HISTORICAL

1. Chemistry of Sesquiterpene Lactones

Sesquiterpene lactones, the derivatives of sesquiterpene, belong to a group of terpenoid or isoprenoid compounds (41, 42). Terpenoids are formed by the polymerization of isoprene units 1 (42). The term sesquiterpene lactone refers to a group of natural products containing 15 carbon atoms which are derived from three isoprene units to form various types of carbocyclic skeleton and the γ-lactone ring. Numbering of the basic carbocyclic ring systems is generally found to be consistent in this thesis with the exception of C-14 and C-15 which are frequently interchanged as shown in chart 9 p. 37 (43).

Most sesquiterpene lactones have the lactone ring either *cis*- or *trans*-fused to the C_6-C_7 or C_8-C_7 position of the carbocyclic skeleton. If the lactone ring is the exocyclic α, β-unsaturated lactone or α-methylene γ-lactone or "active functional group" 2, it can react with thiols *via* Michael addition reaction, and shows biological activities (44, 45). The structural modifications of the basic terpene skeleton involve the incorporation of an epoxide ring, hydroxyl groups, O-acyl groups, side chain esters and a conjugated cyclopentenone (44, 45).

$$H_2C = \overset{\overset{\displaystyle CH_3}{|}}{C} - CH = CH_2$$
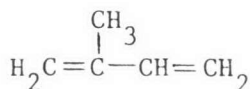
1 isoprene unit
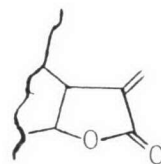
2 α-methylene γ-lactone

2. Classification of Sesquiterpene lactones

The classification of sesquiterpene lactones is based on their carbocyclic skeletons as germacranolides, eudesmanolides, guaianolides, xanthanolides, elemanolides, pseudoguaianolides, eremophilanolides and bakkenolides. The suffix "olide" refers to the lactone group (43, 44).
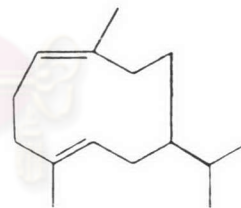
2.1 Germacranolides
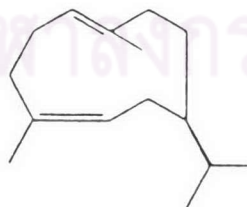
2.1.1 Structural Types of Germacranolides

The germacranolides represent the largest group of sesquiterpene lactones with nearly 300 known naturally occuring members (44). The structural skeleton, a 1(10), 4-cyclodecadiene, has four basic configurational isomers as shown in chart 1 3-6 (p. 20).
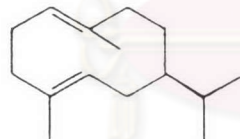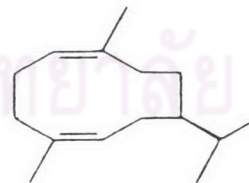

3 germacrolide   4 melampolide

5 heliangolide   6 *cis,cis*-germacranolide

Chart 1. Configurational types of germacranolides

The majority of the germacranolide subgroup represents germacrolides $\underline{3}$, although an increasing number of melampolides $\underline{4}$ and heliangolides $\underline{5}$ have been isolated, and the smallest group is *cis, cis*-germacranolides $\underline{6}$ (43). Most of germacranolides have a **trans**-7, 6 or **trans**-7, 8 lactone ring fusion and the C_6-and C_8-oxygens are alpha configuration (43).

2.1.2 Chemical Transformations of Germacranolides

a. Hydrolysis and Relactonization

The various ester side chains attached to a germacranolide can be hydrolysed by alkaline with a distinct difference in ease (46). For example solution of K_2CO_3 in methanol-water at room temperature hydrolyzes 3-hydroxy-2-methylbut-2-enoate in 20 to 30 minutes whereas the isobutyrate, α-methyl-n-butyrate, tiglate and angelate give no reaction under the same conditions (43).

A general relactonization rule for germacranolides containing C-6 and C-8 α-oxygen functions depends upon strong alkaline treatment followed by acidification; this type of germacranolide always relactonizes to C-8 (43, 47).

b. Reduction and Oxidation

Generally, catalytic hydrogenation of sesquiterpene lactones with Pd-C as a catalyst as well as chemical reduction with $NaBH_4$ in methanol proceed with ease under saturation of the lactonic exocyclic methylene group to form the 11, 13-dihydro derivatives (43).

Reductive transformations of epoxides to alkenes have been used either zinc-copper couple (49) or $CrCl_2$ (43) as reducing agents.

Oxidation reactions have been frequently applied in structural elucidations of various types of germacranolides. MnO_2 oxidations generally transform primary allylic alcohols into α ,β-unsaturated aldehydes, a reaction that can be of considerable use for making configurational assignments to double bonds in the cyclodecadiene skeleton as well as for siting OH groups at C_{14} and/or C_{15} (43).

c. Cyclization Reaction of Germacranolides

Many lewis acid-catalyzed cyclization reactions of the cyclodecadiene or of 1, 10-and 4,5-epoxide derivatives have been studied. In general, cyclization of germacra-1,5-dienes provides eudesmanolides. For example the costunolide 7, when treated with a cation exchange resin (51) or $HClO_4$/AcOH (52), undergoes an acid-initiated cyclization through cation 8 to give a mixture of the eudesmanolides 9 and 10 (chart 2 p.23)

Further examples of the conversion of 1, 10-epoxygermacranolides into eudesmanolides include the derivatives of costunolide 7 (52), epitulipinolide 11 (53), tanacin 12 (54), herbolide B 13 (55) and eriofertin 14 (56).

In contrast, BF_3-catalysed reaction of the 4,5-epoxide dihydroparthenolide 15 gives cation 16 which after the loss of a proton from C-1 now forms the guaianolides 17 (57) (chart 3 p.24).

Further examples of cyclization reaction
of 4,5-epoxides which result in formation of guaianolides include
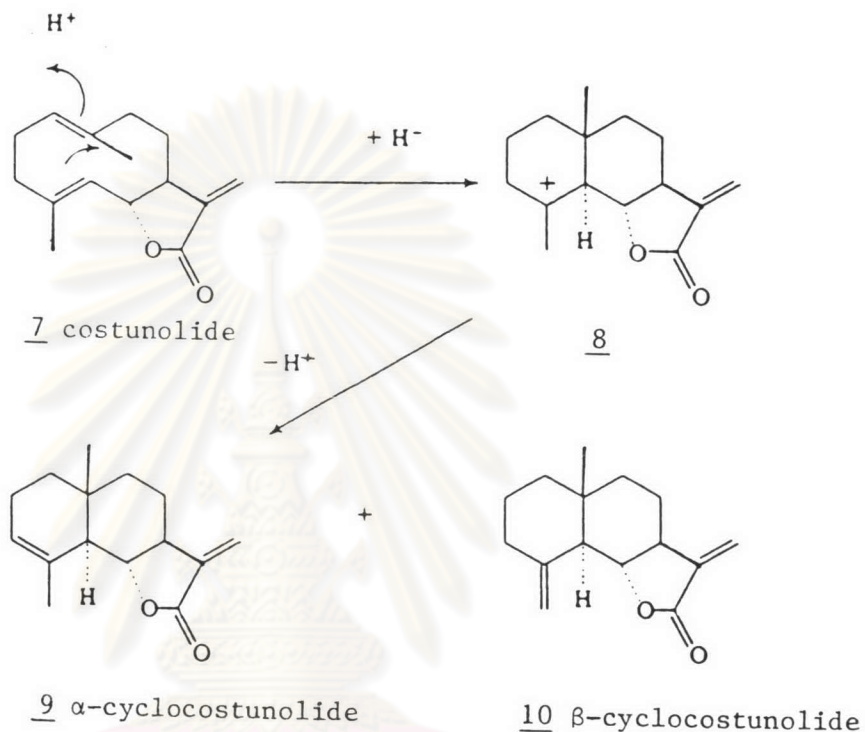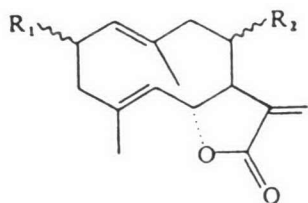parthenolide 18, lanuginolide 19 and derivatives (58).

Chart 2. Cyclization of costunolide

7 costunolide

8

9 α-cyclocostunolide   10 β-cyclocostunolide
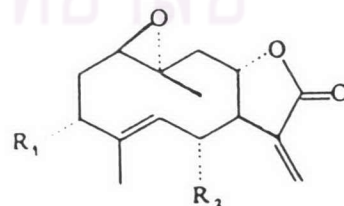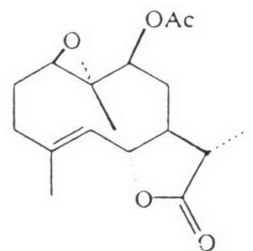

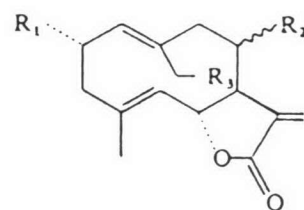11 Tulipinolide, epi; R$_1$=H,R$_2$=β-OAc   12 Tanacin; R$_1$=H,R$_2$=OAng

13 Herbolide B

14 Eriofertin; R_1=OH, R_2=χ-OAng, R_3=OH

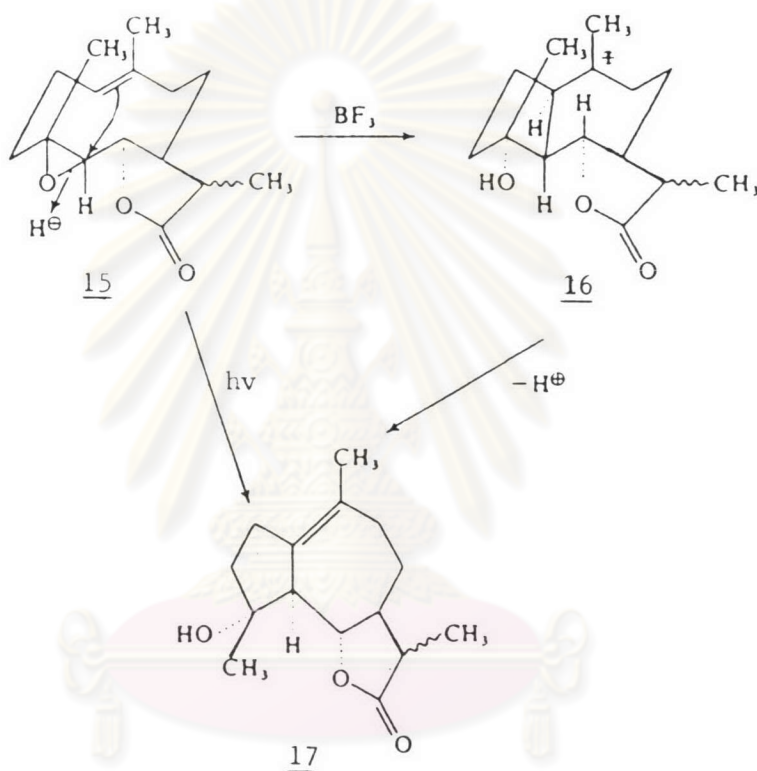15   BF$_3$ 16

hv $-H^{\oplus}$

17

Chart 3.   Cyclization of dihydroparthenolides
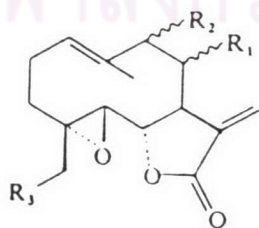
18 Parthenolide; R_1=R_2=R_3=H
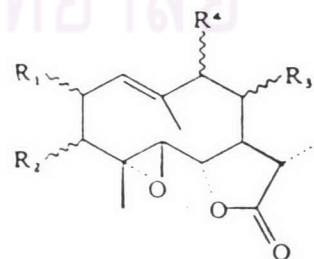
19 Lanuginolide; R_1=R_2=R_4=H, R_3=

α-OAc

d. Cope Rearrangements of Germacranolides

In general, thermal rearrangements of *trans*,*trans*-cyclodeca 1,5-dienic sesquiterpenes proceed in a highly stereospecific manner through a chair-like transition state resulting in a divinylcyclohexane skeleton, elemadiene skeleton.

e. Photochemical Reactions of Germacranolides

Doskotch and coworkers (59) isolated the first hydroperoxide-containing sesquiterpene lactones peroxyferolide 20, peroxycostunolide 21 and peroxyparthenolide 22, compounds of unexpected high thermal stability. Fischer and coworkers (43) were able to prepare the hydroxyperoxides 20 and 21 by a common photooxygenation procedure involving singlet oxygen generated by methylene blue sensitized oxygenation.
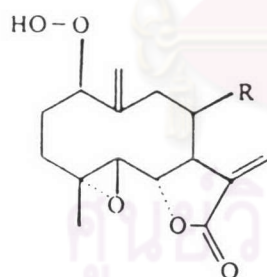
20 1-peroxycostunolide   21 peroxyferolide
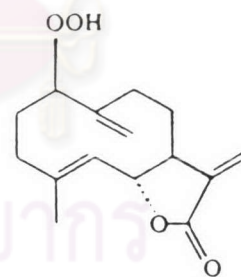
2.2 Eudesmanolides and Biogenetic Derivatives

2.2.1 Structure of Eudesmanolides and Biogenetic

Derivatives

The eudesmanolides (selinanolides) are based on the eudesmane (selinane) skeleton, most of members containing *trans*-7,6-α ,β-unsaturated γ-lactone. Compounds with 7,8-γ-lactone group may occur as *cis*-and *trans*-γ-lactones. Many members contain 3,4-, 4,5-and 4,15 double bonds as well as epoxide derivatives and hydroxyl and/or ketonic oxygen functions predominantly at C_1, C_3 and C_8 (43).

It is interesting that various taxa of the Hepaticae produce the eudesmanolides. The liverworts *Frullania tamarisci* (60) and *F. nisqualensis* contain eudesmanolides such as (-)-frullanolide 23, which are of the skeletal type commonly found in higher plants. However, other liverworts (61) produce the *ent*-eudesmanolides (+)-frullanolide 24 and related compounds.

The biogenetic derivatives of eudesmanolides are three 1,10-secoeudesmanolides eriolanin 25, eriolangin 26 and ivangulin 27; lumisantonin 28 and the phenyl containing vernodesmine 29 represent structural exceptions.
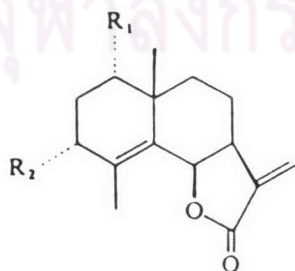
23 (-) Frullania lactone; $R_1=R_2=H$ 24 (+) Frullanolide
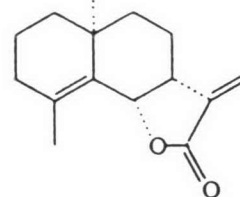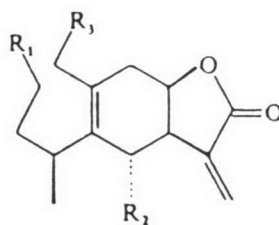
$\underline{25}$ Eriolanin; R_1=CH$_2$OH, R_2=OMac, R_3=OH

$\underline{26}$ Eriolangin; R_1=CH$_2$OH, R_2=OAng, R_3=OH

$\underline{27}$ Ivangulin; R_1=CO$_2$CH$_3$, R_2=R_3=H
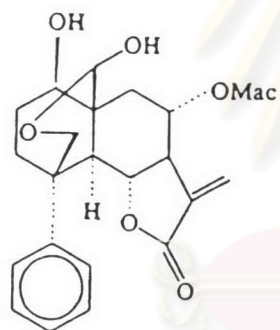
$\underline{29}$ Vernodesmin
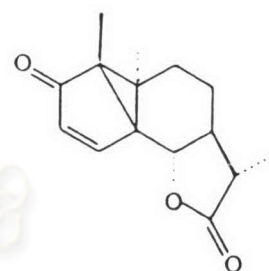
$\underline{28}$ Lumisantonin

2.2.2 <u>Chemical Transformation of Eudesmanolides</u>

a. <u>Dehydrogenation and Hydrogenation</u>

Pyrolysis of alantolactone $\underline{30}$ and isoalantolactone $\underline{31}$ at 350°C in the presence of Pd-C or Se results in the naphthalene derivative eudalene $\underline{32}$ with loss of the C_{10} methyl group (62) (chart 4 p. 28)

Grieco (63) used the dehydrogenation process involving the conversion of α-methyl γ-lactones into α-methylene-γ-lactones.

Catalytic hydrogenation of eudesmanolides results hydroderivatives (43).

$\underline{30}$ alantolactone $\underline{31}$ isoalantolactone

350° Pd-C or Se

$\underline{32}$ eudalene
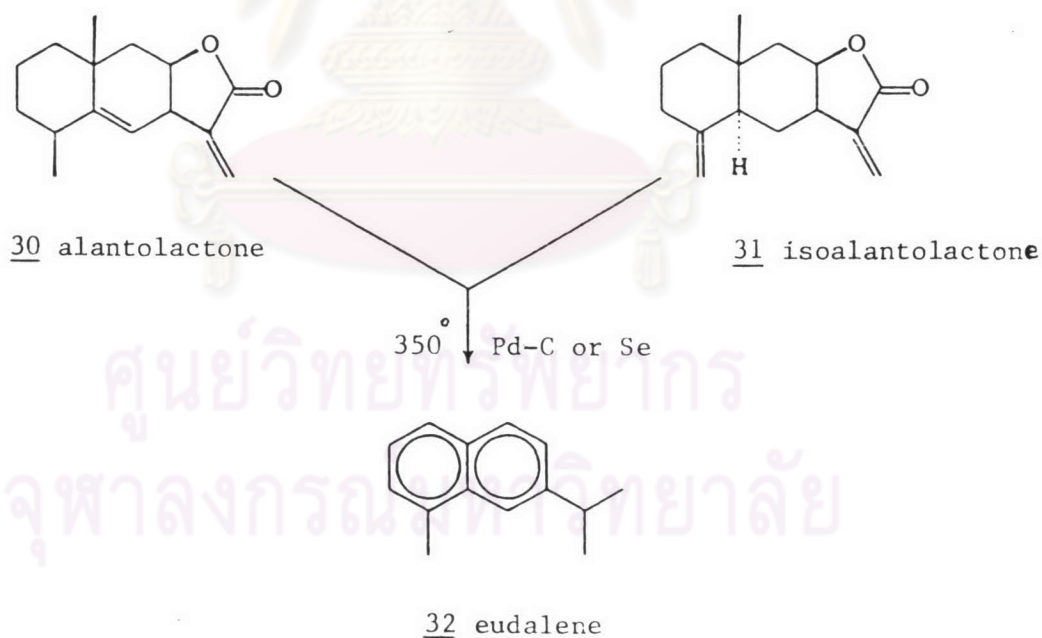
<u>Chart 4</u>. Dehydrogenation of alantolactone and isoalantolactone

b. Selected Chemical and Photochemical Modifications and Transformations of Eudesmanolides

Eudesmanolides have been frequently used as starting material for chemical and photochemical rearrangement processes which lead to other skeletal types of sesquiterpenes guaianolides, pseudoguaianolides, germacranolides and their derivatives (43).

2.3 Guaianolides and Seco-guaianolides (Xanthanolides)

2.3.1 Structural types

The guaianolides together with their seco-derivatives, the xanthanolides, represent one of the largest groups of sesquiterpene lactones with over 200 known naturally occuring compounds (43). The structural skeleton of guaianolides contains the 5,7-ring system and xanthanolides opened ring at C_4-C_5. Most of members contain *trans* 7,6-α,β-unsaturated γ-lactones or their 11,13-dihydroderivatives. Compounds with 7,8 lactone groups may occur as *cis*-and *trans*-γ-lactones.

2.3.2 Selected Chemical Transformations of Guaianolides and Xanthanolides

The simple chemical modifications have been frequently used in structure elucidation and making stereochemical assignment (43). Examples are epoxidation, catalytic hydrogenation, relactonization, oxidation, reduction and hydrolysis (43).

2.4 Elemanolides

2.4.1 Structure of Elemanolides

Elemanolides most likely involve Cope rearrangements of germacranolides which occur under laboratory reactions. It has been suggested that elemanolides isolated from plants are the artifact which formed from the germacranolides during the isolation procedure (43). The structural skeleton is divinylcyclohexane.

2.4.2 Selected Chemical Transformations of Elemanolides

Banker and Kulkarni (64) described monoepoxidations of saussurea lactone 33 and the Lewis acid catalyzed cyclization of the resulting monoepoxides 34, 35. Treatment of the 1,2-epoxide 34 with BF_3 results in the formation of the eudesmanolide dihydrosantamarin 36 and its 4, 15-double bond isomer, dihydroreynosin 37. The cyclization of the 3,4-epoxide 35 is more involved. Most likely, the epoxide ring is isomerized first with formation of an aldehyde at C-3 which is subsequently attacked by C-2 of the 1,2-double bond. Methyl shift from C-10 to C-1 and 1,10-double bond formation finally provide alcohol 38 (chart 5 p. 31)

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

$\underline{33}$

RCO₃H

$\underline{34}$ + $\underline{35}$

BF₃   BF₃

OH

$\underline{36}$ dihydrosantamarin:3.4-d.b. $\underline{38}$

$\underline{37}$ dihydrosantamarin:4.15-d.b.
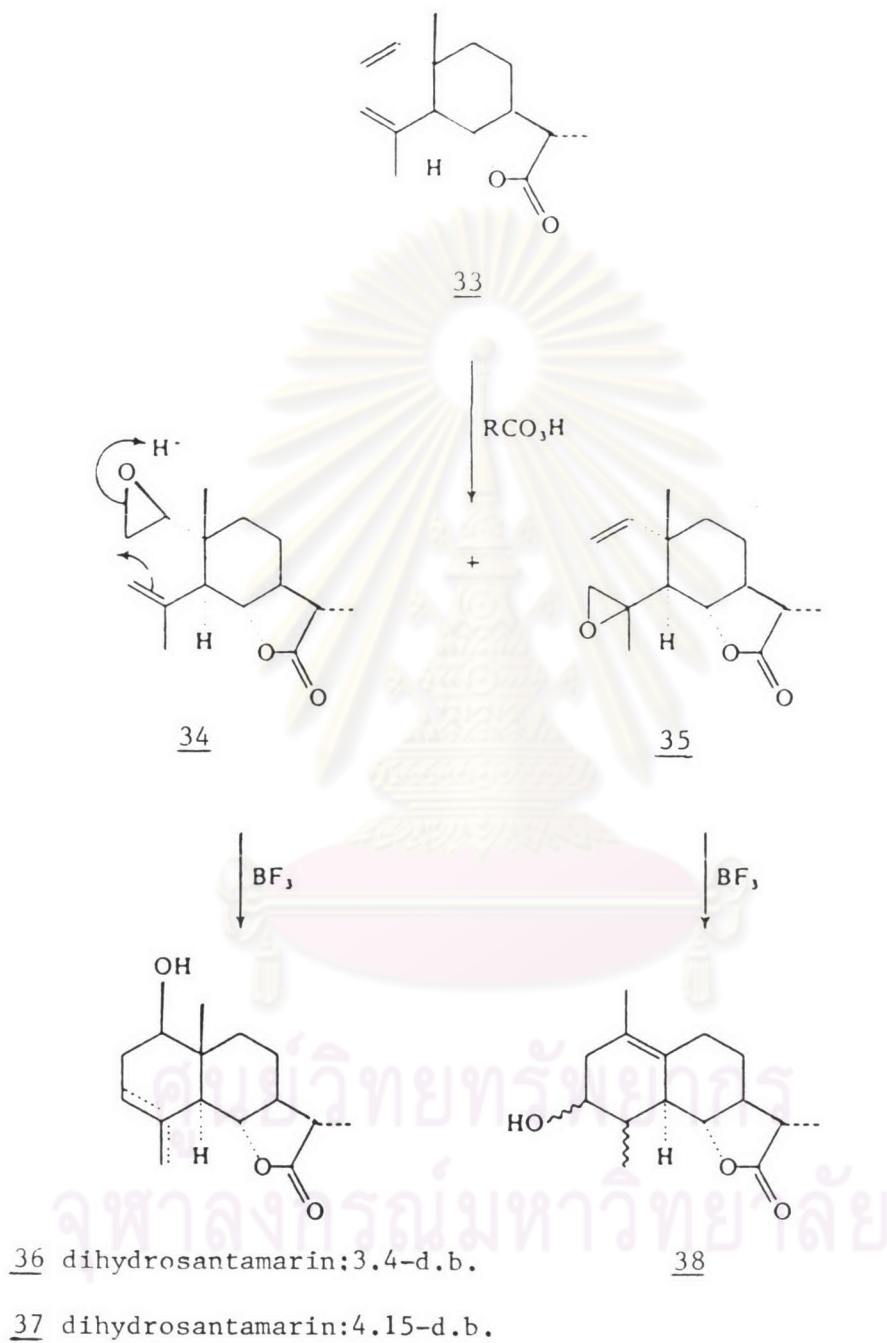
Chart 5. Lewis acid catalysed cyclization of elemanolide monoepoxides

2.5 Pseudoguaianolides and Biogenetic Derivatives

The pseudoguaianolides are based on the 5,7-ring skeleton which typically contain a methyl group at the C-5 ring junction. Formulae 39 and 40 illustrate the two major types of pseudoguaianolides both of which posses a *trans*-fusion of the 5,7-ring system. In the ambrosanolides 39, which usually occur in the subtribe Ambrosiinae and the genus *Parthenium* of the Compositae, the lactone ring is closed predominantly toward 6-β-oxygen. On the other hand, in the helenanolides, the type usually formed in the tribe Heleniae, the lactone ring is closed toward C-8 with the C-8-oxygen bond oriented either α or β(43).

39 ambrosanolide

40 helenanolide

2.6 Eremophilanolides and Bakkenolides

Eremophilanolides are eudesmanolides with methyl migration from C-10 to C-5 (43). Bakkenolides are being considered as derivatives of the eremophilanolides which result from ring contraction of ring B of the eremophilanolane skeleton followed by biomodification (43, 65).

3. Biosynthesis (Biogenesis) of Sesquiterpene Lactones

   3.1 Biosynthesis of Germacranolides

   The formation of germacranolides derived from *trans,* *trans*-farnesylpyrophosphate occurs through three principles stages :

   a. *trans, trans*-Farnesylpyrophosphate Biosynthesis

   The formation of *trans, trans*-farnesylpyrophosphate is through the pathway of acetyl CoA 41, acetoacetyl CoA 42, 3-hydroxy methyl glutaryl CoA 43, mevalonic acid 44, mevalonic acid pyrophosphate 45, isopentenylpyrophosphate 46, 3,3-dimethylallylpyrophosphate 47, geranylpyrophosphate 48 and *trans, trans*-farnesylpyrophosphate 49 (chart 6 p. 34)

   b. Germacrene Cyclization

   The elimination of the pyrophosphate group of the *trans, trans*-farnesylpyrophosphate 49 directly forms *trans, trans*-germacradiene cation 50. The intermediate 50 may be stabilized by elimination of a proton to form germacrene 51 (43, 66) (chart 7,p 35)

$$\text{CH}_3\text{-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-S-CoA} + \text{CH}_3\text{-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-CH}_2\text{-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-S-CoA}$$

<u>41</u> <u>42</u>

$$\text{HO-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-CH}_2\text{-}\overset{\overset{\text{CH}_3}{|}}{\underset{\underset{\text{OH}}{|}}{\text{C}}}\text{-CH}_2\text{-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-S-CoA} \quad \underline{43}$$

$$\text{HO-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-CH}_2\text{-}\overset{\overset{\text{CH}_3}{|}}{\underset{\underset{\text{OH}}{|}}{\text{C}}}\text{-CH}_2\text{-CH}_2\text{-OH} \quad \underline{44}$$

$$\text{HO-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{-CH}_2\text{-}\overset{\overset{\text{CH}_3}{|}}{\underset{\underset{\text{OH}}{|}}{\text{C}}}\text{-CH}_2\text{-CH}_2\text{-OP}_2\text{O}_6\text{H}_3 \quad \underline{45}$$

$$\text{CH}_2\text{=}\overset{\overset{\text{CH}_3}{|}}{\text{C}}\text{-CH}_2\text{-CH}_2\text{-OP}_2\text{O}_6\text{H}_3 \quad \underline{46}$$

$$\text{CH}_3\text{-}\overset{\overset{\text{CH}_3}{|}}{\text{C}}\text{=CH-CH}_2\text{-OP}_2\text{O}_6\text{H}_3 \quad \underline{47}$$

$$\text{CH}_3\text{-}\overset{\overset{\text{CH}_3}{|}}{\text{C}}\text{=CH-CH}_2\text{-CH}_2\text{-}\overset{\overset{\text{CH}_3}{|}}{\text{C}}\text{=CH-CH}_2\text{-OP}_2\text{O}_6\text{H}_3 \quad \underline{48}$$

$$\text{CH}_3\text{-}\overset{\overset{\text{CH}_3}{|}}{\text{C}}\text{=CH-CH}_2\text{-CH}_2\text{-}\overset{\overset{\text{CH}_3}{|}}{\text{C}}\text{=CH-CH}_2\text{-CH}_2\text{-}\overset{\overset{\text{CH}_3}{|}}{\text{C}}\text{=CH}_2\text{CH}_2\text{-OP}_2\text{O}_6\text{H}_3 \quad \underline{49}$$
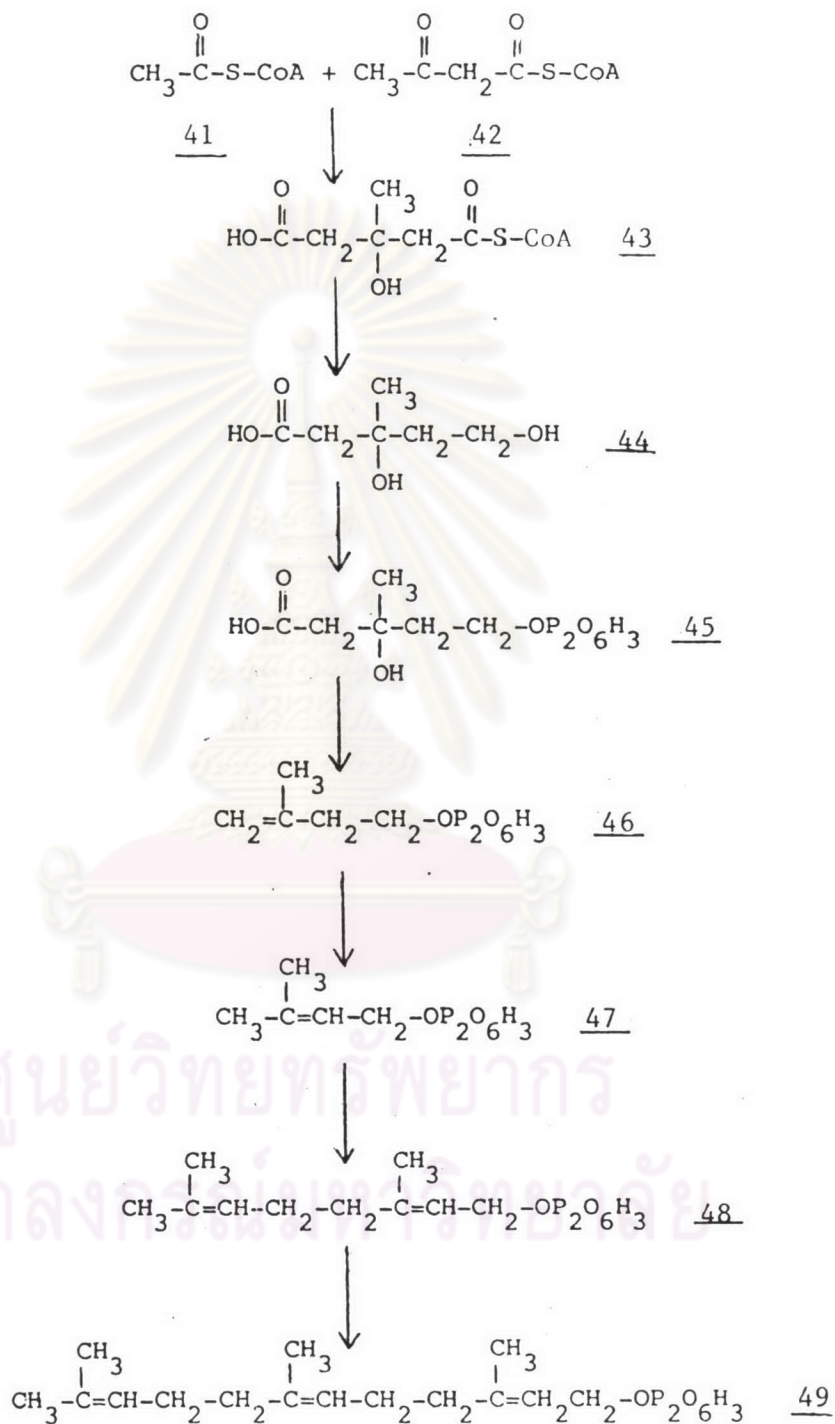
<u>Chart 6</u> *trans,trans*-farnesylpyrophosphate biosynthesis

49 *trans,trans-*

farnesyl pyrophosphate

50

[O]

various skeletal types

of sesquiterpene lactone

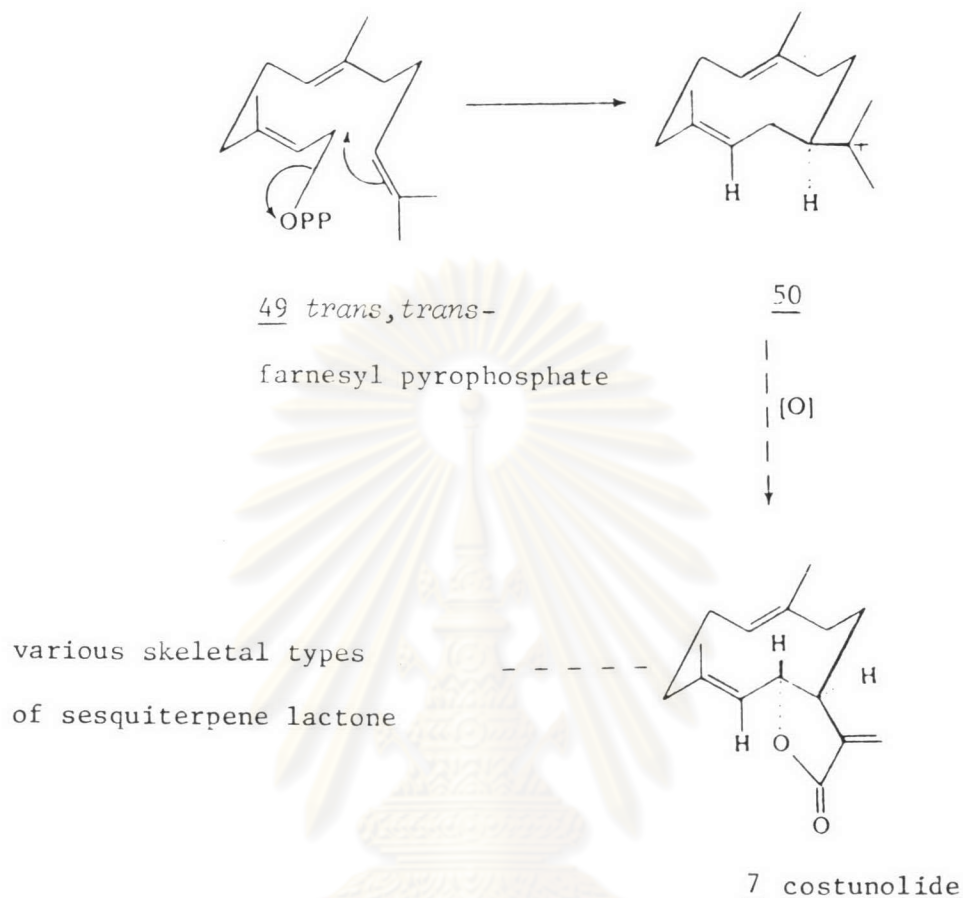- - - - -

7 costunolide

Chart 7. Biogenesis of the germacranolide skeleton

c. Lactone Ring Formation

　　　　The possible biogenetic route has been suggested for
the formation of the lactone ring of germacranolides (67,68,69).
Introduction of an oxygen function at C-12 in 51 to give alcohol 54
could either proceed through epoxide intermediate 52 or could involve
the hydroperoxide 53, the latter being formed by an enzymatically-
mediated reaction mimicking the reaction of singlet oxygen with
olefins.　In either case the process involves migration of a double
bond from what was originally C-11, C-13 to C-11, C-12.　Further
oxidative modifications of 54 through aldehyde 55 and 56 and

hydroxylations at C-6 or C-8 would after lactonization give costunolide
_7_ inunolide _57_ respectively (chart 8 p. 36)

Other skeletal types of sesquiterpene lactones different
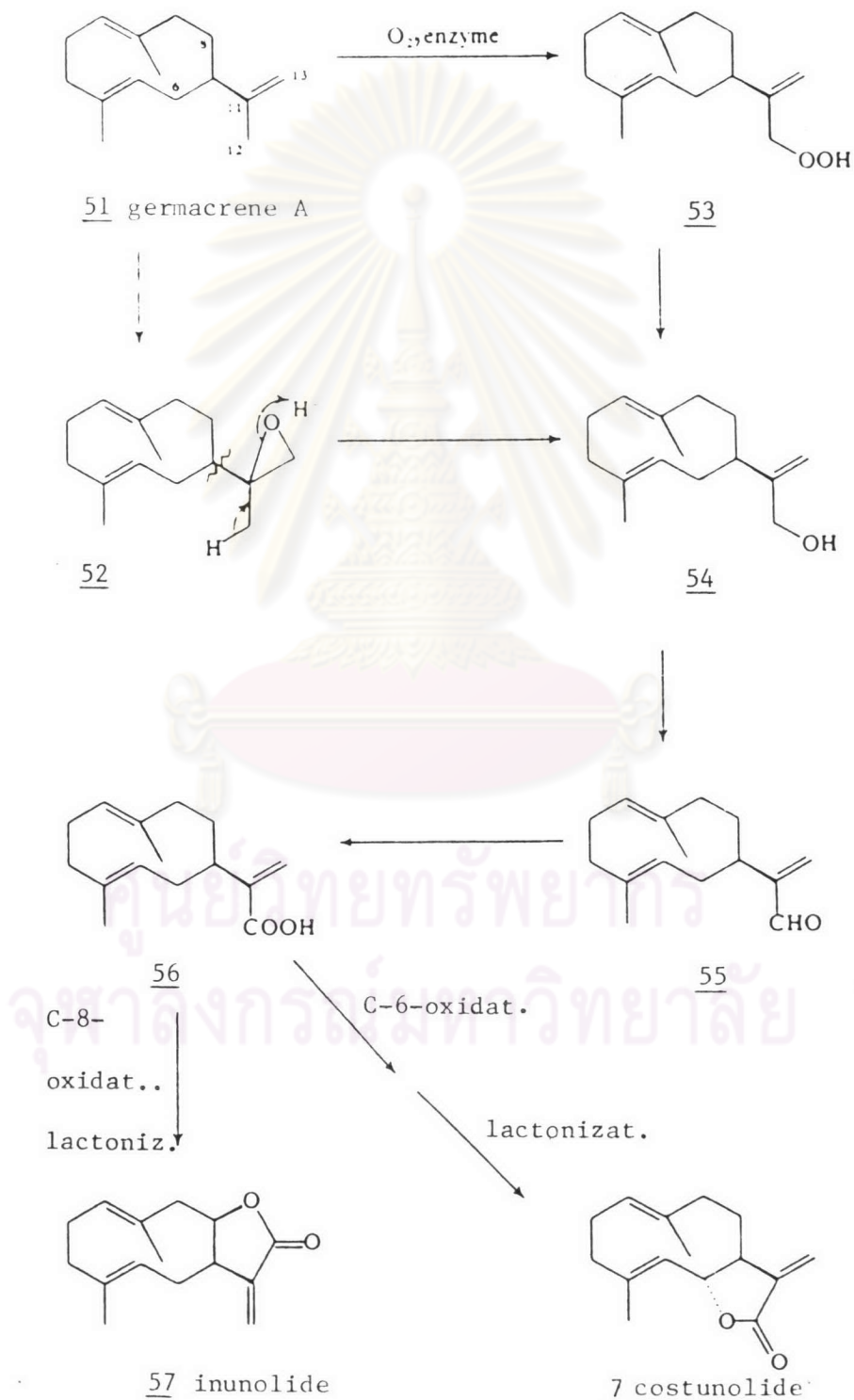from the germacradienes are shown in chart 9 (p. 37)

_51_ germacrene A

_53_

_52_

_54_

_56_

COOH

_55_

CHO

C-8-
oxidat..
lactoniz.

C-6-oxidat.

lactonizat.

_57_ inunolide

7 costunolide

Chart 8. Biogenesis of the lactone ring

Elemanolide   Seco-Eudesmanolide

Eudesmanolide   Eremophilanolide   Bakkenolide

(Fukinanolide)

Germacranolide

Guaianolide   Seco-Guaianolide   Seco-Pseudo-
              (Xanthanolide)   guaianolide

Seco-   Pseudo-   Seco-Pseudo-
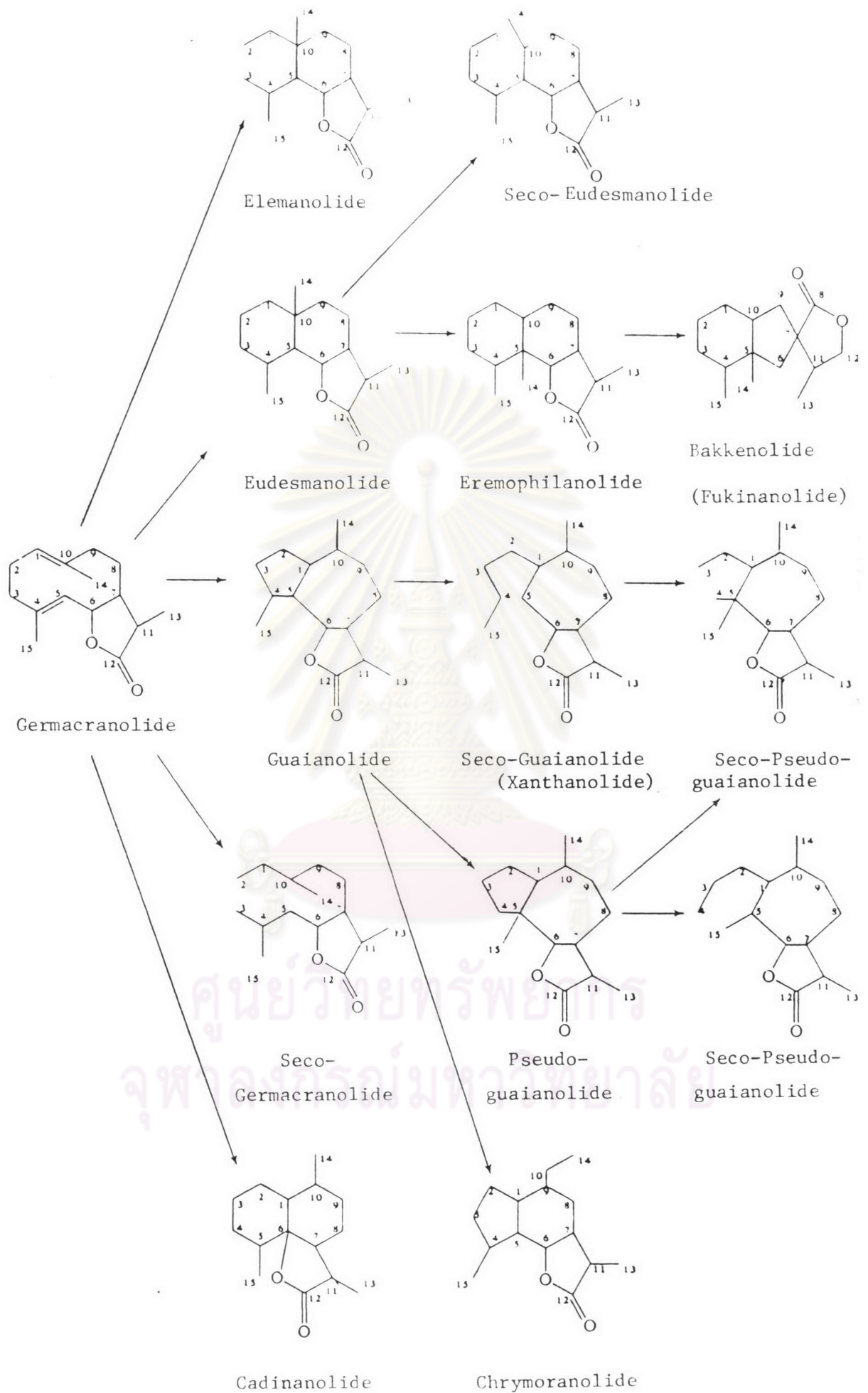Germacranolide   guaianolide   guaianolide

Cadinanolide   Chrymoranolide

<u>Chart 9</u>.   Types and biogenetic relationships of germacranolide-derived

sesquiterpene lactones (after W. Herz)

3.2 Biogenesis of Eudesmanolides

The biogenesis of eudesmanolides undergoes cyclization of germacranolides (chart 2 p. 23) and their epoxide derivatives (50). The acid-catalyzed cyclization of costunolide-1,10-epoxide 58 gives the eudesmanolides reynosin 59 and santamarin 60 through the intermediate cation 61 (70). Ivangulin 27, 1,10-seco-eudesmanolides, could be derived from a eudesmanolides hydroperoxide 62 which by a fragmentation reaction, would provide the aldehyde 63. Further oxidative biomodification followed by methyl ester formation would result in ivangulin 27 (chart 10 p. 39)

3.3 Biogenesis of Guaianolides and Xanthanolides

The Markovnikov type cyclization of germacrolide-4,5-epoxide 64 in a chair-like transition state would lead to the cis-fused guaianolide cation 65 from which the guaianolide skeleton 66 would be formed by an uptake of water. Fragmentation of the 4,5-bond and H-12 to C-10α shift from cation 65, would give the xanthanolide skeleton 67. The diol 66 after water elimination and oxidation at C-8 would provide the dienol 68 which upon intramolecular substitution, C-5 to C-1 hydride shift and uptake of water could provide the cyclopropane guaianolide skeleton 69 from which ivaxillarin 70 might be derived (chart 11 p. 40)

3.4 Biogenesis of Elemanolides

The biogenesis of elemanolides most likely involves Cope rearrangements of germacranolides which occur under laboratory with great ease. The thermal rearrangements of *trans, trans*-cyclodeca-1,5-dienic sesquiterpenes proceed in a highly stereospecific manner

through a chair-like transition state resulting in a divinylcyclohexane skeleton. Short term thermolysis of dihydrotamaulipin A acetate 71 at 220°C gives an 2 : 3 equilibrium mixture of starting material 71 and the divinylcyclohexane derivative 73, the reaction proceeding with high stereospecific through the chair-like transition state 72 (71) (chart 12 p. 41)
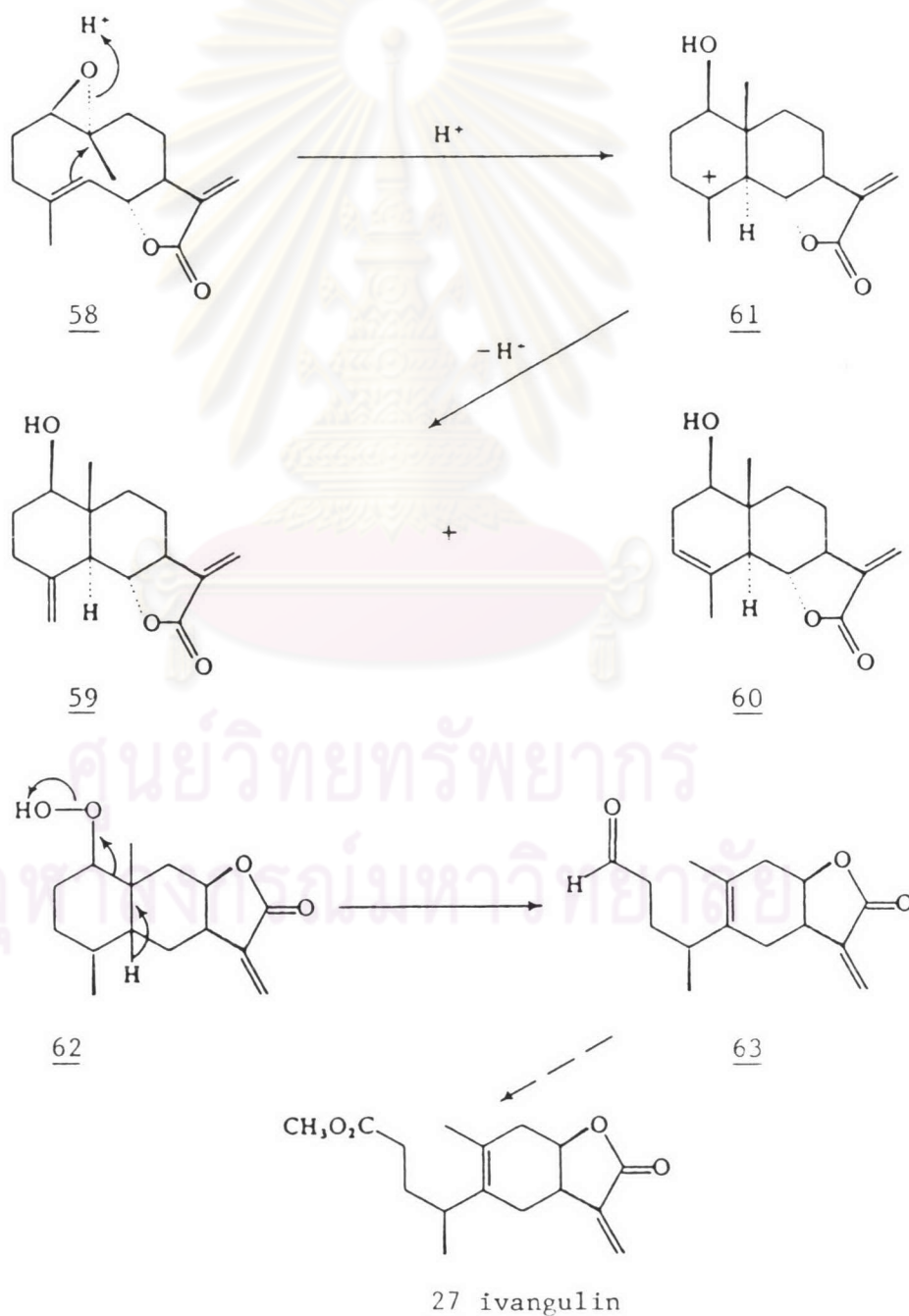

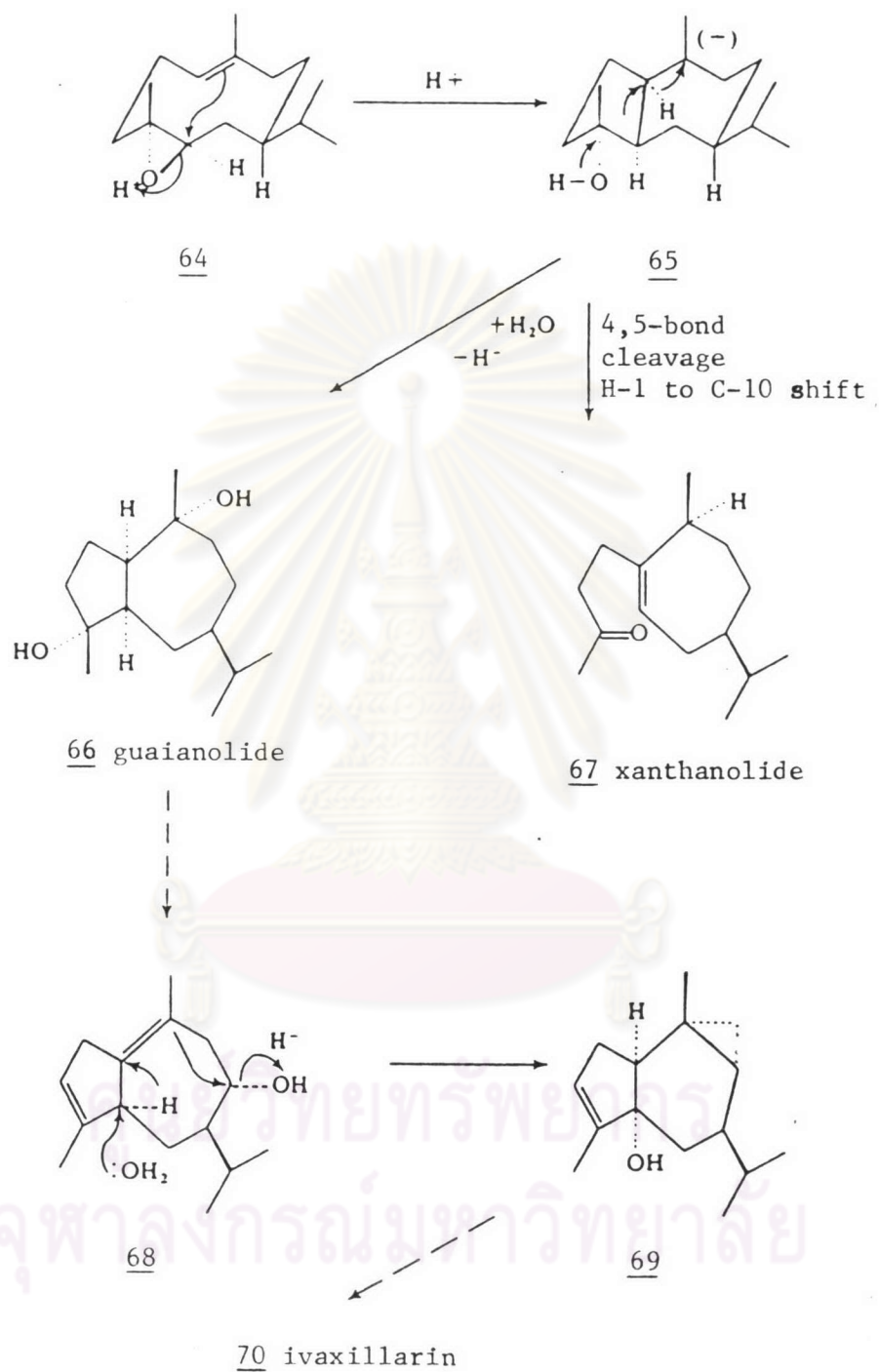Chart 10. Biogenesis of eudesmanolides and 1,10-seco-Eudesmanolides

64   65

+H₂O   4,5-bond
−H⁻   cleavage
        H-1 to C-10 shift

66 guaianolide

67 xanthanolide

68   69

70 ivaxillarin

Chart 11.   Biogenesis of guaianolides and xanthanolides

71 dihydrotamaulipin A
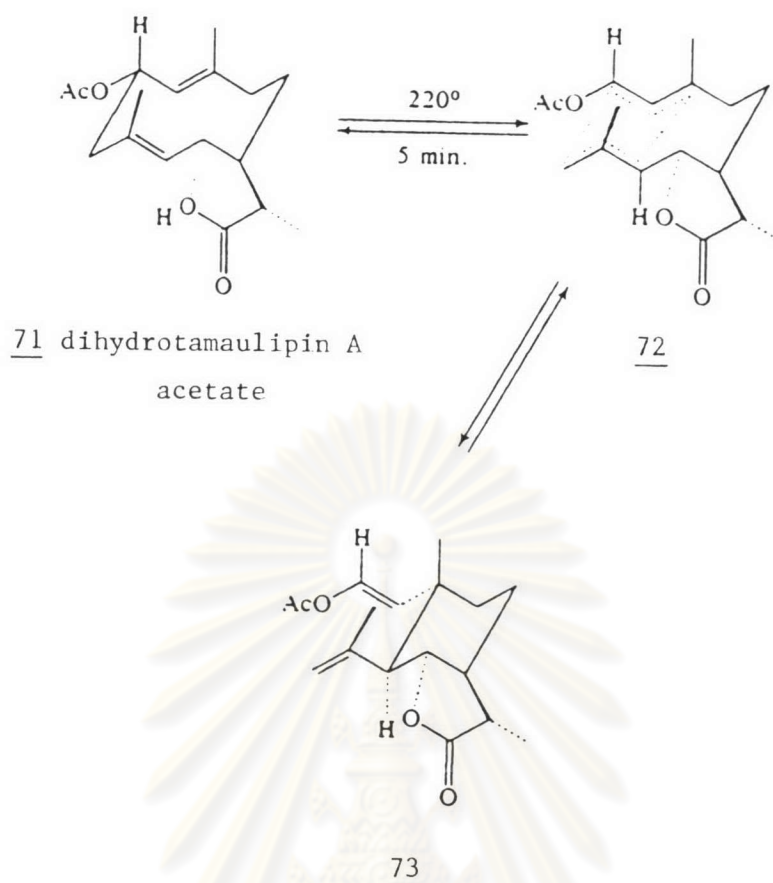   acetate

72

73

Chart 12. Cope rearrangement of dihydrotamaulipin A acetate

3.5 Biogenesis of Pseudoguaianolides

The biogenesis of ambrosanolide skeleton 75 from

the germacrolide-4,5-epoxide 64 will initially undergo Markovnikov

cyclization to the guaianolide type cation 74 which upon double

hydride and methyl shift, gives 75 from which the 7,6-*cis*-lactone

damsin 76 is formed (chart 13 p. 42)

The biogenesis of helenanolides skeleton 40, acid-

induced cyclization of the melampolide-4,5-epoxide 77 and 77' would

give cation 78 from which by the indicated shifts the skeleton 40

results, showing a stereochemical arrangement typical for most
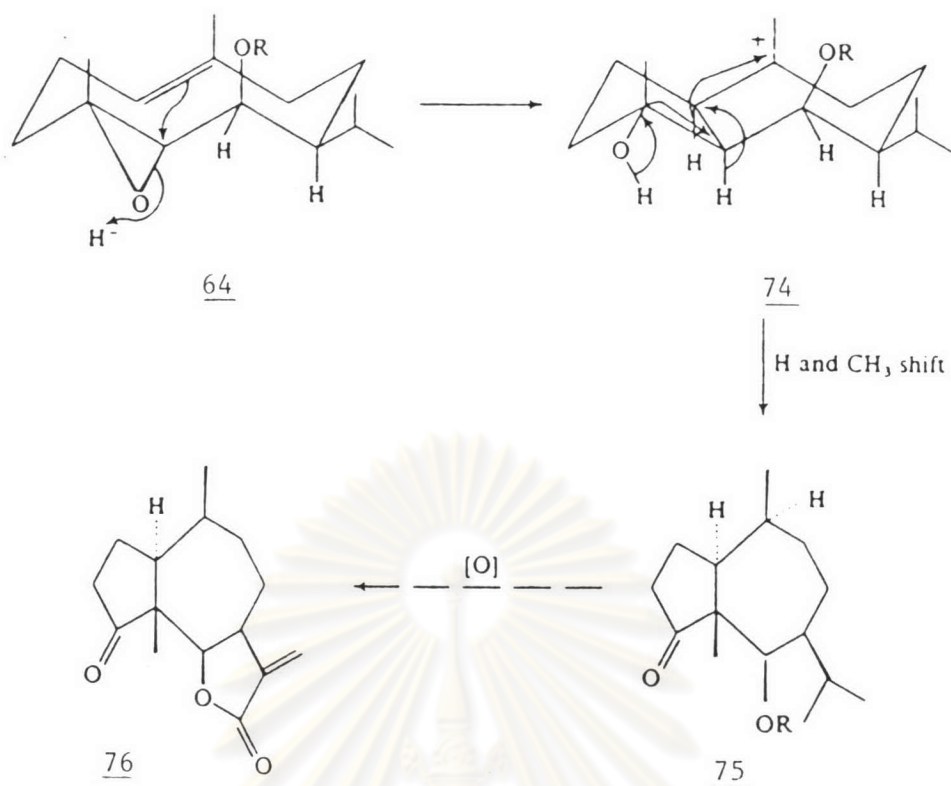
naturally occuring helenanolides (chart 14 p. 42)

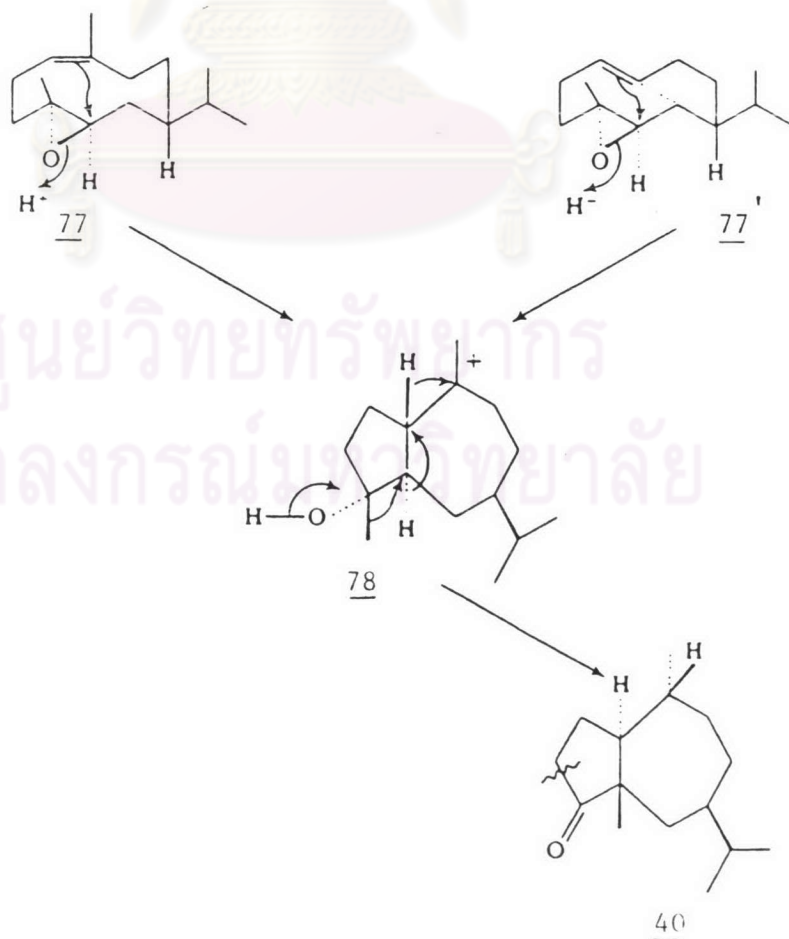Chart 13. Biogenesis of ambrosanolides and psilostachyanolides

Chart 14. Biogenesis of helenanolides

3.6 Biogenesis of Eremophilanolides and Bakkenolides

Reactions mimicking the postulated methyl migration from C-10 to C-5 of a eudesmanolides 79 lead to an eremophilanolide 80 (65). For example, in a biogenetic-type conversion dihydroalantolactone epoxide 79 was transformed to the eremophilanolide 80 upon treatment with formic acid in acetone (72) (chart 15 p. 43)

Oxidative biogenetic conversion of furanoeremophilane 81 would provide the naturally occuring furan derivative 83 which can be transformed in vitro to eremophilenolide 84 through the intermediate 82 (73). The photosensitized autoxidation of the furanolactone 85 leads to the dilactone 86, naturally occuring lactones (chart 16 p. 44)

Bakkenolides are being considered as derivatives of the eremophilanolides which result from ring contraction of ring B of the eremophilane skeleton followed by biomodifications (65). Epoxidation of fukinone 87 gave the α ,β-epoxiketone 88 which upon treatment with base underwent a Favorskii-type rearrangement forming after methylation the ring contraction product 89. Subsequent elimination, SeO_2-oxidation and spontaneous lactonization yeilded bakkenolide A 90 (43) (chart 17 p. 44)
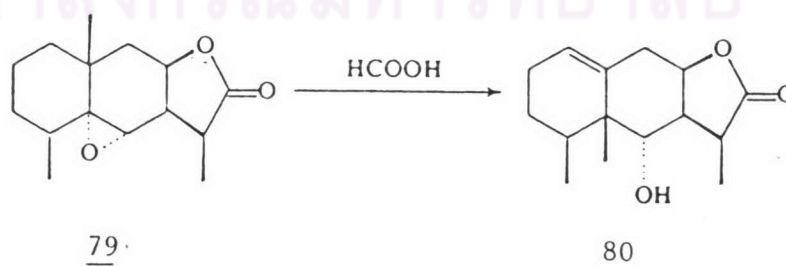

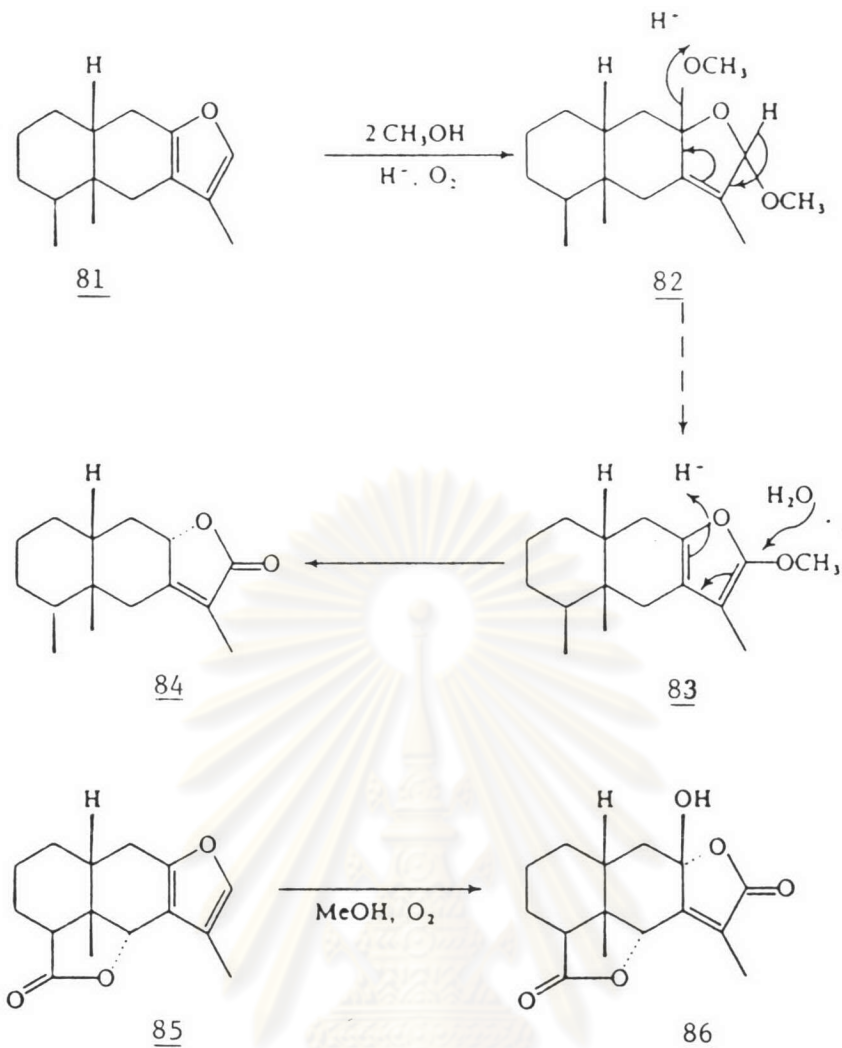Chart 15. Transformation of a eudesmanolide to an eremophilanolide

81   82   84   83   85   86

Chart 16.   Conversion of eremophilanofurans to eremophilanolides
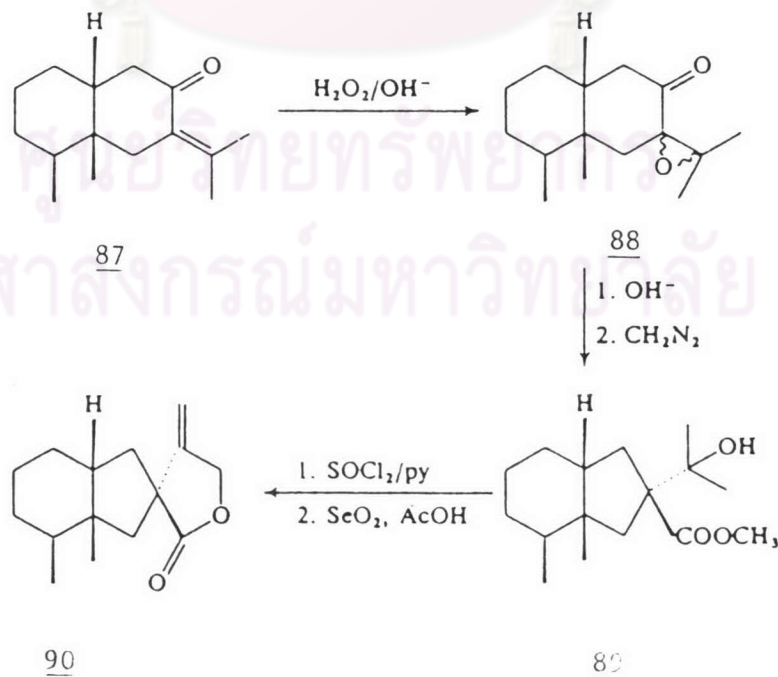

87   88   90   89

Chart 17.   Synthesis of bakkenolide A from fukinone