CHAPTER II

LITERATURE REVIEW

2.1 The previous study of chemical components of genus *Croton*.

The genus *Croton* belongs to the family Euphorbiaceae and has 700 species. They are distributed over all warm countries and are reported to posses important medicinal uses. An extensive literature search revealed that *Croton* has been widely study and many diterpenoid compounds have been isolated. The chemical constituents that were found in *Croton* genus are reported below and the structures of these compounds are shown in Fig 2.

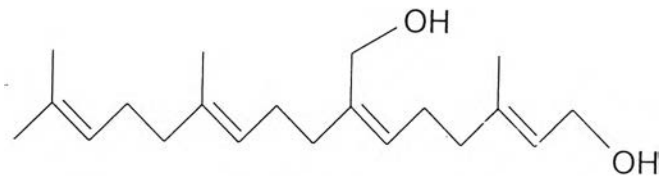
In 1978, Luzbetak and coworkers found furanoid diterpene, (-)-hardwickiic acid, and long chain alcohol, 1-triacontanol from the ethanol extract of the dried whole plants of *C. californicus* [7].

In 1979, Kitazawa and Ogiso isolated two new diterpenelactones named plaunol A and B exhibiting anti-Shay ulcer activity from Thai medicinal plant, *C. sublyratus* [8]. In the next year, During a continuing search for substances of plant origin they found five novel furanoditerpenes of the *ent*-clerodane type, plaunol A, B, C, D and E, which were isolated from acetone extract. They posses potent anti-Shay ulcer activity [9]. In 1981, the isolation and structure elucidation of two diterpene alcohols from the bark of *C. syblyratus* were described. These compounds were *ent*-3α-hydroxy-13-epimanool and *ent*-16β,17-dihydroxykaurane [10].

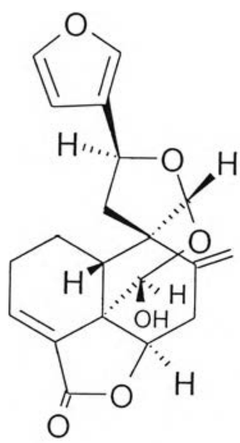
In 1982, Silveira found Sonderianol (12-hydroxy-3-oxo-cleistanth-8,11,13,15-tetraene) and 3,4-seco-sonderianol (methyl-12-hydroxy-3,4-seco-cleistanth-8,11,13,15,18(4)-penten-3-oate), two new diterpenes with cleistanthane skeletons, were isolated from heartwood of *C. sonderianus* [11].

In 1989, McChesney and Silveira found two new neo-clerodane diterpenes, 12-hydroxyhardwickiic acid and sonderianial from the hexane extract of the roots of *C. sonderianus* [12].

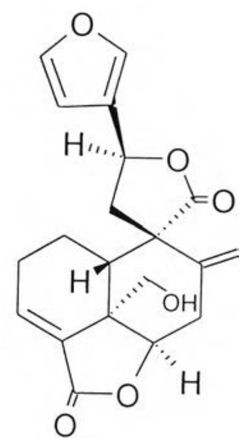
In 1993, The major constituents of the chloroform extract from the bark of *C. lechleri* were found to be 1,3,5-trimethoxybenzene, 2,4,6-trimethoxyphenol, 3,4-dimethoxyphenol, 3,4-dimethoxybenzyl alcohol, 4-hydroxyphenethyl alcohol and its acetate, sitosterol, sitosterol-β-D-glucopyranoside and β-sitostenone. In addition, two new clerodane compounds were found, and they were named as crolechinol and crolechinic acid, respectively [13].



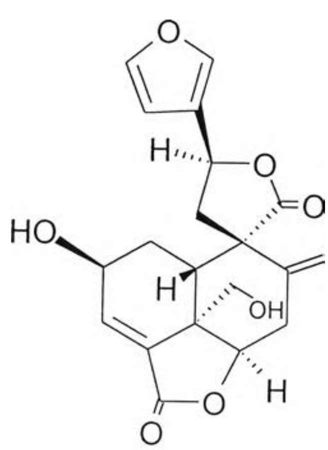
18-hydroxygeranylgeraniol (plaunotol)



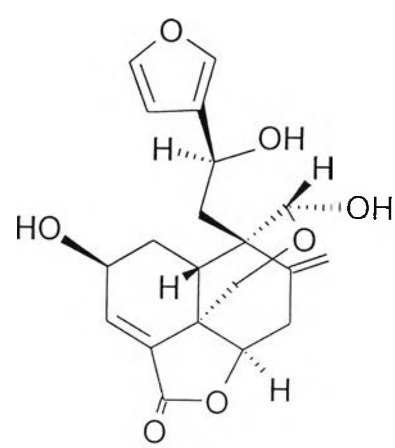
plaunol A



plaunol B

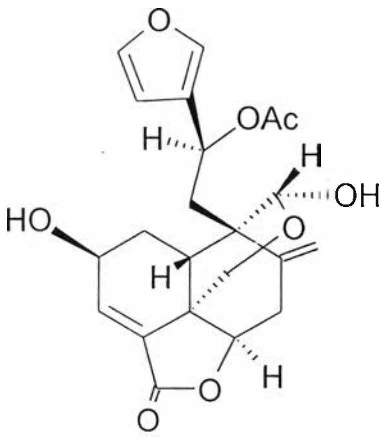


plaunol C

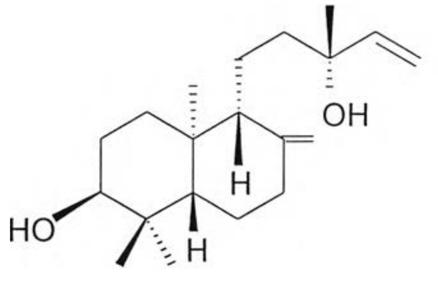


plaunol D

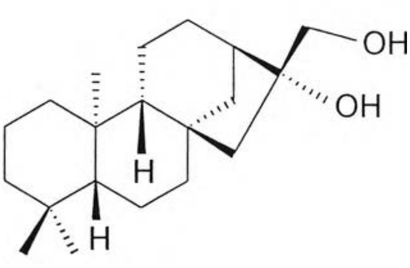
Figure 2 The structure of diterpenoid compounds found in *Croton* genus



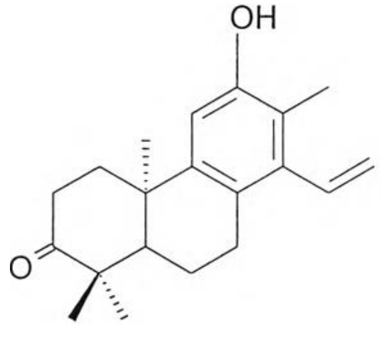
plaunol E



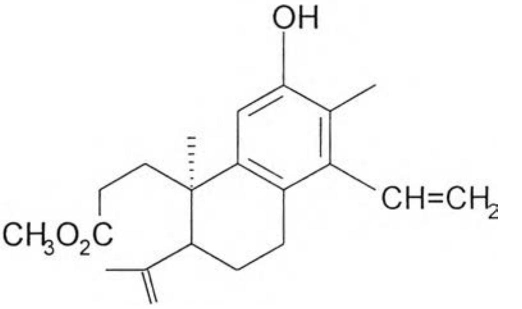
ent-3α-hydroxy-13-epimanool



ent-16β,17-dihydroxykaurane

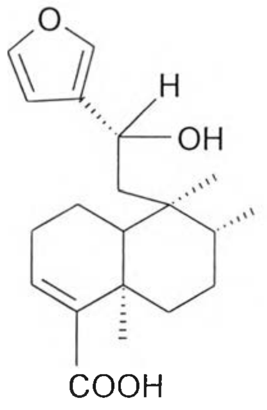


Sonderianol

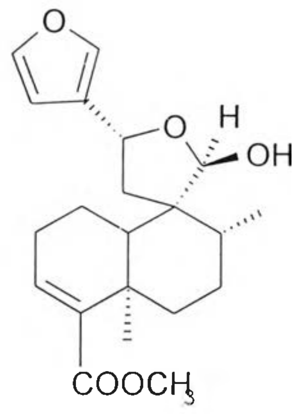


3,4-seco-sonderianol

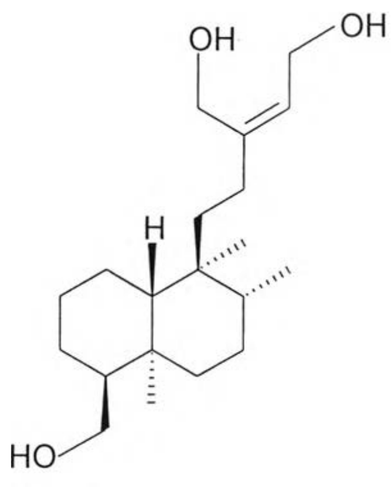
Figure 2 The structure of diterpenoid compounds found in *Croton* genus (continue)



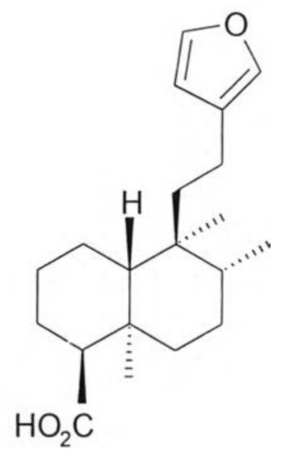
12-hydroxyhardwickic acid



Sonderianial



Crolechinol



Crolechinic acid

Figure 2 The structure of diterpenoid compounds found in *Croton* genus (continue)

2.2 The previous study of chemical constituents of *C. oblongifolius* Roxb.

The chemical constituents of *C. oblongifolius* have been studied for long time by the Indian scientists [14-21]. In Thailand, Roengsumran and coworkers have investigated the chemical constituents of *C. oblongifolius* from various locations in Thailand. They found many new diterpenoid compounds that could be categorized into five groups including clerodane, labdane, cembrane, halimane and isopimarane diterpenoids. The chemical constituents that were found in *C. oblongifolius* are shown below.

In 1968, Rao and coworkers found a new diterpene alcohol, oblongifoliol together with β-sitosterol from the bark of *C. oblongifolius* [14].

In 1969, Aiyar and Seshadri found deoxyoblongifoliol from the stem bark of *C. oblongifolius* Roxb. [15].

In 1970, Aiyar and Seshadri studied the structure of oblogifolic acid, the major diterpene acid component of the bark, it was assigned as (+)-isopimara-7 (8),15-diene-19-oic acid [16].

In 1971, Aiyar and Seshadri found three new minor components from the stem bark. The first one was *ent*-isopimara-7,15-diene, the second was 19-hydroxy-ent-isopimara-7,-15-diene and the last one was *ent*-isopimara-7,15-diene-19-aldehyde [17]. In the same year, based on detailed chemical and spectral data of oblongifoliol and deoxyoblongifoliol. Two components have been assigned their structures as *ent*-isopimara-7,15-diene-3β,19-diol and *ent*-isopimara-7,15-diene-3β-ol, respectively [18]. Moreover, Acetyl aleuritolic acid, 3β-acetoxy-olean-14(15)-ene-28-oic acid, had been obtained from the stem bark also [19].

In 1972, Aiyar and Seshadri found two closly related furanoid diterpenes from the bark. One was *ent*-15,16-epoxy-3,11,13(16),14-clerodatetraen-19-oic acid and given the trivial name 11-dehydro(-)-hardwickiic acid and the second was (-)-hardwickiic acid [20].

In the same year, they studied other parts of *C. oblongifolius* including the root-bark, wood and leaves. Most of the previous isolated compounds from the stem-bark were obtained in poor yield from wood, while the leaves gave only waxy materials [21].

In 1998, Roengsumran and coworkers found two new cembranoids, crotocembraneic acid and neocrotocembraneic acid, isolated from the stem bark of *C. oblongifolius*. Their sturctures were established on the basis of spectroscopic analysis [22].

In the same year, They found four new labdane diterpene compounds, labda-7,12(*E*),14-triene, labda-7,12(*E*),14-triene-17-ol, labda-7,12(*E*),14-triene-17-al and labda-7,12(*E*),14-triene-17-oic acid. These compounds gave effective cytotoxicity against cancer cell lines especially the aldehyde compound, labda-7,12(E),14-triene-17-al [23].

In 1999, Roengsumran and coworkers found a new cembranoid diterpene, neocrotocembranal, isolated from the stem bark of *C. oblongifolius*. This compound inhibited platelet aggregation induced by thrombin, and exhibited cytotoxicity against P-388 cells *in vitro* [24].

There were many diterpenoid compounds isolated and characterized from *C. oblongifolius* and they are tabulated in Table 1.

Table 1 The previous studied of chemical constituents in hexane crude extract from stem bark of *C. oblongifolius* Roxb.

Organic compounds	Area	References
Labda-7,12(*E*),14-triene	Prachubkhirikhan	[2]
Labda-7,12(*E*) 14-triene-17-al	Prachubkhirikhan	[2]
Labda-7,12(*E*),14-triene-17-ol	Prachubkhirikhan	[2]
Labda-7,12(*E*),14-triene-17-oic acid	Prachubkhirikhan	[2]
Poilaneic acid	Prachubkhirikhan	[3]
Crovatin	Kanchanaburi	[3]
Isokolavenol	Kanchanaburi	[3]
Crotocembraneic acid	Petchaboon	[3]
Neocrotocembraneic acid	Petchaboon	[3]
Neocrotocembranal	Petchaboon	[3]
Crotohalimaneic acid	Nakornrachsima	[3]
Benzoyl crotohalimanolic acid	Nakornrachsima	[3]
Crotohalimoneic acid	Nakornrachsima	[3]
Nidorellol	Chonburi	[3]
2-acetoxy-labda-8(17),12(*E*),14-triene-3-ol	Loei	[4]
3-acetoxy-labda-8(17),12(*E*),14-triene-2-ol	Loei	[4]
Labda-8(17),12(*E*),14-triene-2,3-diol	Loei	[4]
(-)-hardwickiic acid	Loei	[4]
Labda-7,13(*Z*)-diene-17,12-olide	Udonthani	[5]
Labda-7,13(*Z*)-diene-17,12-olide-15-ol	Udonthani	[5]
(-)-20-benzoyloxyhardwickiic acid	Udonthani	[5]
(-)-pimara-9(11),15-diene-19-oic acid	Uttaradit	[6]

Table 1 The previous studied of chemical constituents in hexane crude extract from stem bark of *C. oblongifolius* Roxb. (continue)

Organic compounds	Area	References
(2*E*,7*E*,11*E*)-1-isopropyl-1,4-dihydroxy-4,8-dimethylcyclotetradeca-2,7,11-triene-12-carboxylic acid	Uttaradit	[6]
(-)-pimara-9(11),15-diene-19-ol	Uttaradit	[6]
Methyl-15,16-epoxy-12-oxo-3,13(16),14-clerodatriene-20,19-olide-17-oate	Uttaradit	[6]
Oblongifoliol	India	[14]
Deoxyoblongifoliol	India	[15]
Oblongifolic acid	India	[16]
ent-isopimara-7,15-diene	India	[17]
ent-isopimara-7,15-diene-19-aldehyde	India	[17]
11-dehydro(-)-hardwickiic acid	India	[20]

2.3 Literature reviews of biological activity of diterpenoid compounds isolated from *C. oblongifolius* Roxb.

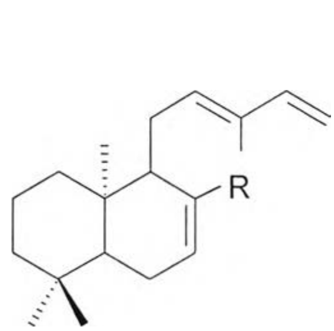
Previous studied in cytotoxic activity of some diterpenoid compounds from stem bark of *C. oblongifolius* against 6 human tumor cell lines, HS 27 (fibroblast), Hep-G2 (hepatoma), SW 620 (colon), Chago (lung), Kato-3 (gastric) and BT 474 (breast) have been assigned in Table 2.

Table 2 Cytotoxic activity against cancer cell lines of some isolated compounds from *C. oblongifolius*

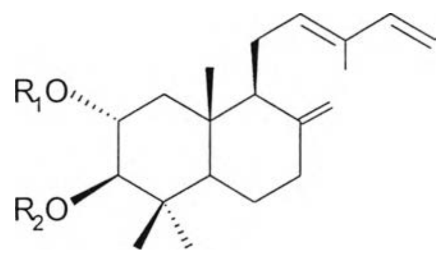
Compound	% Survival					
	HS 27	Hep-G2	SW 620	Chago	Kato-3	BT 474
Labda-7,12(*E*),14-triene-17-ol	64	7	3	82	6	11
Labda-7,12(*E*),14-triene-17-al	6	7	3	3	7	13
Labda-7,12(*E*),14-triene-17-oic acid	73	57	88	59	70	91
Neocrotocembranic acid	46	37	96	97	90	95
Neocrotocembranal	82	71	8	12	10	46
Crotocembraneic acid	82	71	6	3	6	7
Crotohalimaneic acid	64	7	3	82	6	11
Crotohalimoneic acid	91	86	0	0	70	0
(-)20-benzyloxyhardwickiic acid	130	74	84	111	64	109
(-)-pimara-9(11),15-diene-19-ol	89	14	62	66	16	43

Moreover, diterpenoid compounds isolated from *C. oblongifolius* Roxb. have many biological activities such as cAMP phosphodiesterase inhibition, antimicrobial and antiplatelet aggregation etc. For example, (-)-hardwickiic acid showed a significant qualitative antibacterial activity against the Gram-positive bacteria (*B. subtilis*, *St. aureus*) and *M. smegmatis* [25], labdane from Prachubkhirikhan were active against human tumor cell lines [2], neocrotocembranal, neocrotocembraneic acid and poilaneic acid have cAMP phosphodiesterase inhibition activity [3].

Labdane Group



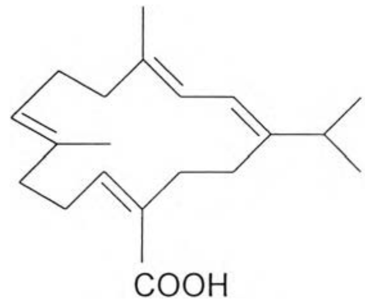
R = CH_3	Labda-7,12(*E*),14-triene
CH_2OH	Labda-7,12(*E*),14-triene-17-ol
CHO	Labda-7,12(*E*),14-triene-17-al
CO_2H	Labda-7,12(*E*),14-triene-17-oic acid



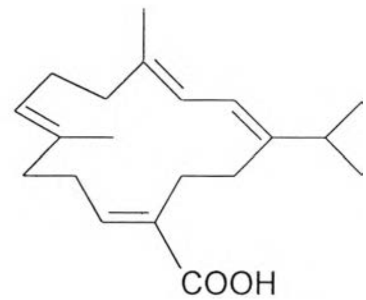
R_1	R_2	
CH_3CO	H	2-acetoxy-labda-8(17),12(*E*),14-triene-3-ol
H	CH_3CO	3-acetoxy-labda-8(17),12(*E*),14-triene-2-ol
H	H	labda-8(17),12(*E*),14-triene-2,3-diol

Figure 3 The structure of the chemical constituents of *C. oblongifolius* Roxb.

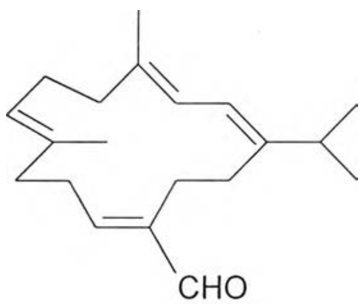
Cembrane Group



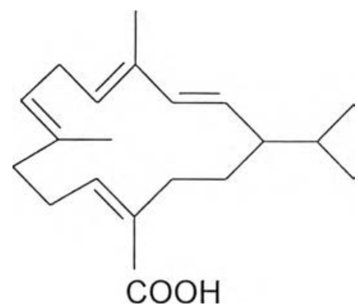
Crotocembraneic acid



Neocrotocembraneic acid

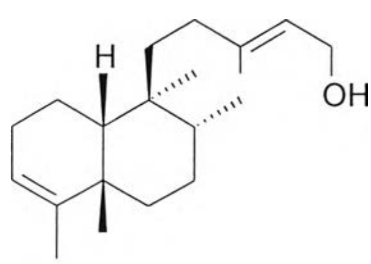


Neocrotocembranal



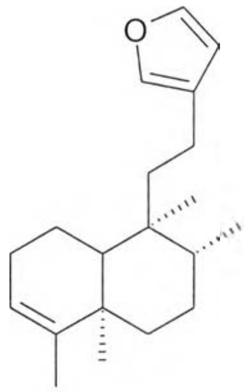
Poilaneic acid

Clerodane Group



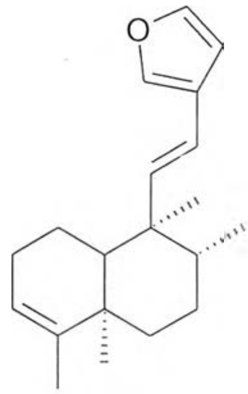
Isokolavenol

Figure 3 The structure of the chemical constituents of *C. oblongifolius* Roxb. (continue)



COOH

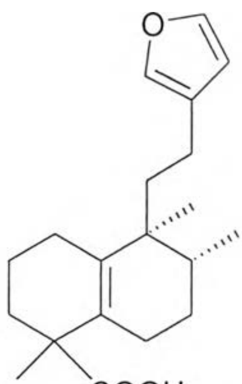
(-)-Hardwickiic acid



COOH

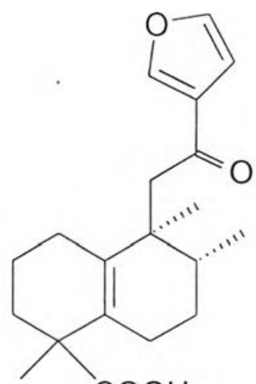
11-Dehydro-(-)-hardwickiic acid

Halimane Group



COOH

Crotohalimaneic acid

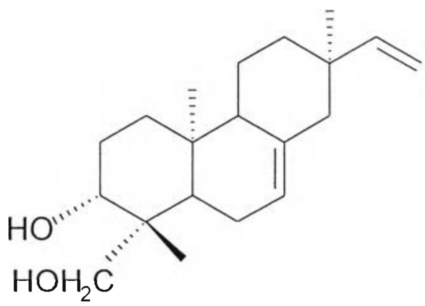


COOH

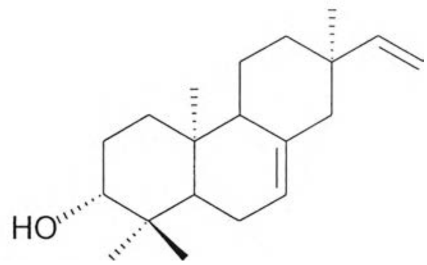
Crotohalimoneic acid

Figure 3 The structure of the chemical constituents of *C. oblongifolius* Roxb. (continue)

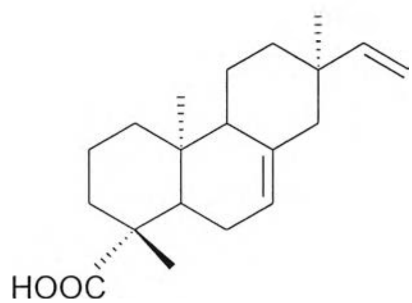
Isopimarane Group



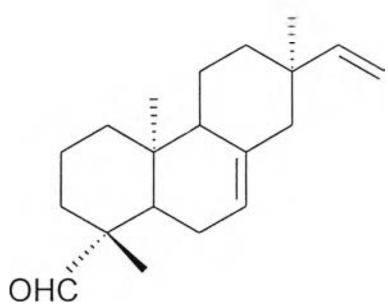
Oblongifoliol



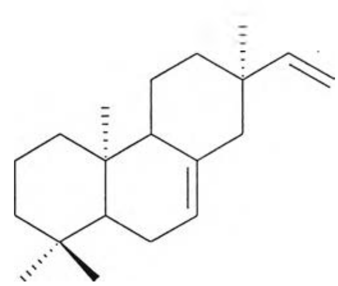
19-Deoxyoblongifoliol



Oblongifolic acid



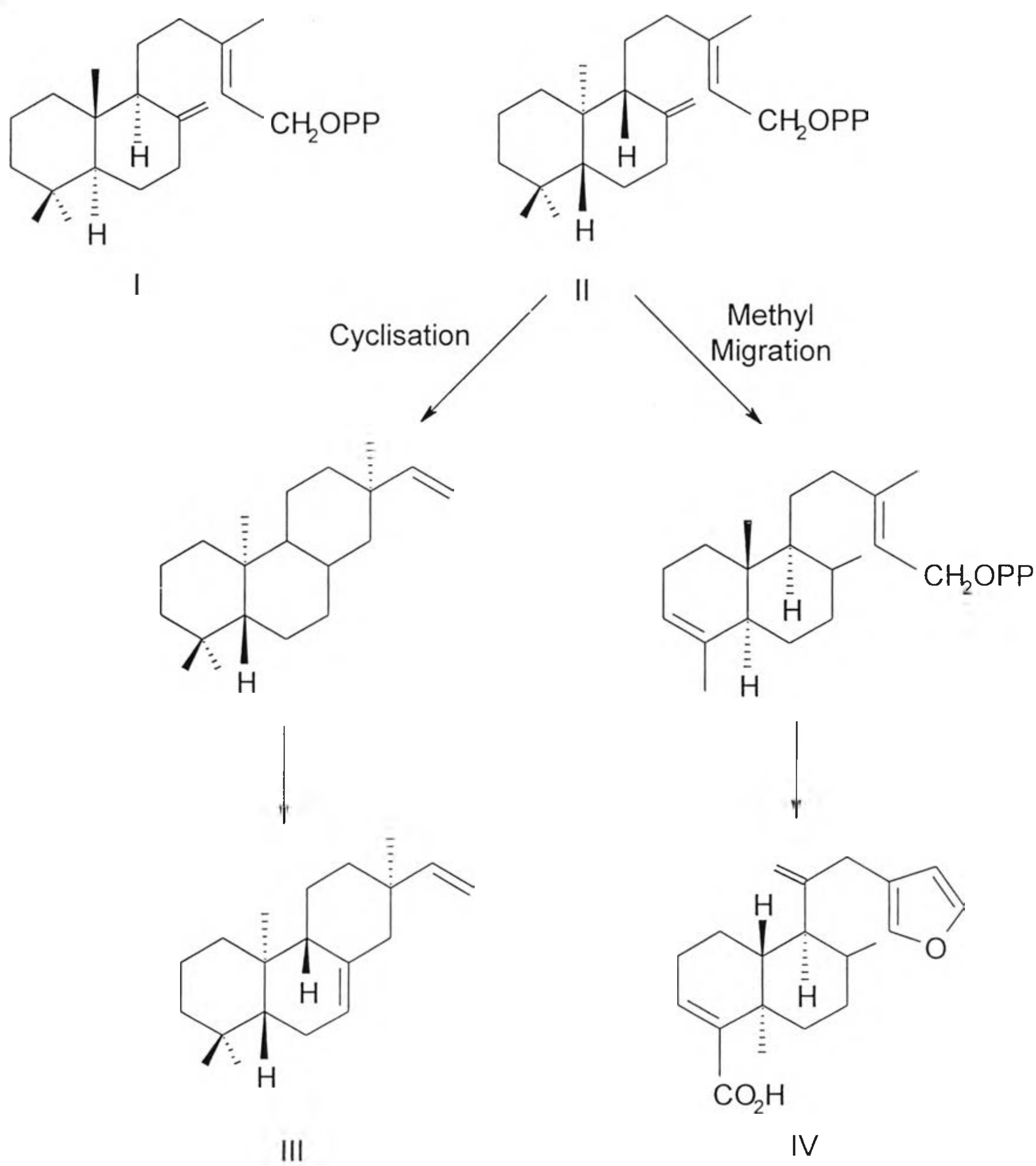
ent-Isopimara-7,15-diene-19-aldehyde



ent-Isopimara-7,15-diene

Figure 3 The structure of the chemical constituents of *C. oblongifolius* Roxb. (continue)

The *Croton* species essentially contain alkaloids, whereas *Croton oblongifolius* has a number of closely related diterpenes. The formation of these diterpenes could be explained as follows. It has been generally accepted that geranyl-geranyl pyrophosphate or its C-13 allylic isomer on cyclisation initiated by proton can give a bicyclic compound of the normal or antipodal type (I, II).



By further cyclisation the latter can yield the mono- and di-hydroxy compounds, aldehyde and the carboxylic acid of the *ent*-isopimara-7,15-dien (III) derivatives whose interrelations have already been discussed. The bicyclic compound (II) can also suffer methyl migration to yield hardwickiic acid (IV) and its 11-dehydro derivative [21].

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