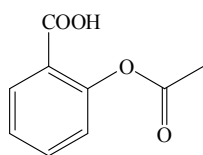


## 1.0 Introduction<sup>1-5</sup>

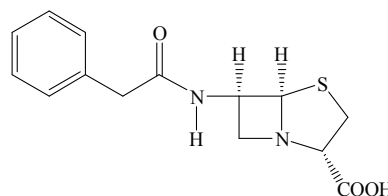
Natural products are naturally derived metabolites and/or byproducts from microorganisms, plants, or animals.<sup>1</sup> In the practice of traditional medicine, natural compounds have been exploited for human use for thousands of years, and plants have been the main source of compounds used to treat various ailments.

Phytochemicals have played a pivotal role in the development of many drugs that have saved millions of lives all over the world, and the hunt for new plant medicines is still on. As more and more habitats of rich biodiversity are threatened by the forces of development, scientists all over the world are racing with time to identify new plant species and to learn about their medicinal uses.

Historically, plants have provided a source of inspiration for novel drug compounds, as plant-derived medicines have large contributions to human health and well-being. Many drugs on the market today were discovered from natural sources; one important example is the analgesic activity of aspirin **1**. Another example is the antibiotic activity of penicillin **2** discovered from the fungus *Penicillium notatum*.

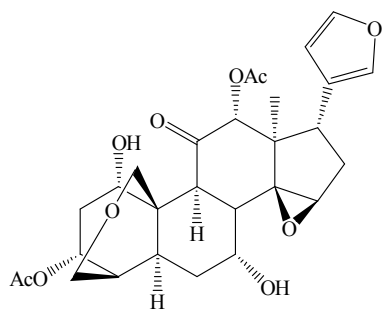


**1**

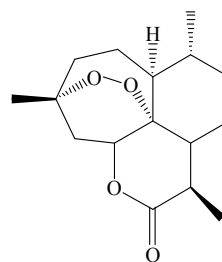


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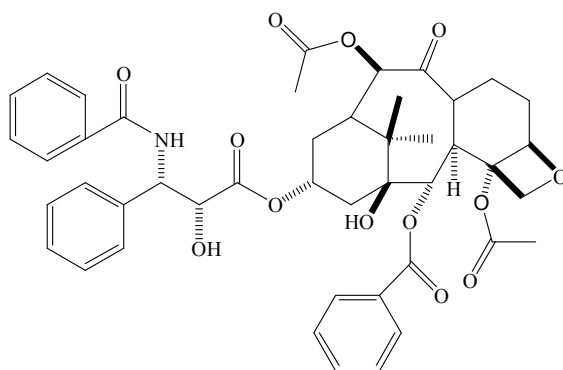
The first generation of plant drugs were usually simple botanicals employed in more or less their crude form. Several medicines used in their natural state such as cinchona, opium, belladonna and aloe were selected as therapeutics agents based on empirical evidence of their clinical application by traditional societies from different parts of the world.<sup>2</sup> After the industrial revolution, a second generation of plant based drugs emerged from the isolation of their active constituent. The second generation phytopharmaceutical agents are pure molecules isolated from plants. Drugs derived from plants, such as toosendanin **3**, artemisinin **4**, and taxol **5**, can serve not only as new drugs but also as leads that can be used to design new pharmaceuticals.



**3**



**4**



**5**

Compounds from natural products have an immense impact on modern medicine. In fact, about 40% of prescription drugs are based on them.<sup>3</sup> From 1981 to 2003, 50% of the anticancer, antimigraine and antihypertensive agents approved by Food and Drug Administration (FDA) were natural products or derivatives thereof.<sup>4</sup>

The number of higher plant species on this planet is estimated at 250,000 and of these, only about 6% have been screened for biological activity, another 15% have been evaluated phytochemically.<sup>5</sup> Thus, plants represent a largely untapped resource. Beside the fact that they are safe and effective products for the use in treatment of illness, medicinal plants are valuable for modern medicine in the four basic ways;<sup>6</sup>

- (1) they are used as a source of direct therapeutic agents,
- (2) they served as raw material base for the elaboration of more complex semi synthetic chemical compounds,
- (3) the chemical structures derived from plants substances can be used as models for new synthetic compounds,
- (4) finally, plants can be used as taxonomic markers for the discovery of new compounds.

Malaysian Rainforests represent one of the twelve mega diversity country in the world where rich ecosystem diversities are recognized. The rich species diversities are important resources for the development of our country and also for the world. Many efforts have been made to carry out the research in the area of natural product for the development of new drugs. In the search of new medicines, large number of plant is being analyzed for their chemical content. The study of the plant species *Aglaia lanuginose* from Malaysian Meliaceae mainly deals with isolation and structural elucidation of chemical compounds. In this research, the plant *Aglaia lanuginose* is studied for its chemical constituents.

## **1.1 Generalities of Meliaceae Family**<sup>13, 14</sup>

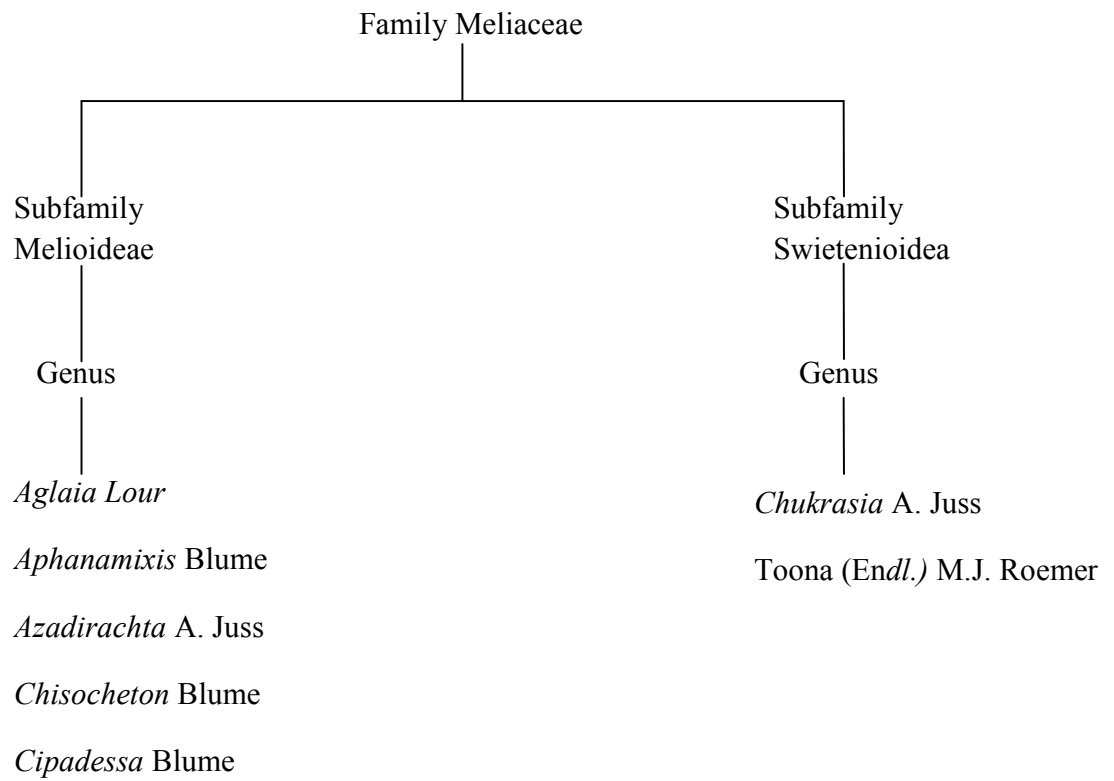
The Meliaceae is a medium sized family of woody plant of both hemispheres, comprising of 51 genera and probably no more than 550 species. The largest genus is *Aglaia* of more than 100 species. They occur in a variety of habitats from rain forests and mangrove swamps to semi deserts. The timbers of certain Meliaceae are some of the most sought after in the world. Other uses of Meliaceae comprise shade and street trees, fruit trees, and last but not least, sources of biologically active compounds.

## 1.2 Botanical Aspects of Meliaceae<sup>7-9</sup>

Many species are deciduous, either in dry season or in winter, but some are evergreen. Mahogany is a very large tree, sometimes reaching over 150 feet in height, with trunks sometimes more than 6 feet in diameter above the large basal buttress. It is generally open crowned tree, with grey to brownish- red fissured bark.

Compared to other groups of similar size, Meliaceae contain relatively wide range of floral, fruit, and seed morphologies. For example, within *Aglaia* alone inflorescence can vary one third to two thirds of a meter long with profuse branching and abundant flowers too much reduced few flowered inflorescence 1-2 cm long. Seeds of Meliaceae are some of the most diverse and intricate in structures that are so far investigated. They are usually pendulous and epittropous in relation to placenta. More detailed botanical aspects of Meliaceae can be explained as below;

Leaves alternate pinnate (rarely simple, *Turraea*, *Beddomea*); leaflets opposite or alternate more or less at base. Flowers bisexual or unisexual regular in axillary panicles usually racemose or spicate, white or yellow in colour. Calyx 3 to 6 lobed rarely entire or with free sepals, usually imbricate in bud. Petals 3-6 free, rarely connate at base. Stamen 3 to 12 insert outside a disc; filament connate in a tube (free in *Cedrela*); anthers sessile in the tube hardly exsert. Disc tubular, annular or obsolete. Ovary 3-celled; ovuled 2 in a cell. Stigma capitate. Fruit capsular, drupaceous or baccate with coriaceous pericarp. Seed arillate.



Scheme 1.1: Classification of Malaysian Meliaceae<sup>7,8</sup>

### 1.3 Generalities of the Genus *Aglaia*<sup>9-12</sup>

The genus *Aglaia* consists of approximately 130 species that are found in the Indo-Malaysian region, in South China and on Pacific Island.<sup>9, 10</sup> *Aglaia* Lour is the largest genus of the subtropical and tropical angiosperm family of Meliaceae. It is estimated that there are about 100 species in the world. The total range of the genus comprises the tropics of the Southeast Asia from Sri Lanka and India to Australia (Queensland, Northern territory, and western Australia) and as far east as the island of Samoa in Polynesia and the north to the Marianne (Saipan, Roti Guam) and (Palu and Panape) in Micronesia.<sup>11</sup>

Out of the 100 species, about 44 indigenous species occur in Malaya. For example, *Aglaia odorata* Lour, is native to Indochina but the male trees are widely distributed in Malaya and throughout Indomalaysia. The Malay name, telur belangkas, means 'king crabs egg' while the Chinese 'me shuilan' is interpreted as fragments of the rice flower; both names refer to the minute flowers characteristic of the genus. The flower of *Aglaia odorata* being strongly fragrant, are use by the Chinese for scenting tea and the Javanese for perfuming clothes.<sup>9</sup> The traditional use of flowers from *A. odorata* in parts of South East Asia as insect repellent is another striking example for the empirical knowledge on the use of plants that can still be accounted in many parts of the world.<sup>12</sup>

## 1.4 Botanical Aspects of *Aglaia* Species<sup>9</sup>

The genus *Aglaia* consists of trees, shrubs or dioecious. The genus can be identified by the bark with scattered large lenticels and smaller one in longitudinal rows, otherwise smooth or in larger species, often with deciduous brittle squarish scale; latex usually present, white, some flowing rapidly from the slash. Indumentums of stellate hairs or stellate or paltate scales on young twigs, the inflorescence and fruits or (occasionally glabrescent) and occasional too dense on leaflet lower surfaces. Apical bud of 2-4 slender and spike like unexpanded leaves which always have dense covering of hairs or scales even when  $\pm$  absent from the leaves. Leaves in spiral, usually imparipinnate with 3-27 leaflets, rarely with a single blade (*A. meliosmoides*). Inflorescence axillary or supra axillary, rarely ramiflorous; male inflorescence large, much divaricately branched and often with several thousand flowers, 1-6 (-9) mm long, subglobose, ellipsoid or obovoid; female inflorescence similar but usually smaller and less- branched, sometimes like a spike (*A. odoratissima*); calyx- cup shape, 3-5 (6) -lobed, petals 3-5 (6) usually free, usually yellow, sometimes pink or white ; staminal tube obovoid with a minute pore or subglobose or cupshape with wider aperture; anthers 5-8 (-10), in a single whorl. Infructescence with one or several fruits; fruit subglobose, obovoid or ellipsoid dehiscent loculicidally or indehiscent containing 1-4 arillate (rarely exarillate, *A. rufibarbis*) seeds.



## 1.5 Botanical Aspects of *Aglaia lanuginosa*



Figure 1.1: Herbarium samples of *Aglaia lanuginosa*. King.

The trees are normally 50 to 70 feet tall and the trunks are 15 to 20 inches in diameter. These plants normally have tomentose branches and their rachises are normally inflorescence. Their leaves are 2 to 4 feet long where their leaflets are dark green above but are soft and velvety brown. The sizes of their leaves are 5 to 15 inches long and 2 to 3.5 inches wide. The petiolous are 2.5 to 4 inches long. The penichles are 12 inches long and the branches are few, short densely and woolly. The globose (rounded) flowers normally grow directly from the stems (sessile). They have calyx covering petals with lobes that are narrow woolly outside. Their flowers have 5 elliptic petals with glabrous stamen tube. They are normally distributed in the dense jungle of low forest. *Aglaia*

*lanuginose* is known to be the woolliest of our species and can be found in Perak, Gunung Bubu and Gunung Pondok.<sup>9</sup>

Table 1.1: Different species of the genus *Aglaia* and their distributions.

Species	Distribution
<i>A. argentia</i> Blume	Lowland forest throughout Malaya and rest of Indomalesia from Burma to Solomon Island. <sup>9</sup>
<i>A. cordata</i> Hiern	Lowland and hill forest , to 1000 m; Penang, Perak, Kelantan, Terengganu, Selangor, Johor, Singapore, Thailand, Sumatra, Anambas Islands, Java, Borneo the Philippines, with allied taxa in New Guinea, Queensland and Fiji. <sup>9</sup>
<i>A. elliptica</i> Blume	Lowland forest; Kedah, Terengganu, Pahang, Johor, Thailand , Sumatra, Java, Borneo, New Guinea, the Philippines, Solomon Islands. <sup>9</sup>
<i>A. forbesii</i> King	Lowland forest, hillside ridges throughout Malaya Burma Thailand Sumatra and Borneo. <sup>9</sup>
<i>A. oligocarpa</i> Miq.	Lowland forest; Perak, Kelantan, China, Indo-China , Thailand , Sumatra, Borneo, New Guinea, the Philippines. <sup>9</sup>
<i>A. ridleiyi</i> King	Lowland and hill forests to 300 m; Perak, Terengganu, Pahang, Selangor. Negeri Sembilan, Melaka, Johor, Singapore Sumatra, Borneo, Sulawesi, New Guinea, Solomon Island with taxa in India Burma and the Philippines. <sup>9</sup>
<i>A. tomentosa</i> Teijsm. & Bin	Lowland and hill forest to 750 m Kedah Penang, Kelantan Terengganu, Pahang, Selangor, Negeri Sembilan. <sup>9</sup>

## 1.6 Medicinal and Biological Activities Found from *Aglaia* Species

Meliaceae synthesise and accumulate bitter and biological active nortriterpenoids, which are known as limonoids and meliacins. These compounds have aroused considerable interest due to their insect antifeedent, insect repellent, molluscicidal, antifungal, bactericidal, and plant antiviral activities as well their numerous medicinal effects in human and animals.

During the past few years, the genus *Aglaia* has received increasing scientific focus due to its bioactivity potentials. Flavaglines especially cyclopentabenzofurans were shown to be potent insecticides. Besides that, cytotoxic and antifungal effects were found for these compounds so far only known to be from *Aglaia* species. Other classes of natural products occurring in *Aglaia* include lignans flavonoids and bisamides. Some of these exhibit cytotoxic antiviral properties. Several species of this genus such as *A. odorata* are traditionally used in folk medicine for example as heart stimulant, febrifuge and for treatment of cough, inflammations and injuries.

High insecticidal activities were found in lipophilic root extract from *Aglaia edulis*. Aglaroxin A and pannelin exhibited the strongest insect toxicity towards neonate larvae of *Spodoptera littoralis*. All naturally occurring rocaglamide derivatives exhibit striking insecticidal activities against pest insects. In addition, they display pronounced cytotoxic activity against human cell lines in vitro. Furthermore, it was shown recently that rocaglamide and several of its congeners inhibit anticancer activity.

Table 1.2: Biologically active compounds from *Aglaia* species<sup>13-15</sup>

<i>Aglaia</i> species	Compounds	Activity
<i>A. odorata</i>	Rocaglamide derivatives	Insecticidal activity <sup>13</sup>
<i>A. elliptifolia</i>	Didesmethylocaglamide	Anti-leukemic MONO-MAC-6(human monocytic leukemia)
<i>A. elagnoidea</i>	Rocaglamide	Anticancer including A-549 (human lung carcinoma ), HCT-8 (human colon carcinoma) RPMI-7951 (human melanoma), TE-671 (human rhabdomyosarcoma) and KB cell(human services carcinoma) <sup>14,15</sup>
<i>A. elliptica</i>	Methyl racoglamide	Cytotoxic activity against KB cell

## 1.7 Objectives of Study

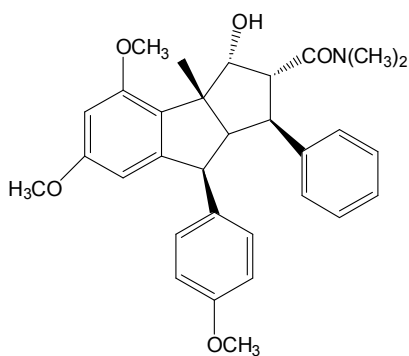
The bark of *Aglaia lanuginosa* (Meliaceae) was studied chemically. The objectives of this study are;

- i) to isolate the chemical constituents from *Aglaia lanuginosa* King,
- ii) to identify each isolated constituent by means of spectroscopic methods: NMR, UV, IR and mass spectroscopy,

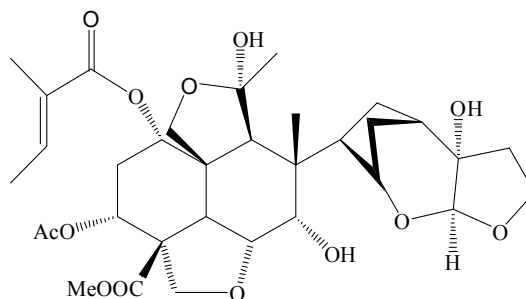
## 2.0 General Chemical Aspects

The family Meliaceae (the mahogany family) provides an example of the high level of phytochemical diversity that can be found in tropical trees. Meliaceae are rich sources of triterpene compounds. Many triterpene compounds reported were isolated from the plants that belong to the Meliaceae family. Besides that, Meliaceae are also rich sources of tetraterpenoids known as limonoids or meliacins.

Another class of compounds called the benzofurans only can be found from *Aglaia* genus.<sup>16</sup> Benzofurans derivatives including rocaglamide **6**, has very strong insecticidal properties similar to azadirachtin **7** isolated from *Azadirachta indica*. In recent studies, rocaglamide were shown to possess high insecticidal activity as well as reported to exhibit cytotoxicity to different cell lines.<sup>16</sup> The Neem tree, *Azadirachta indica*, is a member in this family and its insect antifeedant and growth reducing effects on insects have generated considerable research interest in the defenses of the family against insect.<sup>17</sup> In this section, the general chemical constituents and structure characterization of compounds found in the family Meliaceae will be discussed.



**6**



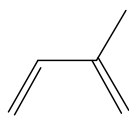
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## 2.2 Terpenes<sup>18, 19</sup>

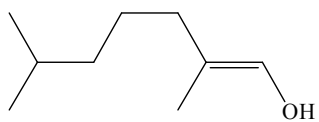
Compounds classified as terpenes constitute what is arguably the largest and most diverse class of natural products. A majority of these compounds are found only in plants, but some of the larger and more complex terpenes (e.g. squalene **11** & cholesterol **20**) occur in animals. Terpenes may be considered to be made up of isoprene units, an empirical feature known as the isoprene rule. Terpenes are natural products structurally related to 2-methylbutadiene **8** or better known as isoprene. According to the isoprene rule, monoterpenes are defined as compounds having two 5 carbon isoprene units, sesquiterpenes with three isoprene units and so on. Among all possible structures of terpene, the favoured one can be devised mechanistically by cyclization of an aliphatic precursor such as geraniol **9**, farnesol **10** and squalene **11**. Each group of terpenes arises from head to tail condensation of variable number of isoprene units.

Table 2.1: Common classification of terpene groups<sup>18</sup>

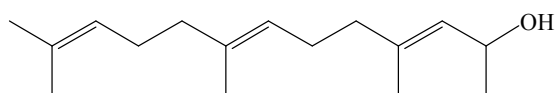
<b>Classification</b>	<b>Isoprene Units</b>	<b>Carbon Atoms</b>	<b>Compounds</b>
Monoterpenes	2	C <sub>10</sub>	Limonane <b>12</b> , 1,8-Cineole <b>13</b> Pinane <b>14</b> , Menthol <b>15</b>
Sesquiterpenes	3	C <sub>15</sub>	$\alpha$ -Bisbolane <b>16</b> , $\gamma$ -Humulene <b>17</b>
Diterpenes	4	C <sub>20</sub>	Taxadiene <b>18</b> , Manool <b>19</b>
Triterpenes	6	C <sub>30</sub>	Cholesterol <b>20</b>



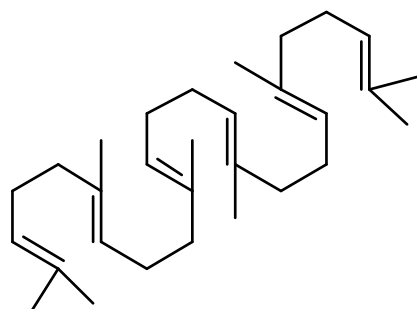
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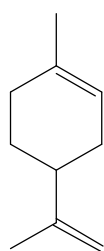
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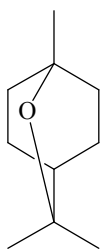
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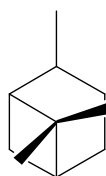
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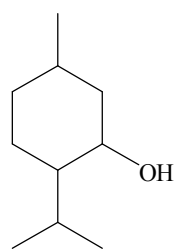
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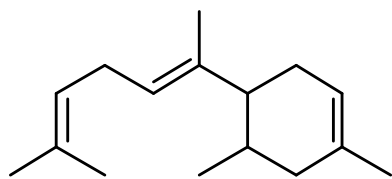


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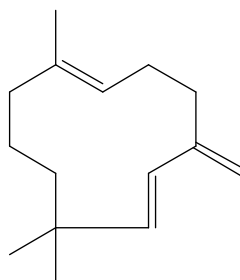


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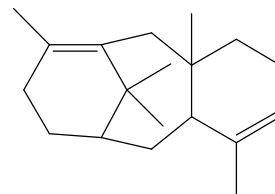




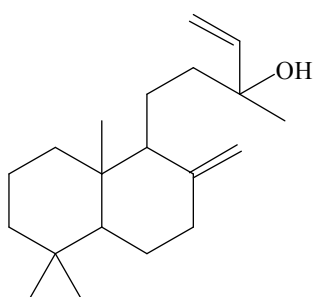
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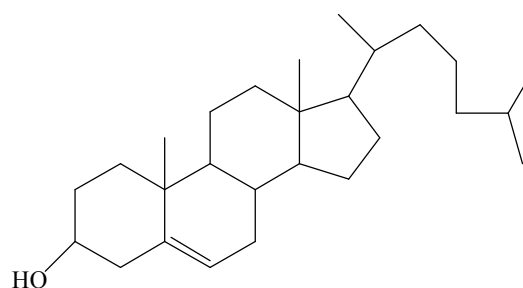
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**18**



**19**



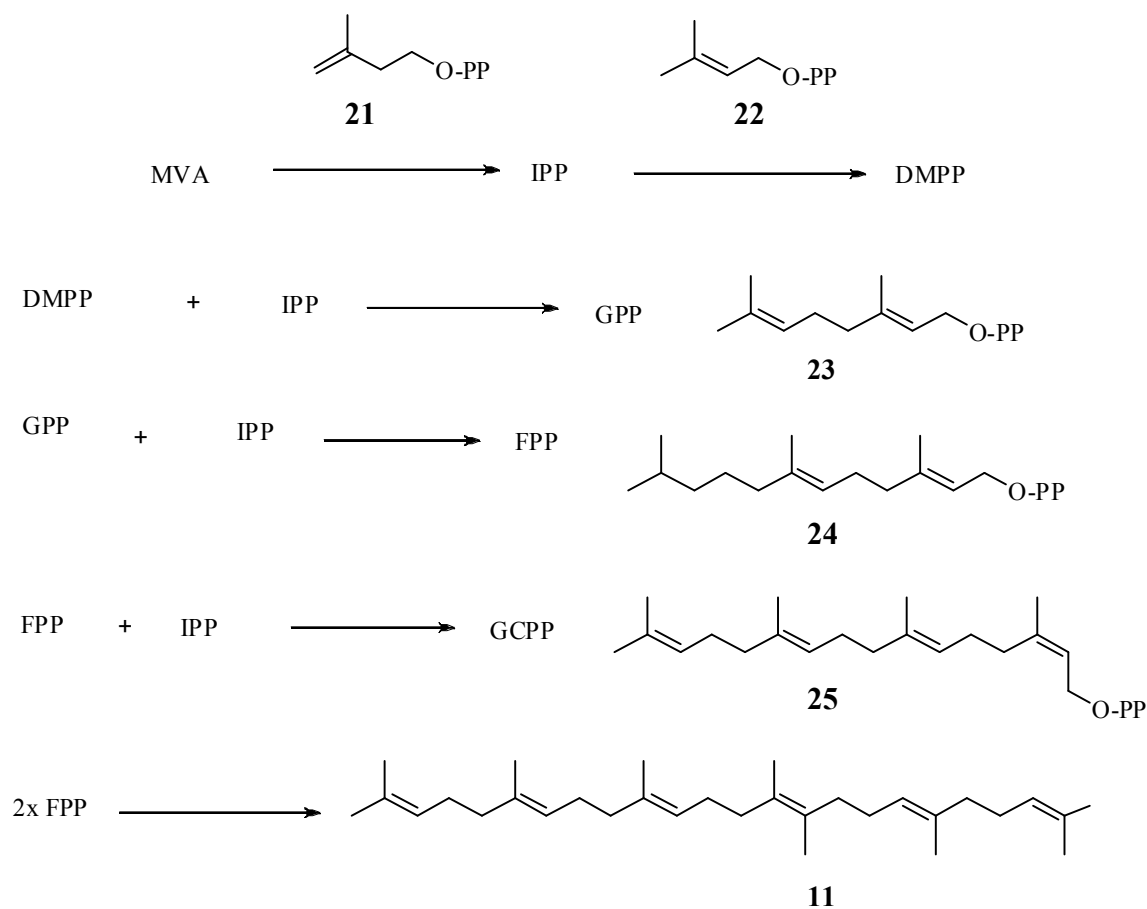
**20**

### 2.3 Biosynthesis of Terpene Molecules

In each group of terpenes, a unique precursor leads to the different known constituent by a succession of classic reactions such as cyclizations, functionlization or rearrangements. The precursor for the chief classes of terpenes are formed by reactions catalyzed by enzymes, and are phosphoric esters of  $(C_5)_n$  alcohols formed by the sequential addition of a  $C_5$  unit, isopentenyl pyrophosphate (IPP) **21** onto a starter molecule, namely an allylic prenyl phyrophosphate, with first unit in the series being dimethyl allyl pyrophosphate (DMAPP) **22**.

Further reaction will then occur where the DMPP reacts with IPP to give FPP. FPP further will react with IPP to form the precursor of a diterpene called GCPP. The precursors of triterpene were formed by two unit of FPP and the mechanism of the reaction is as shown in scheme 2.1. The abbreviations of the precursors are described as below:

- 1) Geranyl pyrophosphate (GPP) **(23)**, precursor of C<sub>10</sub> monoterpenes
- 2) Farnesyl pyrophosphate (FPP) **(24)**, precursor of sesquiterpenes and triterpenes
- 3) Geranylgeranyl pyrophosphate (GCPP) **(25)** precursor of C<sub>20</sub> diterpenes
- 4) Geranylarnesyl pyrophosphate (GFPP) precursor of C<sub>25</sub> sesterpenes



Scheme 2.1: The formation of the monoterpenes, sesquiterpene, diterpene and triterpene precursors

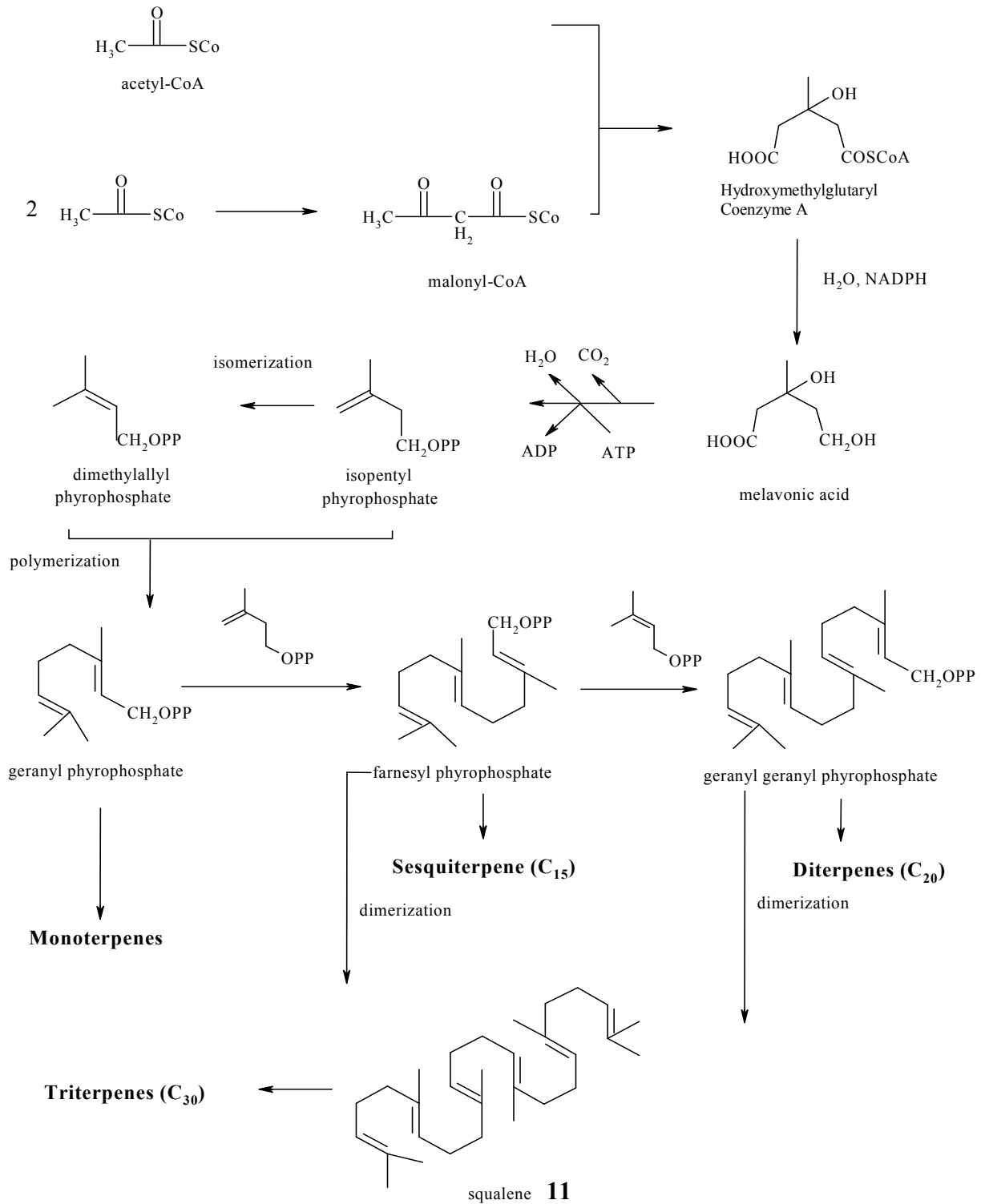
MVA= Methylcrotonyl acid

IPP= isopentenyl pyrophosphate

DMPP=dimethylallyl pyrophosphate

FPP= farnesyl pyrophosphate

GGPP= geranylgeranyl pyrophosphate



Scheme 2.2: Biosynthesis of terpenes<sup>18</sup>

## 2.4 Triterpenes<sup>18-20</sup>

Triterpenes comprise a group of isoprenoids typically containing 30 C-atoms that originate from six isoprenyl residues. The triterpenes form the largest group among the terpene classes, and are widely distributed in the plant kingdom, either in the Free State or as esters or glycosides. Plants contain a huge variety of cyclic triterpenes that do not occur at all in animals and fungi. These triterpenes play an important role mediating plant-plant, plant-insect and plant-pathogen interactions. The corresponding biosynthesis will be discussed in following section.

The triterpenoids are large structurally diversified group of natural products derived from squalene or related acyclic carbon precursor. Triterpenoids with well characterized biological activities include sterols, steroids and saponins. This large group of natural products displays well over 100 distinct skeletons. Most triterpenes are 6-6-6-6 tetracycles, 6-6-6-6-5 pentacycles, or 6-6-6-6-6 pentacycles, but acyclic, monocyclic, bicyclic, tricyclic and hexacyclic triterpenoids have also been isolated from natural sources.

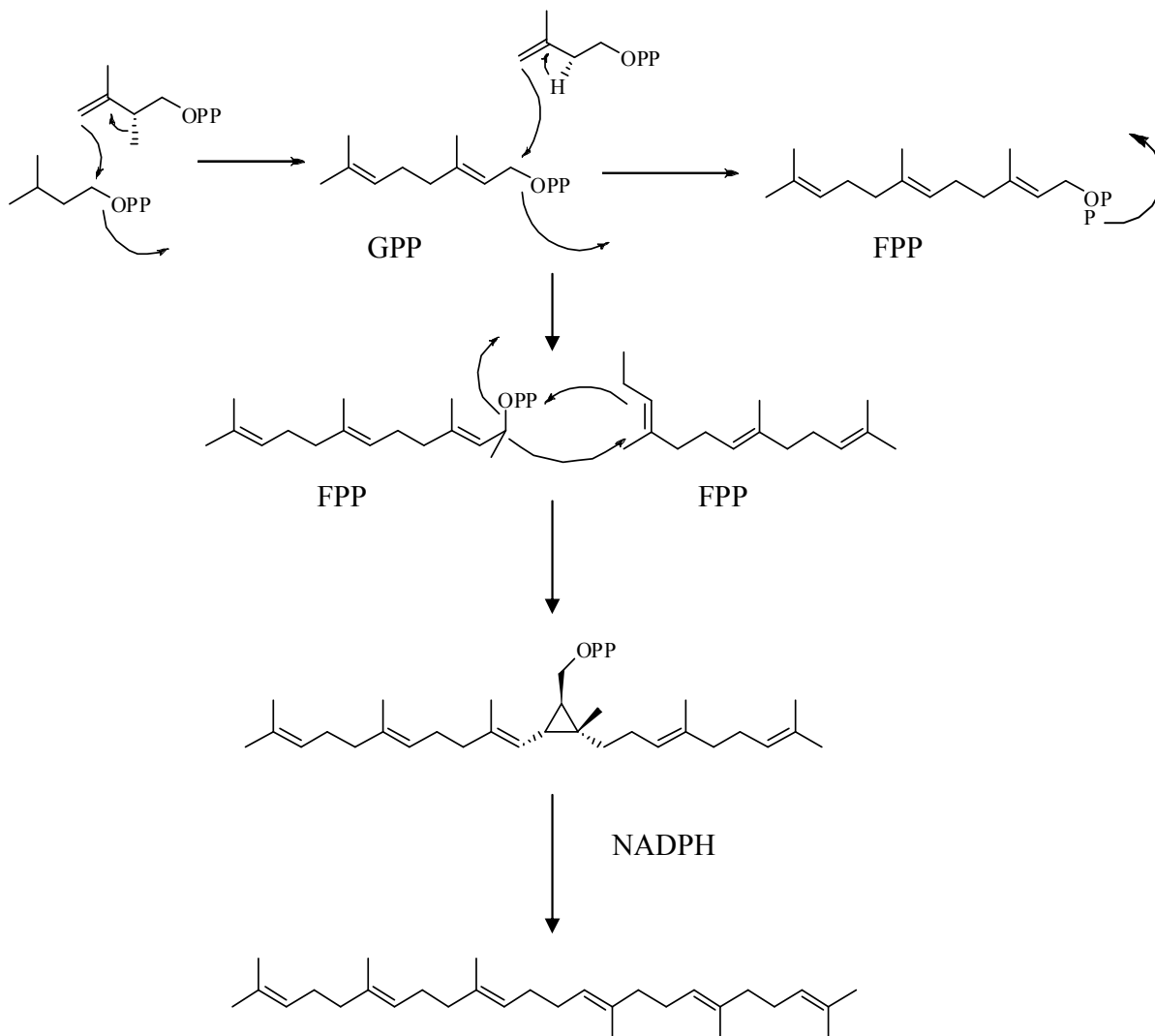
Almost all triterpenoids are hydroxylated at the 3- position (because they arise from opening of the epoxide). Therefore, triterpenes have very high structural homogeneity and the major difference is in the type configuration, depending on to the conformation originally adopted by the squalene epoxide (or by squalene **11** prior to cyclization). The cation resulting from the cyclization can subsequently undergo a series of 1, 2 proton

methyl shifts, which can be used to rationalize the occurrence of different tetra- and pentacyclic skeleton characteristic of this group.

At first glance, it is easy to think that steroids are of triterpene type because of the tetracyclic structure. However, steroids are different from terpenes due to the loss of at least 3 methyl groups at position 4 and 14. The losses of the methyl group are easily identifiable in the  $^1\text{H-NMR}$  spectrum, thereby distinguishing steroids from triterpenes.

#### **2.4.1 Triterpenes Biosynthesis**<sup>18-20</sup>

Triterpene biosynthesis proceeds via the isoprenoid pathway in which 3 isoprene units (molecules containing 5 C – atoms) are first linked in a head to tail manner to each other, resulting in the 15 C atom farnesyl pyrophosphate **24** which are subsequently linked in a tail to tail manner to give a compound of 30 carbon atoms called squalene (Scheme 2.3). Squalene is oxidized into oxidosqualene **26** which is a common starting point for cyclization reactions in triterpenoids biosynthesis.



11

GPP= geranylpyrophosphate

FPP= farnesylpyrophosphate

NADPH= nicotiamide adenine dinucleotide phosphate

Scheme 2.3: Biosynthesis of squalene<sup>18</sup>

Oxidosqualene is converted to cyclic derivative via protonation and epoxide ring opening, which creates a carbocation that can undergo several types of cyclizations reactions. After these cyclizations, subsequent rearrangement can proceed in a different way by a series of hydride shifts and/ or methyl migrations. Finally the carbocations are neutralized by proton elimination to give the double bond or cyclopropyl ring, or by reaction of water to give hydroxyl group.

Cyclizations of oxidosqualene **26** to triterpenes can proceed in two ways, either by chair-chair-chair conformation or chair-boat-chair conformation. An important difference between the two resulting skeletons lies in the stereochemistry, which is clearly shown by the configurations of the C-8 and C-14 atoms. After cyclizations of the chair-chair-chair conformation, the methyl group at C-8 is pointing upward and the one at the C-14 atom is pointing downward, which are opposite to those resulting of the chair-boat-chair conformation (Scheme 2.4 and 2.5).

A proton initiated cyclization of the chair-chair-chair conformation results in the tetracyclic dammaranyl C-20, and all triterpene derived from this carbocation are classified as the dammarane type triterpene. A series of a hydride and methyl shifts in the dammaranyl cations **27** leads to the tirucallanyl C-8 carbocation **28**, and all triterpene that derived from this carbocation are classified as the tirucallane triterpenes (Scheme 2.5)

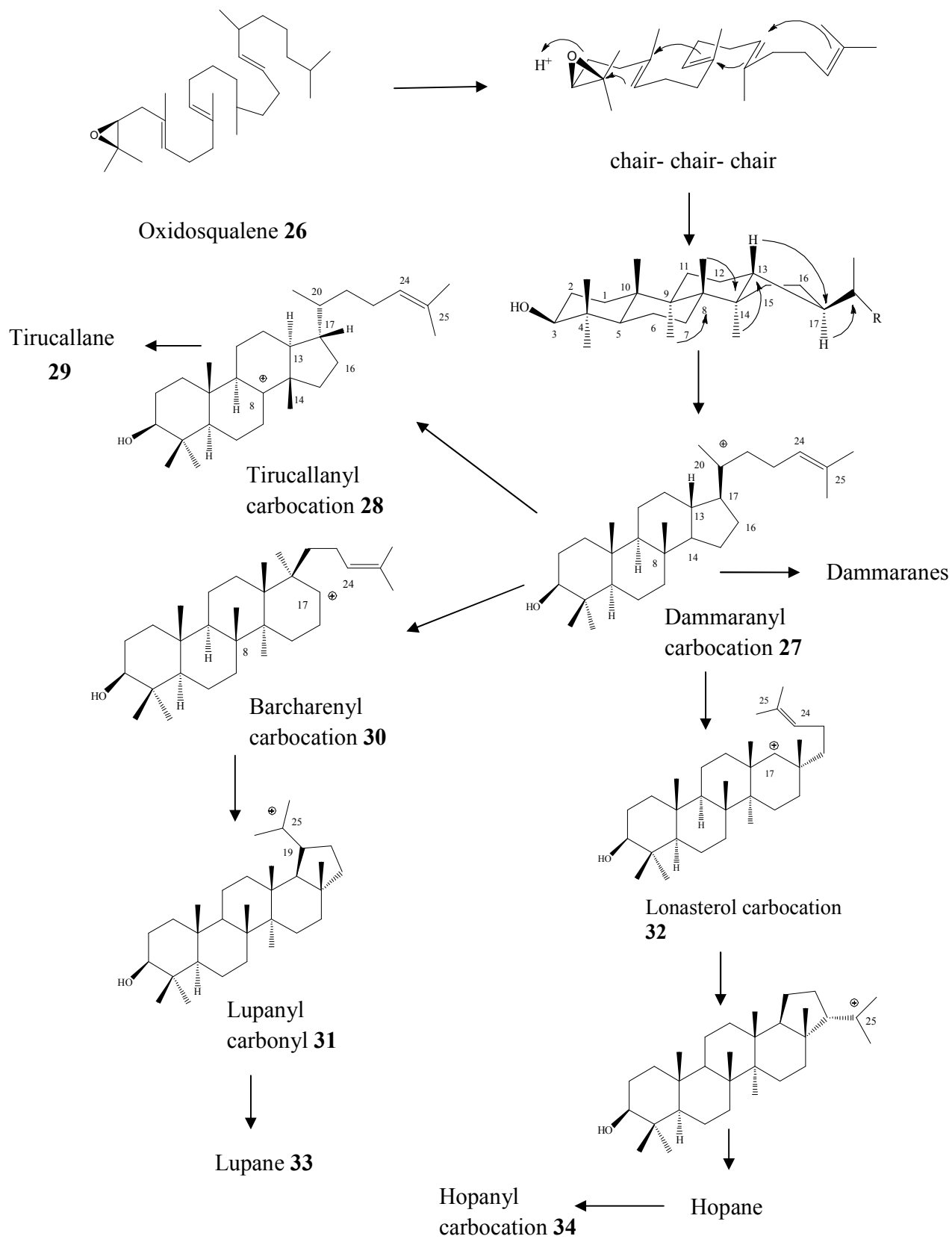




A shift of the C-16 –C-17 bonds leads to the tetracyclic C17 bacharenyl carbocation **30** and can be followed by a reaction with the C-24 –C-25 double bond to produce pentacyclic C25 lupanyl carbocation **33**. All saponins derived from this carbocation are classified as the lupine type triterpenes. A shift of the C13-C17 in the C-20 dammaranyl carbocation leads to a C17 carbocation, which can be cyclized by a reaction with the double bond in the side chain to form the pentacyclic hopanyl carbocation **34**. All triterpenes that are derived from this carbocation are classified as the hopane type triterpenes (Scheme 2.5).

The initial substrate chair-boat chair conformation of 2,3-oxidosqualene to lanosterol, putative conformations after A-ring, B-ring, C-ring closure and skeletal rearrangement of protosterol cation through 1,2 –shifts hydride and methyl group are shown in scheme 2.4. First, (3*S*)-oxidosqualene adopts a pre organized chair boat chair conformation. Protonation of the epoxide ring then triggers a cascade of ring forming reactions to the protosterol cation. Skeletal rearrangement of this intermediate through a series of 1, 2 hydride and 1, 2- methyl group shifts and a final deprotonation step leads to the product lanosterol or cycloartanol.

Deprotonation of lanosteryl carbocation **32** gives lanosterol and all saponins derived from lanosterol are classified as the lanostane type triterpenes. Lanosterol can undergo demethylation and isomerization of the double bond, leading to cholesterol. Triterpene derived from this skeleton are classified as the steroid type triterpene.

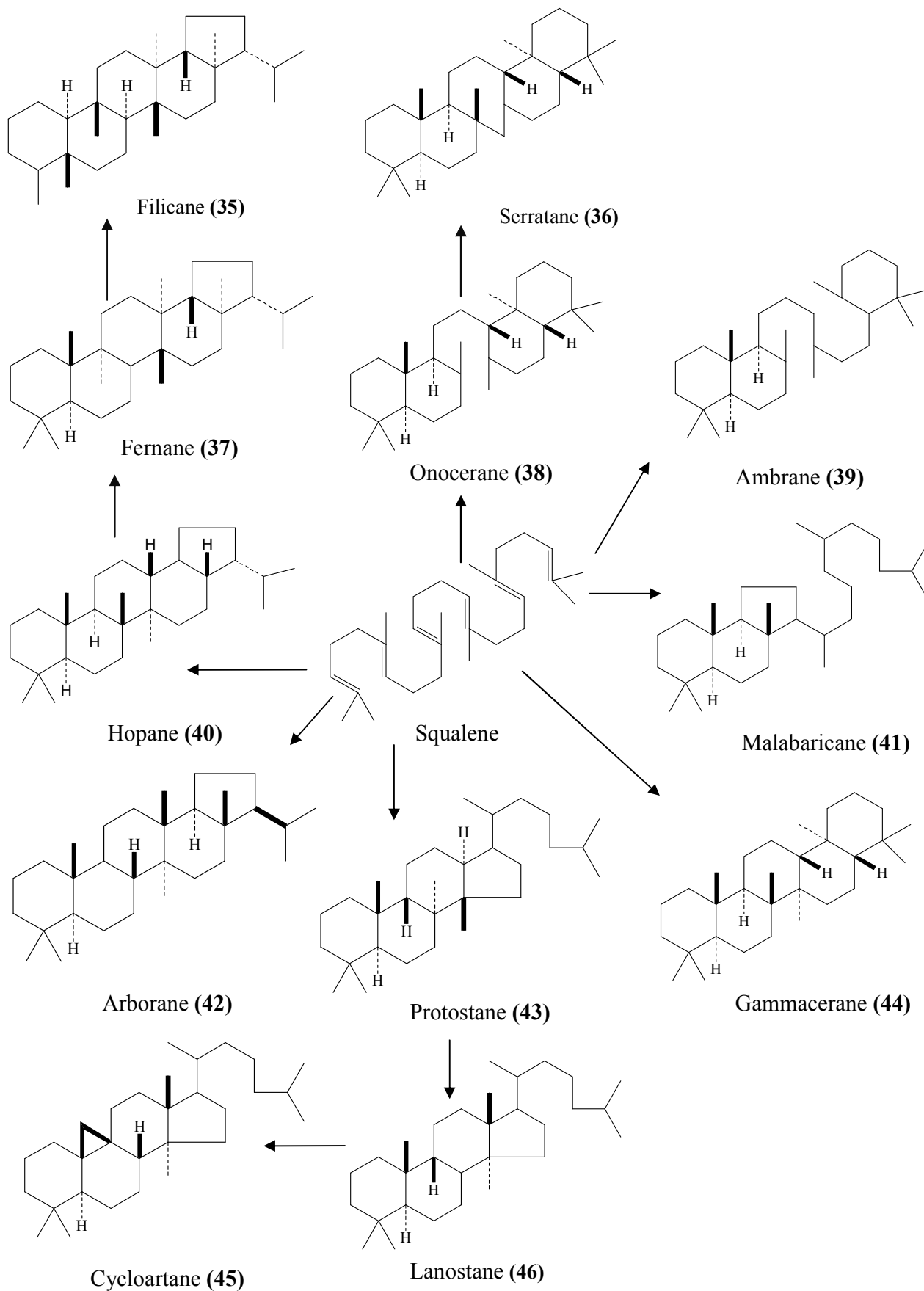


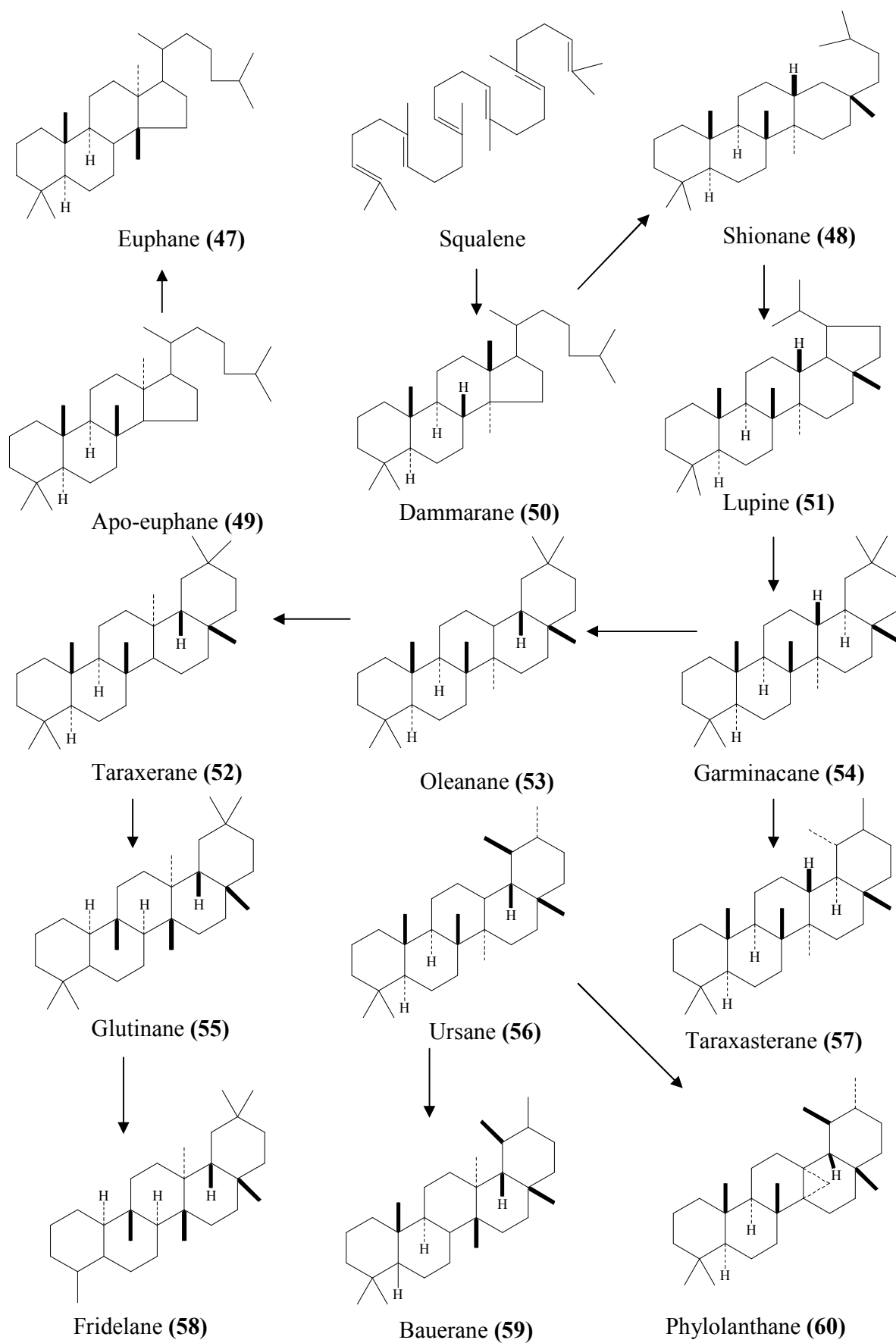
Scheme 2.5: The cyclisation of oxidosqualene to the various triterpenes

## 2.5 Triterpene skeletons<sup>20</sup>

Triterpene structures consist of different skeletons. The dammarane **50**, lupine **51**, hopane **40**, oleanane **53**, taraxasterane **57**, ursane **56**, cycloartane **45**, lanostane **46** and euphane **47** are the most well known triterpenoid skeletons. Other types of skeleton can be found in plants and their structures were illustrated as in figure in page 29 and 30. These skeletons exist as a result of cyclisation, rearrangement and degradation sequence of reaction. There are however several pathways known for the biosynthesis of triterpenoids, leading to different types of triterpenoid skeletons. Several skeletons have been found to undergo ring cleavage leading to seco skeletons, homologation (leading to homo and bis homo skeleton), degradations to nor or bis nor compounds, or minor rearrangement to related skeleton.

The dammarane skeleton can undergo further processing to give the 3, 4 seco dammarane skeleton and the 15, 16 seco dammarane skeleton. The lupane skeleton can be cleaved to give the 3, 4 seco lupane skeleton. The side chain of the 5 member ring in the hopane skeleton can be rearranged to hopenes or to be degraded as bis-nor hopenes. The oleanane skeleton can be fragmented to the 17, 22 seco skeleton or rearranged to a ring A nor-ring B homo skeleton. Degradation of the oleanane skeleton leads to the 23-nor, the 27 nor, the 28 nor or the 30 nor skeletons. The steroid skeleton can be homologated to the 24-bis homo skeletons. Furthermore the steroid skeleton can be degraded in the side chain to the nor skeleton which belongs to the pragnane type steroids, which has been indicated as the 22-homo pragnane skeleton.

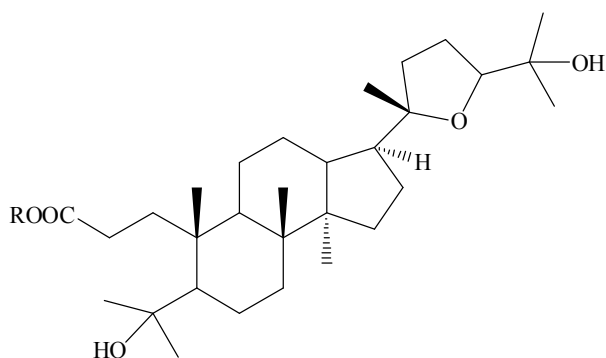
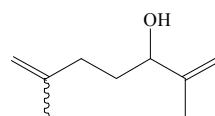
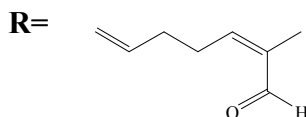
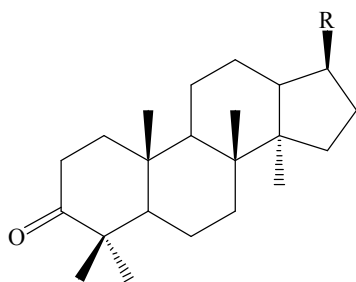




Scheme 2.6: Cyclization of squalene to various triterpene skeletons (pg 29 and 30)

## 2.6.1 Types of triterpenes found in Meliaceae.

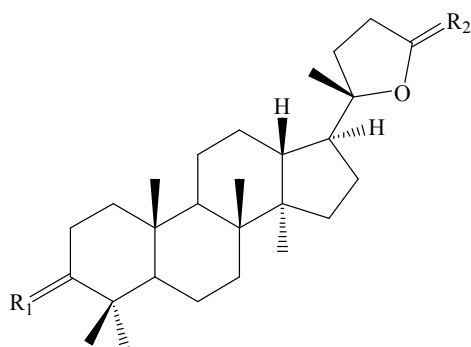
### i) Dammarane type



R=H,24*S* Faveolin A **63**<sup>23</sup>

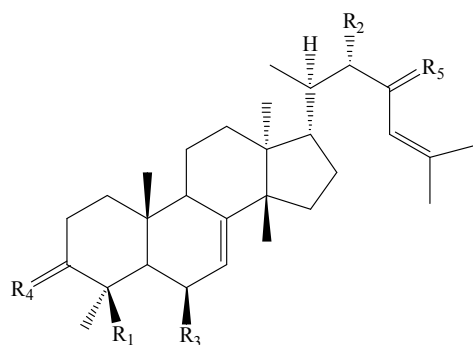
R=Me, 24*S* Dymalol **64**<sup>24</sup>

R=H,24*R* Foveolin B **65**<sup>23</sup>

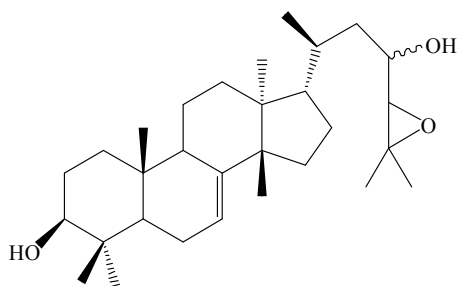


R <sub>1</sub>	R <sub>2</sub>	
O	$\alpha$ -C(Me <sub>2</sub> )OH, $\beta$ -H	Ocotillone <b>66</b> <sup>25</sup>
$\alpha$ -H, $\beta$ -OH	$\alpha$ -C (Me <sub>2</sub> ) OH, $\beta$ -H	Ocotillol-II <b>67</b> <sup>25</sup>
O	O	Cabralealactone <b>68</b> <sup>25</sup>

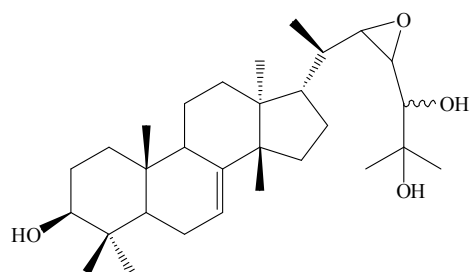
## ii) Tirucallane Type



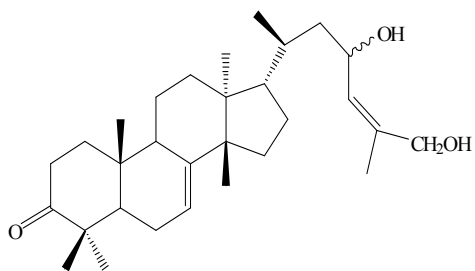
R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	
CH <sub>2</sub> OH	OH	H	O	O	Dymacrin A <b>67</b> <sup>26</sup>
CH <sub>3</sub>	OH	H	O	O	Dymacrin B <b>68</b> <sup>26</sup>
CH <sub>2</sub> OH	OH	H	O	O	Dymacrin C <b>69</b> <sup>26</sup>
CH OH	H	O	O	O	Dymacrin D <b>70</b> <sup>26</sup>



24, 25-epoxy-3 $\beta$ , 23-dihydroxy-7-tirucallene **71**<sup>27</sup>



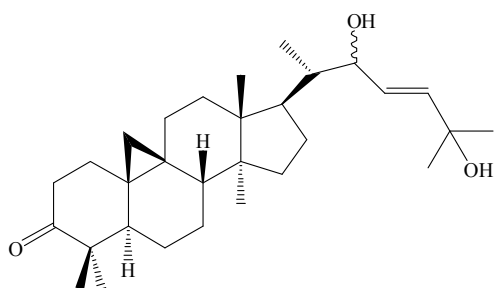
22, 23-epoxy-tirucalla-7-ene-3 $\beta$ , 24, 25-triol **72**<sup>27</sup>



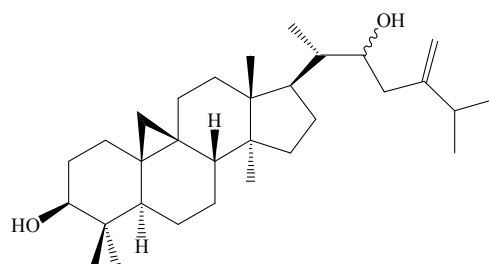
23, 26-dihydroxytirucalla-7, 24-dien-3-one **73**<sup>27</sup>



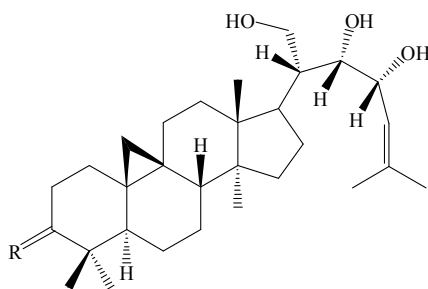
### iii) Cycloartane Type



22, 25-dihydroxycycloart-23E-en-3-one **74**<sup>28</sup>

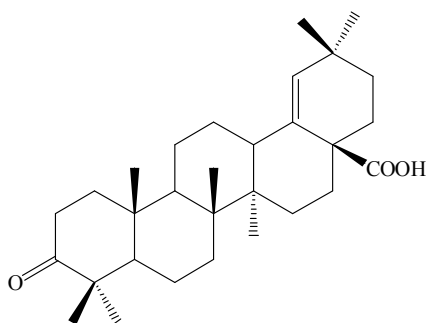


24-methylenecycloartane-3β-22-diol **75**<sup>28</sup>

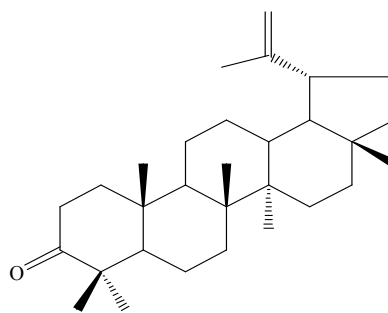


Argenteanone B **76**<sup>29</sup>, R=O  
Argenteanol **77**<sup>29</sup>, R=OH

### iii) Pentacyclic triterpenes



Betulinic acid **78**<sup>30</sup>



Moronic acid **79**<sup>31</sup>

Table 2.2: Occurrence of dammaranes compounds in species of Meliaceae

Compound	OH	Configuration	Sources	References
Aglaiol	3 $\beta$	24,25epoxide	<i>Aglaia odorata</i>	41
Aglaiondiol	3 $\beta$ , 25		<i>Aglaia odorata</i>	44
Aglaitriol	3 $\beta$ , 24R, 25		<i>Aglaia odorata</i>	44
Cabraleadiol	3a, 25	20S, 24R oxide	<i>Cabranea politricha</i>	34
			<i>Cabranea eichleriana</i>	42
			<i>Aglaia tomentosa</i>	39
			<i>Aglaia foveolata</i>	43
Cabraleone	25	20S, 24S oxide	<i>Cabranea politricha</i>	34
			<i>Cabranea eichleriana</i>	42
			<i>Dysoxylum richii</i>	32
			<i>Dysoxylum muelleri</i>	40
			<i>Aglaia lawii</i>	39
			<i>Aglaia elaegnoidea</i>	36
cabraleahydroxy lactone		20S, 24 lactone	<i>Cabranea politricha</i>	42
			<i>Cabranea eichleriana</i>	34
Ocotillol		20S, 24R oxide	<i>Dysoxylum cauliflorum</i>	38
			<i>Aglaia elliptica</i>	35

'Table 2.2, continued'

Ocotillone <b>81</b>	25		<i>Dysoxylum cauliflorum</i>	34
			<i>Dysoxylum richii</i>	32
			<i>Cabrlea eichleriana</i>	38
Cabrlealactone <b>82</b>	20 <i>S</i> , 24 lactone		<i>Aglaia tomentosa</i>	39
			<i>Cabrlea eichleriana</i>	34
Richnone		20 <i>S</i> , 24 <i>S</i> oxide	<i>Dysoxylum richii</i>	32
Richenol		20 <i>S</i> , 24 <i>S</i> oxide	<i>Dysoxylum richii</i>	32
Aglinins C		20 <i>S</i> , 24 oxide	<i>Aglaia tomentosa</i>	39
Aglinins D		20 <i>S</i> , 24 oxide	<i>Aglaia tomentosa</i>	39

Table 2.3: Occurance of 3, 4- secodammaranes in species of Meliaceae

Compound	OH	Configuration	Sources	References
Shoreic acid <b>83</b>	25	20 <i>S</i> , 24 <i>R</i> oxide	<i>Cabrlea eichleriana</i>	34
			<i>Dysoxylum richii</i>	43
			<i>Aglaia foveolata</i>	38
			<i>Dysoxylum cauliflorum</i>	32

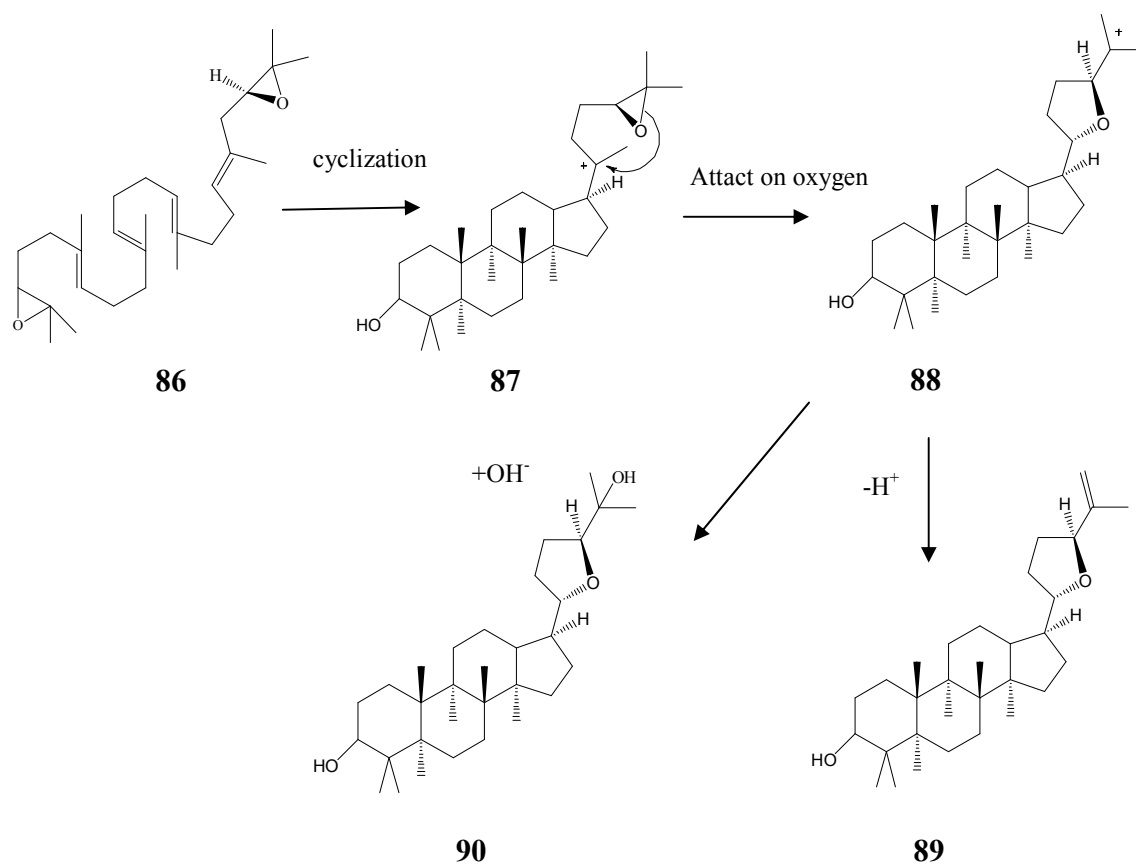
‘Table 2.3, continued’

Eichlerianic acid <b>84</b>	25	20 <i>S</i> , 24 <i>S</i> oxide	<i>Cabrlea eichleriana</i>	34
			<i>Dysoxylum richii</i>	32
			<i>Aglaia elliptica</i>	39
			<i>Aglaia lawii</i>	35
			<i>Aglaia foveolata</i>	43
Dammarenolic acid	20β		<i>Cabrlea eichleriana</i>	34
Eichlerialactone <b>85</b>		20 <i>S</i> , 24 <i>R</i> lactone	<i>Cabrlea eichleriana</i>	38
			<i>Dysoxylum cauliflorum</i>	34
Richenoic acid		20 <i>S</i> , 24 <i>S</i> oxide	<i>Dysoxylum richii</i>	32
Aglinis A	24, 25	20 <i>S</i> , 24 <i>S</i> oxide	<i>Aglaia lawii</i>	39
Aglinis B	4, 24, 25	20 <i>S</i> , 24 oxide	<i>Aglaia lawii</i>	39
Foveolin A	25	20 <i>S</i> , 24 <i>S</i> oxide	<i>Aglaia lawii</i>	39
Foveolin B	4, 25	20 <i>S</i> , 24 <i>S</i> oxide	<i>Aglaia foveolata</i>	43

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## 2.7 The tetrahydrofuran sidechain formation<sup>20</sup>

The cyclization of bis-oxidosqualene **80** to the 17 $\beta$  intermediate cation **81** followed by the 17 $\alpha$ -hydride shift with the side chain *syn* to C16 to generate the 20*S* stereocenter is shown in the first mechanism in scheme 2.7. The attack of oxygen on intermediate cation **81** will form another intermediate cation **82**. The intermediate cation **82** will undergo deprotonation or quenched by hydroxide molecule to form 2 compounds with tetrahydrofuran sidechain **83** and **84**. Scheme 2.7 showing example of the formation of the compounds with tetrahydrofuran sidechain



Scheme 2.7: The formation of tetrahydrofuran sidechain<sup>20</sup>

## 2.8 Aromatic Compounds: The Phenolics<sup>45, 46, 47</sup>

Phenolics are a huge and diverse group of aromatic compounds (containing benzene rings) usually with hydroxyl groups. Many plant phenolics have three carbon side chains and are called phenyl propanoids.

Harborne and Simmonds have divided the phenolic constituents in plants into several families as illustrated in Table 2.4, due to the diverse group of the plant phenolics. Later on, Swain and Bate Smith distinguished between common and less common phenolic constituents. In order to do this, the substances have been assembled into three groups:

- i) The families of widely distributed phenolic constituents.
- ii) The families of less widely distributed constituents.
- iii) Phenolics constituents present in nature in polymeric form.

Table 2.4: Classification of phenolic constituents in plants

Number of carbon atoms	Families of phenols
C <sub>6</sub>	*Simple phenols
C <sub>6</sub> -C <sub>1</sub>	#Phenolic acids and related compounds
C <sub>6</sub> -C <sub>2</sub>	*Acetophenones and phenylacetic acids
C <sub>6</sub> -C <sub>3</sub>	#Cinnamic acid and related compounds
C <sub>6</sub> -C <sub>3</sub>	*Coumarins, isocoumarins and chromones
C <sub>15</sub>	#Flavones
C <sub>15</sub>	#Isoflavones and isoflavonoid
C <sub>15</sub>	#Flavonols, dihydroflavanols and related compounds
C <sub>15</sub>	#Anthocyanidins
C <sub>15</sub>	#Chalcones, aurones and dihydrochalcones.
C <sub>30</sub>	*Biflavonyls
C <sub>6</sub> -C <sub>1</sub> -C <sub>6</sub>	*Benzophenones, xanthenes and stilbenes.
C <sub>6</sub> -C <sub>2</sub> -C <sub>6</sub>	
C <sub>6</sub> , C <sub>10</sub> , C <sub>14</sub>	*Quinones
C <sub>18</sub>	*Bentacyanins

\*The families of widely distributed phenolic constituents.

#The families of less widely distributed phenolic constituents.

The following subchapter will discuss briefly the C<sub>6</sub>-C<sub>3</sub> types of phenolics.

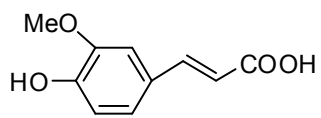
### 2.8.1 The C<sub>6</sub>-C<sub>3</sub> phenolics constituent.<sup>47, 48</sup>

The C<sub>6</sub>- C<sub>3</sub> skeleton is the most common and the most important. Many phenolic compounds reported possess this structure. This group includes, to begin with, the alcohols derived from the cinnamic acids, which is more commonly than their C<sub>6</sub>-C<sub>1</sub> counterparts. Confineryl **91** and sinapyl **92** alcohols are constituents of woody plants: they are regarded as precursors of lignin.

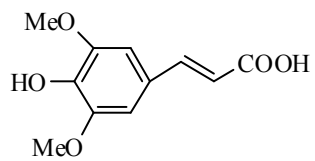
Attention must also be given to two amino acids, which possesses phenolic functions, although they are not usually considered along the phenolic constituents: tyrosine **93** and dihydroxyphenylalanine **94**. In the course of alcoholic fermentation tyrosine is converted into *p*-hydrxyphenylethanol **95**, which is a normal constituent of fermented beverages, beer and wine. To these structures may also be added various aromatic amines, such as tyramines **96**, which are sometimes classified as alkaloids.

Phenolic substances with phenylpropane structures such as eugenol **97** and isoeugenol **98** should be placed in this class of C<sub>6</sub>-C<sub>3</sub> compounds. These are constituents of essential oil. Here also are to be included the lignin, C<sub>6</sub>-C<sub>3</sub> dimers which are heartwood constituents associated with lignin. They are different structural types, such as the dibenzylbutyrolactones (e.g matairesinol **99**), or the diphenyltetrahydrofurofurans (pinoresinol **100**). The last class of C<sub>6</sub>-C<sub>3</sub> to be mentioned is the chromene, which are not commonly found related to the coumarins. The simplest example is that of euginin **95**.

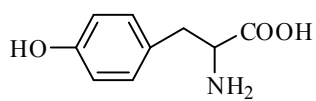




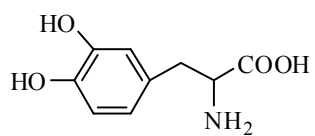
**91**



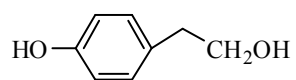
**92**



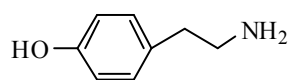
**93**



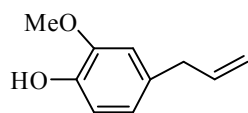
**94**



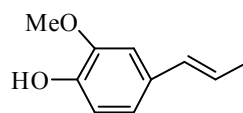
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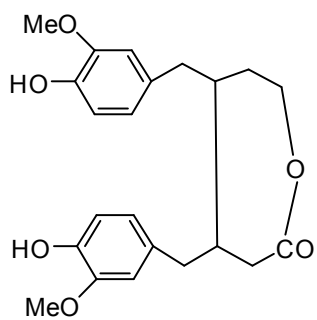
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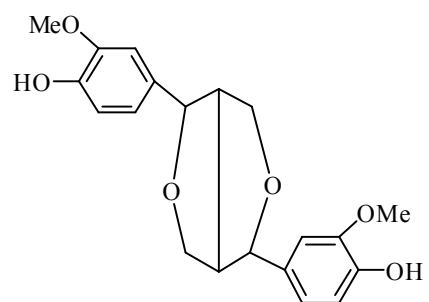
**97**



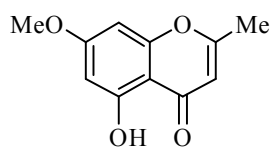
**98**



**99**



**100**



**101**

## 2.9 Biosynthesis/ biogenesis of Plant Phenolics<sup>49</sup>

### i) The shikimic acid pathway

The most common pathway is in the one which, via shikimate (shikimic acid) leads from monosacharides to aromatic amino acids (phenylalanine and tyrosine), then by deamination of the latter, to cinnamic acid and their numerous derivatives including benzoic acids, acetophenones, lignans, lignins and coumarins.

### ii) The acetate or polyketide pathway

The other pathway begins with acetate and leads to poly- $\beta$ -ketonesters, by cyclization (Claisen or aldol condensation), products that are often polycyclic, including chromones, isocaumarins, orcinols, depsides, depsidones, xanthonones and quinines.

### iii) The mevalonic acid pathway

This pathway leads to the formation of aromatic terpenoids and steroids containing aromatic ring.