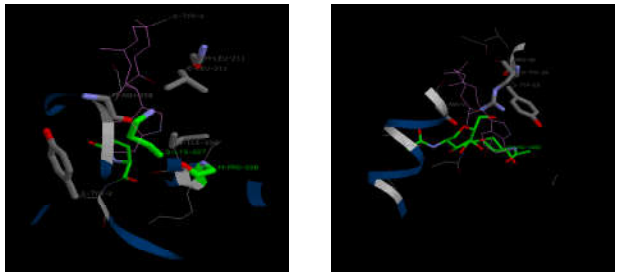


Figure 3.7. Representing the residues on *α*-amylase and *α*-glucosidase to which compound **25a** and zerumbone are bound using Autodock 4.2.a) Compound **25a** to *α*-amylase b) **25a** to *α*-glucosidase c) zerumbone to *α*-amylase d) zerumbone to *α*-glucosidase.

The best pose of **25a** binding to *α*- glucosidase and *α*-amylase using iGEMDOCKv2.1 are shown in figure 3.8. The binding energy of **25a** to α- amylase and α- glucosidase and the amino acids involved in the interaction were also predicted by the iGEMDOCK v2.1 using default docking parameters (Table 3.9).



(a) (b)

Figure 3.8. The best pose and residues on *α*-amylase and *α*- glucosidase to which the molecule binds using iGEMDOCKv2.1. a) **25a** binding to *α*-amylase b) **25a** binding to *α*-glucosidase

Table 3.9. Interaction table showing current binding sites of *α*-amylase and *α*-glucosidase. Energy represents the binding energy (kcal mol^{-1})

Compound	***α*- Amylase-molecule**	**Compound 25a**	***α*-Glucosidase-molecule**
Energy	-69.9	Energy	-78.9
H-S-LYS-227	-3.5	H-M-NAG-1002	-2.5
H-M-PRO-228	-3.41578	H-M-NAG-1002	-8.43492
V-S-TYR-2	-6.85705	V-S-ASN-9	-7.77148
V-M-LEU-211	-11.4169	V-S-ARG-28	-7.03941
V-S-LEU-211	-9.82588	V-M-TYR-29	-7.89761
V-S-LYS-227	-6.5155	V-S-TYR-29	-18.3337
V-S-ILE-230	-5.01057	V-M-NAG-1002	-7.8155
V-M-ASN-250	-6.72715		

3.9.2. Anti-hypertensive activity

Zerumbone-indole derivative were analyzed for ACE inhibitory effect according to procedure discussed in section 2A.8. of chapter 2A. The ACE inhibitory activity was studied using captropril, as a control drug. Among the tested compounds, the maximum inhibition was exhibited by compound **25b** at 1000 μM. The parent molecule zerumbone has inhibited 94% activity of the enzyme, which was found higher than all other molecules. The standard captopril has inhibited 100% at all concentrations screened. Results obtained are tabulated in table 3.10.

Table 3.10. Percentage inhibition of Zerumbone-indole derivative

Compound	% inhibition			
	Concentrations			
	10 µM	**100 µM**	**500 µM**	**1000 µM**
25a	0.00	25.27	52.75	57.14
25b	**24.73**	**45.05**	**65.93**	**80.22**
25d	0.00	0.00	20.88	43.41
25f	0.00	0.00	19.78	23.08
25h	15.38	33.52	57.69	78.02
25i	7.69	18.68	37.36	56.59
25k	**23.63**	**40.66**	**51.10**	**62.09**
25m	**28.57**	**44.51**	**62.64**	**84.07**
Zerumbone	21.98	47.25	68.13	94.51
Captopril	100.55	102.20	100.55	101.10

3.11. Conclusion

In summary, we have developed a synthetic route for the derivatization of zerumbone by Lewis acid catalyzed 1,4-conjugate addition as well as Heck-type reaction. The *in vitro* anti-diabetic screening of the synthesized zerumbone derivatives unveiled that most of the derivatives have superior α-amylase and α-glucosidase inhibition and anti-glycation activity compared to the parent molecular scaffold zerumbone. The compound **25a** demonstrated potential enzymes inhibition activity against digestive enzymes, as compared to the standards. Molecular docking studies were performed to recognize the binding mode of the most active compound **25a.** In addition, we have conducted the *in vitro* inhibitory effect of angiotensin-converting enzyme (anti-hypertensive activity) of the synthesized zerumbone- indole adducts. Compared to zerumbone, some of its indole derivatives showed similar inhibitory activity against angiotensin-converting (ACE) enzyme.

3.12. Experimental Details

General experimental procedures are described in chapter 2A of this thesis.

3.12.1. General Procedure for the Synthesis of indole functionalized zerumbone derivatives.

Zerumbone **24** (0.137 mmol) and indole **1a** (0.137 mmol) were taken in a Schlenk tube. Scandium triflate (5 mol %) was added as catalyst and acetonitrile (2 mL) was added as solvent. The reaction was stirred for 12 h. at room temperature. After the completion of the reaction as monitored by TLC, the reaction mixture was concentrated

and the crude product was purified by column chromatography on silica gel (100-200 mesh) and hexane: ethylacetate as the eluent to afford the product as a crystalline solid.

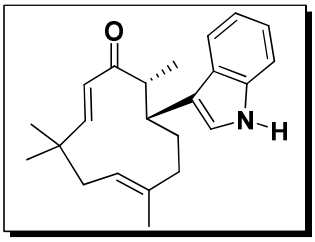
3.12.2. Synthesis of indole functionalized zerumbone derivatives *via* Heck-type reaction

Zerumbone **24** (30 mg, 0.137 mmol), indole **1a** (16.1 mg, 0.137 mmol), palladium acetate (20 mol %) and hydrated copper acetate (1.8 equiv.) in DMSO:DMF (1:20, 3 mL) solvent mixture under argon atmosphere and stirred for 12 h at 80 ^{o}C. After the completion of the reaction as monitored by TLC, the reaction mixture was extracted with ethylacetate and dried over anhydrous sodium sulphate and concentrated under vacuum in an rotary evaporator and the crude product was purified by column chromatography on silica gel (100-200 mesh) using hexane: ethylacetate as eluent gave the coupled product **31a**.

3.13. Spectral Details of Compounds 25a-31p

(2E,6E)-10-(1H-indol-3-yl)-4,4,7,11-tetramethylcycloundeca-2,6-dienone (25a)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), indole **1a** (16.05 mg, 0.137 mmol), $Sc(OTf)_3$ (3.4 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **25a** as white solid (41.5 mg, 90%).



R_f: 0.18 (ethylacetate/hexane = 1:3).

Mp: 155-160 ^{o}C.

IR (neat) υ_{max}: 3410, 3345, 3043, 2961, 2932, 2856, 1682, 1624, 1455, 1369, 1301, 1265, 1047, 908, 788, 739, 665, 610, 556 cm^{-1}.

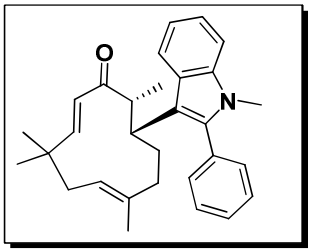
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (brs, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 8 Hz, 1H), 7.27-7.17 (m, 2H), 7.08 (s, 1H), 6.53 (d, *J* = 16 Hz, 1H), 6.33 (d, *J* = 16 Hz, 1H), 5.14 (dd, J_1 = 11.5 Hz, J_2 = 3.5 Hz, 1H), 3.76-3.74 (m, 1H), 2.98-2.95 (m, 1H), 2.38- 2.32 (m, 1H), 2.07-2.03 (m, 1H), 1.95-1.92 (m, 1H), 1.88-1.81 (m, 1H), 1.66-1.59 (m, 1H), 1.53 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H), 1.12-1.07 (m, 1H), 0.91 (d, *J* = 7 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.7, 151.4, 138.0, 136.8, 128.4, 127.4, 122.3, 122.2, 121.5, 119.6, 118.5, 118.3, 111.5, 51.8, 41.7, 40.0, 38.3, 37.4, 29.1, 25.5, 23.3, 16.9, 7.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{29}NNaO$: 358.21468, Found: 358.21594 $[M+Na]^+$.

(2E,6E)-4,4,7,11-tetramethyl-10-(1-methyl-2 phenyl- 1H-indol-3-yl)cycloundeca-2,6-dienone (25b)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), indole **1b** (28.49 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **25b** as white solid (42 mg, 72%).



R_f: 0.45 (ethylacetate/hexane = 1:3).

Mp: 185-190 ^oC.

IR (neat) υ_{max}: 3731, 3335, 3051, 2930, 2855, 2378, 2349, 2312, 1689, 1655, 1513, 1464, 1367, 1335, 1265, 1111, 1046, 1021, 909, 790, 743, 704, 667, 610, 556 cm^{-1}.

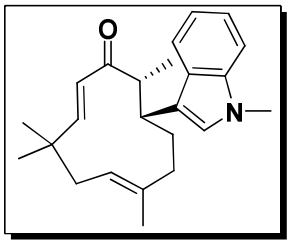
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8 Hz, 1H), 7.58-7.45 (m, 5H), 7.36-7.35 (m,1H), 7.27-7.24 (m, 1H), 7.16-7.13 (m, 1H), 6.15 (d, *J* = 16 Hz, 1H), 5.65 (d, *J* = 16 Hz, 1H), 4.55-4.53 (m, 1H), 3.48 (s, 3H), 3.28-3.26 (m, 1H), 2.76-2.72 (m, 1H), 2.38-2.32 (m, 1H), 2.12-2.07 (m, 1H), 1.88-1.84 (m, 1H), 1.68-1.64 (m, 1H), 1.50-1.48 (m, 1H), 1.35 (s, 3H), 1.24-1.23 (m, 3H), 1.08 (s, 3H), 0.88-0.86 (m, 1H), 0.61 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.5, 151.4, 137.9, 137.2, 136.3, 133.0, 131.2, 129.0, 128.9, 128.1, 127.2, 121.8, 121.6, 121.4, 119.1, 115.5, 109.5, 55.7, 41.4, 39.7, 38.6, 30.5, 29.2, 24.8, 23.0, 16.7, 10.7 ppm.

HRMS (ESI): *m/z* Calcd for $C_{30}H_{35}NNaO$: 434.24598, Found: 434.24539 $[M+Na]^+$.

(2E,6E)-4,4,7,11-tetramethyl-10-(1-methyl-1H-indol-3-yl)cycloundeca-2,6-dienone (36c)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), indole **1c** (17.967 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **25c** as a colourless liquid (42 mg, 86%).



R_f: 0.35 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 3424, 2926, 2856, 1640, 1459, 1420, 1266, 1155, 1123, 1044, 737, 665, 611,560 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.32-7.29 (m, 1H), 7.24-7.21 (m, 1H),

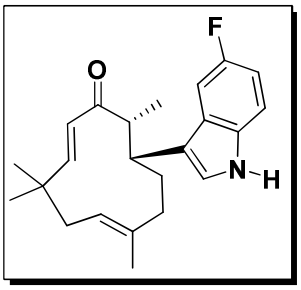
6.95 (s, 1H), 6.56 (d, *J* = 16 Hz, 1H), 6.36 (d, *J* = 16 Hz, 1H) 5.18-5.16 (m, 1H), 3.83 (s, 3H), 3.78-3.77 (m, 1H), 2.97-2.94 (m, 1H), 2.41-2.35 (m, 1H), 2.10-2.06 (m, 1H), 1.98-1.94 (m, 1H), 1.88-1.82 (m, 1H), 1.69-1.64 (m, 1H), 1.57 (s, 3H), 1.37 (s, 3H), 1.30 (s, 3H), 1.16-1.11 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.6, 151.2, 138.0, 137.5, 128.5, 127.9, 126.4, 122.2, 121.9, 119.1, 118.4, 117.0, 109.6, 52.1, 41.8, 40.1, 38.4, 37.4, 32.8, 29.2, 25.6, 23.3, 17.0, 8.0 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{31}NNaO$: 372.23033, Found: 372.23068 $[M+Na]^+$.

(2E,6E)-10-(5-fluoro-1H-indol-3-yl)-4,4,7,11-tetramethylcycloundeca-2,6 dienone (25d)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), indole **1d** (18.51 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **25d** as a white solid (35.84 mg, 74%).



R_f: 0.12 (ethylacetate/hexane = 1:3).

Mp: 155-160 ^oC.

IR (neat) υ_{max}: 3346, 3044, 2963, 2935, 2870, 2312, 1683, 1625, 1583, 1485, 1455, 1367, 1300, 1271, 1221, 1166, 1083, 1041, 998, 944, 911, 841, 794, 765, 732, 666, 615, 557 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (brs, 1H), 7.31 (dd, 1H, J_1 = 4.5 Hz, J_2 = 8.5 Hz), 7.27 (dd, J_1 = 2.5 Hz, J_2 = 9.5 Hz, 1H), 7.11 (d, *J* = 2 Hz, 1H), 7.00-6.96 (m, 1H), 6.47 (d, *J* = 16 Hz, 1H), 6.31 (d, *J* = 16 Hz, 1H), 5.12 (dd, J_1 = 4.5 Hz, J_2 = 12 Hz, 1H), 3.64-3.62 (m, 1H), 2.89-2.87 (m, 1H), 2.32 (t, *J* = 12.5 Hz, 1H), 2.05-2.01 (m, 1H), 1.93-1.90 (m, 1H), 1.84-1.77 (m, 1H), 1.62-1.61 (m, 1H), 1.50 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H), 1.10-1.05 (m, 1H), 0.89 (d, *J* = 6.5 Hz, 3H) ppm.

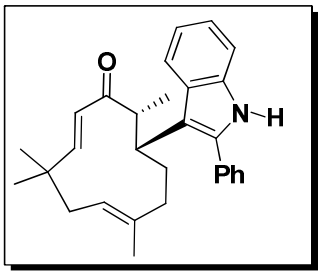
^{13}C NMR (125 MHz, $CDCl_3$): δ 203.6, 157.8 (d, $^1J_{C\text{-}F}$ = 233.8 Hz), 151.6, 137.9, 133.2, 128.3, 127.8 (d, $^2J_{C\text{-}F}$ = 8.8 Hz), 123.4, 122.2, 118.6 (d, $^4J_{C\text{-}F}$ = 5 Hz), 112.1 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 110.6 (d, $^2J_{C\text{-}F}$ = 26.3 Hz), 103.3 (d, $^2J_{C\text{-}F}$ = 23.8 Hz), 51.7, 41.6, 40.0, 38.3, 37.5, 29.1, 25.5, 23.2, 16.9, 7.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{28}FNNaO$: 376.20526, Found: 376.20480 $[M+Na]^+$.

(2E, 6E)-4,4,7,11-tetramethyl-10-(2-phenyl-1H-indol-3-yl)cycloundeca-2,6-dienone (25e)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol),

indole **1e** (26.441 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **25e** as a colourless liquid (45 mg, 80%).



R_f: 0.3 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 3733, 3330, 2923, 2853, 2377, 2309, 1747, 1680, 1654, 1585, 1513, 1457, 1369, 1159, 1117, 1058, 667, 610, 555 cm^{-1}.

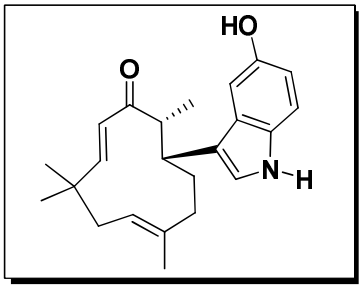
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (brs, 1H), 7.70 (d, *J* = 8 Hz, 1H), 7.51-7.50 (m, 2H), 7.48-7.45 (m, 2H), 7.40 (t, *J* = 7 Hz, 1H), 7.30 (d, *J* = 8 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.13 (d, *J* = 16 Hz, 1H), 5.84 (d, *J* = 16 Hz, 1H), 4.50-4.47 (m, 1H), 3.38-3.37 (m, 1H), 2.79-2.76 (m, 1H), 2.31-2.25 (m, 1H), 2.06-2.01 (m, 1H), 1.80-1.72 (m, 1H), 1.61-1.59 (m, 2H), 1.28 (s, 3H), 1.19 (s, 3H), 1.04 (s, 3H), 0.82-0.77 (m, 1H), 0.67(s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.4, 151.6, 137.9, 136.5, 136.0, 133.9, 129.7, 128.9, 128.6, 128.1, 127.6, 121.8, 121.7, 119.5, 115.8, 111.1, 55.4, 41.4, 39.9, 38.7, 38.5, 29.2, 24.9, 23.1, 16.8, 10.8 ppm.

HRMS (ESI): *m/z* Calcd for $C_{29}H_{33}NNaO$: 434.24598, Found: 434.24539 $[M+Na]^+$.

(2E,6E)-10-(5-hydroxy-1H-indol-3-yl)-4,4,7,11-tetramethylcycloundeca-2,6-dienone (25f)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), indole **1f** (18.24 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **25f** as a brownish viscous liquid (33.33 mg, 69%).



R_f: 0.15 (ethylacetate/hexane = 2:3).

IR (neat) υ_{max}: 3349, 2963, 2935, 2857, 1678, 1623, 1584, 1457, 1366, 1303, 1265, 1221, 1181, 1105, 1083, 1048, 998, 944, 910, 877, 841, 791, 732, 666, 613, 517 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.24 (d, *J* = 9 Hz, 1H), 7.08 (d, *J* = 1.5 Hz, 1H), 7.02 (d, *J* = 1.5 Hz, 1H),6.84 (dd, J_1 = 2 Hz, J_2 = 8.5 Hz, 1H), 6.48 (d, *J* = 16.5 Hz, 1H), 6.32 (d, *J* = 16 Hz, 1H), 5.92 (brs, 1H), 5.10 (dd, J_1 = 3.5 Hz, J_2 = 11.5 Hz, 1H), 3.62-3.60 (m, 1H), 2.88-2.86 (m, 1H), 2.37-2.28 (m, 1H), 2.07-2.02 (m, 1H), 1.91-1.87 (m, 1H), 1.85-1.79 (m,

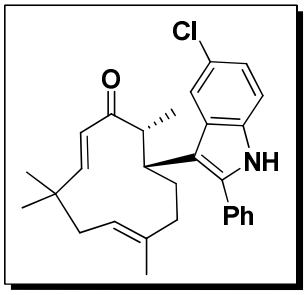
1H), 1.64-1.59 (m, 1H), 1.50 (s, 3H), 1.27 (s, 3H), 1.18 (s, 3H), 1.06-1.04 (m, 1H), 0.85 (d, J = 7 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 204.9, 151.8, 149.6, 138.0, 132.0, 128.4, 128.0, 122.1, 117.5, 112.2, 112.1, 103.3, 51.6, 41.6, 40.0, 38.3, 37.5, 28.8, 25.4, 23.2, 16.9, 7.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{29}NNaO_2$: 374.20960, Found: 374.20981 $[M+Na]^+$.

(2E,6E)-10-(5-chloro-2-phenyl-1H-indol-3-yl)-4,4,7,11-tetramethylcycloundeca-2,6-dienone (25g)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), indole **1g** (31.22 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **25g** as a brown solid (5 mg, 8%).



R_f: 0.25 (ethylacetate/hexane = 1:3).

Mp: 230-235 ^oC.

IR (neat) υ_{max}: 3339, 2922, 2853, 2378, 2311, 1731, 1589, 1455, 1366, 1314, 1158, 1117, 1048, 796, 746, 666, 609, 555 cm^{-1}.

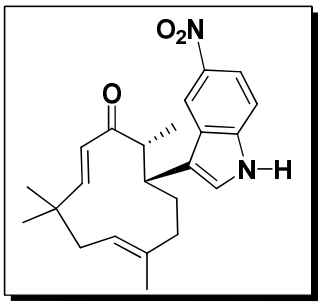
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (brs, 1H), 7.72 (s, 1H), 7.59-7.54 (m, 4H), 7.52-7.50 (m, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 6.20 (d, J = 16 Hz, 1H), 5.87 (d, J = 16 Hz, 1H), 4.55 (dd, J_1 = 3.5Hz, J_2 = 11.5 Hz, 1H), 3.43–3.41 (m, 1H), 2.83-2.81 (m, 1H), 2.31-2.25 (m, 1H), 2.15-2.10 (m, 1H), 1.92-1.88 (m, 1H), 1.71-1.67 (m, 1H), 1.47-1.42 (m, 1H), 1.38 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H), 0.91-0.86 (m, 1H), 0.75 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 202.7, 151.5, 138.1, 137.7, 134.4, 133.4, 129.6, 129.0, 128.9, 128.7, 128.0, 125.3, 122.2, 121.7, 121.1, 115.8, 111.9, 55.2, 41.4, 39.9, 38.5, 29.7, 24.8, 23.1, 16.8, 10.8 ppm.

HRMS (ESI): *m/z* Calcd for $C_{29}H_{32}ClNNaO$: 468.20701, Found: 468.20660 $[M+Na]^+$.

(2E,6E)-4,4,7,11-tetramethyl-10-(5-nitro-1H-indol-3-yl)cycloundeca-2,6-dienone (25h)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), indole **1h** (22.21 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **25h** as a yellow solid (10.45 mg, 20%).



R_f: 0.22 (ethylacetate/ hexane = 4:6).

Mp: 215-225 ^oC.

IR (neat) υ_{max}: 3354, 2961, 2935, 2857, 2375, 2313, 2252, 1732, 1685, 1625, 1578, 1547, 1519, 1472, 1381, 1332, 1256, 1096, 1047, 999, 909, 587, 839, 813, 789, 737, 684, 666, 553 cm^{-1}.

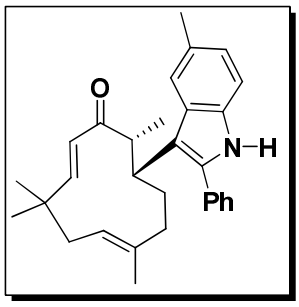
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.02 (brs, 1H), 8.69 (d, *J* = 1.5 Hz, 1H), 8.18-8.16 (m, 1H), 7.48 (d, *J* = 9 Hz, 1H), 7.27 (s, 1H), 6.57 (d, *J* = 16 Hz, 1H), 6.36 (d, *J* = 16 Hz, 1H), 5.17 (dd, J_1 = 6.5 Hz, J_2 = 11.5 Hz, 1H), 3.82-3.80 (m, 1H), 2.90-2.86 (m, 1H), 2.38-2.33 (m, 1H), 2.08-2.04 (m, 1H), 1.98-1.95 (m, 1H), 1.86-1.80 (m, 1H), 1.60-1.55 (m, 1H), 1.52 (s, 3H), 1.41 (s, 3H), 1.26 (s, 3H), 1.19-1.14 (m, 1H), 0.95 (d, *J* = 7 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.4, 152.2, 141.6, 139.6, 137.5, 128.2, 127.0, 124.7, 122.7, 121.2, 117.9, 115.5, 111.5, 52.1, 41.7, 40.2, 38.3, 37.2, 29.0, 25.7, 23.0, 16.9, 7.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{28}N_2NaO_3$: 403.19976, Found: 403.19937 $[M+Na]^+$.

(2E,6E)-4,4,7,11-tetramethyl-10-(5-methyl-2-phenyl-1H-indol-3-yl)cycloundeca-2,6-dienone (25i)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), indole **1i** (28.36 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **25i** as an yellow crystalline solid (16.38 mg, 28%).



R_f: 0.32 (ethylacetate/hexane = 1:3).

Mp: 225-230 ^oC.

IR (neat) υ_{max}: 3734, 3329, 2924, 2354, 2347, 2306, 1867, 1731, 1681, 1621, 1512, 1455, 1370, 1315, 1160, 1056, 798, 766, 666, 610, 556 cm^{-1}.

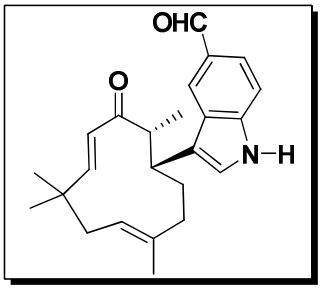
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.59-7.58 (m, 2H), 7.55-7.52 (m, 3H), 7.49-7.46 (m, 1H), 7.26 (t, *J* = 8.5 Hz, 1H), 7.03 (d, *J* = 8.5 Hz, 1H), 6.20 (d, *J* = 16 Hz, 1H), 5.92 (d, *J* = 16 Hz, 1H), 4.56 (dd, J_1 = 3.5 Hz, J_2 = 11 Hz, 1H), 3.44-3.42 (m 1H), 2.86-2.84 (m, 1H), 2.50 (s, 3H), 2.44-2.35 (m, 1H), 2.15-2.10 (m, 1H), 1.90-1.86 (m, 1H), 1.71-1.67 (m, 1H), 1.56-1.44 (m, 1H), 1.38 (s, 3H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.14 (s, 3H), 0.91-0.86 (m, 1H), 0.76 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.1, 151.3, 138.0, 136.4, 134.4, 134.2, 129.6, 128.9, 128.5, 128.2, 127.9, 123.5, 121.7, 115.5, 110.8, 55.4, 41.4, 39.9, 38.6, 29.2, 24.8, 23.1, 21.9, 16.8, 10.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{30}H_{35}NNaO$: 448.26163, Found: 448.26117 $[M+Na]^+$.

3-((4E,8E)-2,6,6,9-tetramethyl-3-oxocycloundeca-4,8-dienyl)-1H-indole-5-carbaldehyde (25j)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), indole **1j** (19.959 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **25j** as a white solid (6 mg, 12%).



R_f: 0.18 (ethylacetate/hexane = 2:3).

Mp: 205-210 ^oC.

IR (neat) υ_{max}: 3727, 3285, 2378, 2307, 1681, 1611, 1579, 1511, 1450, 1380, 1301, 1170, 1107, 1049, 912, 799, 665, 610, 556, 515 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.09 (s, 1H), 8.41 (brs, 1H), 8.23 (s, 1H), 7.82-7.78 (m, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.19 (s,1H), 6.56 (d, J = 16 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 5.16 (dd, J_1 = 11.5 Hz, J_2 = 3 Hz, 1H), 3.82-3.80 (m, 1H), 2.93-2.91 (m, 1H), 2.38-2.33 (m, 1H), 2.09-2.05 (m, 1H), 1.97-1.94 (m, 1H), 1.87-1.81 (m, 1H), 1.62-1.60 (m, 1H), 1.5 (s, 3H), 1.39 (s, 3H), 1.27 (s, 3H), 1.15-1.08 (m, 1H), 0.93 (d, J = 6.5 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 202.9, 191.6, 151.7, 140.1, 137.7, 129.5, 128.2, 127.5, 123.4, 123.1, 122.8, 122.5, 120.8, 111.9, 52.0, 41.7, 40.1, 38.3, 37.3, 29.7, 29.1, 23.2, 16.9, 7.9 ppm.

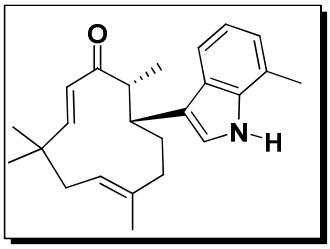
HRMS (ESI): *m/z* Calcd for $C_{24}H_{29}NNaO_2$: 386.20960, Found: 386.20938 $[M+Na]^+$.

(2E,6E)-4,4,7,11-tetramethyl-10-(7-methyl-1H-indol-3-yl)cycloundeca-2,6-dienone (25k)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), indole **1k** (17.97 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **25k** as a white solid (45.63 mg, 95%).

R_f: 0.45 (ethylacetate/hexane = 1:3).

Mp: 150-155 ^oC.



IR (neat) υ_{max}: 3856, 3329, 2956, 2924, 2854, 2355, 2314, 1859, 1678, 1611, 1577, 1534, 1437, 1362, 1303, 1262, 1175, 1100, 1125, 1043, 891, 809, 772, 652, 613, 547, 514 cm^{-1}.

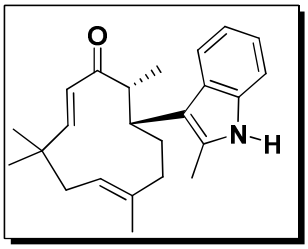
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (brs, 1H), 7.52 (d, *J* = 10 Hz, 1H), 7.11 (t, *J* = 10 Hz, 1H), 7.06 (d, *J* = 5 Hz, 1H,), 7.02 (d, *J* = 5 Hz, 1H), 6.50 (d, *J* = 16.5 Hz, 1H), 6.29 (d, *J* = 16.5 Hz, 1H), 5.11 (dd, J_1 = 12 Hz, J_2 = 4.5 Hz, 1H), 3.73-3.71(m, 1H), 2.94-2.90 (m, 1H), 2.52 (s, 3H), 2.32 (t, 1H, *J* = 12.5 Hz), 2.02-2.01 (m, 1H), 1.92-1.90 (m,1H), 1.85-1.78 (m, 1H), 1.60 (t, *J* = 12 Hz, 1H), 1.50 (s, 3H), 1.32 (s, 3H), 1.24 (s, 3H), 1.10-1.04 (m, 1H), 0.87 (d, *J* = 6.5 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.5, 151.2, 138.0, 136.3, 128.4, 127.0, 122.9, 122.2, 121.1, 120.5, 119.9, 119.2, 116.0, 51.8, 41.8, 40.0, 37.5, 29.1, 25.5, 23.2, 16.9, 16.6, 7.8 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{31}NNaO$: 372.23033, Found: 372.23068 $[M+Na]^+$.

(2E,6E)-4,4,7,11-tetramethyl-10-(2-methyl-1H-indol-3-yl)cycloundeca-2,6-dienone (25l)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), indole **1l** (17.97 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **25l** as a white solid (45.14 mg, 94%).



R_f: 0.47 (ethylacetate/hexane = 1:3).

Mp: 130-135 ^oC.

IR (neat) υ_{max}: 3856, 3329, 2956, 2924, 2854, 2355, 2314, 1859, 1678, 1611, 1577, 1534, 1437, 1362, 1303, 1262, 1175, 1100, 1125, 1043, 891, 809, 772, 652, 613, 547, 514 cm^{-1}.

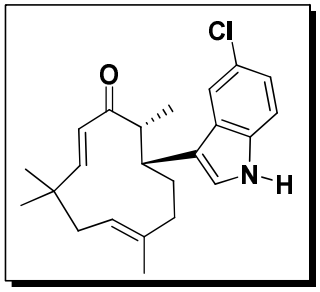
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (brs, 1H), 7.62 (d, J = 8 Hz, 1H), 7.10-7.06 (m, 3H), 6.35-6.34 (m, 2H), 5.13 (dd, J_1 = 11.5 Hz, J_2 = 4.5 Hz, 1H), 3.57-3.55 (m, 1H), 2.72-2.70 (m, 1H), 2.55 (s, 3H), 2.35-2.30 (m, 3H), 1.94-1.91 (m, 2H), 1.49 (s, 3H), 1.43 (t, J = 5.2 Hz, 1H), 1.27 (s, 3H), 1.25 (s, 3H), 1.16 (d, J = 7 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 202.1, 152.5, 138.2, 137.6, 127.6, 127.2, 122.6, 120.7, 119.2, 112.5, 110.3, 55.7, 41.7, 40.4, 40.2, 38.7, 37.8, 30.9, 20.7, 28.9, 24.3, 23.3, 16.9, 10.0 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{31}NNaO$: 372.23033, Found: 372.23068 $[M+Na]^+$.

(2E,6E)-10-(5-chloro-1H-indol-3-yl)-4,4,7,11-tetramethylcycloundeca-2,6-dienone (25m)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), indole **1m** (20.76 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **25m** as a white solid (42.14 mg, 83%).



R_f: 0.50 (ethylacetate/hexane = 1:3).

Mp: 180-183 ^oC.

IR (neat) υ_{max}: 3856, 3329, 2956, 2924, 2854, 2355, 2314, 1859, 1678, 1611, 1577, 1534, 1437, 1362, 1303, 1262, 1175, 1100, 1125, 1043, 891, 809, 772, 652, 613, 547, 514 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (brs, 1H), 7.59 (d, J =2 Hz, 1H), 7.31(d, J = 8.5 Hz, 1H), 7.19-7.17 (m, 1H), 7.08 (d, J = 2.5 Hz, 1H), 6.48 (d, J = 16.5 Hz, 1H), 6.31 (d, J = 16.5 Hz, 1H), 5.12 (dd, J_1 = 12 Hz, J_2 = 4.5 Hz, 1H), 3.66-3.64 (m, 1H), 2.87-2.84 (m, 1H), 2.32 (t, J = 13 Hz, 1H), 2.05-2.01(m, 1H), 1.94-1.91(m, 1H), 1.82-1.76 (m, 1H), 1.60-1.56 (m, 1H), 1.50 (s, 3H), 1.33 (s, 3H), 1.24 (s, 3H), 1.10-1.05 (m, 1H), 0.88 (d, J = 7 Hz, 3H) ppm.

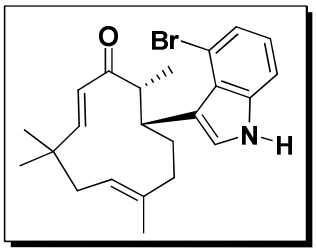
^{13}C NMR (125 MHz, $CDCl_3$): δ 203.4, 151.6, 137.8, 135.0, 128.6, 128.3, 125.4, 122.8, 122.6, 122.4, 118.4, 117.9, 112.4, 51.8, 41.7, 40.1, 38.3, 37.4, 29.1, 25.5, 25.5, 23.1, 16.9, 7.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{28}ClNNaO$: 392.17571, Found: 392.17566 $[M+Na]^+$.

(2E,6E)-10-(4-bromo-1H-indol-3-yl)-4,4,7,11-tetramethylcycloundeca-2,6-dienone (25n)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol),

indole **1n** (26.85 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **25n** as a white solid (9.09 mg, 16%).



R_f: 0.61 (ethylacetate/hexane = 1:3).

Mp: 180-184 ^oC.

IR (neat) υ_{max}: 3856, 3329, 2956, 2924, 2854, 2355, 2314, 1859, 1678, 1611, 1577, 1534, 1437, 1362, 1303, 1262, 1175, 1100, 1125, 1043, 891, 809, 772, 652, 613, 547, 514 cm^{-1}.

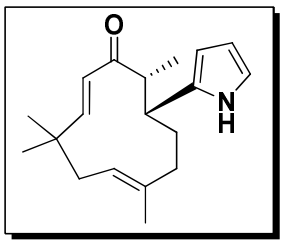
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (brs, 1H), 7.34-7.31 (m, 2H), 7.16 (d, J = 2.5 Hz, 1H), 7.04-7.01(m, 1H), 6.82 (d, J = 16 Hz, 1H), 6.28 (d, J = 16 Hz, 1H), 5.24 (dd, J_1 = 11.5 Hz, J_2 = 5 Hz, 1H), 4.35-4.32 (m, 1H), 3.06-3.01 (m, 1H), 2.32 (t, J = 12.5 Hz, 1H), 2.01-1.98 (m, 1H), 1.92-1.89 (m, 2H), 1.70-1.66 (m, 1H), 1.49 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H), 1.04-0.99 (m, 1H), 0.84 (d, J = 7 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 204.3, 151.0, 138.2, 138.0, 128.8, 125.3, 124.6, 124.4, 122.8, 121.8, 118.5, 113.7, 110.8, 52.3, 41.1, 40.0, 38.2, 37.0, 29.6, 27.5, 23.8, 17.2, 7.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{28}BrNNaO$: 436.12520, Found: 436.12511 $[M+Na]^+$.

(2E, (2E,6E)-4,4,7,11-tetramethyl-10-(1H-pyrrol-2-yl)cycloundeca-2,6-dienone (27a)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), pyrrole **26a** (18.36 mg, 0.274 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **27a** as a colourless liquid (6 mg, 76%).



R_f: 0.2 (ethylacetate/hexane = 1:2.3).

IR (neat) υ_{max}: 3349, 2959, 2872, 1709, 1690, 1625, 1453, 1365, 1302, 1265, 1221, 1180, 1142, 1083, 1045, 1001, 978, 909, 877, 859, 841, 787, 725, 664, 568, 531 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 9.20 (brs, 1H), 6.69 (dd, J_1 = 4.5 Hz, J_2 = 2.5 Hz, 1H), 6.44 (d, J = 16.5 Hz, 1H), 6.17 (d, J = 16 Hz, 1H), 6.02-6.00 (m, 1H), 5.94 (d, J = 1.5 Hz, 1H), 5.12 (dd, J_1 = 12 Hz, J_2 = 4.5 Hz, 1H), 3.36-3.33 (m, 1H), 2.84-2.79 (m, 1H), 2.31-2.26 (m, 1H), 2.09-2.02 (m, 1H), 1.89-1.85 (m, 1H), 1.80-1.73 (m, 1H), 1.57-1.52 (m, 1H), 1.43 (s, 3H), 1.21 (s, 3H), 1.19 (s, 3H), 0.91-0.86 (m, 1H), 0.77 (d, J = 6.5 Hz,

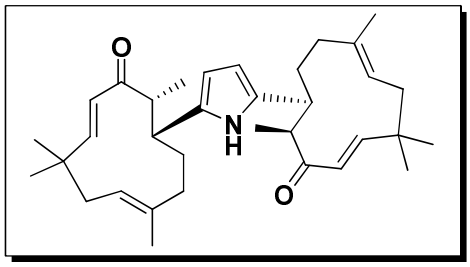
3H) ppm.

^{13}C NMR (125 MHz, CD_3CN): δ 202.4, 150.6, 137.2, 133.6, 128.0, 121.9, 107.0, 104.9, 52.0, 40.6, 39.3, 39.1, 37.9, 27.9, 24.6, 22.1, 15.6, 6.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{19}H_{27}NNaO$: 308.19903, Found: 308.19947 $[M+Na]^+$.

(2E,2'E,6E,6'E)-10,10'-(1H-pyrrole-2,5-diyl)bis(4,4,7,11-tetramethylcycloundeca-2,6-dienone) (28a)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), pyrrole **26a** (18.36 mg, 0.274 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **28a** as a colourless liquid (42 mg, 59%).



R_f: 0.13 (ethylacetate/hexane = 1:2.3).

IR (neat) υ_{max}: 3378, 3054, 2962, 2873, 1686, 1625, 1454, 1383, 1366, 1303, 1267, 1219, 1176, 1143, 1083, 1044, 1001, 909, 875, 859, 783, 737, 703, 568 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (brs, 1H), 6.29 (d, J = 16 Hz, 2H), 6.23 (d, J = 16 Hz, 2H), 5.91 (d, J = 2.5 Hz, 2H), 5.10 (dd, J_1 = 11.5 Hz, J_2 = 4.5 Hz, 2H), 3.34-3.30 (m, 2H), 2.87-2.83 (m, 2H), 2.29-2.24 (m, 2H), 2.14-2.10 (m, 2H), 1.91-1.88 (m, 2H), 1.78-1.65 (m, 4H), 1.46 (s, 6H), 1.21 (s, 6H), 1.20 (s, 6H), 1.05-0.98 (m, 2H), 0.95 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 202.5, 151.6, 137.9, 137.8, 133.3, 129.0, 128.2, 127.8, 125.3, 122.1, 122.0, 105.8, 52.6, 41.4, 39.8, 39.7, 38.7, 29.7, 29.0,25.4, 23.0, 21.4, 16.8, 8.4, 8.3 ppm.

HRMS (ESI): *m/z* Calcd for $C_{34}H_{49}NNaO_2$: 526.36610, Found: 526.36661$[M+Na]^+$.

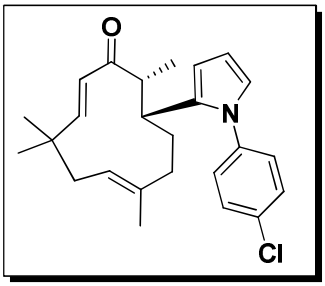
(2E,6E)-10-(1-(4-chlorophenyl)-1H-pyrrol-2-yl)-4,4,7,11- tetramethylcycloundeca-2,6-dienone (27b)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), compound **26b** (48.67 mg, 0.274 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **27b** as a colourless crystalline solid (44.03 mg, 81%).

R_f: 0.75 (ethylacetate/hexane = 1:3).

Mp: 175-180 ^oC.

IR (neat) υ_{max}: 3355, 2959, 2935, 2871, 1690, 1625, 1596, 1495, 1454, 1383, 1327, 1302, 1267, 1215, 1177, 1093, 1040, 1015, 907, 876, 839, 785, 738, 714, 557, 520 cm^{-1}.



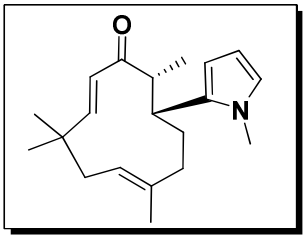
^{1}H NMR (500 MHz, CD_3CN): δ 7.59 (d, J_1 = 6.5 Hz, J_2 = 2 Hz, 2H), 7.43 (dd, J_1 = 6.5 Hz, J_2 = 2 Hz, 2H), 6.74 (dd, J_1 = 2.5 Hz, J_2 = 2 Hz, 1H), 6.19-6.16 (m, 2H), 6.03 (d, J = 16 Hz, 1H), 5.34 (d, J = 16 Hz, 1H), 4.78 (dd, J_1 = 11.5 Hz, J_2 = 4 Hz, 1H), 3.13-3.11 (m, 1H), 2.46-2.43 (m, 1H), 2.20-2.15 (m, 1H), 2.01-1.96 (m, 1H), 1.83-1.80 (m, 1H), 1.77-1.74 (m, 1H), 1.53-1.48 (m, 1H), 1.36 (s, 3H), 1.09 (s, 3H), 0.92-0.85 (m, 1H), 0.82-0.80 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 202.9, 152.0, 140.2, 138.5, 136.8, 135.0, 130.8, 130.5, 130.2, 128.5, 123.8, 123.0, 108.9, 52.1, 41.7, 40.3, 38.8, 38.5, 29.1, 27.7, 23.2, 16.9, 7.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{25}H_{30}ClNNaO$: 418.19136, Found: 418.19204 $[M+Na]^+$.

(2E,6E)-4,4,7,11-tetramethyl-10-(1-methyl-1H-pyrrol-2-yl)cycloundeca-2,6-dienone (27c)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), compound **26c** (22.23 mg, 0.274 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **27c** as a white solid (19.5 mg, 47%).



R_f: 0.57 (ethylacetate/hexane = 2:3).

Mp: 130-135 °C.

IR (neat) υ_{max} (CaF_2): 3365, 3100, 2958, 2872, 2376, 2150, 1692, 1628, 1490, 1454, 1382, 1366, 1300, 1266, 1245, 1214, 1176, 1138, 1084, 1042, 999, 978, 936, 907, 874, 857, 840 cm^{-1}.

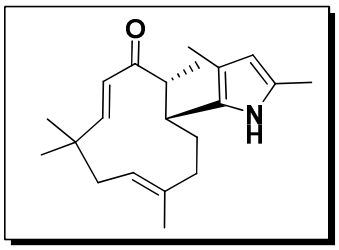
^{1}H NMR (500 MHz, CD_3CN): δ 6.62 (s, 1H), 6.36 (d, J = 16 Hz, 1H), 6.18 (d, J = 16 Hz, 1H), 5.97-5.96 (m, 2H), 5.17 (dd, J_1 = 11.5 Hz, J_2 = 4.5 Hz, 1H), 3.72 (s, 3H), 3.36-3.34 (m, 1H), 2.64-2.63 (m, 1H), 2.35-2.30 (m, 1H), 2.01-1.97 (m, 1H), 1.91-1.88 (m, 1H), 1.83-1.76 (m, 1H), 1.46 (s, 3H), 1.44-1.41 (m, 1H), 1.20 (s, 3H), 1.19 (s, 3H), 0.94-0.91 (m, 1H), 0.79 (d, J = 13 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.0, 151.9, 138.4, 134.4, 127.7, 122.0, 121.8, 107.2, 106.6, 51.3, 41.6, 40.0, 38.4, 37.8, 33.9, 28.9, 26.1, 23.2, 16.9, 7.4 ppm.

HRMS (ESI): *m/z* Calcd for $C_{20}H_{29}NNaO$: 322.21468, Found: 322.21528 $[M+Na]^+$.

(2E,((2E,6E)-10-(3,5-dimethyl-1H-pyrrol-2-yl)-4,4,7,11-tetramethylcycloundeca-2,6-dienone (27d)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), compound **26d** (26.08 mg, 0.274 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **27d** as a colourless viscous liquid (34.03 mg, 79%).



R_f: 0.42 (ethylacetate/hexane = 2:3).

IR (neat) υ_{max}: 3372, 3049, 2933, 2870, 1685, 1627, 1454, 1384, 1301, 1267, 1220, 1142, 1083, 1042, 1001, 908, 876, 842, 786, 736, 702, 567 cm^{-1}.

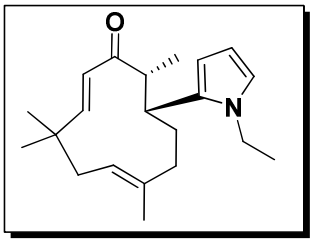
^{1}H NMR (500 MHz, CD_3CN): δ 8.59 (brs, 1H), 6.33 (d, *J* = 16 Hz, 1H), 6.16 (d, *J* = 16.5 Hz, 1H), 5.56 (s, 1H), 5.14 (dd, J_1 = 11.5 Hz, J_2 = 4.5 Hz, 1H), 3.40-3.38 (m,1H), 2.63-2.58 (m,1H), 2.32-2.29 (m, 2H), 2.14 (s, 3H), 2.09 (s, 3H), 1.94-1.93 (m, 2H), 1.69-1.66 (m, 1H), 1.44 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H), 0.91 (d, *J* = 7 Hz, 3H), 0.86-0.83 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 208.3, 156.2, 142.7, 133.7, 133.2, 130.7, 127.7, 119.4, 112.9, 58.0, 46.5, 45.0, 43.0, 42.5, 33.4, 30.1, 27.7, 21.3, 17.2, 16.0, 13.3 ppm.

HRMS (ESI): *m/z* Calcd for $C_{21}H_{31}NNaO$: 336.23033, Found: 336.23041 $[M+Na]^+$.

(2E,((2E,6E)-10-(1-ethyl-1H-pyrrol-2-yl)-4,4,7,11-tetramethylcycloundeca-2,6-dienone (27e)

Following the general experimental procedure, zerumbone **24** (30 mg, 0.137 mmol), compound **26e** (26.06 mg, 0.274 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **27e** as a white solid (23.69 mg, 55%).



R_f: 0.68 (ethylacetate/hexane = 1:3).

Mp: 85-90 ^oC.

IR (neat) υ_{max} (CaF_2): 3370.7, 3099.8, 3040.3, 2964.5, 2936.6, 2872.5, 1693.5, 1627.6, 1540.3, 1483.5, 1451.3, 1379.3, 1365.0, 1299.4, 1288.7, 1245.2, 1232.8, 1213.8, 1176.1, 1136.6, 1100.8, 1081.2, 1041.0, 997.9, 977.0, 927.2, 906.4, 873.3, 855.8, 837.4 cm^{-1}.

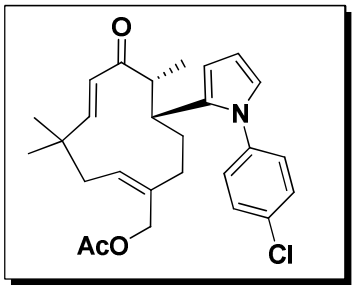
^{1}H NMR (500 MHz, CD_3CN): δ 6.70-6.69 (m, 1H), 6.33 (d, *J* = 16.5 Hz, 1H), 6.19 (d, *J* = 16 Hz, 1H), 6.02-6.00 (m, 1H), 5.97-5.96 (m, 1H), 5.14 (dd, J_1 = 11.5 Hz, J_2 = 4.5 Hz, 1H), 4.09-3.99 (m, 2H), 3.34-3.32 (m, 1H), 2.63-2.60 (m,1H), 2.35-2.30 (m, 1H), 2.02-1.99 (m, 1H), 1.92-1.88 (m, 1H), 1.85-1.79 (m, 1H), 1.46 (s, 3H), 1.44-1.43 (m, 3H), 1.39-1.33 (m, 1H), 1.20 (s, 3H), 1.19 (s, 3H), 0.95-0.90 (m, 1H), 0.81 (d, *J* = 6.5 Hz, 3H) ppm.

^{13}C NMR (125 MHz, CD_3CN): δ 203.5, 152.2, 138.9, 134.3, 129.2, 123.1, 121.0, 107.8, 107.7, 52.2, 42.0, 41.9, 40.7, 39.0, 38.3, 29.0, 26.9, 23.3, 17.9, 17.0, 7.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{21}H_{31}NNaO$: 336.23033, Found: 336.23076.

(((1Z,5E)-9-(1-(4-chlorophenyl)-1H-pyrrol-2-yl)-4,4,8-trimethyl-7-oxocycloundeca-1,5-dienyl)methyl acetate (30b)

Following the general experimental procedure, zerumbone acetate, **29** (30 mg, 0.1087 mmol), **26b** (38.486 mg, 0.2174 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00544 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **30b** as a white solid (16.74 mg, 34%).



R_f: 0.46 (ethylacetate/hexane = 1:3).

Mp: 95-100 ^oC.

IR (neat) υ_{max} (CaF_2): 3366.2, 3099.7, 3046.6, 2959.5, 2870.5, 1736.7, 1691.5, 1626.3, 1496.1, 1454.1, 1369.7, 1327.1, 1298.8, 1231.1, 1175.6, 1141.6, 1094.1, 1034.9, 908.9, 841.6 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 7.62 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 4.5 Hz, 2H), 6.77-6.76 (m, 1H), 6.22-6.20 (m, 2H), 5.96 (d, *J* = 16 Hz, 1H), 5.39 (d, *J* = 16 Hz, 1H), 5.04-5.01 (m, 1H), 4.48 (d, *J* = 12 Hz, 1H), 4.28 (d, *J* = 12.5 Hz, 1H), 3.13-3.11 (m,1H), 2.49-2.47 (m, 1H), 2.35-2.30 (m,1H), 2.24-2.20 (m,1H), 1.99 (s, 3 H), 1.90-1.84 (m, 2H), 1.50-1.46 (m, 1H), 1.30-1.19 (m, 1H), 1.12 (s, 3H), 0.87 (s, 3H), 0.83 (d, *J* = 6.5 Hz, 3H) ppm.

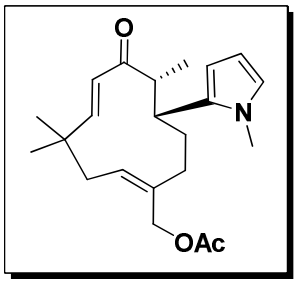
^{13}C NMR (125 MHz, CD_3CN): δ 202.9, 171.6, 152.7, 140.1, 137.1, 136.4, 135.0, 130.8, 130.5, 129.1, 128.6, 123.9, 118.3, 108.9, 61.9, 52.1, 41.2, 39.4, 38.2, 34.0, 29.0, 27.7, 23.2, 21.0, 7.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{27}H_{32}ClNNaO_3$: 476.19684, Found: 476.19749 $[M+Na]^+$.

((1Z,5E)-4,4,8-trimethyl-9-(1-methyl-1H-pyrrol-2-yl)-7-oxocycloundeca-1,5-dienyl)methyl acetate (30c)

Following the general experimental procedure, zerumbone acetate, **29** (30 mg, 0.1087

mmol), **26c** (22.22 mg, 0.2174 mmol), $Sc(OTf)_3$ (2.67 mg, 0.00544 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **30c** as a colourless liquid (13.5 mg, 29%).



R_f: 0.5 (ethylacetate/hexane = 2:3).

IR (neat) υ_{max}: 2918, 2848, 2392, 2355, 1649, 1590, 1415, 1276, 1118, 1035, 751 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 6.63-6.62 (m, 1H), 6.38 (d, *J* = 16.5 Hz, 1H), 6.10 (d, *J* = 16.5 Hz, 1H), 5.98-5.97 (m, 2H), 5.42 (dd, J_1 = 12 Hz, J_2 = 5 Hz, 1H), 4.55 (d, *J* = 12 Hz, 1H), 4.33 (d, *J* = 12.5 Hz, 1H), 3.73 (s, 3H), 3.34-3.31 (m, 1H), 2.66-2.64 (m, 1H), 2.46-2.41 (m, 1H), 2.01-1.98 (m, 1H), 1.98 (s, 3H), 1.86-1.79 (m, 1H), 1.42-1.36 (m, 1H), 1.24 (s, 3H), 1.20 (s, 3H), 0.95-0.89 (m, 1H), 0.79 (d, *J* = 7 Hz, 1H) ppm.

^{13}C NMR (125 MHz, CD_3CN): δ 205.5, 171.6, 152.7, 137.2, 134.8, 129.4, 129.2, 123.2, 107.7, 107.2, 61.9, 51.5, 41.5, 39.8, 38.1, 34.4, 34.0, 28.9, 27.1, 23.4, 21.1, 7.7 ppm.

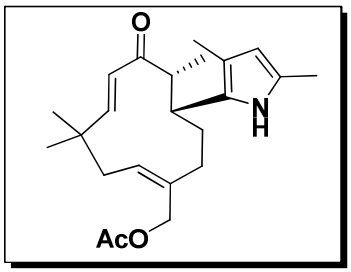
HRMS (ESI): *m/z* Calcd for $C_{22}H_{31}NNaO_3$: 380.22016, Found: 380.21973 $[M+Na]^+$.

(2E,(((1Z,5E)-9-(3,5-dimethyl-1H-pyrrol-2-yl)-4,4,8-trimethyl-7-oxocycloundeca-1,5-dienyl)methyl acetate (30d)

Following the general experimental procedure, zerumbone acetate **29** (30 mg, 0.1087 mmol), compound **26d** (20.67 mg, 0.2174 mmol), Sc $(OTf)_3$ (2.67 mg, 0.00544 mmol), in 3 mL acetonitrile at room temperature for 12 h gave the product **30d** as colourless liquid (13 mg, 33%).

R_f: 0.13 (ethylacetate/hexane = 1:2.3).

IR (neat) υ_{max}: 3356, 3054, 2933, 2871, 1627, 1455, 1368, 1302, 1237, 1122, 1079, 1038, 910, 856, 785, 736, 702, 609 cm^{-1}.



^{1}H NMR (500 MHz, CD_3CN): δ 8.58 (brs, 1H), 6.36 (d, *J* = 16.5 Hz, 1H), 6.07 (d, *J* = 16.5 Hz, 1H), 5.57 (d, *J* = 2 Hz, 1H), 5.39 (dd, J_1 = 12.5 Hz, J_2 = 5 Hz, 1H), 4.54 (d, *J* = 12.5 Hz, 1H), 4.32 (d, *J* = 12.5 Hz, 1H), 3.37-3.34 (m, 1H), 2.64-2.62(m, 1H), 2.43-2.41 (m,1H), 2.19-2.14 (m, 1H), 2.14 (s, 3H), 2.11-2.10 (m, 1H), 2.09 (s, 3H), 2.02-2.00 (m, 1H), 1.99 (s, 3H), 1.74-1.68 (m, 1H), 1.39-1.35 (m, 1H), 1.24 (s, 3H), 1.19 (s, 3H), 0.90 (d, *J* = 7 Hz, 3H) ppm.

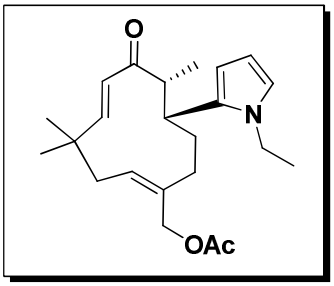
^{13}C NMR (125 MHz, CD_3CN): δ 202.4, 170.3, 151.0, 135.6, 128.2, 127.2, 125.1, 113.9, 107.3, 60.5, 52.3, 40.3, 38.5, 36.4, 32.5, 27.6, 24.8, 22.0, 19.8, 11.5, 10.4, 7.6 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{32}NO_3$: 371.2460, Found: 370.23822 (M-1 peak).

(2E,(((1Z,5E)-9-(1-ethyl-1H-pyrrol-2-yl)-4,4,8-trimethyl-7-oxocycloundeca-1,5-dienyl)methyl acetate (30e)

Following the general experimental procedure, zerumbone acetate **29** (30 mg, 0.1087 mmol), compound **26e** (20.67 mg, 0.2174 mmol), Sc $(OTf)_3$ (2.67 mg, 0.00544 mmol), in 3 mL acetonitrile at room temperature for 12 h gave the product **30e** as colourless liquid (22 mg, 55%).

R_f: 0.4 (ethylacetate/hexane = 1:3).



IR (neat) υ_{max}: 3375, 3101, 3046, 2969, 2873, 1738, 1693, 1628, 1453, 1369, 1235, 1137, 1102, 1078, 1039, 908, 861, 782, 735, 709, 613, 554 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 6.72-6.71 (m, 1H), 6.36 (d, *J* = 16.5 Hz, 1H), 6.10 (d, *J* = 16 Hz, 1H), 6.02-6.01 (m, 1H), 5.97-5.96 (m, 1H), 5.38 (dd, J_1 = 12.5 Hz, J_2 = 5 Hz, 1H), 4.55 (d, *J* = 12.5 Hz, 1H), 4.34 (d, *J* = 12.5 Hz, 1H), 4.08-4.00 (m, 2H), 3.32-3.29 (m, 1H), 2.65-2.61 (m, 1H), 2.47-2.42 (m, 1H), 2.26-2.21 (m, 1H), 2.03-2.00 (m, 1H), 1.99 (s, 3H), 1.89-1.82 (m, 1H), 1.45 (t, *J* = 7 Hz, 3H), 1.42-1.33 (m, 1H), 1.24 (s, 3H), 1.20 (s, 3H), 0.96-0.90 (m, 1H), 0.80 (d, *J* = 6.5 Hz, 3H) ppm.

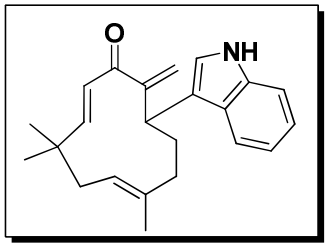
^{13}C NMR (125 MHz, CD_3CN): δ 203.3, 171.6, 152.7, 137.4, 133.9, 129.2, 129.1, 121.2, 107.9, 107.7, 61.8, 52.1, 42.0, 41.4, 39.8, 37.9, 34.1, 28.9, 27.3, 23.3, 21.1, 17.9, 7.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{33}NNaO_3$: 394.23581, Found: 394.23505 $[M+Na]^+$.

(2E,6E)-10-(1H-indole-3-yl)-4,4,7-trimethyl-11-methelenecycloundeca-2,6-dienone (31a)

Following the general procedure, zerumbone **24** (30 mg, 0.137 mmol), indole **1a** (16.1 mg, 0.137 mmol), palladium acetate (6.16 mg, 0.274 mmol) and hydrated copperacetate (44.95 mg, 0.079 mmol) in mixture of DMSO:DMF (1:20, 3 mL) under argon atmosphere and stirred for 12 h at 80 ^{0}C gave the coupled product **31a** as colourless liquid (28%).

R_f: 0.34 (ethylacetate/hexane = 1:4).



IR (neat) υ_{max}: 3861, 3561, 3377, 3058, 2958, 2926, 2853, 2127, 1737, 1663, 1545, 1511, 1491, 1457, 1384, 1366, 1337, 1302, 1265, 1229, 1095, 1013, 993, 974, 928, 880, 844, 740, 700, 665, 595, 531, 515 cm^{-1}.

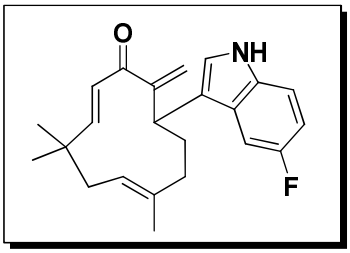
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 brs (s, 1H), 7.48 (d, *J* = 8 Hz, 1H), 7.37 (d, *J* = 8 Hz, 1H), 7.20-7.11 (m, 3H), 6.48 (d, *J* = 16.5 Hz, 1H), 6.26 (d, *J* = 16 Hz, 1H), 5.63 (s, 1H), 5.23 (dd, 1H, J_1 = 11.5 Hz, J_2 = 5 Hz), 4.90 (s, 1H), 4.08 (d, *J* = 6.5 Hz, 1H), 2.30-2.28 (m, 1H), 2.25-2.19 (m, 1H), 2.17-2.14 (m, 1H), 2.07-1.98 (m, 1H), 1.97-1.94 (m, 1H), 1.88-1.84 (m, 1H), 1.53 (s, 3H), 1.52 (m, 3H), 1.25 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.7, 154.9, 150.9, 137.8, 137.0, 128.8, 127.1, 122.8, 122.3, 121.9, 119.5, 119.4, 118.6, 117.4, 111.3, 41.3, 39.3, 38.3, 32.5, 30.9, 29.3, 23.9, 17.0 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{27}NNaO$: 356.19903, Found: 356.19913 $[M+Na]^+$.

(2E,6E)-10-(5-fluoro-1H-indol-3-yl)-4,4,7-trimethyl-11-methylenecycloundeca-2,6-dienone (31c)

Following the general procedure, zerumbone **24** (30 mg, 0.137 mmol), 5-fluoro indole **1c** (15.58 mg, 0.115 mmol), palladium acetate (6.16 mg, 0.274 mmol) and hydrated copper acetate (44.95 mg, 0.079 mmol) in mixture of DMSO:DMF (1:20, 3 mL) under argon atmosphere and stirred for 12 h at 80 ^oC gave the coupled product **31c** as colourless liquid (34%).



R_f: 0.26 (ethylacetate/hexane = 1:4).

IR (neat) υ_{max}: 3806, 3753, 3878, 3656, 3363, 2956, 2919, 2851, 2349 2310, 1737, 1664, 1627, 1531, 1550, 1464, 1377, 1265, 1181, 1115, 1080, 971, 890, 850, 877, 741, 670, 619,567, 515 cm^{-1}.

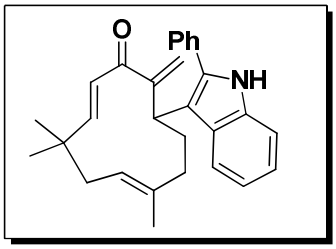
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (brs, 1H), 7.32 (dd, J_1= 9 Hz, J_2 = 4.5 Hz, 1H), 7.17-7.11 (m, 2H), 6.97-6.96 (m, 1H), 6.42 (d, *J* = 16 Hz, 1H), 6.27 (d, *J* = 16.5 Hz, 1H), 5.65 (d, *J* = 1Hz, 1H), 5.22 (dd, J_1 = 11 Hz, J_2 = 5 Hz, 1H), 4.90 (s, 1H), 4.01 (d, *J* = 7 Hz, 1H), 2.31-2.26 (m, 2H), 2.18-2.13 (m, 2H), 1.99-1.97 (m,1H), 1.88-1.82 (m, 1H), 1.54 (s, 3H), 1.25 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 189.5, 154.7, 150.8, 138.1, 137.5, 128.7, 127.2, 117.2, 110.7, 41.3, 39.5, 38.1, 32.4, 29.2, 25.2, 17.1, 11.8 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{26F}NNaO$: 374.18961, Found: 374.18845 $[M+Na]^+$.

(2E,6E)-4,4,7-trimethyl-11-methylene-10-(2-phenyl-1H-indol-3-yl)cycloundeca-2,6-dienone (31d)

Following the general procedure, zerumbone **24** (30 mg, 0.137 mmol), 2-phenyl indole **1d** (26.47 mg, 0.115 mmol), palladium acetate (6.16 mg, 0.274 mmol) and hydrated copper acetate (44.95 mg, 0.079 mmol) in mixture of DMSO:DMF (1:20, 3 mL) under argon atmosphere and stirred for 12 h at 80 ^oC gave the coupled product **31d** as yellow liquid (2.8 mg, 5%).



R_f: 0.12 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 3419, 2097, 1639, 1452, 1307, 1266, 1094, 742, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (brs, 1H), 7.66 (d, *J* = 8 Hz, 1H), 7.52-7.51 (m, 4H), 7.46-7.40 (m, 2H), 7.24-7.20, (m, 1H), 7.14-7.11 (m, 1H), 6.26 (d, *J* = 16 Hz, 1H), 6.11 (d, *J* = 16 Hz, 1H), 5.59 (s, 1H), 5.27 (d, *J* = 1.5 Hz, 1H), 4.59 (dd, J_1 = 11.5 Hz, J_2 = 5 Hz, 1H), 4.89 (s, 1H), 3.95 (d, *J* = 7 Hz, 1H), 2.49-2.43 (m, 1H), 2.13-2.08 (m, 1H), 1.89-1.85 (m, 1H), 1.76-1.72 (m, 1H), 1.52-1.43 (m, 2H), 1.34 (s, 3H), 1.16 (s, 3H), 0.92 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 198.4, 155.4, 151.8, 138.0, 136.4, 136.0, 133.3, 129.0, 128.9, 128.4, 128.3, 127.8, 122.1, 121.9, 121.6, 119.6, 118.0, 113.8, 111.2, 40.9, 39.7, 39.4, 39.1, 31.8, 29.3, 24.0, 16.9 ppm.

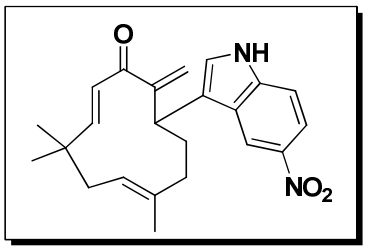
HRMS (ESI): *m/z* Calcd for $C_{29}H_{31}NNaO$: 432.23033, Found: 432.23083$[M+Na]^+$.

(2E,6E)-4,4,7-trimethyl-11-methylene-10-(5-nitro-1H-indol-3-yl)cycloundeca-2,6-dienone (31f)

Following the general procedure, zerumbone **24** (30 mg, 0.137 mmol), 5-nitroindole **1f** (22.29 mg, 0.137 mmol), palladium acetate (6.16 mg, 0.274 mmol) and hydrated copper acetate (44.95 mg, 0.079 mmol) in mixture of DMSO:DMF (1:20, 3 mL) under argon atmosphere and stirred for 12 h at 80 ^oC gave the coupled product **31f** as a colourless liquid (17 mg, 33%).

R_f: 0.12 (ethylacetate/hexane = 1:4).

IR (neat) υ_{max}: 3737, 3392, 3306, 3245, 2957, 2918, 2851, 2356, 2316, 1882, 1788, 1731, 1712, 1638, 1645, 1615, 1590, 1534, 1379, 1331, 1171, 1079, 1042, 970, 932, 848, 813, 771, 721, 672, 611 cm^{-1}.



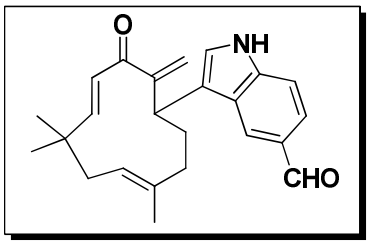
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (s, 2H), 8.16-8.14 (m, 1H), 7.44-7.28 (m, 2H), 6.44 (d, *J* = 16.5 Hz, 1H), 6.33 (d, *J* = 16 Hz, 1H), 5.67 (s, 1H), 5.28 (dd, J_1 = 11.5 Hz, J_2 = 5 Hz, 1H), 4.95 (s, 1H), 4.13 (d, *J* = 7 Hz, 1H), 2.35-2.30 (m, 1H), 2.25-2.21 (m, 1H), 2.19-2.14 (m, 1H), 2.05-2.00 (m, 1H), 1.94-1.91 (m, 1H), 1.88-1.86 (m, 1H), 1.58 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.4, 154.3, 152.3, 141.7, 139.6, 137.2, 128.1, 126.3, 125.1, 123.3, 118.0, 116.2, 111.3, 41.6, 39.5, 38.1, 34.5, 29.6, 29.1, 25.3, 23.9, 17.1, 11.5 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{26}N_2NaO_3$:401.18411, Found: 401.18447 $[M+Na]^+$.

3-((4E,8E)-6,6,9-trimethyl-2-methylene-3-oxocycloundeca-4,8-dien-1-yl)-1H-indole-5-carbaldehyde (31g)

Following the general procedure, zerumbone **24** (30 mg, 0.137 mmol), indole-5-carboxaldehyde **1g** (19.88 mg, 0.137 mmol), palladium acetate (6.16 mg, 0.274 mmol) and hydrated copperacetate (44.95 mg, 0.079 mmol) in mixture of DMSO:DMF (1:20, 3 mL) under argon atmosphere and stirred for 12 h at 80 ^oC gave the coupled product as a colourless liquid **31g** (2.48 mg, 5%).



R_f : 0.14 (ethylacetate/hexane = 1:4)

IR (neat) υ_{max}: 3856, 3329, 2956, 2924, 2854, 2355, 2314, 1859, 1678, 1611, 1577, 1534, 1437, 1362, 1303, 1262, 1175, 1100, 1125, 1043, 891, 809, 772, 652, 613, 547, 514 cm^{-1}.

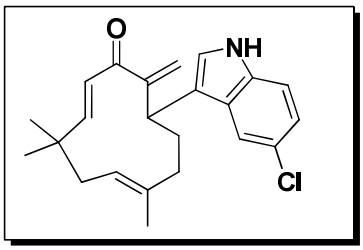
^{1}H NMR (500 MHz, $CDCl_3$): δ 10.04 (s, 1H), 8.36 (brs,1H), 8.02 (s, 1H), 7.80 (d, *J* = 8.5 Hz , 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* =1.5 Hz, 1H), 6.44 (d, *J* = 16 Hz, 1H), 6.31 (d, *J* =16.5 Hz, 1H), 5.67 (s, 1H), 5.26 (dd, J_1 = 11.5 Hz, J_2 = 5 Hz, 1H), 4.94 (s, 1H), 4.13 (d, *J* = 6.5 Hz, 1H), 2.34-2.29 (m, 1H), 2.24-2.20 (m, 1H), 2.19-2.16 (m, 1H), 2.03-2.00 (m, 1H), 1.99-1.87 (m, 1H), 1.69-1.64 (m, 1H), 1.58 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.4, 170.8, 154.4, 151.6, 140.2, 137.5, 129.6, 128.1, 123.7, 123.3, 112.1, 41.3, 39.6, 38.3, 29.5, 29.2, 25.1, 23.9, 17.9, 14.2 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{27}NNaO_2$: 384.19395, Found: 384.1930 $[M+Na]^+$.

(2E,6E)-10-(5-chloro-1H-indol-3-yl)-4,4,7-trimethyl-11-methylenecycloundeca-2,6-dienone (31j)

Following the general procedure, zerumbone **24** (30 mg, 0.137 mmol), 5-chloro indole **1j** (20.76 mg, 0.137 mmol), palladium acetate (6.16 mg, 0.274 mmol) and hydrated copperacetate (44.95 mg, 0.079 mmol) in mixture of DMSO:DMF (1:20, 3 mL) under argon atmosphere and stirred for 12 h at 80 ^{o}C gave the coupled product **31j** as colourless liquid (10 mg, 20%).



R_f: 0.88 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 3434, 2929, 2126, 1640, 1549, 1380, 1267, 1096, 891, 798, 751, 601 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (brs, 1H), 7.41 (s, 1H), 7.29-7.28 (m, 1H), 7.16- 7.12 (m, 2H), 6.40 (d, *J* = 16 Hz, 1H), 6.26 (d, *J* =16.5 Hz, 1H), 5.63 (s. 1H), 5.22 (dd, J_1 = 11 Hz, J_2 = 4.5 Hz, 1H), 4.89 (s, 1H), 4.00 (d, *J* = 7 Hz, 1H), 2.36-2.26 (m, 2H), 2.18-2.11 (m, 2H), 1.99-1.96 (m, 1H), 1.87-1.81 (m, 1H), 1.54 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H) ppm.

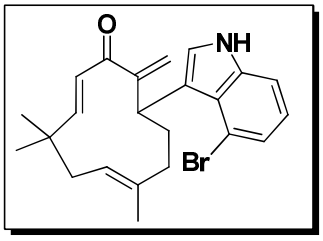
^{13}C NMR (125 MHz, $CDCl_3$): δ 197.9, 154.6, 151.8, 137.7, 135.3, 128.4, 125.3, 123.5, 123.0, 122.7, 119.0, 118.6, 117.3, 112.4, 41.2, 39.6, 39.3, 38.4, 32.7, 29.7, 29.2, 24.0, 17.0 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{26}ClNNaO$: 390.16006, Found: 390.16068 $[M+Na]^+$.

(2E,6E)-10-(4-bromo-1H-indol-3-yl)-4,4,7-trimethyl-11-methylenecycloundeca-2,6-dienone (31k)

Following the general procedure, zerumbone **24** (30 mg, 0.137 mmol), 4-bromo indole **1k** (26.86 mg, 0.137 mmol), palladium acetate (6.16 mg, 0.274 mmol) and hydrated copperacetate (44.95 mg, 0.079 mmol) in mixture of DMSO:DMF (1:20, 3 mL) under argon atmosphere and stirred for 12 h at 80 ^{o}C gave the coupled product **31k** as colourless liquid (11.9 mg, 21%).

R_f : 0.46 (ethylacetate/hexane = 1:4)



IR (neat) υ_{max}: 3424, 2091, 1641, 1502, 1423, 1123, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (brs, 1H), 7.35-7.28 (m, 1H), 7.22-7.19 (m, 2H), 7.04-7.01 (m, 1H), 6.70 (d, *J* = 16 Hz, 1H), 6.32 (d, *J* = 16.5 Hz, 1H), 5.61 (s, 1H), 5.28 (dd, J_1 = 7.5 Hz, J_2 = 3.5 Hz, 1H), 4.75 (d, *J* = 8 Hz, 1H),

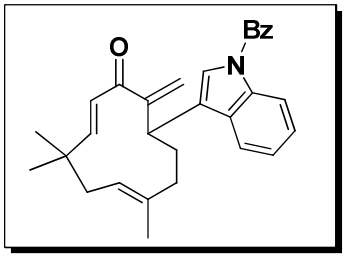
4.59 (s, 1H), 2.38-2.20 (m, 3H), 2.14-2.01 (m, 2H), 1.91-1.86 (m, 1H), 1.25 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 198.1, 156.4, 151.2, 138.2, 137.8, 129.0, 124.6, 124.5, 123.0, 122.7, 118.7, 116.9, 113.9, 110.8, 40.6, 39.6, 38.1, 38.0, 34.6, 29.7, 29.1, 25.1, 17.8 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{26}BrNNaO$: 434.10955, Found: 434.10983 $[M+Na]^+$.

(2E,6E)-10-(1-benzoyl-1H-indol-3-yl)-4,4,7-trimethyl-11-methylenecycloundeca-2,6-dienone (31m)

Following the general procedure, zerumbone **24** (30 mg, 0.137 mmol), N-benzylindole **1m** (30.28 mg, 0.137 mmol), palladium acetate (6.16 mg, 0.274 mmol) and hydrated copperacetate (44.95 mg, 0.079 mmol) in mixture of DMSO:DMF (1:20, 3 mL) under argon atmosphere and stirred for 12 h at 80 ^oC gave the coupled product **31m** as a colourless liquid **(**2.4 mg, 4%).



R_f: 0.46 (ethylacetate/hexane = 1:4).

IR (neat) υ_{max}: 3806, 3754, 3720,3677, 3666, 3634, 3572, 3343, 3060, 2957, 2926, 2855, 2311, 1728, 1666, 1604, 1550, 1531, 1450, 1362, 1332, 1262, 1208, 1151, 1085, 1046, 1022, 909, 872, 794, 749, 701, 670, 621, 566, 579 $cm^{-1.}$

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7 Hz, 1H), 7.78 (d, *J* = 7 Hz, 1H), 7.66-7.63 (m, 1H), 7.59-7.56 (m, 3H), 7.47-7.32 (m, 3H), 7.25 (s, 1H), 6.43 (d, *J* = 16 Hz, 1H), 6.27 (d, *J* = 16 Hz, 1H), 5.68 (s, 1H), 5.22 (dd, J_1 = 11 Hz, J_2 = 4.5 Hz, 1H), 4.97 (s, 1H), 4.01 (d, *J* = 7 Hz, 1H), 2.31-2.26 (m, 1H), 2.20-2.16 (m, 1H), 2.08-2.03 (m, 1H), 2.00-1.96 (m, 1H), 1.87-1.82 (m, 1H), 1.71-1.70 (m, 1H), 1.52 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H) ppm.

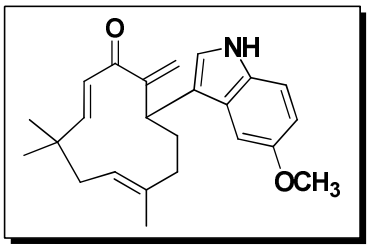
^{13}C NMR (125 MHz, $CDCl_3$): δ 197.4, 191.8, 154.4, 151.6, 140.2, 137.5, 129.6, 128.1, 123.7, 123.3, 112.1, 41.3, 39.5, 38.3, 29.5, 29.2, 25.1, 23.9, 17.1, 14.1 ppm.

HRMS (ESI): *m/z* Calcd for $C_{30}H_{31}NNaO_2$: 460.22525, Found: 459.90640 $[M+Na]^+$.

(2E,6E)-10-(5-methoxy-1H-indol-3-yl)-4,4,7-trimethyl-11-methylenecycloundeca-2,6-dienone (31o)

Following the general procedure, zerumbone **24** (30 mg, 0.137 mmol), 4-methoxy indole **1o** (20.14 mg, 0.137 mmol), palladium acetate (6.16 mg, 0.274 mmol) and hydrated copperacetate (44.95 mg, 0.079 mmol) in mixture of DMSO:DMF (1:20, 3 mL) under

argon atmosphere and stirred for 12 h at 80 ^{o}C gave the coupled product **31o** as a colourless liquid (5 mg, 10%).



R_f: 0.88 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 3362, 2932, 2867, 1622, 1485, 1454, 1363, 1265, 1214, 1172, 1088, 795, 773, 764, 748, 742, 737, 724, 714 cm^{-1}.

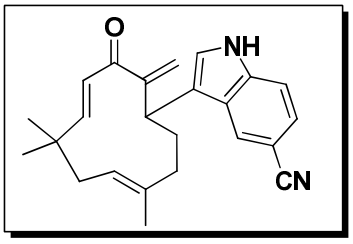
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (brs, 1H), 7.27-7.26 (m, 1H), 7.09 (d, *J* = 2.5 Hz, 1H), 6.91 (d, *J* = 2 Hz, 1H), 6.87- 6.85 (m, 1H), 6.46 (d, *J* = 16 Hz, 1H), 6.25 (d, *J* = 16 Hz, 1H), 5.63(d, *J* = 1.5 Hz, 1H), 5.22 (dd, J_1 = 11 Hz, J_2 = 4.5 Hz, 1H), 4.93 (s, 1H), 4.03 (d, *J* = 6.5 Hz, 1H), 3.84 (s, 3H), 2.31-2.14 (m, 4H), 1.98-1.95 (m, 1H), 1.87-1.81 (m, 1H), 1.53 (s, 3H), 1.25 (s, 3H), 1.25 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 198.0, 154.8, 153.9, 151.2, 138.0, 132.2, 128.7, 127.6, 122.9, 122.8, 118.6, 117.1, 112.2, 112.0, 101.7, 55.9, 41.3, 39.7, 39.3, 38.4, 32.5, 29.7, 29.2, 23.8, 16.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{29}NNaO_2$: 386.20960, Found: 386.21011 $[M+Na]^+$.

3-((4E,8E)-6,6,9-trimethyl-2-methylene-3-oxocycloundeca-4,8-dienyl)-1H-indole-5-carbonitrile (31p)

Following the general procedure, zerumbone **24** (30 mg, 0.137 mmol), 5-cyano indole **1p** (19.45 mg, 0.137 mmol), palladium acetate (6.16 mg, 0.274 mmol) and hydrated copperacetate (44.95 mg, 0.079 mmol) in mixture of DMSO:DMF (1:20, 3 mL) under argon atmosphere and stirred for 12 h at 80 ^{o}C gave the coupled product **31p** as a colourless liquid (3 mg, 6%).



R_f: 0.88 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 3331, 2930, 2220, 1617, 1472, 822, 811, 805, 797, 794, 783, 780, 776, 769, 767, 764, 756, 749, 745, 740, 735, 728, 722, 713, 709, 707 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (brs, 1H), 7.81 (s, 1H), 7.46-7.44 (m, 3H), 6.35 (d, *J* = 16 Hz, 1H), 6.28 (d, *J* = 16 Hz, 1H), 5.64 (s, 1H), 5.22 (dd, J_1 = 11 Hz, J_2 = 2.5 Hz, 1H), 4.87 (s, 1H), 4.02 (d, *J* = 7.5 Hz, 1H), 2.31-2.27 (m, 1H), 2.22-2.20 (m, 1H), 2.14-2.11 (m, 1H), 2.01-1.98 (m, 1H), 1.91-1.82 (m, 1H), 1.67-1.62 (m, 1H), 1.55 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.7, 152.4, 137.5, 128.0, 125.4, 125.1, 124.3, 123.2,

118.5, 112.3, 102.8, 41.0, 39.6, 38.4, 32.5, 30.9, 29.8, 28.9, 24.2, 16.8 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{26}N_2NaO$: 381.19428, Found: 381.19490 $[M+Na]^+$.

3.14. Procedure for biological assays

Refer: Chapter 2A, Procedure for various biological assays, 2A.10.

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CHAPTER 4

Part A

Lewis Acid Catalyzed Transannular Cyclization of Indole Functionalized Zerumbone derivatives to [5.3.0] Decane Skeleton

4A.1. Introduction

Natural products offer a rich source for novel therapeutic agents with enormous structural diversity. About 34% of all the drugs approved by FDA in the past three decades are based on natural products and in many cases, the structurally complex natural products are altered from their core structure to a distinct framework using known synthetic methodologies.[1-2] In this line sustainable utilization of abundant natural products as a renewable resource for structurally diverse small molecules with intrinsic bioactivity is highly demanding. The fascinating eleven membered structural motif of zerumbone has elicited lot of interest from its synthetic viewpoint.[3-14] Hence, we focused on utilising zerumbone and its derivatives in annulation reactions by employing rare earth based metal catalysts for organic transformations.[15-18] This chapter describes our efforts in constructing 5-7 fused sesquiterpenoid frameworks *via* Lewis acid catalyzed cyclization reaction of zerumbone. Representative examples of the biologically active compounds having [5.7] fused ring systems are shown in figure 4A.1.

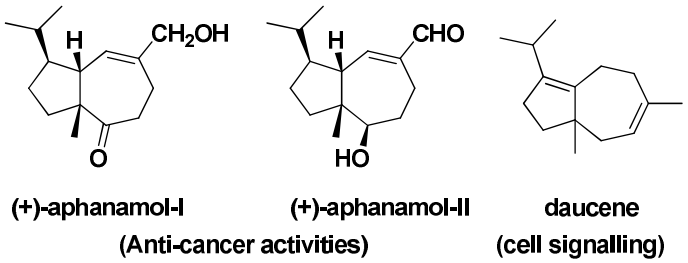
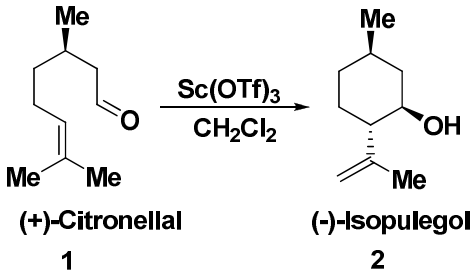


Figure 4A.1. Examples of the biologically active compounds having [5.7] fused ring systems

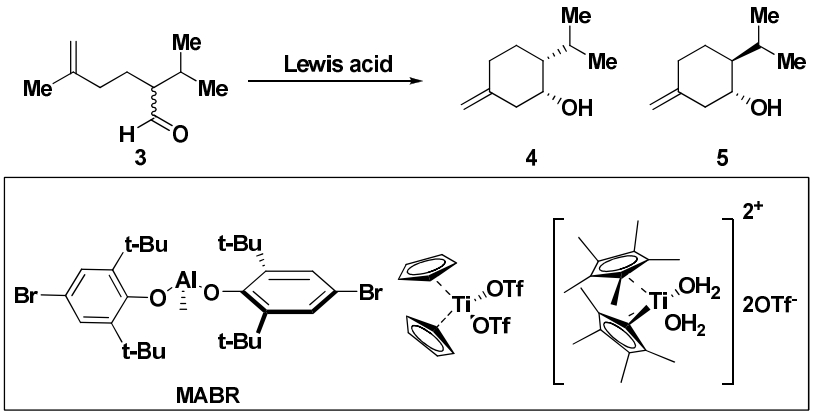
4A.2. Intramolecular Cyclization using Lewis Acid Catalyst

Aggarwal *et al.* reported the synthesis of isopulegol, **2** *via* Lewis acid catalyzed intramolecular cyclization of (+)-citronellal, **1** (Scheme 4A.1).[19] The reaction was catalyzed by one equivalent of zinc bromide in benzene, resulting in the formation of a single isomer, (-)-isopulegol **2** in 70% yield. Most of the other Lewis acids gave the product in moderate yields and selectivity. Later Aggarwal found that usage of scandium triflate as catalyst reduce the catalyst loading to 5 mol %.



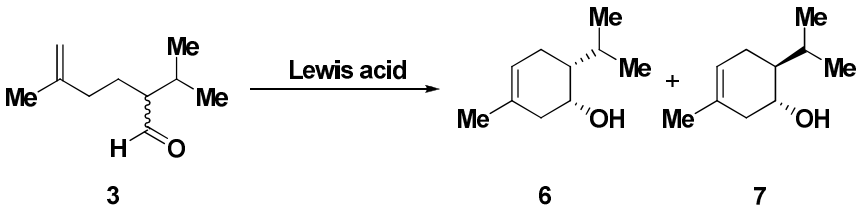
Scheme 4A.1.

Brown and co-workers utilized BCl_3, $SnCl_4$, methyl-aluminium bis(4-bromo-2,6-di-tertbutylphenoxide (MABR), $Sc(OTf)_3$ and titanocenes as catalysts in the intramolecular carbonyl ene-reactions of aldehyde **3** (Scheme 4A.2).[20] In presence of BCl_3 or $SnCl_4$ as catalysts, the intramolecular carbonyl-ene reaction of **3** proceeded to yield a mixture of **4** and **5** in 9:1 ratio.



Scheme 4A.2

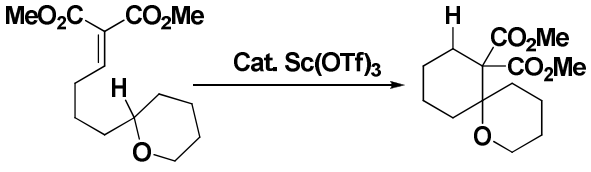
Lewis acids such as $Sc(OTf)_3$ and titanocenes mediated intramolecular carbonyl ene-reactions of aldehyde have also been reported (Scheme 4A.3), and the reaction afforded ene products with an internal alkene, **6** and **7**, instead of the "normal" ene products **4** and **5**.



3 6 7

Scheme 4A.3

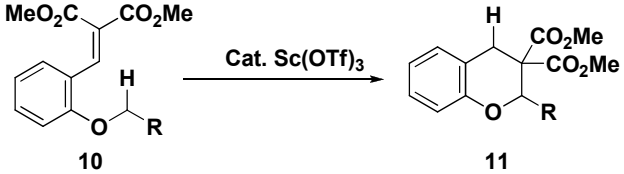
In 2005, Pastine and co-workers have reported a Lewis acid-catalyzed intramolecular hydroalkylation reaction of tetrahydropyran substrate containing isolated electron-deficient olefins **8** (Scheme 4A.4).[21]



8 9

Scheme 4A.4

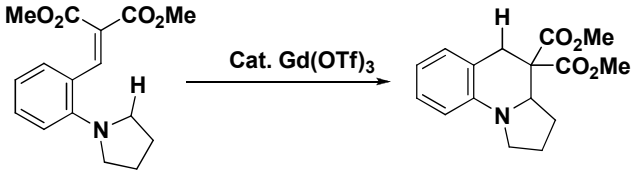
McQuaid and co-workers have reported the synthesis of dihydrobenzopyrans **11** through the hydride transfer initiated cyclization ("HT-cyclization") of vinylaryl alkyl ethers **10** and the reaction is illustrated in scheme 4A.5.[22-23]



10 11

Scheme 4A.5

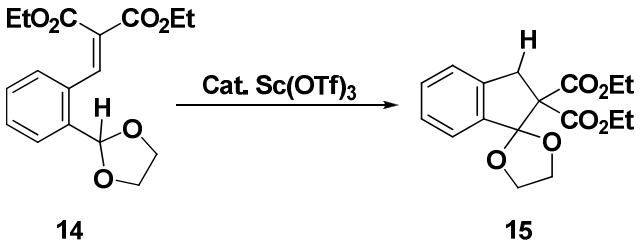
Murarka *et al.* presented the synthesis of polycyclic tetrahydroquinolines **13** *via* an efficient Lewis acid catalyzed 1,5-hydride shift, ring closure sequence of N-aryl amine-enone **12** (Scheme 4A.6).[24]



12 13

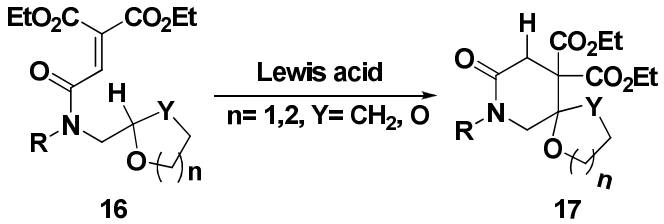
Scheme 4A.6

Alajarin and co-workers documented the synthesis of 1,2-dihydroindane derivatives *via* a one-pot hydride shift/cyclization process facilitated by the hydricity of the acetalic CH bonds, with benzylidenemalonate fragments as electrophilic hydride acceptors, and the catalysis of scandium(III) triflate (Scheme 4A.7).[25]



Scheme 4A.7

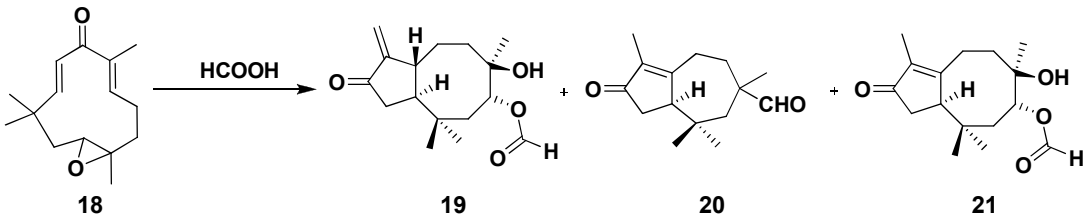
Recently, Yamazaki and co-workers reported the Lewis acid catalyzed cyclization of amides of ethenetricarboxylate bearing cyclic acetal and ether groups **16** *via* intramolecular hydride transfer. The reaction furnished the spirocyclic piperidine derivatives **17** in good yield (Scheme 4A.8).[26]



Scheme 4A.8

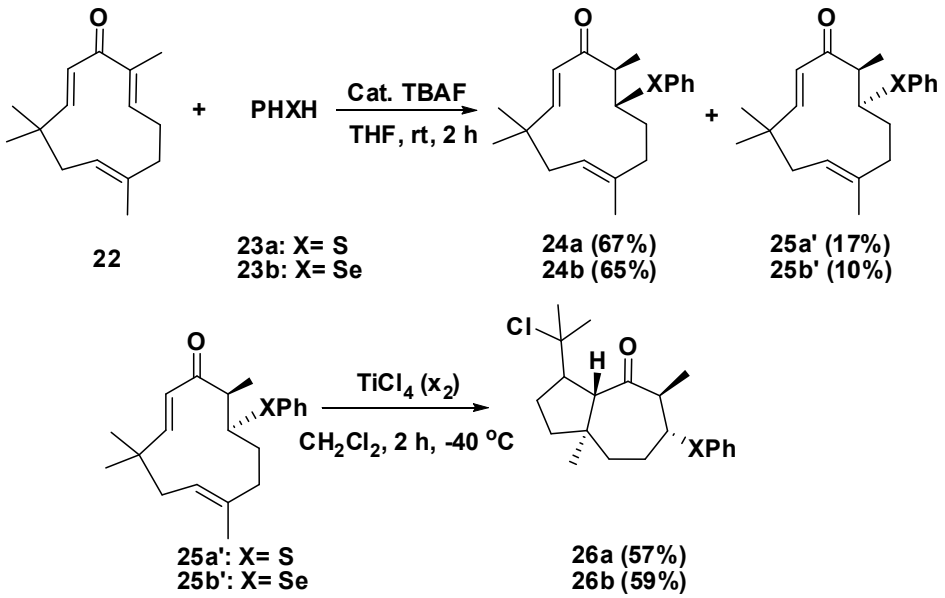
4A.2.1. Transannular cyclization

In 1982, Luu and co-workers reported the synthesis of bicyclo[6.3.0]undecane and bicyclo[5.3.0]decane skeletons *via* Bronsted acid catalyzed Nazarov-type cyclization of zerumbone epoxide **18** (Scheme 4A.9).[27]



Scheme 4A.9

The Michael/conjugate addition of zerumbone with thiophenol and benzeneselenol and further cyclization with Lewis acids such $TiCl_4$ leading to the bicyclic systems was reported by Ohe and co-workers (Scheme 4A.9).[28] Groups of Joshi,[29] Ohe[28] and Minassi,[30] also reported synthesis of rare bicyclo[6.3.0]decane skeletons from zerumbone analogues.



Scheme 4A.10

4A.3. Definition of the Problem

A close look at the single crystal X-ray structure of zerumbone prompted us to presume that the strained 11-membered puckered structure can be activated with Lewis acids for triggering transannular cyclizations leading to structurally diverse frame works. Annulation or cyclization of zerumbone, if achieved by mild chemical reagent or simple chemical reactions, it would lead to a more atom-economical synthetic method. The X-ray structure of the Michael adduct showed a considerable conformational difference in comparison to that of zerumbone (Figure 4A.2), which encouraged us to explore the feasibility of annulation of the adduct under Lewis acid catalysis. With this in mind, we undertook the Lewis acid catalyzed cyclization studies of zerumbone-indole Michael adducts.

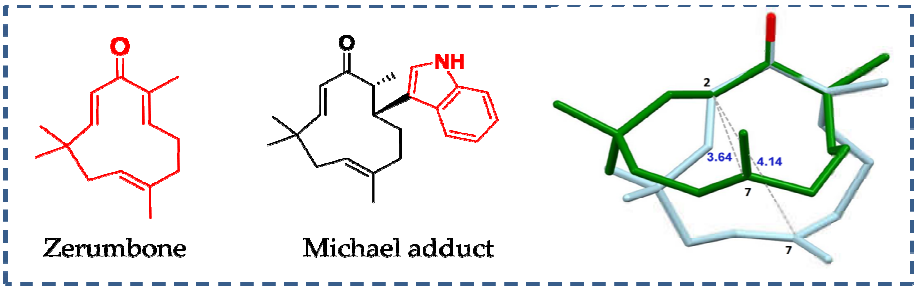
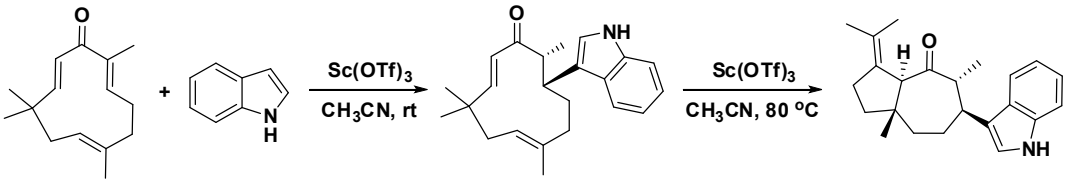


Figure 4A.2. Structure overlay of zerumbone **22** (light blue) and Michael adduct (green). Hydrogen atoms and indole (in Michael adduct) were omitted for clarity.

4A.4. Results and Discussion

We initiated with our investigations by exploring the reaction of Michael adduct **28a,** in the presence of 5 mol % of $Sc(OTf)_3$ in CH_3CN at 80 ^oC. Indole substituted isodaucane skeleton **29a** was obtained in 33% yield (Scheme 4A.11). The structure and stereochemistry of the product was confirmed by various spectroscopic techniques.



Scheme 4A.11

The structure was assigned to the product on the basis of spectral analysis. The IR spectrum of the compound showed characteristic carbonyl absorption at 1744 cm^{-1}. The ^1H NMR spectrum showed the presence of NH proton, resonated at δ 9.08 ppm, the aromatic protons were resonated between δ 7.64-7.02 ppm range and the proton at the bridge near the carbonyl group appeared as singlet at δ 3.96 ppm. The proton attached to the carbon bearing an indolyl group resonated as triplet at δ 3.19 ppm having coupling constant J = 11Hz and the proton at the carbon, having a methyl group appeared as a multiplet in between δ 2.65-2.61 ppm. The CH_2 protons resonated in the region δ 2.36-1.52 ppm. The ^1H NMR spectrum of compound **29a** is shown in the figure 4A.3.

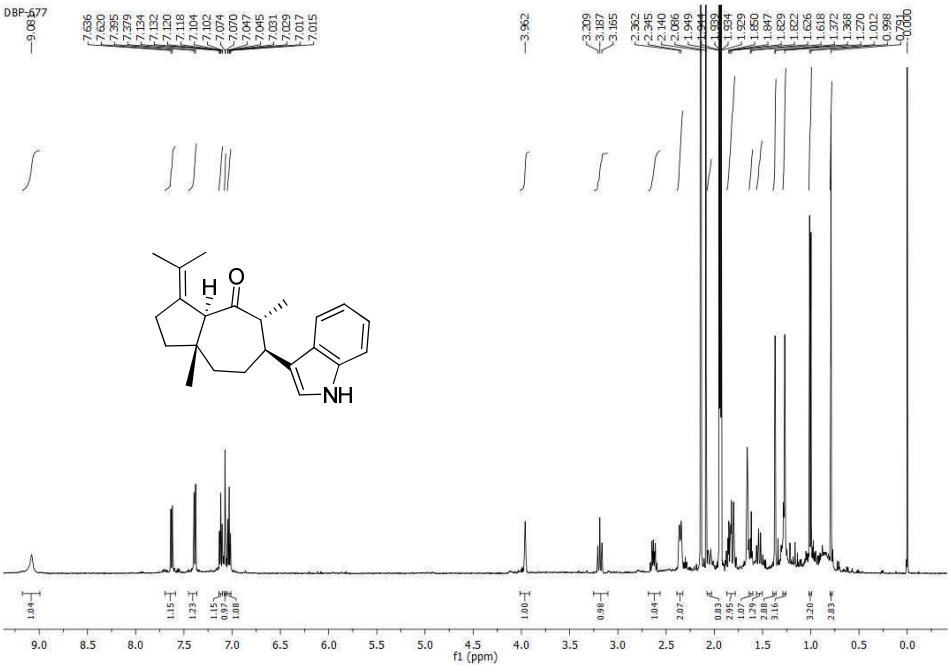


Figure 4A.3. ^1H NMR of compound **29a**

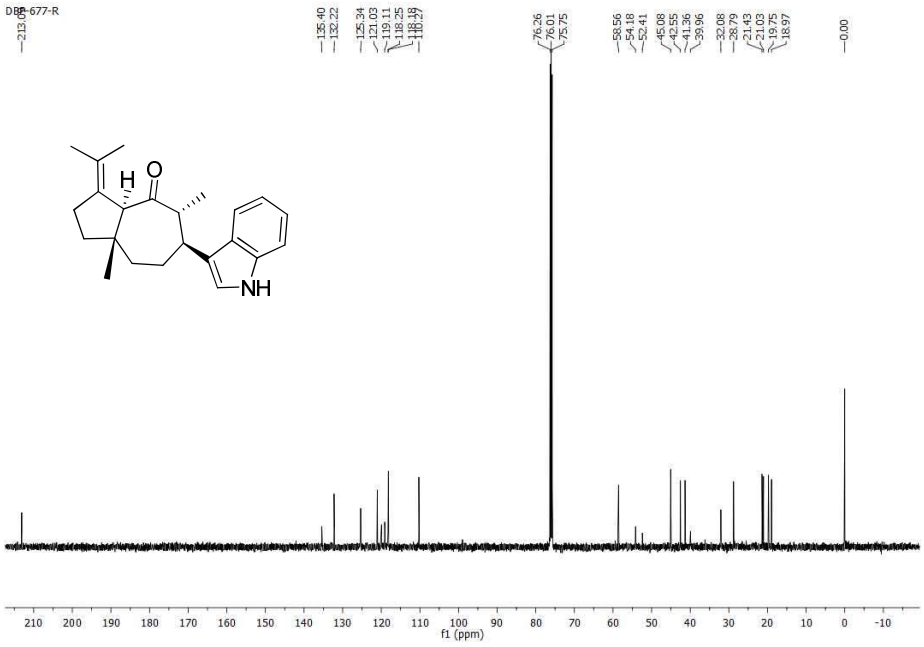


Figure 4A.4. ^{13}C NMR of compound **29a**

The ^{13}C NMR showed the characteristic carbonyl peak at δ 213.1 ppm. The ^{13}C NMR spectrum of compound **29a** is shown in the figure 4A.4. All the peaks were in well agreement with the desired structure of the product **29a**. Final evidence for the structure was obtained from the high resolution mass spectral analysis, which displayed a peak at *m/z* =358.2139 $[M+Na]^+$ (Figure 4A.5).

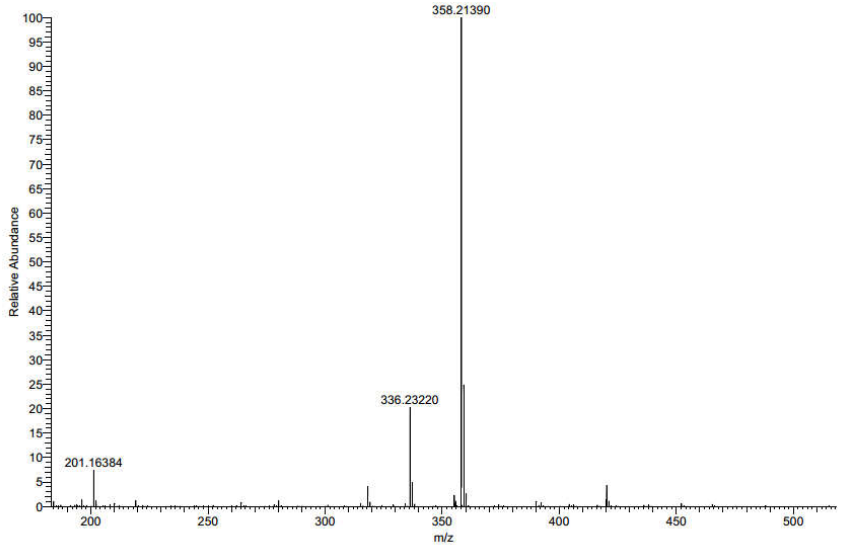


Figure 4A.5. HRMS of compound **29a**

4A.4.1. Optimization Studies

Detailed optimization studies were carried out for the annulation reaction with the Michael adduct **28a**. The catalytic activity of different Lewis acids such as $Sc(OTf)_3$, $Yb(OTf)_3$, $Cu(OTf)_2$, $La(OTf)_3$, $Hf(OTf)_3$, $Zn(OTf)_2$, $BF_3.(OEt)_2$, $AlCl_3$, $In(OTf)_3$, were studied, out of which the best transformation was obtained with 10 mol % $Sc(OTf)_3$ (Table 4A.1, entry 14). Among the several solvents screened, CH_3CN was found to be the ideal medium for the reaction. From the detailed optimization studies, 1 equivalent of Michael adduct **28a** in presence of 10 mol % of $Sc(OTf)_3$ in CH_3CN at 80 ^oC was found to be the best condition for the reaction. The results are summarized in table 4A.1.

Table 4A.1. Optimization studies for a suitable catalyst system for [5.7] fused core **29a**.

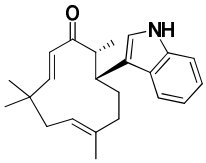
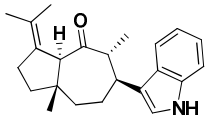
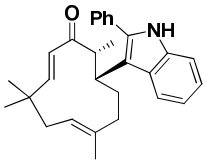
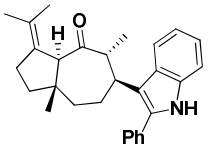
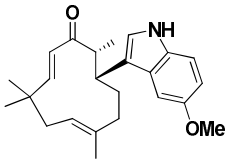
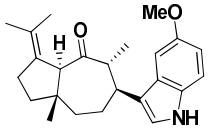
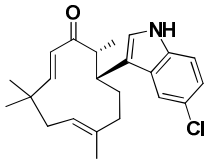
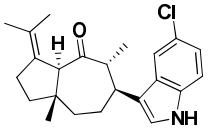
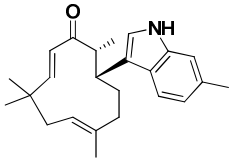
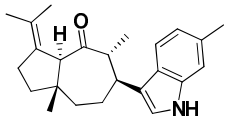
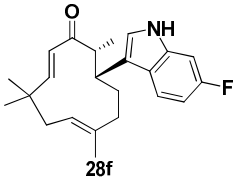
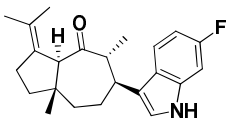
Entry [a]	Lewis acid	Solvent	Temp. (^oC)	Yield (%)[d]
1	$Sc(OTf)_3$	CH_3CN	80 ^oC	33
2	$Yb(OTf)_3$	CH_3CN	80 ^oC	NR
3	$Cu(OTf)_2$	CH_3CN	80 ^oC	7
4	$La(OTf)_3$	CH_3CN	80 ^oC	NR
5	$Hf(OTf)_4$	CH_3CN	80 ^oC	NR
6	$Zn(OTf)_2$	CH_3CN	80 ^oC	NR
7	BF_3-OEt_2	CH_3CN	80 ^oC	NR
8	$AlCl_3$	CH_3CN	80 ^oC	NR
9	$In(OTf)_3$	CH_3CN	80 ^oC	7
10	$Sc(OTf)_3$	DCE	80 ^oC	NR
11	$Sc(OTf)_3$	THF	60 ^oC	NR
12	$Sc(OTf)_3$	DMF	80 ^oC	NR
13	$Sc(OTf)_3$	Toluene	80 ^oC	NR
14 [b]	**$Sc(OTf)_3$**	**CH_3CN**	**80 ^oC**	**53**
15 [c]	$Sc(OTf)_3$	CH_3CN	80 ^oC	27

[a]Reaction conditions: Michael adduct (1 equiv.), Lewis acid (5 mol %), Solvent 2 mL, 80 ^oC, 12 h, [b]10 mol % $Sc(OTf)_3$ was used, [c]20 mol % $Sc(OTf)_3$ was used, [d]Isolated yield.

The generality of the reaction was studied under the optimized conditions and the results are depicted in table 4A.2. The annulation with the Michael adduct **28b** of 2-phenylindole furnished the annulation product **29b** in only 26% yield, which might be due to the steric

influence of the phenyl ring in indole. The ring closing reaction of other Michael adducts with indole containing both electron-withdrawing and releasing substituents also afforded the products in similar yields. The final confirmation of the structure and stereochemistry of indole substituted isodaucane skeleton was obtained from single crystal X-ray analysis of compound **29f** (Figure 4A.5).

Table 4A.2. Generality of the reaction

Entry	Michael adduct	Product	Yield (%)
1	 **28a**	 **29a**	53
2	 **28b**	 **29b**	26
3	 **28c**	 **29c**	44
4	 **28d**	 **29d**	42
5	 **28e**	 **29e**	33
6	 **28f**	 **29f**	45

Reaction conditions: Michael adduct **28** (1 equiv.), $Sc(OTf)_3$ (10 mol%), CH_3CN (2 mL), 80 °C, 12 h

4A.4.2. Spectroscopic Evidence for Assigned Stereochemistry

To ascertain the structure and stereochemistry of the 5-7 fused product, we have carried out various 2D NMR experiments of one of the synthesized derivative **29f**.

The ^{1}H NMR spectrum showed the presence of NH proton, resonated at δ 8.12 ppm, the aromatic protons were resonated between δ 7.29-6.92 ppm range and the proton at the bridge near the carbonyl group appeared as singlet at δ 3.88 ppm. The proton attached to the carbon bearing an indolyl group appeared as multiplet and resonated between δ 3.04-2.99 ppm. The proton at the C2 carbon appeared as a multiplet in between δ 2.74-2.71 ppm. The CH_2 protons resonated in the region δ 2.43-1.52 ppm. The ^{1}H NMR spectrum of compound **29f** is shown in the figure 4A.6.

The ^{13}C NMR showed the characteristic carbonyl peak at δ 213.9 ppm. The carbon (C7) resonated at δ 59.6 ppm. The carbon (C2) and carbon (C3) resonated at δ 55.2 ppm and 40.9 ppm respectively. ^{13}C NMR spectrum of compound **29f** is shown in the figure 4A.7.

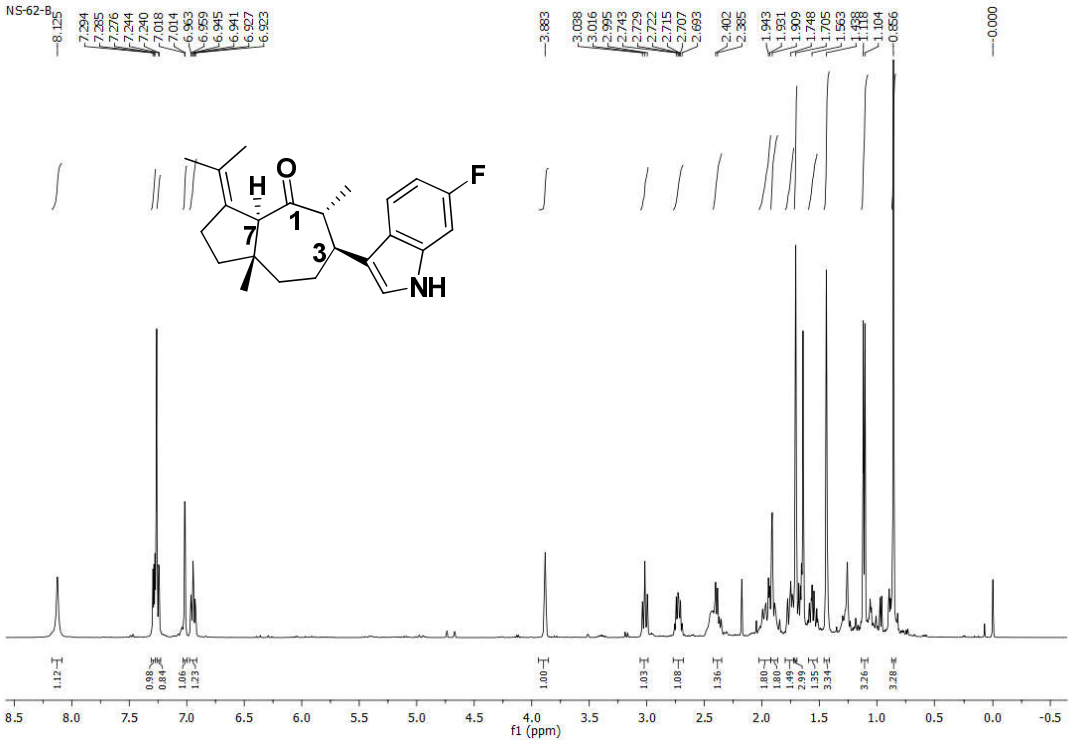


Figure 4A.6. ^{1}H NMR of compound **29f**

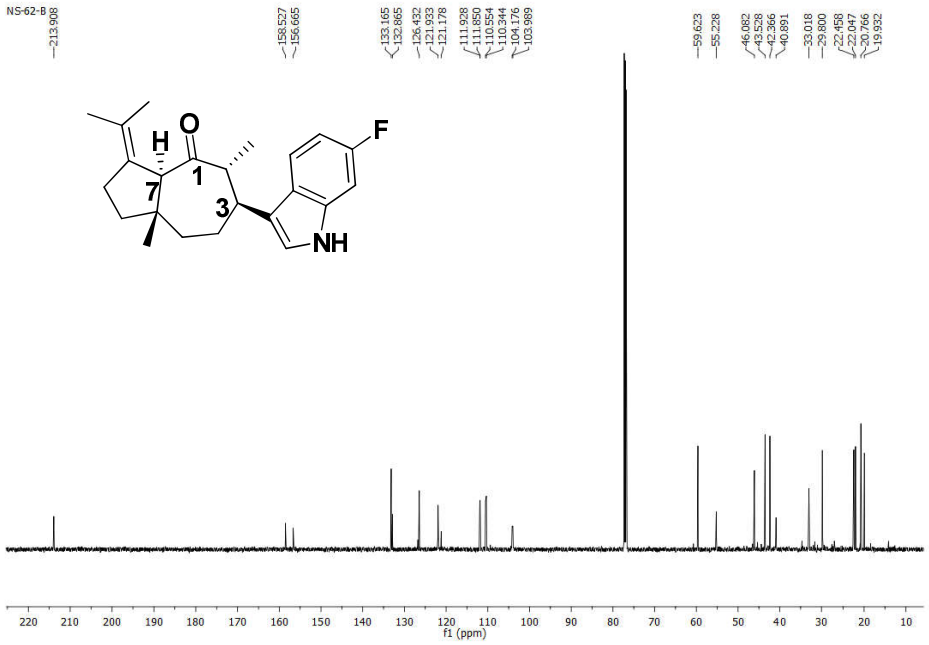


Figure 4A.7. ^{1}H NMR of compound **29f**

We are able to identify the –NH proton of the indole moiety and the quaternary carbons from the HMQC spectral analysis (Figure 4A.11). The ^{1}H-^{1}H COSY of compound is given in figure 4A.8. Finally, the stereochemistry of the product was unambiguously confirmed by single crystal analysis of compound **29f** (Figure 4A.14)

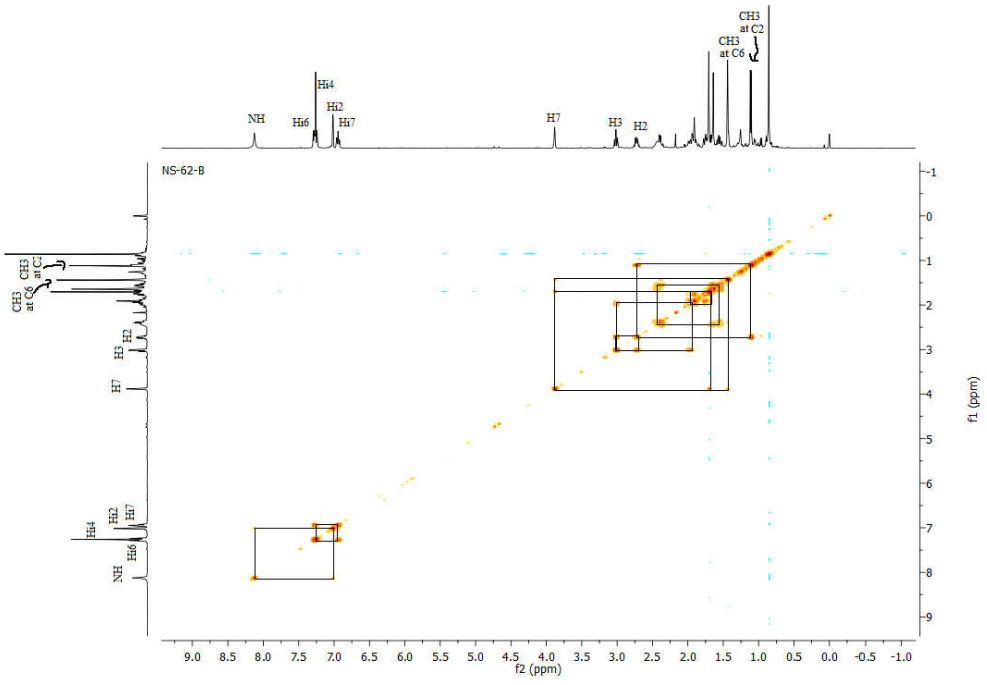


Figure 4A.8. ^{1}H-^{1}H COSY NMR of compound **29f**

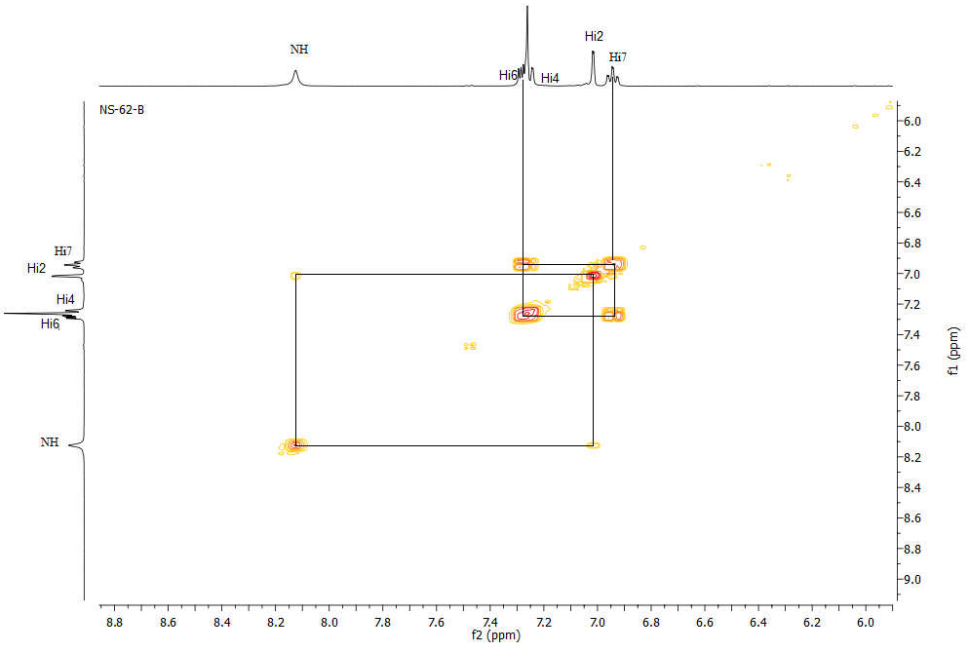


Figure 4A.9. ^{1}H-^{1}H COSY NMR of **29f** showing correlation between (i) NH and Hi2 (ii) Hi6 and Hi7

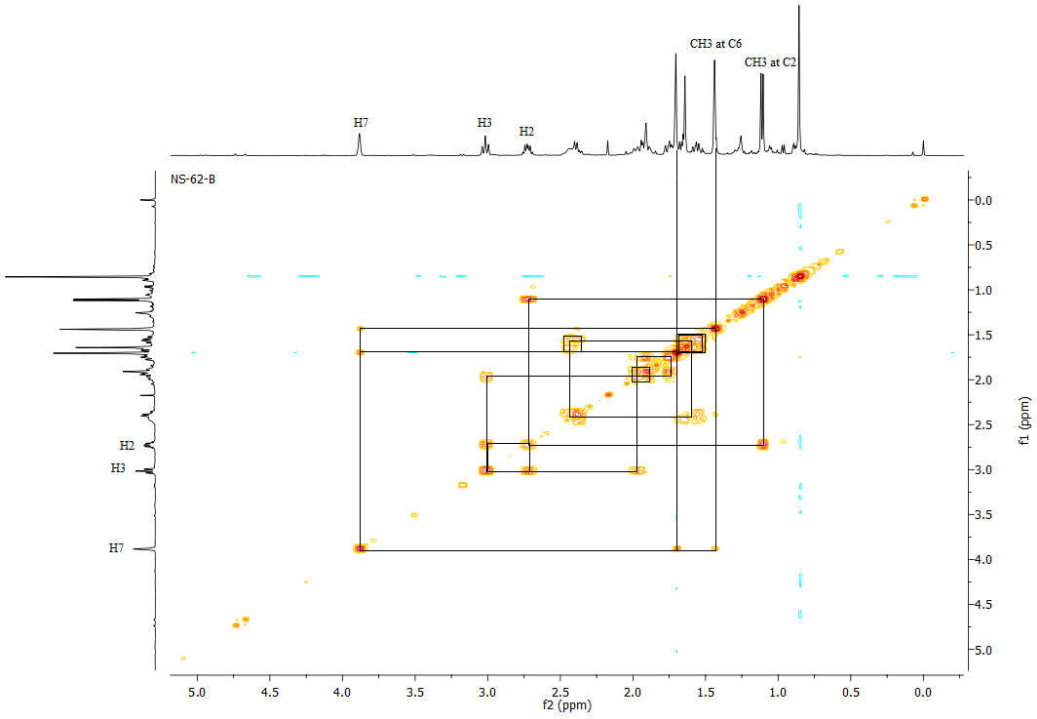


Figure 4A.10. ^{1}H-^{1}H COSY NMR of **29f** showing correlation between (i) H7 and CH_3 at C6 (ii) H2 and CH_3 at C2

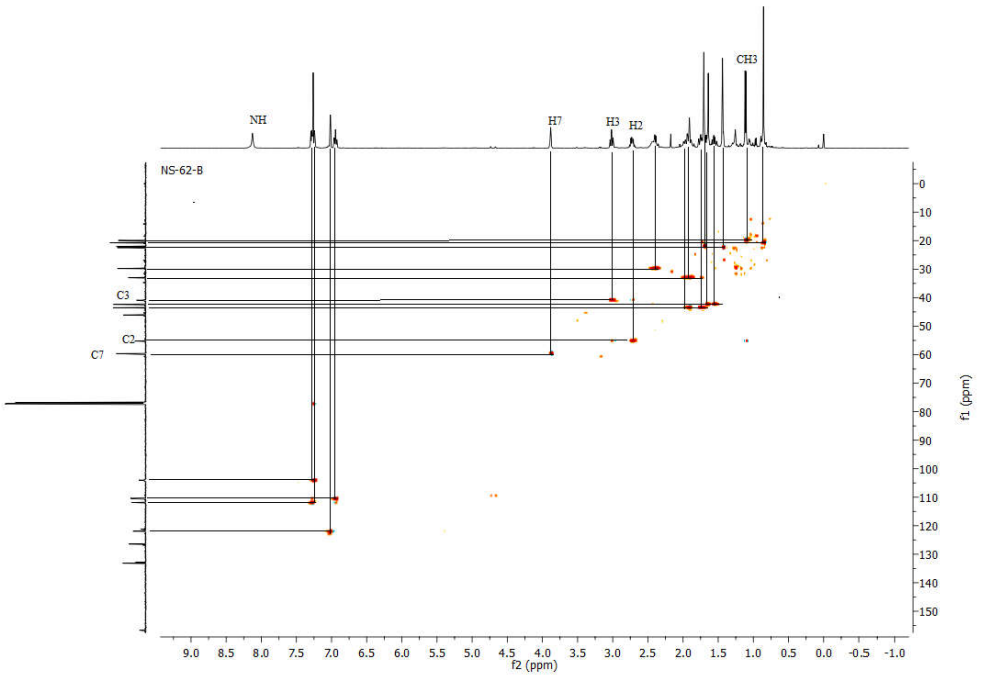


Figure 4A.11. HMQC Spectrum of **29f**

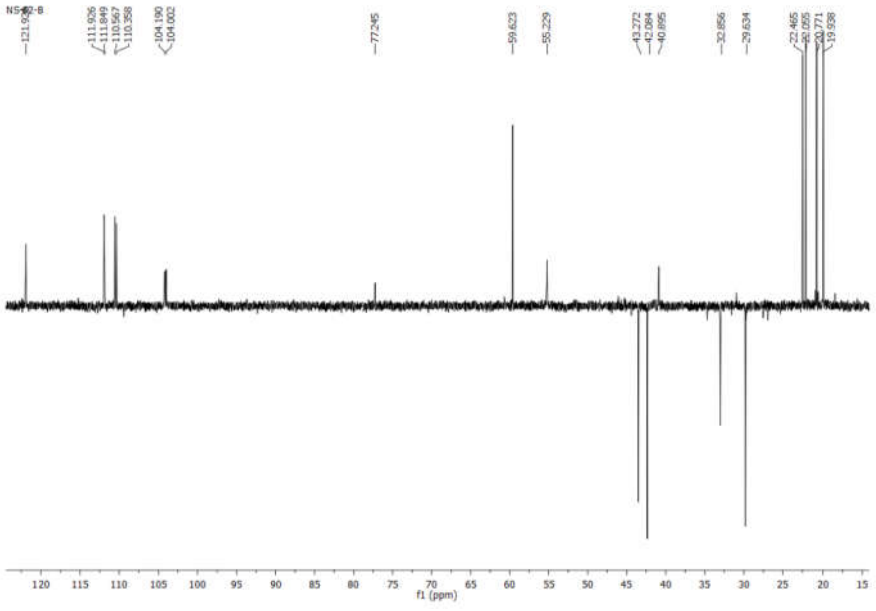


Figure 4A.12. DEPT-135 of compound **29f**

The DEPT-135 NMR spectrum (Figure 4A.12) gave signals for four –CH_2-groups, four CH_3 groups in the aliphatic region.

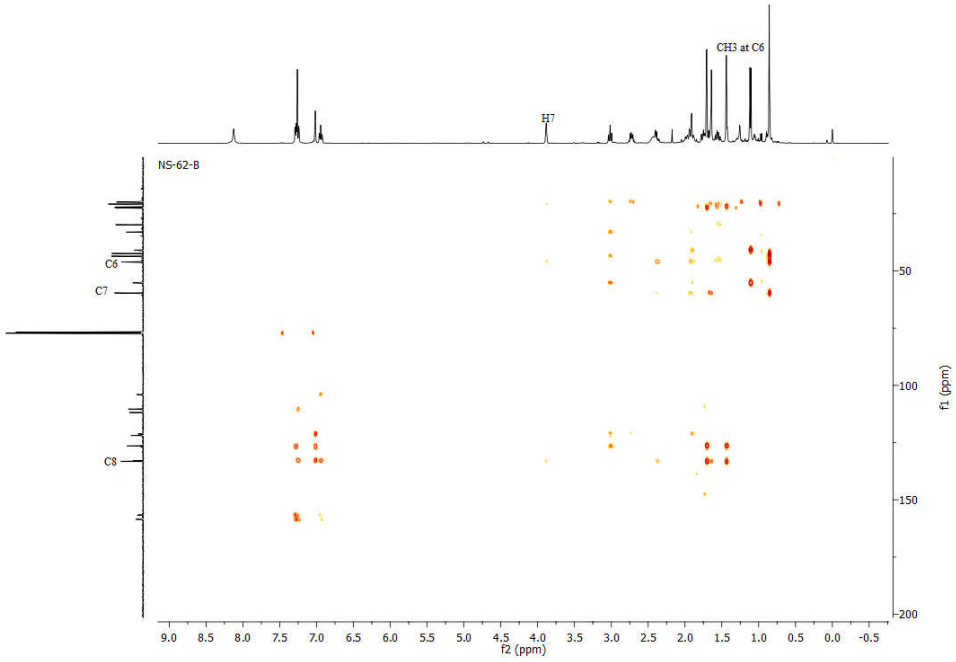


Figure 4A.13. HMBC spectrum of compound **29f**

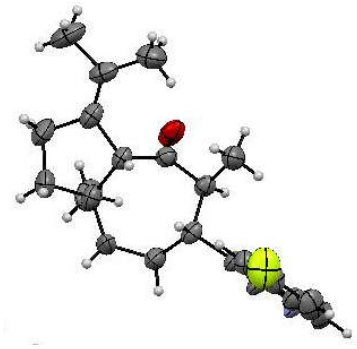
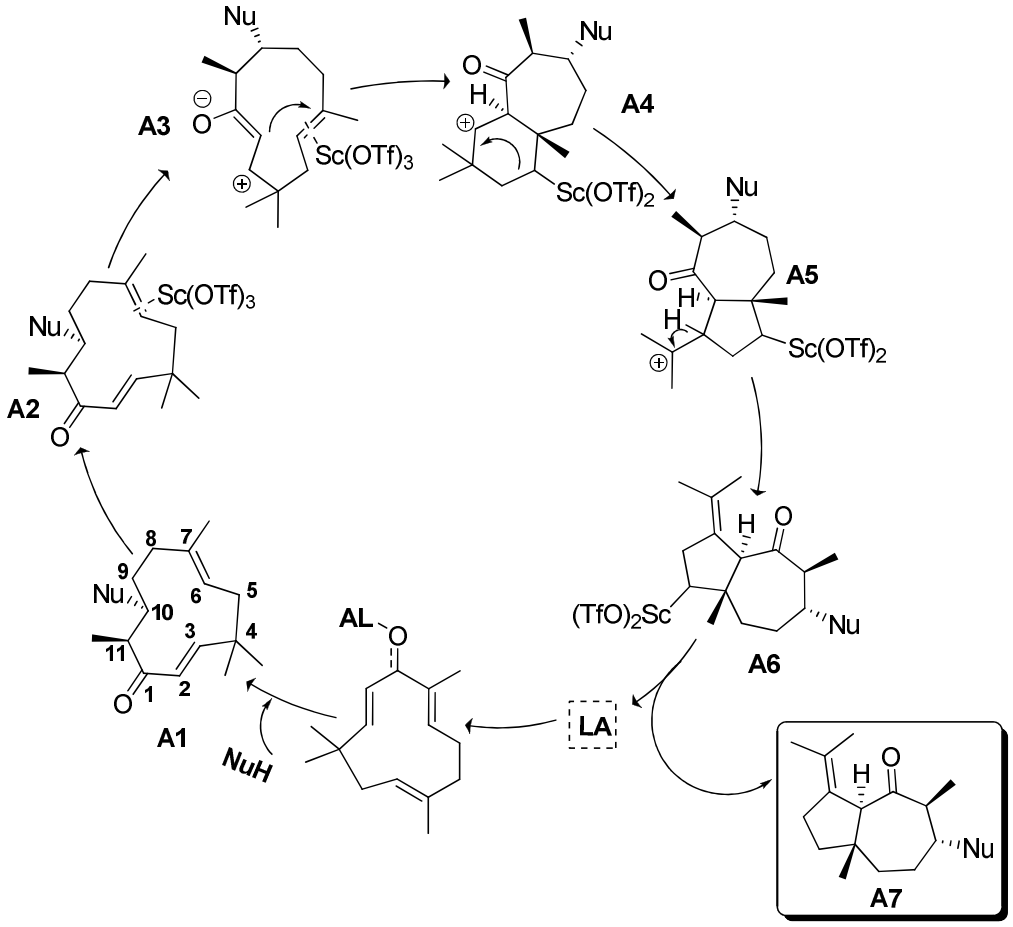


Figure 4A.14. ORTEP diagram of compound **29f** (CCDC number-1573651)

4A.5. Proposed Mechanism

Based on the literature reports, we propose a plausible mechanism for the annulations reaction of zerumbone derivatives (Scheme 4A.12). The mechanism for the formation of [5.7] fused product involve the initial coordination of $Sc(OTf)_3$ with the unactivated double bond, which trigger the subsequent cyclization to provide a [6.7] bicyclic intermediate with a cationic centre (intermediate A4). A close look at the structure overlay of zerumbone and Michael adduct **A1** shows that the C-2 and C-7 in **A1** are closer than that in zerumbone thereby facilitating the initial ring-closing through these centres (Figure 4A.2).The subsequent migration of the adjacent bond to this cationic centre in the intermediate furnishes the [5.7] bicyclic skeleton with a more stable exocyclic tertiary carbocation (intermediate **A5**). Finally, the elimination of a proton

occurs followed by the decomplexation of scandium triflate providing the [5.7] fused bicyclic compound **A7** (product **29**).



Scheme 4A.12

4A.6. Conclusion

In conclusion, we have developed Lewis acid catalyzed annulation reactions of zerumbone-indole derivatives to access structurally diverse polycyclic compounds. The core structures of synthesized molecules i.e. [5.7] fused rings are found in many biologically active natural products. The highlight of the novel methodology is the utilisation of renewable resources to generate complex fused skeletons. It is to be noted that *Z. zerumbet*, the tropical ginger can be cultivated on a large scale yielding the mature rhizome in seven month period. Under Lewis acid catalysis, we could easily synthesize indole substituted isodaucane moiety from zerumbone-indole adduct.

4A.7. Experimental Section

General information about the experiment is given in section 2A.8 of chapter **2A**.

4A.7.1. Procedure for the synthesis of Michael adduct

Procedure for the synthesis of Michael adduct of zerumbone is given in section 3.12 of chapter 3.

4A.7.2. Procedure for the synthesis of [5.7] fused ring system

The reaction was commenced with one equivalent of Michael adduct in the presence of 10 mol % of $Sc(OTf)_3$ in 2 mL CH_3CN at 80 ^oC for 12 hours. After the completion of the reaction as monitored by TLC, the reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (100-200 mesh) and hexane: ethylacetate as the eluent to afford the product.

4A.7.3. Spectral Details of compounds

(2E,6E)-10-(1H-indol-3-yl)-4,4,7,11-tetramethylcycloundeca-2,6-dienone (28a)

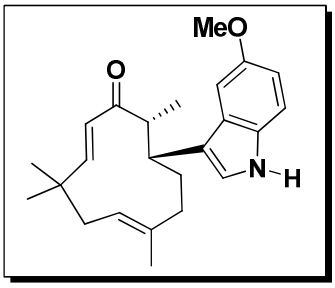
Spectral details of compound **28a** are described in section 3.12.3 of chapter 3.

(2E, 6E)-4,4,7,11-tetramethyl-10-(2-phenyl-1H-indol-3-yl)cycloundeca-2,6-dienone (28b)

Spectral details of compound **28b** are described in section 3.12.3 of chapter 3.

(2E,6E)-10-(5-methoxy-1H-indol-3-yl)-4,4,7,11-tetramethylcycloundeca-2,6-dienone (28c)

Following the general experimental procedure, zerumbone **22** (30 mg, 0.137 mmol), 5-methoxy indole **27c** (20.16 mg, 0.137 mmol), $Sc(OTf)_3$ (3.4 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **28a** as colourless viscous liquid (32.6 mg, 65%).



R_f: 0.20 (ethylacetate/hexane = 1:3).

IR (neat) υ_{max}: 3355.2, 3042.4, 2936.1, 2874.0, 1684.6, 1625.5, 1585.3, 1485.3, 1485.2, 1453.2, 1382.2, 1365.9, 1298.9, 1279.9, 1213.6, 1171.8, 1082.6, 1048.1, 1027.3, 998.4, 976.8, 907.9, 875.0, 840.1, 820.6, 795.2, 783.4, 764.0, 753.9, 729.1, 705.5, 696.3, 686.3 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (brs, 1H), 7.28-7.24 (m, 1H), 7.10-7.09 (m, 1H), 7.03-7.02 (m, 1H), 6.89-6.87 (m, 1H), 6.51 (d, J = 16 Hz, 1H), 6.31 (d, J = 16 Hz, 1H), 5.13 (dd, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 3.90 (s, 3H), 3.68-3.66 (m, 1H), 2.90-2.88 (m, 1H), 2.35-2.30 (m, 1H), 2.04-2.00 (m, 1H), 2.35-2.30 (m, 1H), 2.04-2.00 (m, 1H), 1.93-1.92 (m, 1H), 1.80-1.76 (m, 1H), 1.69-1.58 (m, 1H), 1.50 (s, 3H), 1.31 (s, 3H), 1.23 (s, 3H), 1.10-1.03 (m, 1H), 0.90 (d, J = 6.5 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.7, 154.0, 151.3, 138.1, 131.9, 129.0, 128.4, 127.9, 122.2, 118.1, 112.2, 112.1, 100.3, 55.6, 51.7, 41.8, 40.0, 38.4, 37.4, 29.0, 25.5, 23.0, 16.9, 7.9 ppm.

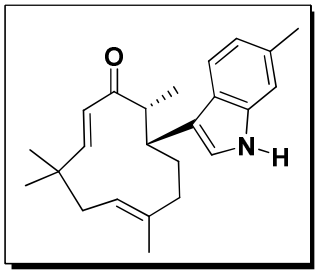
HRMS (ESI): *m/z* Calcd for $C_{24}H_{31}NNaO_2$: 388.22525, Found: 388.22606 $[M+Na]^+$.

(2E,6E)-10-(5-chloro-1H-indol-3-yl)-4,4,7,11-tetramethylcycloundeca-2,6-dienone (28d)

Spectral details of compound **28d** are described in section 3.12.3 of chapter 3.

(2E,6E)-4,4,7,11-tetramethyl-10-(6-methyl-1H-indol-3-yl)cycloundeca-2,6-dienone (28e)

Following the general experimental procedure, zerumbone **22** (30 mg, 0.137 mmol), 6-methyl indole **27e** (20.16 mg, 0.137 mmol), $Sc(OTf)_3$ (3.4 mg, 0.00685 mmol), in 2 mL acetonitrile at room temperature for 12 h gave the product **28e** as a white solid (45.62 mg, 95%).



R_f: 0.58 (ethylacetate/hexane = 1:3).

Mp: 190-193 ^oC.

IR (neat) υ_{max}: 3353, 2936, 2870, 1684, 1625, 1547, 1452, 1382, 1365, 1339, 1301, 1265, 1229, 1177, 1154, 1083, 1047, 998, 792, 680, 593, 517 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (brs, 1H), 7.54 (d, J = 8 Hz, 1H), 7.19 (s, 1H), 7.03-7.01 (m, 1H), 6.98 (d, J = 2 Hz, 1H), 6.49 (d, J = 16 Hz, 1H), 6.29 (d, J = 16.5 Hz, 1H), 5.10 (dd, J_1 = 11.5, J_2 = 4 Hz, 1H), 3.70-3.68 (m, 1H), 2.95-2.90 (m,1H), 2.49 (s, 3H), 2.34-2.29 (m, 1H), 2.04-2.00 (m, 1H), 1.92-1.89 (m, 1H), 1.83-1.77 (m, 1H), 1.63-1.58 (m, 1H), 1.50 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H), 1.08-1.03 (m, 1H), 0.987 (d, J = 7 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 203.6, 151.2, 138.0, 137.2, 132.0, 128.4, 125.3, 122.1, 121.3, 120.8, 118.4, 118.0, 111.4, 51.8, 41.7, 40.0, 38.3, 37.5, 29.1, 25.4, 21.7, 16.9, 7.9 ppm.

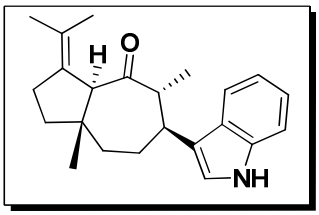
HRMS (ESI): *m/z* Calcd for $C_{24}H_{31}NNaO$: 372.23033, Found: 372.23159 $[M+Na]^+$.

(2E,6E)-10-(5-fluoro-1H-indol-3-yl)-4,4,7,11-tetramethylcycloundeca-2,6dienone (28f)

Spectral details of compound **28f** are described in section 3.11.3 of chapter 3.

(6-(1H-indol-3-yl)-5,8a-dimethyl-3-(propan-2-ylidene)octahydroazulen-4(5H)-one (29a)

Following the general procedure, Michael adduct **24a** (30 mg, 1 equiv.) and 10 mol % of $Sc(OTf)_3$ (4.4 mg) were taken in Schlenk tube. 2 mL acetonitrile was added as solvent under argon atmosphere and stirred for 12 h at 80 ^oC gave the cyclized product **29a** as colourless liquid in 53% yield (16 mg).



R_f: 0.43 (ethylacetate/hexane = 2:3).

IR (neat) υ_{max}: 3717, 2921, 2309, 1744, 1593, 1514, 1267, 751 cm^{-1}.

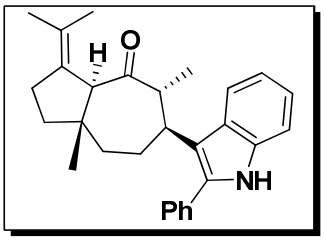
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.08 (brs, 1H), 7.63 (d, *J* = 8 Hz, 1H), 7.39 (d, *J* = 8 Hz, 1H), 7.13-7.10 (m, 1H), 7.07 (d, *J* = 2 Hz, 1H), 7.05-7.02 (m, 1H), 3.96 (s, 1H), 3.19 (t, *J* = 11 Hz, 1H), 2.65-2.61 (m, 1H), 2.36-2.34 (m, 2H), 2.06-2.04 (m, 1H), 1.85-1.82 (m, 3H), 1.63-1.61 (m, 1H), 1.56-1.52 (m, 1H), 1.37 (d, *J* = 2 Hz, 3H), 1.27 (s, 3H), 1.01 (d, *J* = 7 Hz, 3H), 0.79 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 213.1, 135.4, 132.2, 125.3, 121.0, 119.1, 118.2, 118.1, 110.3, 58.6, 54.2, 52.4, 45.1, 42.6, 41.4, 40.0, 32.1, 28.8, 21.4, 21.0, 19.8, 19.0 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{29}NNaO$: 358.21468, Found: 358.21390 $[M+Na]^+$.

5,8a-dimethyl-6-(2-phenyl-1H-indol-3-yl)-3-(propan-2-ylidene)octahydroazulen-4(5H)-one (29b)

Following the general procedure, Michael adduct **28b** (30 mg, 1equiv.) and 10 mol % of $Sc(OTf)_3$ (4.4 mg) were taken in Schlenk tube. 2 mL acetonitrile was added as solvent under argon atmosphere and stirred for 12 h at 80 ^oC gave the cyclized product **29b** as colourless viscous liquid in 26% (7.8 mg).



R_f: 0.18 (ethylacetate/hexane = 3:7).

IR (neat) υ_{max}: 3425, 2372, 2096, 1641, 1423, 1374, 1270, 1039, 929, 752, 608, 558 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 9.43 (brs, 1H), 7.71-7.69 (m, 1H), 7.52-7.49 (m, 2H), 7.44-7.40 (m, 3H), 7.22-7.21 (m, 1H), 7.15-7.12 (m, 1H), 6.99-6.97 (m, 1H), 3.82-3.81 (m, 1H), 3.23-3.16 (m, 1H), 2.58-2.53 (m, 1H), 2.39-2.32 (m, 2H), 1.84-1.82 (m, 2H), 1.76 (s, 3H), 1.62-1.58 (m, 1H), 1.48- 1.46 (m, 1H), 1.27 (s, 3H), 1.15-1.13 (m, 2H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.58 (s, 3H) ppm.

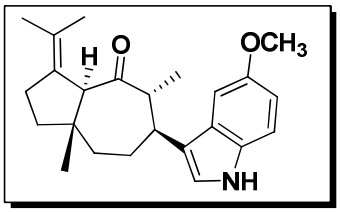
^{13}C NMR (125 MHz, CD_3CN): δ 210.7, 137.8, 137.7, 137.3, 134.0, 129.8, 129.8, 129.2, 128.1, 122.9, 120.4, 119.8, 118.3, 112.4, 55.3, 53.9, 46.7, 41.1, 37.9, 37.6, 37.3, 34.6, 31.8, 31.6, 31.5, 30.3, 28.7, 24.4, 23.7, 8.6 ppm.

HRMS (ESI): *m/z* Calcd for $C_{29}H_{34}NO$: 412.26404, Found: 412.26275$[M+Na]^+$.

6-(5-methoxy-1H-indol-3-yl)-5,8a-dimethyl-3-(propan-2-ylidene)octahydroazulen-4(5H)-one (29c)

Following the general procedure, Michael adduct **28** (30 mg, 1 equiv.) and 10 mol % of

$Sc(OTf)_3$ (4.4 mg) were taken in Schlenk tube. 2 mL acetonitrile was added as solvent under argon atmosphere and stirred for 12 h at 80 ^oC gave the cyclized product **29c** as colourless liquid in 44% (13.2 mg).



R_f: 0.11 (ethylacetate/hexane = 3:7).

IR (neat) υ_{max}: 3424, 2088, 1638, 1457, 1418, 1316, 1267, 1122, 1041, 857, 752, 556 cm^{-1}.

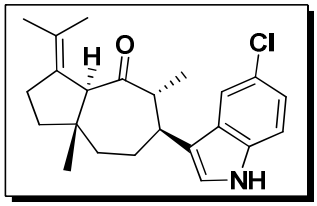
^{1}H NMR (500 MHz, $CDCl_3$): δ7.91 (brs, 1H), 7.29-7.26 (m, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.88-6.86 (m, 1H), 3.91-3.90 (m, 4H), 3.06-3.02 (m, 1H), 2.78-2.73 (m, 1H), 2.44-2.36 (m, 3H), 1.99-1.90 (m, 3H), 1.71 (s, 3H), 1.68-1.64 (m, 1H), 1.55-1.52 (m, 1H), 1.44 (s, 3H), 1.13 (d, *J* = 7 Hz, 3H), 0.86 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 213.7, 153.8, 133.2, 131.6, 126.3, 120.8, 111.9, 111.8, 101.5, 100.0, 59.5, 56.0, 55.3, 46.0, 43.6, 42.4, 40.9, 33.1, 29.8, 29.7, 22.4, 22.0, 20.8, 19.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{31}NNaO_2$: 388.22525, Found: 388.22437 $[M+Na]^+$.

6-(5-chloro-1H-indol-3-yl)-5,8a-dimethyl-3-(propan-2-ylidene)octahydroazulen-4(5H)-one (29d)

Following the general procedure, Michael adduct **28d** (30 mg, 1 equiv.) and 10 mol % of $Sc(OTf)_3$ (4.4 mg) were taken in Schlenk tube. 2 mL acetonitrile was added as solvent under argon atmosphere and stirred for 12 h at 80 ^oC gave the cyclized product **29d** as colourless crystalline solid in 42% yield (12.6 mg).



R_f: 0.21 (ethylacetate/hexane = 3:7).

Mp: 82-84 ^oC.

IR (neat) υ_{max}: 3365, 3025, 2964, 2926, 2872, 1731, 1463, 1369, 1336, 1302, 1238, 1146, 1005, 896, 834, 804 cm^{-1}.

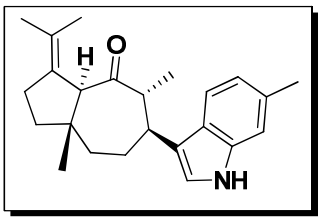
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (brs, 1H), 7.57(d, *J* = 2 Hz, 1H), 7.29-7.27 (m, 1H), 7.16-7.14 (m, 1H), 6.99 (d, *J* = 2 Hz, 1H), 3.88 (s, 1H), 3.06-3.01 (m, 1H), 2.74-2.70 (m, 1H), 2.43-2.35 (m, 2H), 1.99-1.87 (m, 3H), 1.81-1.75 (m, 1H), 1.71 (s, 3H), 1.68-1.64 (m, 1H), 1.57-1.52 (m, 1H), 1.43 (s, 3H), 1.10 (d, *J* = 7 Hz, 3H), 0.86 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 213.7, 133.1, 126.4, 125.1, 122.4, 121.5, 120.9, 118.6, 112.3, 59.6, 55.2, 46.1, 43.5, 42.4, 33.1, 29.8, 22.4, 22.0, 20.8, 19.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{28}ClNO$: 369.18594, Found: 369.18582 $[M+Na]^+$.

5,8a-dimethyl-6-(6-methyl-1H-indol-3-yl)-3-(propan-2-ylidene)octahydroazulen-4(5H)-one (29e)

Following the general procedure, Michael adduct **28e** (30 mg, 1 equiv.) and 10 mol % of $Sc(OTf)_3$ (4.4 mg) were taken in Schlenk tube. 2 mL acetonitrile was added as solvent under argon atmosphere and stirred for 12 h at 80 ^oC gave the cyclized product **29e** as colourless viscous liquid in 33% yield (9.9 mg).



R_f: 0.67 (ethylacetate/hexane = 3:7).

IR (neat) υ_{max}: 3384.2, 3054.2, 2960.4, 2924.1, 2870.0, 1729.3, 1461.3, 1368.0, 1333.7, 1306.3, 1236.4, 1148.4, 1007.6, 893.7, 837.6, 801.5 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (brs, 1H), 7.48 (d, *J* = 8 Hz, 1H), 7.14 (s, 1H), 6.93 (d, *J* = 8 Hz, 1H), 6.89 (d, *J* = 2 Hz, 1H), 3.87 (s, 1H), 3.06-3.01 (m, 1H), 2.77-2.74 (m, 1H), 2.46 (s, 3H), 2.37-2.35 (m, 2H), 2.02-2.00 (m, 1H), 1.92-1.91 (m, 2H), 1.77-1.74 (m, 1H), 1.70 (s, 3H), 1.66-1.63 (m, 2H) 1.42 (s, 3H), 1.10 (d, *J* = 7 Hz, 3H), 0.85 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 214.7, 131.8, 123.9, 121.2, 119.7, 118.6, 116.2, 111.2, 57.5, 48.3, 41.5, 36.9, 29.4, 24.8, 21.8, 19.1 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{31}NNaO$: 372.23033, Found: 372.23113 $[M+Na]^+$.

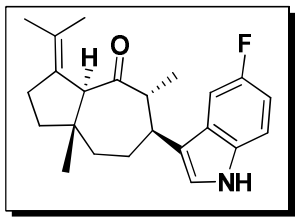
6-(5-fluoro-1H-indol-3-yl)-5,8a-dimethyl-3-(propan-2-ylidene)octahydroazulen-4(5H)-one (29f)

Following the general procedure, Michael adduct **28f** (30 mg, 1equiv.) and 10 mol % of $Sc(OTf)_3$ (4.4 mg) were taken in Schlenk tube. 2 mL acetonitrile was added as solvent under argon atmosphere and stirred for 12 h at 80 ^oC gave the cyclized product **29f** as colourless crystalline solid in 45% (13.5 mg).

R_f: 0.17 (ethylacetate/hexane = 3:7).

Mp: 195-197 ^oC.

IR (neat) υ_{max}: 3424, 2372, 2096, 1641, 1423, 1374, 1270, 1039, 929, 752, 608, 558 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (brs, 1H), 7.29-7.24 (m, 2H), 7.02-7.01 (m, 1H), 6.96-6.92 (m, 1H), 3.88 (s, 1H), 3.04-2.99 (m, 1H), 2.74-2.71 (m, 1H), 2.43-2.38 (m, 2H), 1.94-1.91 (m, 4H), 1.78-1.75 (m, 1H), 1.70 (s, 3H), 1.59-1.52 (m, 1H), 1.44 (s, 3H), 1.11 (d, *J* = 7 Hz, 3H), 0.86 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 213.9, 157.6 (d, $^1J_{C\text{-}F}$ = 232.8 Hz), 133.0 (d, $^2J_{C\text{-}F}$ = 37.5 Hz), 126.8 (d, $^3J_{C\text{-}F}$ = 9.4 Hz), 126.4, 121.9, 121.2 (d, $^4J_{C\text{-}F}$ = 4.9 Hz), 111.9 (d, $^4J_{C\text{-}F}$ = 9.8 Hz), 110.4 (d, $^2J_{C\text{-}F}$ = 26.2 Hz), 104.1 (d, $^2J_{C\text{-}F}$ = 23.4 Hz), 59.6, 55.2, 46.1, 43.5, 42.4, 40.9, 33.0, 29.8, 22.5, 22.0, 20.8, 19.9 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{28}FNNaO$: 376.20526, Found: 376.20574 $[M+Na]^+$.

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CHAPTER 4

Part B

Interrupted Nazarov Cyclization of Zerumbone in presence of Indole Leading to [6.3.0] Decane Skeleton

4B.1. Introduction

Annulation reactions or cyclization reactions of polyolefins are always an interesting area to fascinate organic chemists. The propensity of medium-sized compounds to undergo transannular cyclization has been deftly harnessed by nature to build thousands of polycyclic sesquiterpenoids from various classes of medium-sized and macrocyclic precursors. Isoprenoids, the most diverse class of natural products can be synthesized *via* the electrophilic cyclization of polyolefins or medium-sized polyolefins. Nazarov cyclization, is one among the cyclization and has long been regarded as a versatile method to construct five-membered carbocycles which are ubiquitous in nature. This chapter describes the synthesis of [6.3.0] decane system *via* Lewis acid catalyzed interrupted Nazarov cyclization of zerumbone. Representative examples of the biologically active compounds having 5-8 fused ring systems are shown in figure 4B.1.

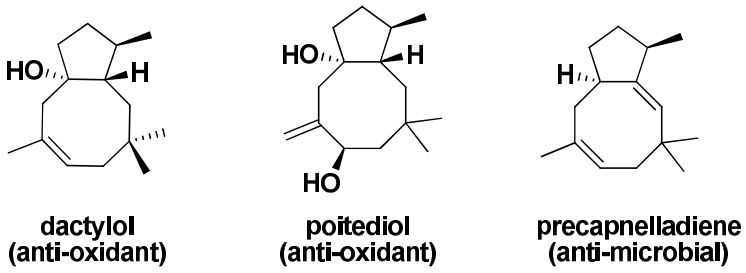
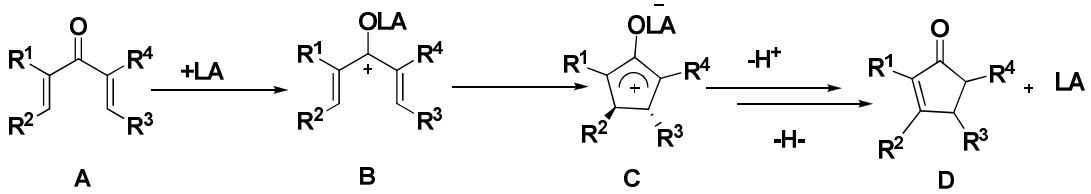


Figure 4B.1. Examples of the biologically active compounds having 5-8 fused ring systems

4B.2. Nazarov cyclization

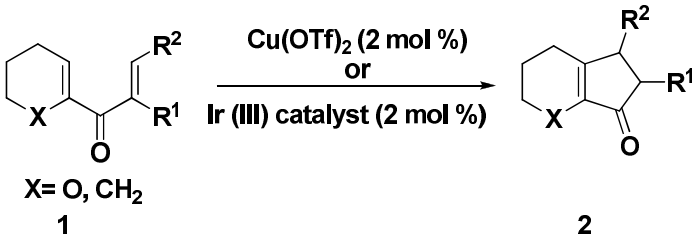
The acid-catalyzed cyclization of a doubly *α,β*-unsaturated ketone, referred to as the Nazarov reaction[1-3], is a powerful method for the construction of five-membered carbocycles.[4-6] Nazarov reaction chemistry has been developed since 1994.[7] In Nazarov reaction, upon treatment of the divinyl ketone with either a mineral or a Lewis acid results the conrotatory electrocyclic ring closure process (Scheme 4B.1).



Scheme 4B.1

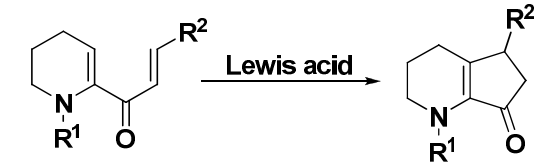
The individual steps involved in the transformation are thought to proceed as follows: a divinyl ketone (**A**) complexes to the Lewis acid to give a pentadienyl cation (**B**); cyclization gives an oxyallyl cation (**C**); elimination of a proton gives a Lewis-acid bound enolate and finally, protonation of the enolate gives a cyclopentenone product (**D**).

In 2003, Frontier and co-workers reported Lewis acid-catalyzed procedure for Nazarov cyclization of polarized divinyl ketones **1** using $Cu(OTf)_2$ or Ir(III) catalyst (Scheme 4B.2).[8, 9]



Scheme 4B.2

Later in 2006, Occhiato and co-workers reported the Nazarov cyclization of 2-(N-methoxycarbonylamino)-1, 4-pentadien-3-ones **3** (Scheme 4B.3) The reaction is an easy route for the construction of pyrindine systems.[10]



$R^1 = CO_2Me$, R^2 = alkyl, aryl

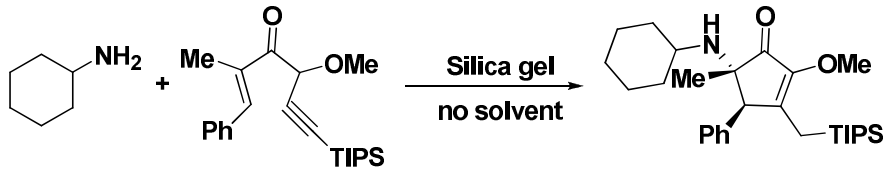
3 4

Scheme 4B.3

4B.3. Interrupted Nazarov cyclization

In Nazarov cyclization, if the oxyallyl cation intermediate is stable enough to trap the nucleophilic species, then it was termed as 'interrupted' Nazarov cyclization.

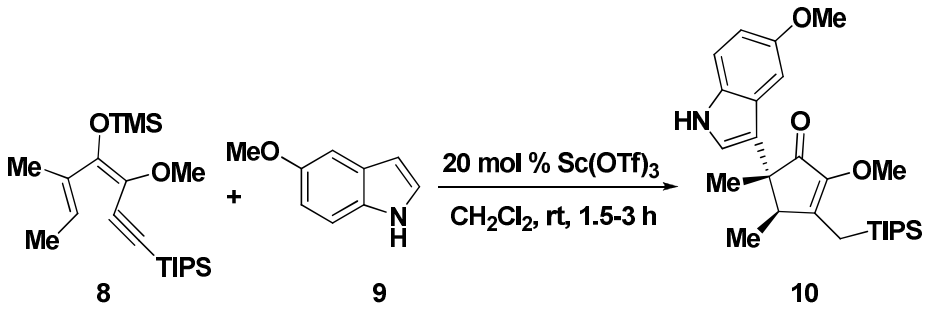
In 2005, Tius and co-workers reported an interrupted Nazarov cyclization of propargyl vinyl ketone **6** with primary or secondary amine **5**, affording aminocyclopentenone **7**. The reaction is outlined in scheme 4B.4.[11]



5 6 7

Scheme 4B.4

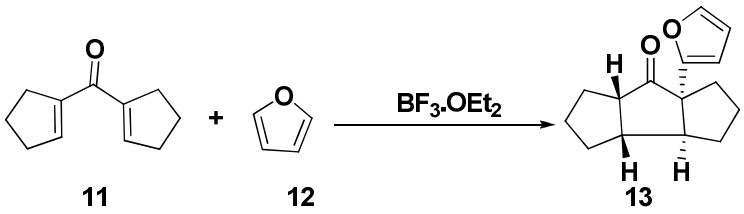
Later, the same group reported a Lewis acid catalyzed interrupted Nazarov cyclization of allenyl ether **8** with indoles **9,** affording indole substituted cyclopentenone **10** (Scheme 4B.5).[12]



8 9 10

Scheme 4B.5

α-Arylated cyclopentanones **13** was prepared by West and co-workers in 2008, by carrying out an intermolecular trapping of arene (furan **12**) with bis(cycloalkenyl) ketones **11** (Scheme 4B.6).[13]



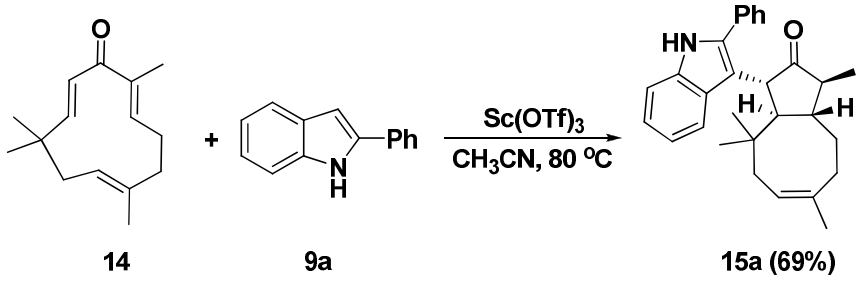
Scheme 4B.6

4B.4. Definition of the Problem

At room temperature, zerumbone reacts with indole in presence of Lewis acid, which resulted in the formation of zerumbone-indole Michael adducts. The synthesis of zerumbone-indole Michael adducts is discussed in chapter 3. Nazarov cyclization of divinyl ketone plays a pivotal role for the synthesis of cyclopentenones. Bronsted acid catalyzed reaction of zerumbone epoxide to [5.3.0] and [6.3.0] decane skeletons are known. In this work, we disclose our efforts towards developing a new and general method to synthesize [6.3.0] decane skeletons *via* the Lewis acid catalyzed interrupted Nazarov cyclization of zerumbone.

4B.5. Results and Discussion

The first reaction was carried out with 1.0 equivalent of both zerumbone **14** and indole **9a** in the presence of 5 mol % of $Sc(OTf)_3$ at 80 ^oC in CH_3CN. To our excitement, an indole substituted 5-8 fused compound 1**5a** was obtained in 69% yield from the reaction rather than the expected isodaucane skeleton (Scheme 4B.7). By looking at the structure of the product obtained, it was confirmed that the transformation that had taken place was an interrupted Nazarov cyclization.



Scheme 4B.7

The structure of **15a** was assigned on the basis of various spectral analyses. The IR spectrum of the compound showed characteristic carbonyl absorption at 1729 cm^{-1}.

The ^{1}H NMR spectrum showed the presence of NH proton, resonated at δ 9.42 ppm as broad singlet. The aromatic protons were resonated between δ 7.62-7.04 ppm ranges. The unactivated olefinic proton was resonated between δ 5.15-5.12 ppm. The proton attached to the carbon bearing an indolyl group resonated as doublet at δ 3.84 ppm having coupling constant J = 9.5 Hz and and the proton at the carbon, having a methyl group appeared as a multiplet in between δ 2.61-2.58 ppm. And all other peaks are in well agreement with the desired structure of the product. The ^{1}H NMR spectrum of compound **15a** is shown in the figure 4B.2.

The ^{13}C NMR showed the characteristic carbonyl peak at δ 222.2 ppm. The ^{13}C NMR spectrum of compound **15a** is shown in the figure 4B.3. All the peaks were in well agreement with the desired structure of the product **15a**. Final evidence for the structure was obtained from the high resolution mass spectral analysis, which displayed a peak at m/z = 434.2445.

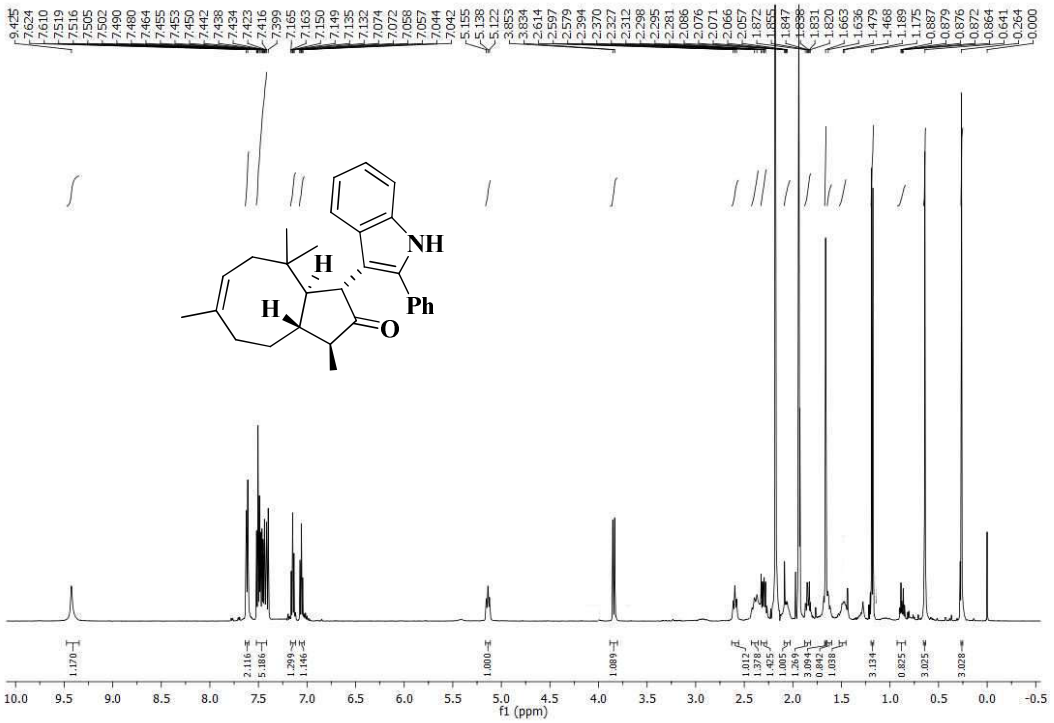


Figure 4B.2. ^{1}H NMR of compound **15a**

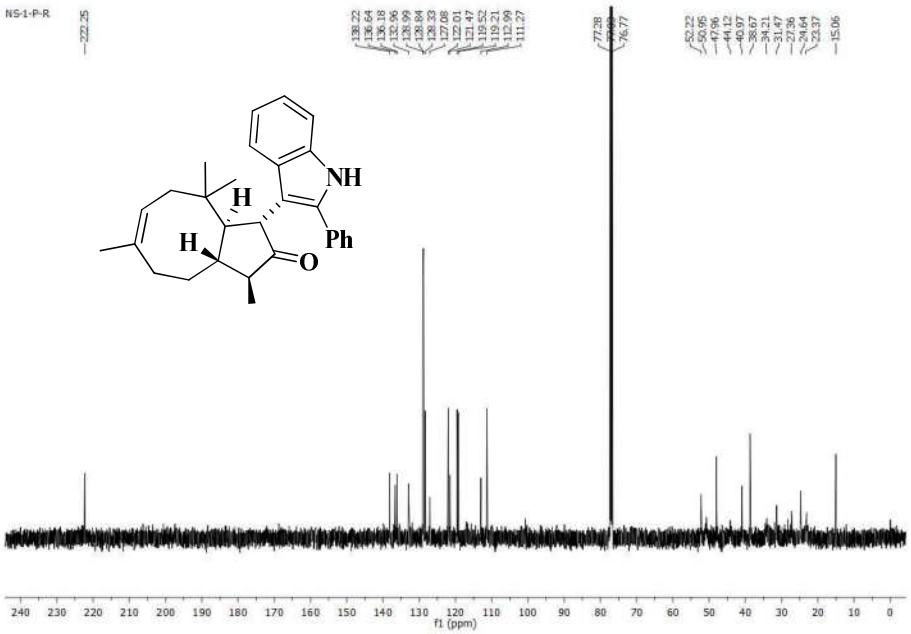


Figure 4B.3. ^{13}C NMR of compound **15a**

DEPT-135 spectrum confirmed the presence of three -CH_2 groups (Figure 4B.4). The figure 4B.5 shows the ^{1}H-^{1}H correlation by HOMO COSY. Also, the figure 4B.6 shows the ^{1}H-^{13}C correlation by HMQC.

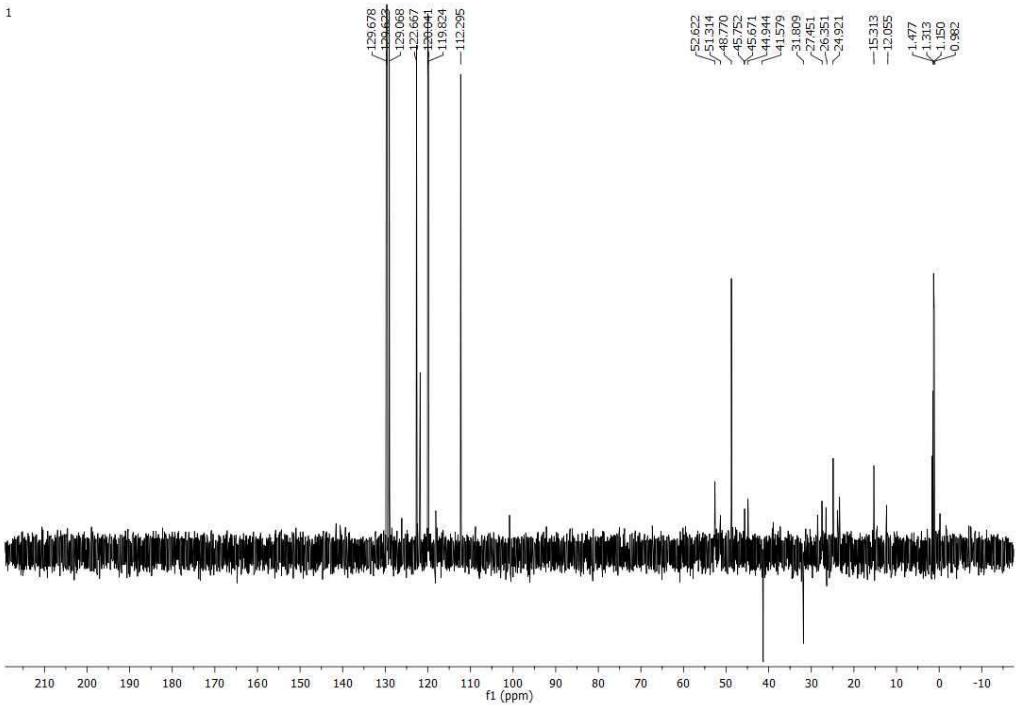


Figure 4B.4. DEPT-135 spectrum of compound **15a**

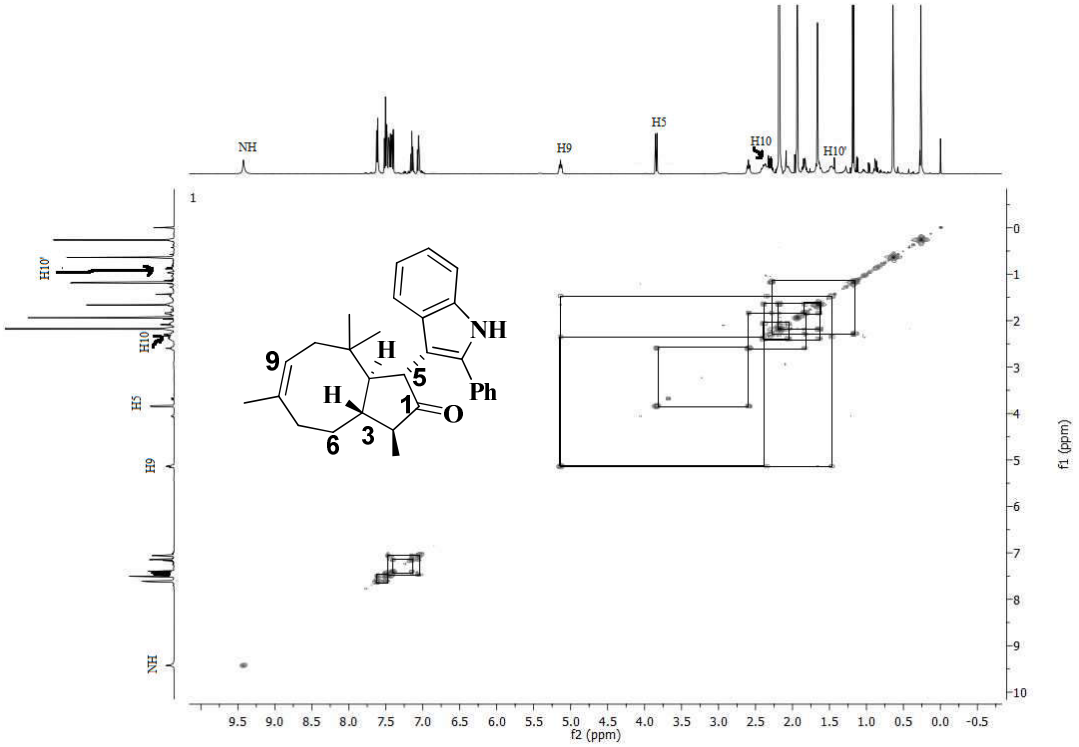


Figure 4B.5. ^{1}H-^{1}H COSY NMR of compound **15a**

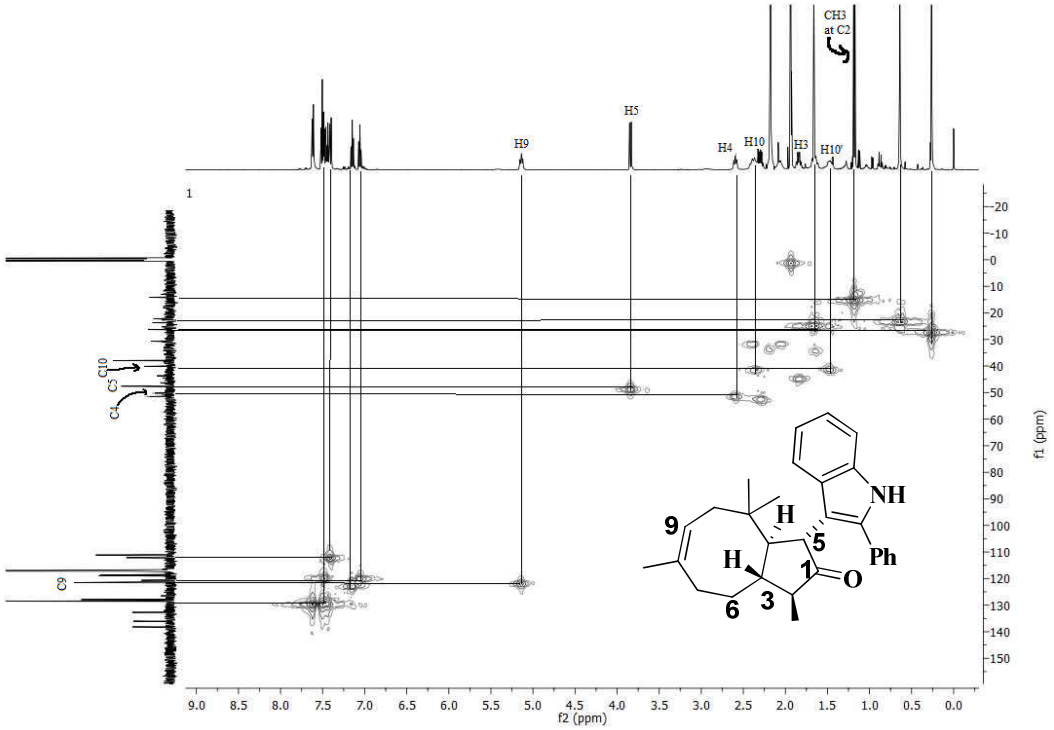


Figure 4B.6. HMQC Spectrum of **15a**

Finally, the structure of the product was unambiguously proved by single crystal X-ray analysis of compound **15j** (Figure 4B.7).

Figure 4B.7. Single crystal X-ray structure of **15j** (CCDC number – 1571495)

To find out the best catalytic condition for this transformation, we have carried out detailed optimization studies (Table 4B.1.). Various Lewis acids such as $Sc(OTf)_3$, $Yb(OTf)_3$, $Cu(OTf)_2$, $La(OTf)_3$ etc. and solvent systems such as CH_3CN, DCE, THF, DMF, Toluene etc.were screened. A combination of $Sc(OTf)_3$ in CH_3CN was found to be the best condition for the cyclization affording 1**5a** in 78% yield (Table 4B.1., entry 15).

Table 4B.1. Optimisation studies

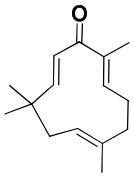
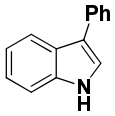
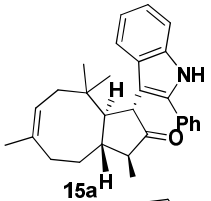
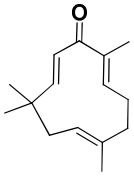
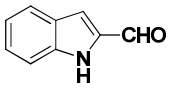
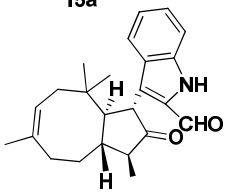
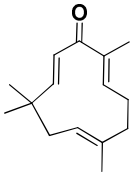
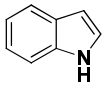
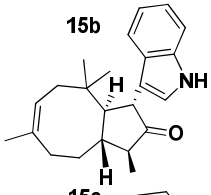
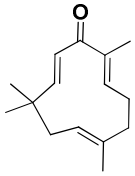
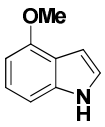
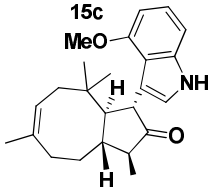
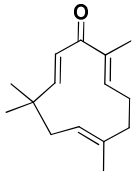
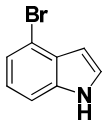
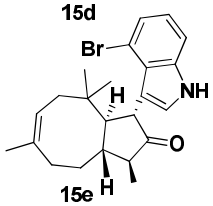
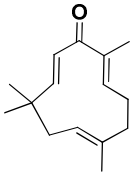
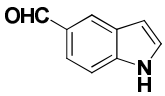
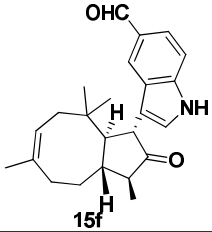
Entry [a]	Lewis acid	Solvent	Temp. (^oC)	Yield (%)[c]
1	$Sc(OTf)_3$	CH_3CN	80 ^oC	69
2	$Yb(OTf)_3$	CH_3CN	80 ^oC	NR
3	$Cu(OTf)_2$	CH_3CN	80 ^oC	42
4	$La(OTf)_3$	CH_3CN	80 ^oC	NR
5	$Hf(OTf)_4$	CH_3CN	80 ^oC	28
6	AgOTf	CH_3CN	80 ^oC	NR
7	$Zn(OTf)_2$	CH_3CN	80 ^oC	NR
8	BF_3-OEt_2	CH_3CN	80 ^oC	16
9	$AlCl_3$	CH_3CN	80 ^oC	19
10	$In(OTf)_3$	CH_3CN	80 ^oC	44
11	$Sc(OTf)_3$	DCE	80 ^oC	21
12	$Sc(OTf)_3$	THF	60 ^oC	11
13	$Sc(OTf)_3$	DMF	80 ^oC	NR
14	$Sc(OTf)_3$	Toluene	80 ^oC	12
[b]15	**$Sc(OTf)_3$**	**CH_3CN**	**80 ^oC**	**78**
16	-	CH_3CN	80 ^oC	NR

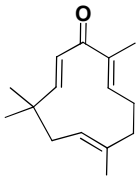
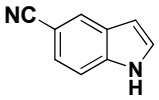
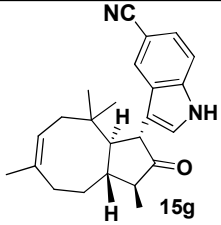
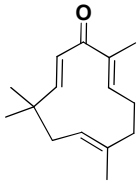
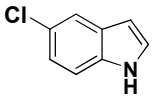
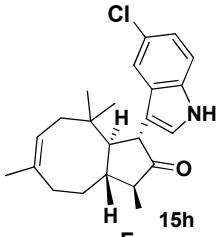
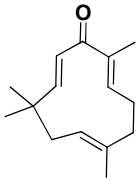
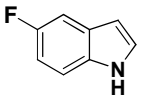
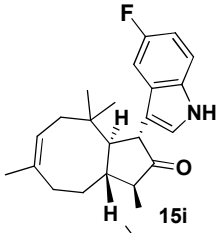
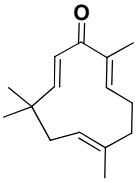
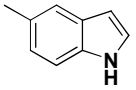
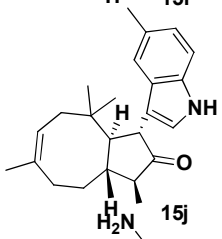
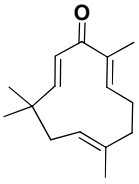
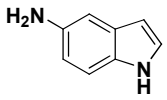
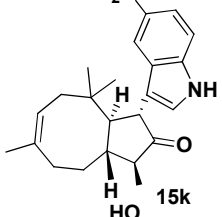
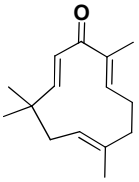
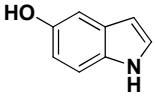
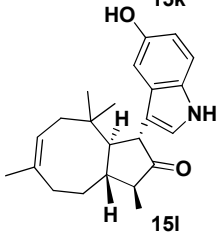
[a]Reaction condition: Zerumbone (1 equiv.), 2-Phenyl indole (1 equiv.), Lewis acid (5 mol %), [b] Zerumbone: 2-Phenyl indole = 1.2:1, [c] Isolated yield

The generality of the reaction was examined with different substituted indoles (Table 4B.2.).The reaction with 2-formyl indole failed to afford the product, which might be due to the less nucleophilicity of C-3 position (Table 4B.2, entry 2). The interrupted Nazarov cyclization worked well with unsubstituted indole furnishing the compound **15c**

in 60% yield. Next, we studied the reactivity of 4-substituted indoles and the corresponding 5-8 fused compounds were obtained in low yields. Both electron-donating and withdrawing substituents on C-5 position of indole did not influence the outcome of the reaction considerably affording the expected products in moderate to good yields (Table 4B.2., entries 1**5f**-1**5j**). Both 5-amino and 5-hydroxy indoles completely failed to furnish expected products. The structure and stereochemistry of [5.8] fused skeleton was confirmed from single crystal X-ray analysis of compound **15j**.[9]

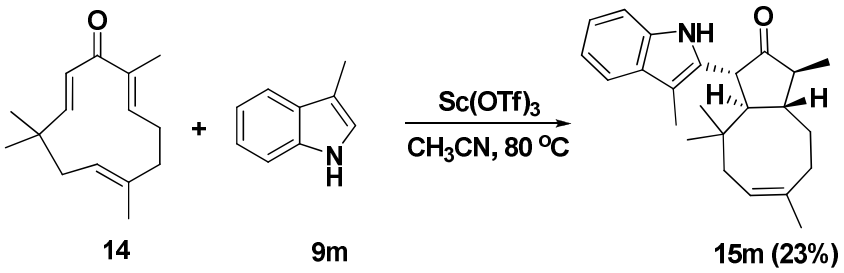
Table 4B.2. Generality of interrupted Nazarov cyclization

Entry	Zerumbone (14)	Indole (9)	Product (15)	Yield (%)[b]
1		 9a	 15a	78
2		 9b	 15b	NR
3		 9c	 15c	60
4		 9d	 15d	22
5		 9e	 15e	22
6		 9f	 15f	17

Entry	Zerumbone (14)	Indole (9)	Product (15)	Yield (%)[b]
7		 9g	 15g	63
8		 9h	 15h	47
9		 9i	 15i	33
10		 9j	 15j	56
11		 9k	 15k	NR
12		 9l	 15l	NR

Reaction condition: Zerumbone (1 equiv.), Indole (1 equiv.), $Sc(OTf)_3$ (5 mol %), CH_3CN (2 mL), 80 ^oC

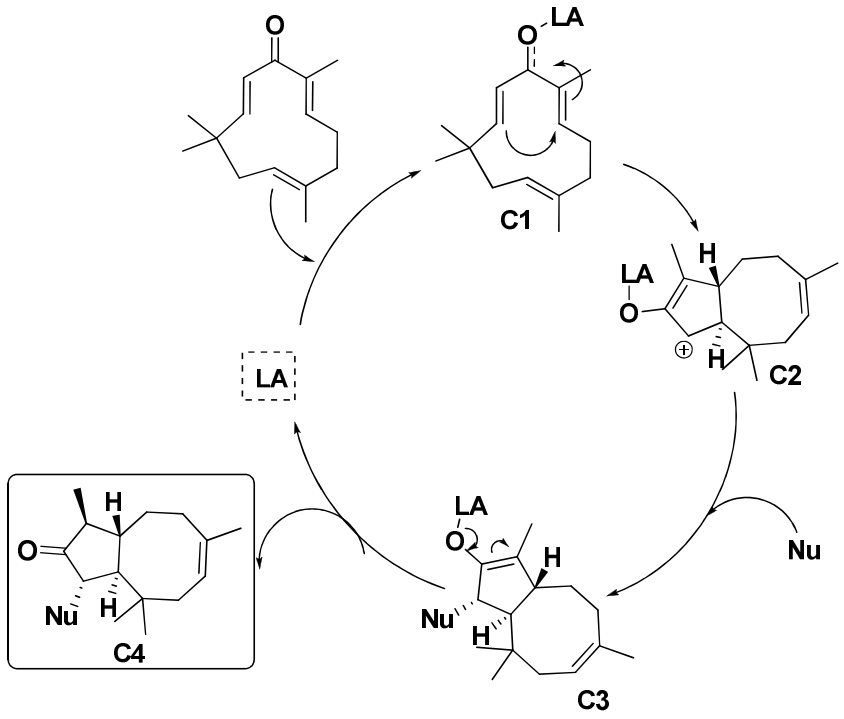
It was interesting to check the reactivity of C-3 substituted indole with the intention of finding the possibility of C-2 activation under the reaction conditions. As expected, the reaction proceeded to furnish the C-2 substituted [5.8] fused compound **15m** in 23% yield (Scheme 4B.8).



Scheme 4B.8

4B.6. Proposed Mechanism

The mechanism follows the Nazarov type cyclization. Initially the Lewis acid coordinates to the carbonyl oxygen of zerumbone, thereby creating an allyl carbocation (intermediate C2). This carbocation is then trapped by an external nucleophile (indole) followed by tautomeric rearrangements resulting in the formation of the product C4 (Scheme 4B.9).



Scheme 4B.9

4B.7. Conclusion

In conclusion, we have developed Lewis acid catalyzed annulation reactions of zerumbone to access structurally diverse polycyclic compounds. Under Lewis acid

catalysis, we could easily synthesize [5.8] fused ring system starting from zerumbone and indole.

4B.8. Experimental Section

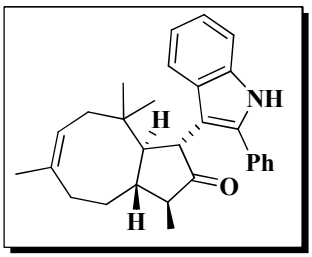
General information about the experiments is given in section 2A.8 of Chapter 2A.

4B.8.1. General Procedure for the Synthesis of [5.8] Fused Ring System

The reaction was carried out with 1.0 equivalents of both zerumbone and indole in the presence of 5 mol % of $Sc(OTf)_3$ at 80 ^oC in CH_3CN for 12 hours. After the completion of the reaction as monitored by TLC, the reaction mixture was concentrated and the crude product was purified by column chromatography on silica gel (100-200 mesh) using hexane: ethylacetate as the eluent.

1,4,4,7-tetramethyl-3-(2-phenyl-1H-indol-3-yl)-3,3a,4,5,9,9a-hexahydro-1H-cyclopenta[8]annulen-2(8H)-one (15a)

Following the general experimental procedure, zerumbone **14** (30 mg, 0.137 mmol), 2-phenyl indole **9a** (26.441 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at 80 ^oC for 12 h gave the product **15a** as white crystalline solid (44 mg, 78 %).



R_f: 0.83 (ethylacetate/hexane = 3:7).

Mp: 207-209 ^oC.

IR (neat) υ_{max}: 3361.4, 3056.3, 2957.9, 2924.2, 1729.9, 1606.7, 1453.3, 1369.4, 1309.4, 1244.4, 1149.6, 893.2 cm^{-1}.

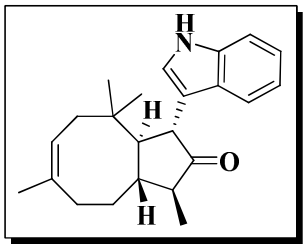
^{1}H NMR (500 MHz, CD_3CN): δ 9.42 (brs, 1H), 7.62-7.61 (m, 2H), 7.52-7.40 (m, 5H), 7.16-7.13 (m, 1H),7.07-7.04 (m, 1H), 5.15-5.12 (m, 1H), 3.84 (d, *J* = 9.5 Hz, 1H), 2.61-2.58 (m, 1H), 2.39-2.37 (m, 1H), 2.33-2.28 (m, 1H), 2.09-2.06 (m, 1H), 1.87-1.81 (m, 1H), 1.66 (s, 3H), 1.64-1.62 (m, 1H), 1.49-1.47 (m, 1H), 1.18 (d, *J* = 7 Hz, 3H), 0.89-0.86 (m, 1H), 0.64 (s, 3H), 0.26 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 222.2, 138.2, 136.6, 136.2, 133.0, 129.0, 128.8, 128.3, 127.1, 122.0, 121.5, 119.5, 119.2, 113.0, 111.3, 52.2, 50.9, 48.0, 44.1, 41.0, 38.7, 34.2,31.5,27.4, 24.6, 23.4, 15.1 ppm.

HRMS (ESI): *m/z* Calcd for $C_{29}H_{33}NNaO$: 434.24598, Found: 434.24454 $[M+Na]^+$.

(3-(indole)-1,4,4,7-tetramethyl-3,3a,4,5,9,9a-hexahydro-1H-cyclopenta[8]annulen-2(8H)-one (15c)

Following the general experimental procedure, zerumbone **14** (30 mg, 0.137 mmol), indole **9c** (16.5 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at 80 ^oC for 12 h gave the product **15a** as white crystalline solid (27.66 mg, 60 %).



R_f: 0.67 (ethylacetate/hexane = 3:7).

Mp: 173-175 ^oC.

IR (neat) υ_{max}: δ 3296.2, 2959.9, 1724.7, 1581.8, 1509.6, 1450.2, 1354.5, 1265.6, 1241.4, 1184.7, 1086.3, 971.2, 825.9, 807.4, 795.3 cm^{-1}.

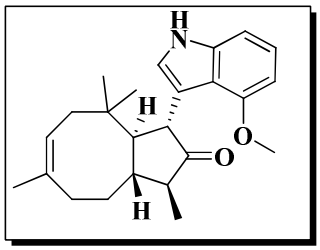
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (brs, 1H), 7.82 (d, *J* = 8 Hz, 1H), 7.32-7.31 (m, 1H), 7.20-7.12 (m, 2H), 6.98 (s, 1H), 5.41-5.38 (m, 1H), 3.59 (d, *J* = 4.5 Hz, 1H), 2.45-2.43 (m, 2H), 2.39-2.30 (m, 2H), 2.17-2.08 (m, 2H), 1.84 (s, 3H), 1.72-1.69 (m, 2H), 1.55-1.53 (m,1H), 1.05 (d, *J* = 12 Hz, 3H), 0.90 (s, 3H), 0.83 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 217.3, 138.6, 136.5, 126.4, 122.5, 121.9, 121.1, 119.9, 119.8, 117.3, 111.1, 51.5, 48.3, 47.8, 44.0, 40.3, 38.4, 34.8, 31.9, 27.1, 24.9, 22.7, 12.6 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{29}NNaO$: 358.21468, Found: 358.21339 $[M+Na]^+$.

3-(4-methoxy-1H-indol-3-yl)-1,4,4,7-tetramethyl-3,3a,4,5,9,9a-hexahydro-1H-cyclopenta[8]annulen-2(8H)-one (15d)

Following the general experimental procedure, zerumbone **14** (30 mg, 0.137 mmol), 4-methoxy indole **9d** (20.16 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at 80 ^oC for 12 h gave the product **15d** as white crystalline solid (11.05 mg, 22 %).



R_f: 0.67 (ethylacetate/ hexane = 3:7).

Mp: 150-152 ^oC.

IR (neat) υ_{max}: 3296.2, 2959.9, 1724.7, 1581.8, 1509.6, 1450.2, 1354.5, 1265.6, 1241.4, 1184.7, 1086.3, 971.2, 825.9, 807.4, 795.3 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$ + MeOH, 7:3 %): δ 10.61 (brs, 1H), 6.97-6.94 (m, 2H), 6.82 (s,1H), 6.43-6.41 (m,1H), 5.26-

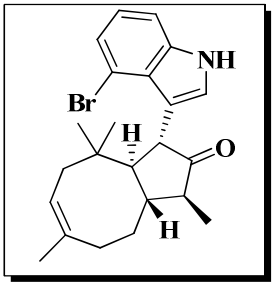
5.24 (m, 1H), 3.99 (brs, 1H), 3.87(s, 3H), 2.43-2.38 (m, 2H), 2.27-2.24 (m, 2H), 2.14-2.06 (m, 2H), 1.75-1.72 (m, 4H), 1.59-1.56 (m, 2H), 1.09-1.08 (m, 3H), 0.95 (s, 3H), 0.71 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$ + MeOH, 7:3 %): δ 224.3, 159.0, 142.9, 126.8, 126.3, 120.9, 110.0, 104.0, 83.7, 83.4, 83.1, 59.7, 54.0, 48.6, 45.0, 44.8, 44.7, 44.5, 44.3,43.3, 36.3, 34.2, 32.4, 29.9, 28.2, 19.2 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{31}NNaO_2$: 388.22525, Found: 388.22503 $[M+Na]^+$.

3-(4-bromo-1H-indol-3-yl)-1,4,4,7-tetramethyl-3,3a,4,5,9,9a-hexahydro-1H-cyclopenta[8]annulen-2(8H)-one (15e)

Following the general experimental procedure, zerumbone **14** (30 mg, 0.137 mmol), 2-phenyl indole **9e** (26.441 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at 80 ^oC for 12 h gave the product **15e** as white crystalline solid (12.5 mg, 22 %).



R_f: 0.38 (ethylacetate/hexane = 3:7).

Mp: 256-258 ^oC.

IR (neat) υ_{max}: 3340.4, 2956.8, 2922.8, 2868.8, 2852.4, 1722.1, 1558.7, 1468.0, 1422.9, 1365.9, 1337.1, 1265.0, 1184.2, 1076.1, 1043.1, 911.1, 814.6 cm^{-1}.

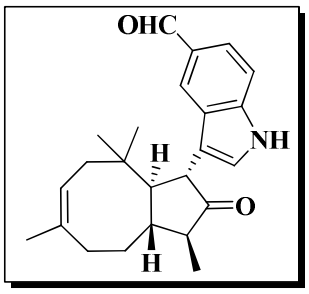
^{1}H NMR (500 MHz, $CDCl_3$ + DMSO-d_6, 8:2 %): δ 10.62 (brs, 1H), 7.84 (s, 1H), 7.26-7.24 (m, 1H), 7.18-7.16 (m, 1H), 7.01 (s, 1H), 5.40-5.36 (m, 1H), 3.46 (d, *J* = 4.5 Hz, 1H), 2.59-2.58 (m, 1H), 2.46-2.30 (m, 3H), 2.16-2.08 (m, 2H), 1.85 (s, 3H), 1.71-1.67 (m, 2H), 1.02 (d, *J* = 7 Hz, 3H), 0.89 (s, 3H), 0.80 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6, 8:2 %): δ 216.8, 138.4, 135.3, 127.9, 124.2, 122.9, 121.7, 121.6, 119.9, 115.5, 113.1, 111.9, 47.9, 47.4, 38.2, 34.5, 31.6, 29.4, 24.8, 22.4, 12.4 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{28}BrNNaO$: 436.12520, Found: 436.12581 $[M+Na]^+$.

3Z-3,6,9,9-tetramethyl-2-oxo-2,3,3a,4,5,8,9,9a-octahydro-1H-cyclopenta[8]annulen-1-yl)-1H-indole-5-carbaldehyde (15f)

Following the general experimental procedure, zerumbone **14** (30 mg, 0.137 mmol), indole-5-carbaldehyde **9f** (19.959 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at 80 ^oC for 12 h gave the product **15f** as colourless oily liquid (8.49 mg, 17 %).



R_f: 0.26 (ethylacetate/hexane = 3:7)

IR (neat) υ_{max}: 3336.0, 2958.7, 2926.5, 2870.7, 2731.2, 1731.1, 1681.5, 1610.9, 1576.7, 1439.4, 1368.0, 1312.1, 1266.8, 1178.3, 798.7 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.06 (brs, 1H), 8.45-8.36 (m, 2H), 7.78-7.77 (m, 1H), 7.40-7.39 (m, 1H), 7.09(s, 1H), 5.42-5.39 (m,1H), 3.65 (d, *J* = 5 Hz, 1H), 2.48-2.47(m, 2H), 2.35-2.32 (m, 2H), 2.13-2.11 (m, 2H), 1.85 (s, 3H), 1.79-1.71 (m, 2H), 1.07 (d, *J* = 7 Hz, 3H), 0.93 (s, 3H), 0.82 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ217.0, 192.5, 139.9,138.7,129.8, 126.3, 126.0, 122.6, 122.4, 121.8, 119.2, 111.8, 77.2, 51.5, 48.1, 44.0, 40.3, 38.4, 34.7, 31.5, 29.8, 27.1, 24.8, 22.7, 12.7 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{29}NNaO_2$: 386.20960, Found: 386.20942 $[M+Na]^+$.

3Z-3,6,9,9-tetramethyl-2-oxo-2,3,3a,4,5,8,9,9a-octahydro-1H-cyclopenta[8]annulen-1-yl)-1H-indole-5-carbonitrile (15g)

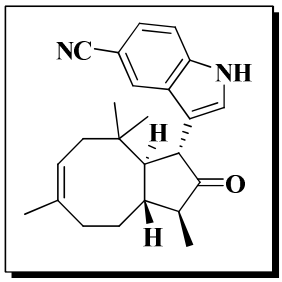
Following the general experimental procedure, zerumbone **14** (30 mg, 0.137 mmol), 5-cyano indole **9g** (19.47 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at 80 ^oC for 12 h gave the product **15g** as white crystalline solid (31.21 mg, 63 %).

R_f: 0.5 (ethylacetate/hexane = 3:7).

Mp: 235-237 ^oC.

IR (neat) υ_{max}: 3333.4, 2959.2, 2925.8, 2870.7, 2220.3, 1731.7, 1618.3, 1579.1, 1544.9, 1471.0, 1438.3, 1387.6, 1366.4, 1326.9, 1265.7, 1174.7, 1184.9, 1097.3, 1052.4, 1007.6, 920.2, 892.4, 799.5 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (brs, 1H), 8.19 (s, 1H), 7.41-7.35 (m, 2H), 7.10 (s, 1H), 5.41-5.38 (m, 1H), 3.57 (d, *J* = 5 Hz, 1H), 2.48-2.41 (m, 2H), 2.32-2.26 (m, 2H),



2.12-2.10 (m, 2H), 1.86 (s, 3H), 1.77-1.71 (m, 1H), 1.60-1.47 (m, 1H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 3H), 0.80 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 216.9, 138.7, 138.2, 126.3, 125.8, 125.4, 123.1, 121.8, 118.2, 112.0, 103.1, 51.6, 48.3, 48.0, 43.9, 40.1, 38.4, 34.9, 31.6, 27.2, 24.8, 22.7, 12.8 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{28}N_2NaO$: 383.20993, Found: 383.21068 $[M+Na]^+$.

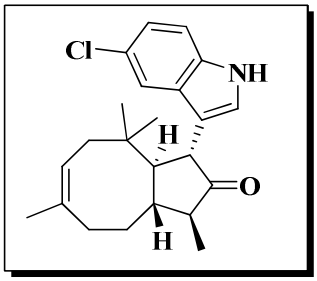
3-(5-chloro-1H-indol-3-yl)-1,4,4,7-tetramethyl-3,3a,4,5,9,9a-hexahydro-1H-cyclopenta[8]annulen-2(8H)-one (15h)

Following the general experimental procedure, zerumbone **14** (30 mg, 0.137 mmol), 5-chloro indole **9h** (20.76 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at 80 ^oC for 12 h gave the product **15a** as colourless crystalline solid (23.87 mg, 47%).

R_f: 0.30 (ethylacetate/hexane = 3:7).

Mp: 236-237 ^oC.

IR (neat) υ_{max}: 3354.6, 2957.8, 2922.8, 2854.9, 1724.6, 1588.5, 1458.6, 1419.2, 1315.9, 1269.2, 1116.8, 1018.3, 885.8, 820.7, 793.9 cm^{-1}.



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (brs, 1H), 7.80 (d, *J* = 1.5 Hz, 1H), 7.24-7.22 (m, 1H), 7.14-7.13 (m, 1H), 7.01 (d, *J* = 2 Hz, 1H), 5.41-5.38 (m, 1H), 3.52 (d, *J* = 5 Hz, 1H), 2.43-2.34 (m, 2H), 2.32-2.30 (m, 2H), 2.17-2.09 (m, 2H), 1.85 (s, 3H), 1.72-1.69 (m, 2H), 1.53-1.51 (m, 1H), 1.06 (d, *J* = 1.5 Hz, 3H), 0.90 (s, 3H), 0.81 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 217.0, 138.6, 134.9, 127.5, 125.7, 122.9, 122.3, 121.9,119.5, 117.2, 112.1, 48.0, 40.3, 38.4, 34.8, 32.0, 25.1, 22.6, 12.7 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{28}ClNNaO$: 392.17571, Found: 392.17556 $[M+Na]^+$.

3-(5-fluoro-1H-indol-3-yl)-1,4,4,7-tetramethyl-3,3a,4,5,9,9a-hexahydro-1H-cyclopenta[8]annulen-2(8H)-one (15i)

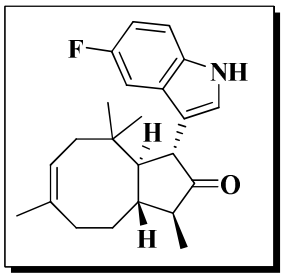
Following the general experimental procedure, zerumbone **14** (30 mg, 0.137 mmol), 5-flouro indole **9i** (18.51 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at 80 ^oC for 12 h gave the product **15a** as white crystalline solid (16.03 mg, 33 %).

R_f: 0.67 (ethylacetate/hexane = 3:7).

Mp: 175-177 ^oC.

IR (neat) υ_{max}: 3365.2, 2959.6, 2924.4, 2868.2, 1727.4, 1581.1, 1485.0, 1457.2, 1369.5, 1286.5, 1168.2, 1094.8, 935.2, 844.0, 796.1 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.96 (brs,1H), 7.06-6.99 (m, 2H), 6.82-6.81 (m,1H), 6.60-6.56 (m, 1H), 5.06-5.02 (m, 1H), 3.16 (d, *J* = 5.5 Hz, 1H), 2.14-2.10 (m, 1H), 2.04-1.96 (m, 3H), 1.76-1.72 (m,2H), 1.48 (s, 3H), 1.43-1.36 (m, 2H), 1.26-1.20 (m, 1H),



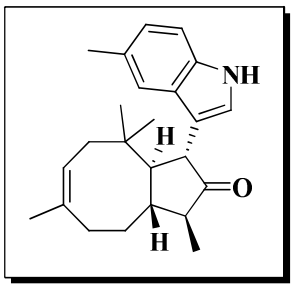
0.66 (d, J = 6.5 Hz, 3H), 0.55 (s, 3H), 0.43 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 211.1, 159.8 (d, $^1J_{C\text{-}F}$ = 262.5 Hz), 138.7, 133.0, 126.7 (d, $^2J_{C\text{-}F}$ = 10 Hz), 122.8, 121.9, 117.4, 111.7 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 110.9 (d, $^2J_{C\text{-}F}$ =26.2 Hz), 104.9 (d, $^2J_{C\text{-}F}$ = 23.8 Hz), 51.5, 48.2, 48.0, 40.2, 38.4, 34.8, 31.8, 27.2, 24.9, 22.9, 12.6 ppm.

HRMS (ESI): *m/z* Calcd for $C_{23}H_{28}FNNaO$: 376.20526, Found: 376.20454 $[M+Na]^+$.

1,4,4,7-tetramethyl-3-(5-methyl-1H-indol-3-yl)-3,3a,4,5,9,9a-hexahydro-1H-cyclopenta[8]annulen-2(8H)-one (15j)

Following the general experimental procedure, zerumbone **14** (30 mg, 0.137 mmol), 5-methyl indole **9j** (17.967 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at 80 ^oC for 12 h gave the product **15j** as colourless amorphous solid (26.9 mg, 56%).



R_f: 0.70 (ethylacetate/hexane = 3:7).

IR (neat) υ_{max}: 3402.8, 2959.1, 2924.9, 2860.0, 1728.3, 1690.7, 1666.3, 1621.6, 1587.3, 1455.3, 1368.5, 1311.6, 1266.1, 1222.7, 1179.9, 1097.2, 1038.0, 986.5, 894.3, 793.5 cm^{-1}.

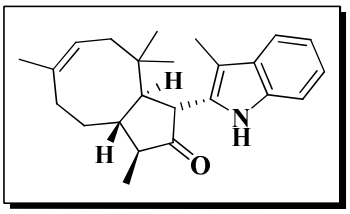
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (brs, 1H), 7.61 (s, 1H), 7.26-7.20 (m, 1H), 7.02-7.00 (m, 1H), 6.96 (brs, 1H), 5.41-5.39 (m, 1H), 3.56 (d, J = 4.5 Hz, 1H), 2.46 (s, 3H), 2.45-2.40 (m, 1H), 2.38-2.34 (m, 1H), 2.29-2.28 (m, 1H), 2.10-2.05(m, 1H), 1.85 (s, 3H), 1.73-1.66 (m, 2H), 1.55-1.51 (m, 1H), 1.26-1.24 (m, 1H), 1.04 (d, J = 7 Hz, 3H), 0.90 (s, 3H), 0.83 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 217.3, 138.6, 134.9, 129.1, 126.6, 124.1, 122.0, 121.1, 119.5, 116.9, 110.7, 51.5, 48.3, 47.7, 40.2, 38.4, 34.8, 24.9, 21.6, 12.5 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{31}NNaO$: 372.23033, Found: 372.22909.

1,4,4,7-tetramethyl-3-(3-methyl-1H-indol-2-yl)-3,3a,4,5,9,9a-hexahydro-1H-cyclopenta[8]annulen-2(8H)-one (15m)

Following the general experimental procedure, zerumbone **14** (30 mg, 0.137 mmol), 2-methyl indole **9m** (26.441 mg, 0.137 mmol), $Sc(OTf)_3$ (3.37 mg, 0.00685 mmol), in 2 mL acetonitrile at 80 ^oC for 12 h gave the product **15m** as white colourless solid (11.05 mg, 23%).



R_f: 0.52 (ethylacetate: hexane = 3:7).

Mp:190-192 ^oC

IR (neat) υ_{max}: 3384.2, 3054.2, 2960.4, 2924.1, 2870.0, 1729.3, 1461.3, 1368.0, 1333.7, 1306.3, 1236.4, 1148.4, 1007.6, 893.7, 837.6, 801.5 cm^{-1}.

^{1}H NMR (500 MHz, CD_3CN): δ 8.83 (brs, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.39-7.36 (m, 1H), 7.30 (d, *J* = 8 Hz, 1H), 7.08-7.04 (m, 1H), 7.02-6.99 (m, 1H), 5.33-5.29 (m, 1H), 3.67 (d, *J* = 9.5 Hz, 1H), 2.46-2.36 (m, 3H), 2.23 (s, 3H), 2.19-2.14 (m, 3H), 1.89-1.83 (m, 1H), 1.78 (s, 3H), 1.72-1.65 (m, 2H), 1.11 (d, *J* = 7 Hz, 3H), 0.98 (s, 3H), 0.62 (s, 3H) ppm.

^{13}C NMR (125 MHz, CD_3CN): δ 218.4, 139.9, 136.8, 135.3, 130.3, 122.1, 121.9, 119.8, 118.9, 111.5, 111.4, 108.3, 52.6, 51.9, 50.4, 41.3, 39.2, 36.9, 32.2, 31.8, 24.8, 23.5, 12.4, 9.2 ppm.

HRMS (ESI): *m/z* Calcd for $C_{24}H_{31}NNaO$:372.23033, Found: 372.23113 $[M+Na]^+$.

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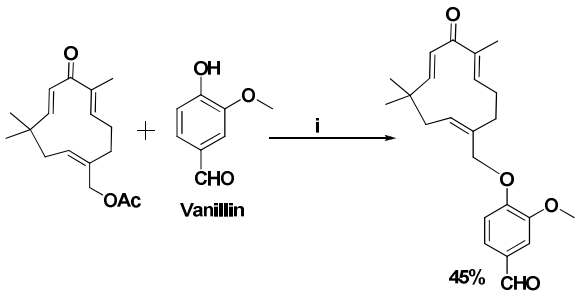
Summary and Conclusion

Natural products offer a rich source for novel therapeutic agents with enormous structural diversity. About 34% of all the drugs approved by FDA in the past three decades are based on natural products and in many cases, the structurally complex natural products are altered from their core structure to a distinct framework using known synthetic methodologies. Zerumbone, isolated from *Zingiber zerumbet* Smith (L). is a naturally occurring humulane-type sesquiterpene which constitutes 4% of the dry weight of this tropical ginger. It has attracted much attention of the scientific community because of its interesting biological properties and chemical reactivity. The **Chapter 1** gives an overview of synthetic transformations of zerumbone.

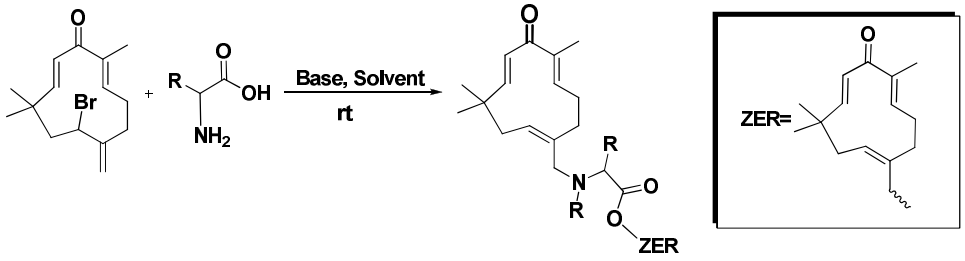
Chapter 2 is divided into two parts. First part describes the palladium catalyzed Tsuji-Trost coupling of phenols/arene carboxylic acids with zerumbone to provide a new class of zerumbone pendant derivatives (Scheme 1). Preliminary *in vitro* α-glucosidase inhibition assays revealed that the synthesized zerumbone pendant derivatives have potent inhibitory activity than the parent molecule zerumbone (IC_{50}, 271.053 ± 0.332 μM) and the standard acarbose (81.3 ± 1.10 μM). Also, the zerumbone derivatives showed significantly improved α-amylase inhibitory activity (IC_{50}, 12-43 μM range) as compared to zerumbone (51.070 ± 0.254 μM). The derivatives of zerumbone were evaluated for its ability to prevent the protein glycation reaction, all the derivatives showed superior anti-glycation property than zerumbone (104.86 ± 0.183 μM) and the standard ascorbic acid (165.11 ± 0.2306 μM). Molecular docking studies were performed to recognize the binding mode along with activity comparison of derivatives. The zerumbone pendant derivatives were tested for cytotoxicity against selected human cancer cells *viz*., A549 (human lung adenocarcinoma), HCT116 (human colon carcinoma), HeLa (Human cervix carcinoma), HT1080 (human Fibrosarcoma) and MDAMB231 (human breast adenocarcinoma) using MTT assay. Among tested compounds, two derivatives showed significant anti-proliferative effect in some cancer cells. In addition, we have checked the antihypertensive activity of some selected zerumbone derivatives and most of the derivatives showed better inhibition against angiotensin-converting (ACE) enzyme than zerumbone.



i = $Pd_2(dba)_3.CHCl_3$(10 mol %), PPh_3 (40 mol %), Cs_2CO_3 (2.0 equiv.), THF, rt, 12h

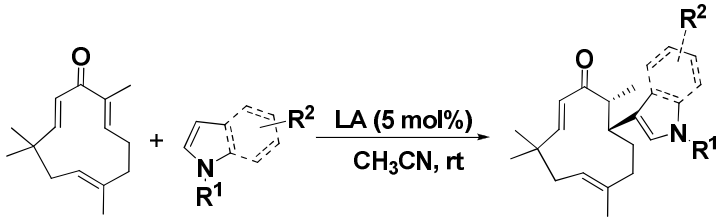
Scheme 1

The second part deals with the synthesis of a new class of zerumbone derivatives by incorporating amino acids as well as nucleobases (adenine, thymine, uracil *etc*.) to zerumbone *via* base catalysed reaction (Scheme 2). Two of the zerumbone pendant amino acid derivatives were tested for cytotoxicity against some of the selected human cancer cells using MTT assay. Among them, valine derivative of zerumbone showed significant growth inhibition activity (IC_{50} = 11.0 ± 1.10 μM) against HeLa cells.



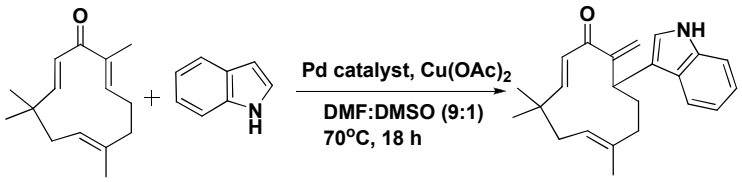
Scheme 2

Chapter 3 describes a synthetic route for the derivatizations of zerumbone by Lewis acid catalyzed 1,4-conjugate addition, with biologically important heterocycles such as indole/pyrrole (Scheme 3). The method provides a straightforward access to conjugate addition product of zerumbone with indole under mild reaction condition.



Scheme 3

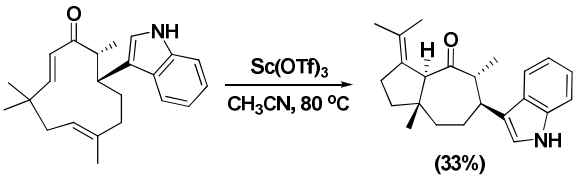
This chapter also describes the synthesis of indole functionalized zerumbone derivatives using palladium catalyst (Scheme 4).



Scheme 4

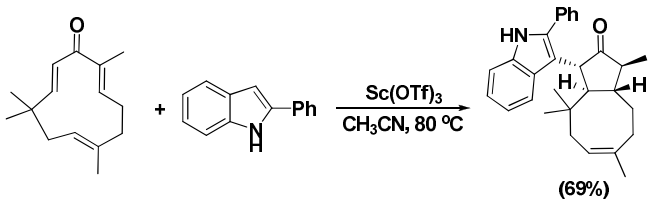
We have conducted the *in vitro* anti-diabetic screening of the synthesized indole functionalized zerumbone derivatives as well as inhibitory effect of angiotensin-converting enzyme (anti-hypertensive activity) of the synthesized zerumbone-indole adducts. The studies revealed that indole functionalized zerumbone derivatives have superior inhibitory activity against digestive enzymes such as α-glucosidase and α-amylase enzymes. Also the synthesized indole functionalized zerumbone derivatives showed improved anti-glycation property compared to the parent molecule zerumbone. Molecular docking studies were performed to recognize the binding mode of zerumbone-indole to the enzyme. Compared to zerumbone, some of its indole derivatives showed similar inhibitory activity against angiotensin-converting (ACE) enzyme.

A facile Lewis acid catalysed methodology towards structurally diverse sesquiterpenoid derivatives from readily available and abundant 11-membered natural product, zerumbone is discussed in **chapter 4**. The chapter is divided into two parts. First part explains the Lewis acid catalysed synthesis of indole functionalized [5.7] fused systems (Scheme 5). We have developed Lewis acid catalyzed annulation reactions of Michael adduct of zerumbone to access structurally diverse polycyclic compounds. The core structures of synthesised molecules, [5.7] fused rings are found in a number of biologically active natural products. The highlight of the novel methodology is the utilisation of renewable resources to generate complex fused skeletons.



Scheme 5

The part B of **chapter 4** deals with synthesis of indole functionalized [5.8] fused systems using Lewis acid catalyst (Scheme 6). Here we describe our efforts in constructing a sesquiterpenoid [5.8] frameworks *via* Lewis acid catalysed cyclisation reaction of zerumbone.



Scheme 6

Under Lewis acid catalysis, we could easily synthesise indole substituted isodaucane moiety from zerumbone-indole adduct and also a [5.8] fused ring system starting from zerumbone and indole.

Natural products, especially plant-derived compounds occupy a proficient position in the development of numerous useful drugs. Diversity oriented synthesis has been used in success for the generation of biologically relevant/drug-like molecules *via* simple chemical transformation of readily available natural products. In this line, zerumbone, a humulenoid sesquiterpene which is the major component of essential oils of Zingiber zerumbet Smith., has attracted much attention of the scientific community because of its interesting biological properties. We have presented some general strategy for the synthesis of zerumbone derivatives *via* simple chemical transformation. *In vitro* biological screening of the zerumbone derivatives are also discussed.

List of Publications

1. **Dhanya, B. P.;** Gopalan, G.; Sasikumar, P.; Neethu, S.; Meenu, M. T.; Sharathna, P. John, J.; Varughese, S.; Sabu , M.; Dan, Mathew ; Radhakrishnan, K. V. 'Lewis Acid Catalysed Activation of Zerumbone towards Sesquiterpenoid Derivatives: Sustainable Utilisation of Abundant Natural Resources towards Chemically Diverse Architectures' ***Asian JOC.*** **2018**, *7*, 471–476.
2. Sithara, Thomas; **Dhanya, B. P.,** K B, Arun; Mathew, Dan; Radhakrishnan, K. V.; Slini, Suresh; Nisha, P.'Zerumbone, a Cyclic Sesquiterpene from *Zingiber zerumbet* Induces Apoptosis, Cell Cycle Arrest, and Antimigratory Effects in SW480 Colorectal Cancer Cells' ***J. Agric. Food Chem.*** **2018**, *66*, 602–612.
3. Saranya, J.; **Dhanya, B.P.;** Gopalan, G.; Radhakrishnan, K.V.; Priya, S. 'Effects of a new synthetic zerumbone pendant derivative (ZPD) on apoptosis induction and anti-migratory effects in human cervical cancer cells' ***Chem. Biol. Interact.*** **2017***, 278,* 32-39.
4. **Dhanya, B. P.**; Gopalan, G. ; Reshmitha, T. R.; Saranya, J. ; Sharathna, P.; Shibi, I. G. Nisha, P.; Radhakrishnan, 'Synthesis and in vitro evaluation of zerumbone pendant derivatives: potent candidates for anti-diabetic and anti-proliferative activities' K. V. ***New J. Chem.*** **2017**, *41*, 6960-6964.
5. Gopalan, G. ; **Dhanya, B. P**.; Saranya, J.; Reshmitha, T. R.; Baiju, T. V.; Meenu, M. T.; Nair, M. S.; Nisha, P.; Radhakrishnan, K. V. 'Metal-free *trans*- aziridination of zerumbone: Synthesis and biological evaluation of aziridine derivatives of zerumbone' ***Eur. J. Org. Chem.*** **2017**, *2017*, 3072-3077.
6. Sasikumar,P.; Prabha, B.; Reshmitha, T.R.; Sheeba Veluthoor,; Pradeep, A. K., Rohit, K.R.; **Dhanya, B. P**.; Sivan, V.V.; Jithin, M.M.; Anilkumar, N.; Shibi, I.G.; Nisha, P.; Radhakrishnan, K.V. 'Comparison of antidiabetic potential of (+) and (-)- Hopeaphenol, a pair of enantiomers isolated from Ampelocissus indica (L.) and Vateria indica Linn, with respect to inhibition of digestive enzymes and induction of glucose uptake in L6 myotubes*'* ***RSC Adv.*** **2016**,*6*, 77075-77082.
7. Ajish, K. R.; Antu, K. A.; Riya, M. P.; Preetharani, M. P.; Raghu, K. G.; **Dhanya, B. P.;** Radhakrishnan, K. V. 'Studies on α-glucosidase, aldose reductase and glycation inhibitory properties of sesquiterpenes and flavonoids of Zingiber zerumbet Smith., ***Nat. Prod. Res.*** **2015**, *29*, 947-952.

8. Ajish, K. R.; **Dhanya, B. P.**; Joseph, N.; Rani, P.; Raghu, K. G.; Vineetha, V. P.; Radhakrishnan, K. V. 'Synthesis of novel zerumbone derivatives via regioselective palladium catalyzed decarboxylative coupling reaction: a new class of α-glucosidase inhibitors' ***Tetrahedron Lett.*** **2014**, *55*, 665-670.
9. Chand, S. S.; Saranya, S., Preethanuj, P.; **Dhanya, B. P.;** Jijy, E.; Prakash, P; Sasidhar, B. S.; Szymoniak, J.; Santhini, P. V.; Radhakrishnan, K. V. 'Trapping the Lewis acid generated transient species from pentafulvene derived diazanorbornenes with ortho-functionalized aryl iodides and aliphatic alcohols***' Org. Biomol. Chem***. **2014**, *12*, 3045-3061.
10. Chand, S. S.; Jijy, E.; Prakash, P.; Szymoniak, J.; Preethanuj, P.; **Dhanya, B. P.;** Radhakrishnan, K. V. 'Radhakrishnan, K. V., Palladium / Lewis Acid mediated domino reaction of pentafulvene derived diazabicyclic olefins: Efficient access to spiropentacyclic motif with an Indoline and Pyrazolidine fused to cyclopentene' ***Org. Lett.*** **2013**, *15*, 3338-3341.
11. **Dhanya, B. P.;** Gopalan, G.; Baiju, T. V.; Arun, K. B.; Reshmitha, T. R.; Arya A. Das; Radhakrishnan, K. V.; Nisha, P., 'Synthesis of Zerumbone – Indole/Pyrrole hybrids by Lewis acid/Transition metal catalyzed reactions and their *in vitro* anti-diabetic screening' (To be communicated)
12. **Dhanya, B. P.;** Sharathna, P.; Prabha, B.; Gopalan, G.; Greeshma Gopalan, Sabu, M.; Nisha, P.; Radhakrishnan, K. V. 'Copper Catalyzed Synthesis of Triazole-Linked Zerumbone/Humulene Analogues and their Activity Antidiabetic against Digestive Enzymes' (**To be communicated**)
13. **Dhanya, B. P.;** Gopalan, G.; Saranya J.; Radhakrishnan, K. V. 'Facile synthesis and biological evaluation of zerumbone pendant derivatives: an easy access to biologically relevant motifs' (**To be communicated**)

Contributions to Academic Conferences

1. *Transition metal catalysed regio- and stereoselective 1,4 – conjugate addition of boronic acids to zerumbone: A facile route towards novel zerumbone derivatives.* K. R. Ajish, **B. P. Dhanya**, K. V. Radhakrishnan, a poster presented at National seminar On Emerging Trends in Chemical Sciences (ETCS-2013), during May 29-31, 2013 held at University of Kerala, Kariavattom, Thiruvananthapuram.

2. *Synthesis of Novel α-Glucosidase Inhibitors of Zerumbone Derivatives via Regioselective Palladium Catalyzed Decarboxylative Coupling Reaction.* **B. P. Dhanya,** K. R. Ajish., Nayana Joseph, K. G. Raghu and K. V. Radhakrishnan., a poster presented at National Conference on entitled "Transcending Frontiers in Organic Chemistry (TFOC-2014)"during October 09-11, 2014 held at CSIR-NIIST, Thiruvananthapuram.

3. *Synthesis and evaluation of anti-diabetic activity of indole functionalized zerumbone derivatives.* **B. P. Dhanya,** Greeshma Gopalan, P. Nisha and K. V. Radhakrishnan a poster presented at International symposium on phytochemistry & Dr. Hisham endowment award ceremony, April 25, 2015 heldat Kerala State Science and Technology Museum, Thiruvananthapuram.

4. *Synthesis and evaluation of anti-diabetic activity of indole functionalized zerumbone derivatives.* **B. P. Dhanya,** Greeshma Gopalan, P. Nisha and K. V. Radhakrishnan, a poster presented at International Conference on "*Nascent Developments in Chemical Sciences: Opportunities for Academia-Industry Collaboration (NDCS-2015)*" during October 16-18, 2015 held at BITS Pilani, Pilani.

5. *Regioselective palladium catalyzed decarboxylative coupling for the synthesis of zerumbone derived α-glucosidase inhibitors* **B. P. Dhanya,** K. R. Ajish., Nayana Joseph, K. G. Raghu and K. V. Radhakrishnan, a poster presented at the 6th International Symposium on "Current Trends in Drug Discovery Research" (CTDDR-2016) during 25th-28th February 2016 held at CDRI, Lucknow.

6. *Synthesis of Novel Zerumbone Derivatives as α-glucosidase Inhibitors via Regioselective Palladium Catalyzed Decarboxylative Coupling Reaction.* **B. P. Dhanya,** K. R. Ajish, Nayana Joseph, K. G. Raghu and K. V. Radhakrishnan, a poster presented at 19th CRSI National Symposium in Chemistry (NSC-19), during July14-16, 2016 held at North Bengal University (NBU), West Bengal.

7. *Synthesis and in vitro evaluation of zerumbone pendant derivatives: Potent candidates for anti-diabetic and anti-proliferative activities,* **B. P. Dhanya**, P.Nisha, K. V. Radhakrishnan, a poster presented at 2nd International Conference on "Nutraceuticals and Chronic Diseases" during September 1-3, 2017 held at Goa, India.

8. Oral presentation titled "*Facile Lewis Acid Catalyzed Route towards Chemically Diverse Five-Eight, Five-Seven and Five-Eight-Three Fused Sesquiterpenoids from Abundant Natural Product Zerumbone"* **B. P. Dhanya**, Greeshma Gopalan, M.Sabu, Mathew Dan and K. V. Radhakrishnan at International Seminar on Phytochemistry-2018, during March 26-27, 2018 held at Jawaharlal Nehru Tropical Botanic Garden and Research Institute, Thiruvananthapuram, Kerala,