CHAPTER I

INTRODUCTION

PLAUNOTOL

Plaunotol ((*E,Z,E*) -7- Hydroxymethyl-3,11,15-trimethyl-2,6,10,14-hexadeca tetraen-1-ol) (Figure 1) was isolated as the principle component from leaves of Plaunoi (*Croton sublyratus* Kurz) and it has the following formula :

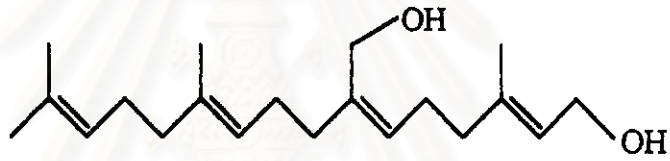
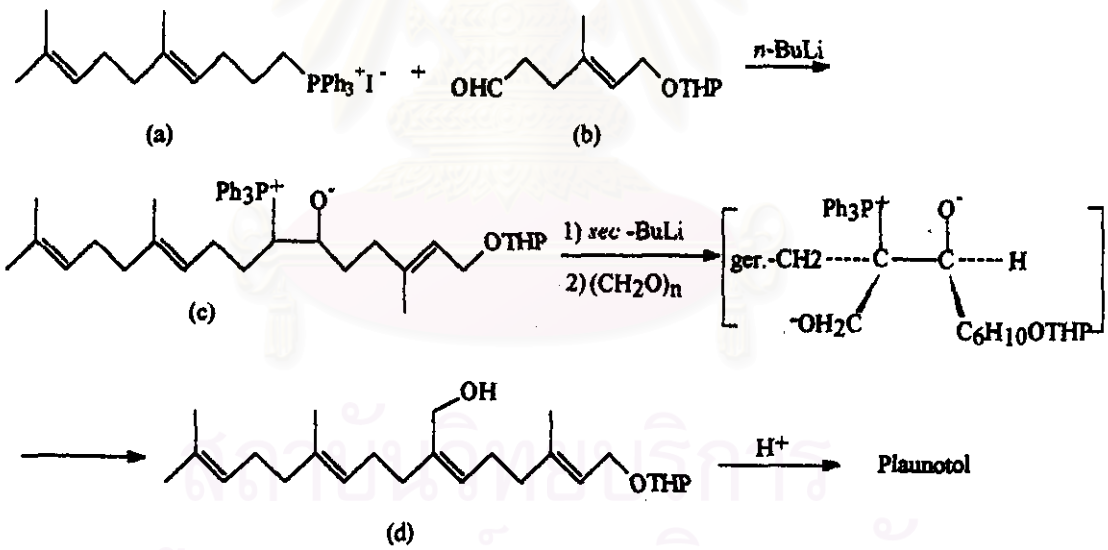


Figure 1 : The structure of Plaunotol

Plaunotol is acyclic diterpene alcohol. Not only it shows broad spectrum of inhibition against acute gastric and duodenal ulcers but it also facilitates the healing of chronic gastric ulcer. A drug made from Plaunotol reduced the ulcer size and induced regeneration of mucosa, reduced the volume of gastric juice, and also reduced acid and pepsin secretion. Additionally, the compound facilitated biosynthesis of mucosal substances and prostaglandins in the mucosa and also protected the break down of the mucous barrier and acted mainly on the mucosal site in the unchanged form. It showed no side effect or toxicity. At present, trade name of this drug is Kelnac.® [1-5] Furthermore, in 1996 - 1997, plaunotol was observed to have bactericidal activity against *Helicobacter pylori* (*H. pylori*) which has been associated with various gastrointestinal diseases such as gastritis, peptic ulcer and gastric cancer. [6-8]

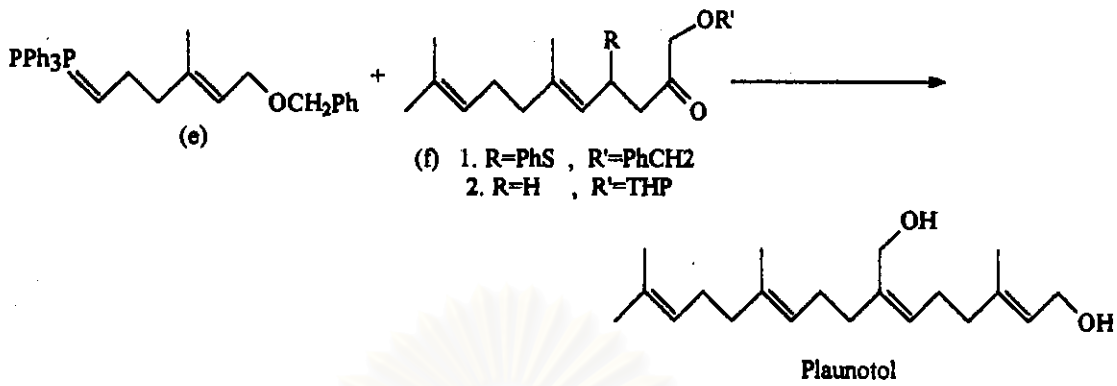
From the interesting biological activities of plaunotol as mentioned above, it has been a target of many syntheses.

In 1978 Akira Ogiso and co-workers [9] prepared plaunotol by appling a method which was developed by E.J. Corey and H.Yamamoto [10] as depicted in Scheme 1. This synthetic route used Indirect Wittig Reaction which involved a stereospecific sequence for trisubstituted olefins having an allylic alcohol *via* β-oxido phosphonium ylide. Reaction of phosphonium iodide (a) with aldehyde (b) obtained by ozonolysis of geranyl 2-tetrahydropyranyl ether, in the presence of *n*- butyllithium in tetrahydrofuran gave a Wittig betaine (c). Subsequent reaction of the betaine with *sec*-butyllithium and dried paraformaldehyde followed by treatment of the resulting tetrahydropyranyl ether (d) with acid furnished the desired compound bearing (*E,Z,E*)-7-Hydroxymethyl-3,11,15 - trimethyl-2,6,10,14-hexadecatetraen-1-ol.
Plaunotol was obtained in 37.70 % overall yield from 6 steps. This reaction is indeed highly stereoselective, but the product selectivity is insufficient to obtain a single product in a good yield.



Scheme 1

In 1988 and 1990 Kikumasa Sato and co-workers [11,12] reported that the direct Wittig reaction between unstabilized phosphorus ylides and α -alkoxyacetones led to a protection of trisubstituted allylic alcohols with high stereoselectivity for the *Z* isomer as shown in scheme 2.



Scheme 2

The intermediate α - alkoxy ketones (f) having a geranylacetone skeleton could be prepared either by three - carbon elongation from geranyl sulfide or by regioselective oxidation of geranylacetone. The phosphorus ylide (e) could also be prepared from geraniol according to a sequence similar to the synthesis of the stereoisomeric ylide, which was used for preparing a difunctional *cis*-terpenoid building block in our hand. After that, the reaction of phosphorus ylide and the counterpart ketones were carried out by the direct Wittig olefination to elaborate the plaunotol skeleton. This method afforded plaunotol in 40.25 % overall yield from 9 steps. On the synthesis of plaunotol as a single product in a good yield, an efficient stereoselective procedure was provided by the direct Wittig reaction employing α - alkoxy ketones and phosphorus ylide.

However, these methods were very complicated and composed of several complex steps which were inappropriate for industrial applications. Therefore, *Croton sublyratus* Kurz, was still an important source for antiulcer drugs at the present time.

In consideration of plaunotol's structure, we saw that the distance of two hydroxyl groups was composed of 8 carbon atoms separated by olefinic groups and methyl group. On the other side it was geranyl group which was hydrophobic group. From the study of Hiroshi Mishima and co-workers [1], they synthesized polyprenyl derivatives, which have the formula shown in figure 2 and there compounds exhibited different anti-reserpine ulcer activity such as :

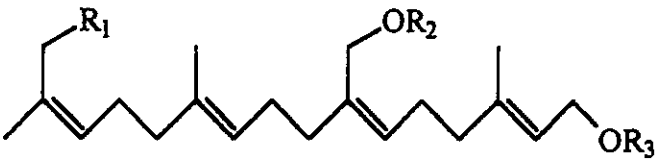


Figure 2 : The structure of polyprenyl derivatives

1. If R_1, R_2, R_3 represented hydrogen atom, isomer (*E,E,E*), (*Z,Z,E*), (*Z,E,E*) would have less activity than plaunotol (*E,Z,E*).

2. If R_1 represented hydrogen atom; R_2, R_3 which represented hydrogen atom would have more activity than any other groups such as acyl group.

3. If R_1 represented alcohol group, R_2 and R_3 represented hydrogen atom, the compounds which had two or three alcohol groups would have the same activity.

4. If hydrophobic group was farnesol, this compound would have more activity than plaunotol which hydrophobic group was geraniol.

5. If R1, R2 and R3 represented hydrogen atom, the distance of two hydroxyl groups having 8 carbon atoms would have more activity than the compound having 12 carbon atoms.

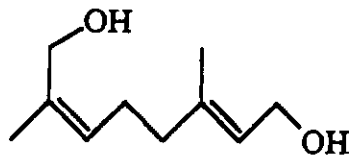
So that, the compound whose structure was similar to plaunotol may have interesting biological activity. This research is aimed to synthesize plaunotol analogues from geraniol and tested for biological activity.

Objective and scope of the Research

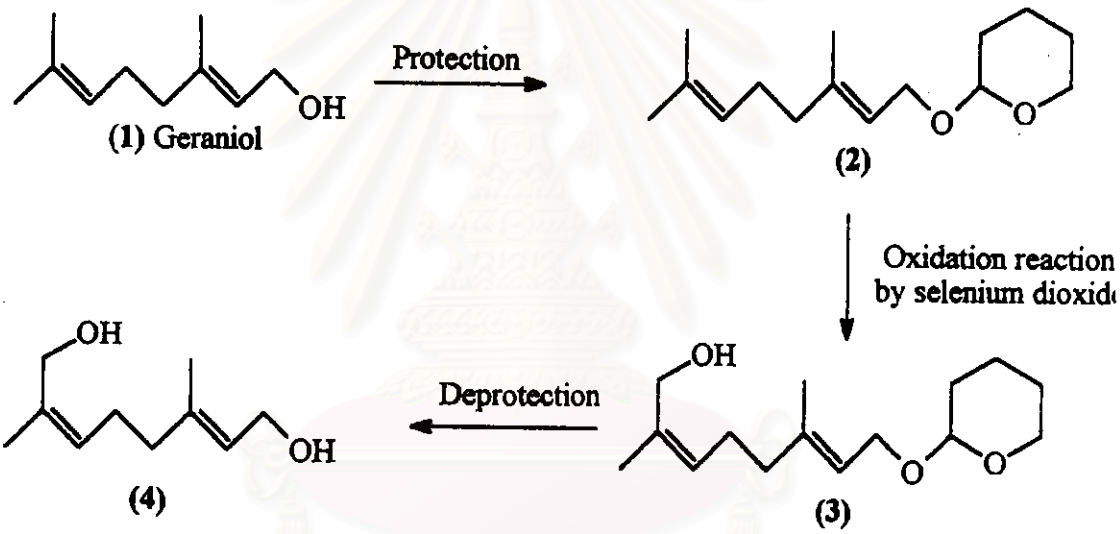
The objective of this research is to synthesize plaunotol analogues from geraniol for studying correlation between structure and biological activity of these compounds.

Synthesized plaunotol analogues can be divided into 3 types.

Type I :



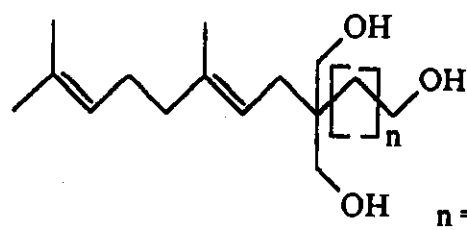
The compound (type I) differs from plaunotol in that this compound has methyl group as hydrophobic group while plaunotol has geranyl group as hydrophobic group. This compound is prepared by following experimental of Camps, L. and co-workers [25] by oxidation reaction of 3,7- Dimethyl -2,6- octadienyl tetrahydro pyranyl ether (2) with selenium dioxide according to Scheme 3.



Scheme 3

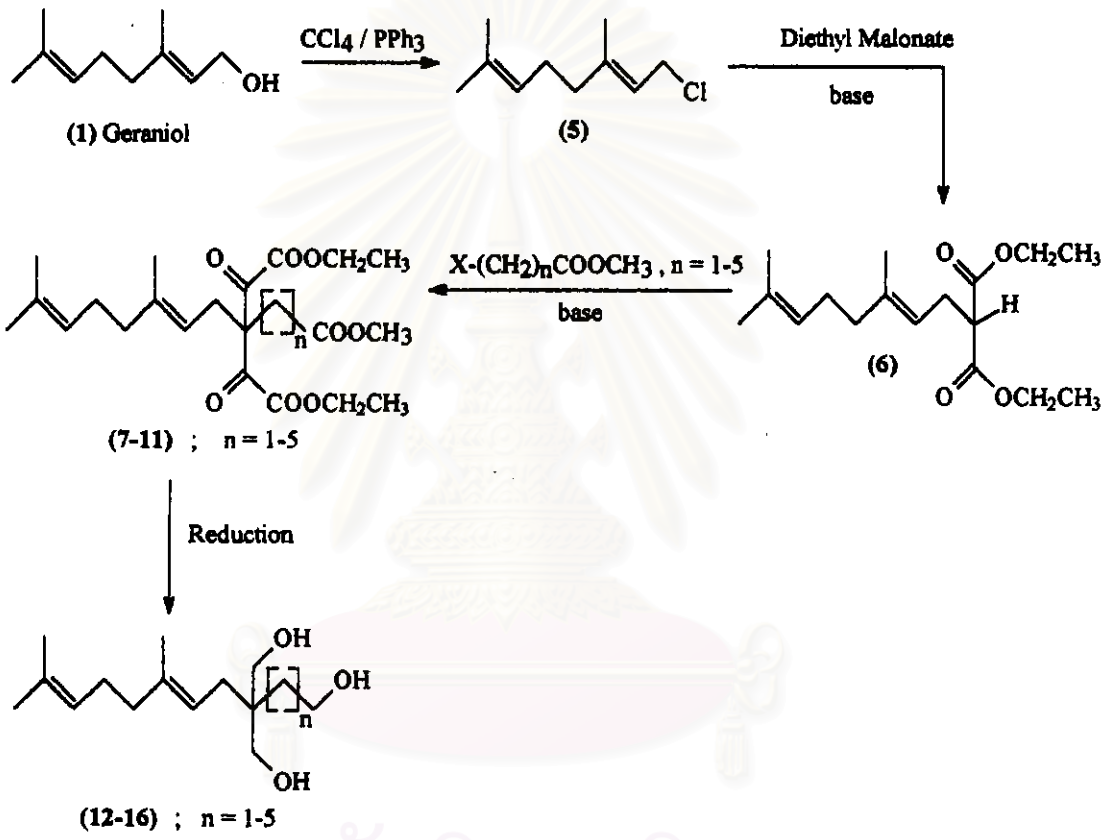
Type I was synthesized in order to study the correlation between the effect of hydrophobic group and biological activity by using methyl group instead of geranyl group.

Type II :



n = 1 - 5

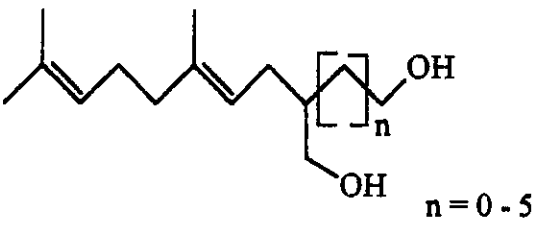
The compounds (Type II) differ from plaunotol in that these compounds have three hydroxyl groups and the distance between the two hydroxyl groups comprising of 4-8 carbon atoms which belong to alkyl chain group while plaunotol has two hydroxyl groups and the distance between the two hydroxyl groups comprising exactly 8 carbon atoms including olefinic groups. These compounds are prepared by Malonic Ester Synthesis reaction.(Scheme 4)



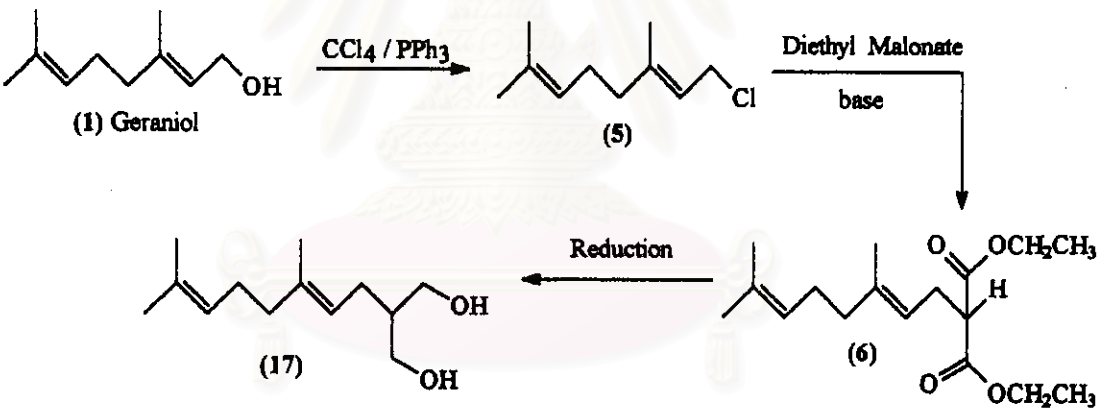
Scheme 4

Type II was synthesized in order to study the correlation between the effect of olefinic groups which is between two hydroxyl groups, the effect of the distance between the two hydroxyl groups which comprises 4-8 carbon atoms of alkyl chain group and the effect of the number of hydroxyl groups which composes of three hydroxyl groups when these three groups were compared with biological activity.

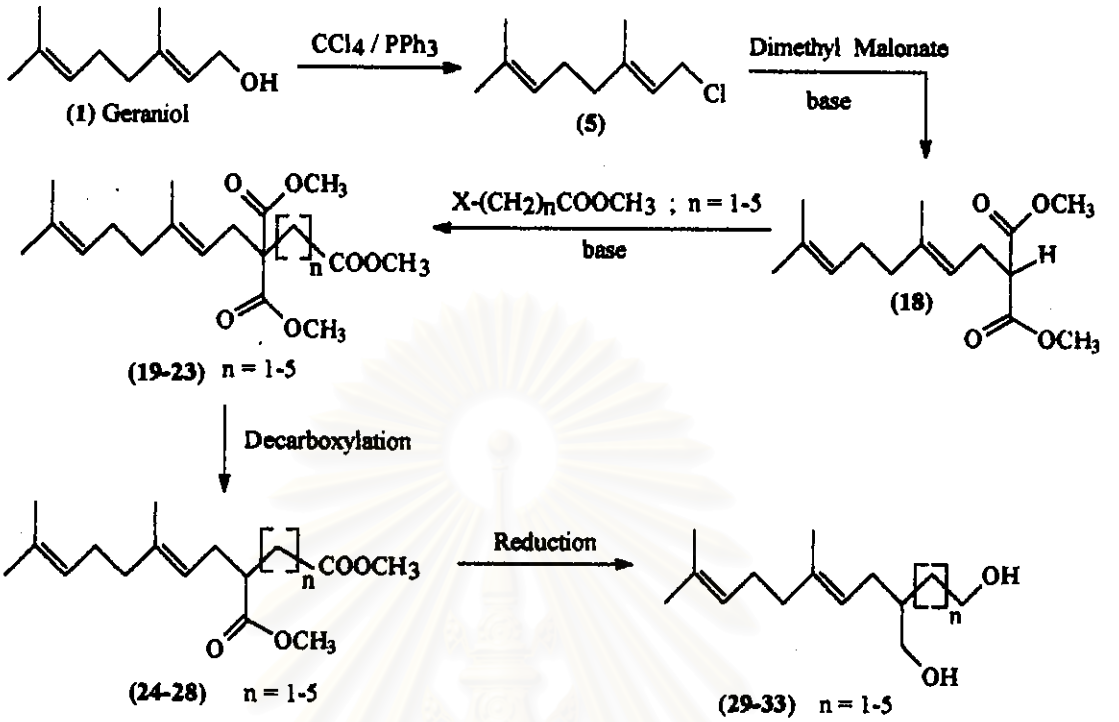
Type III :



These compounds (Type III) differ from plaunotol in that these compounds have the distance between the two hydroxyl groups comprising of 3-8 carbon atoms which are in the group of alkyl chain group while plaunotol has the distance between the two hydroxyl groups comprising of exactly 8 carbon atoms and contains olefinic groups. These compounds are prepared by Malonic Ester synthesis and decarboxylation reaction. (Scheme 5-6)



Scheme 5



Scheme 6

Type III was synthesized in order to study the correlation between the effect of olefinic groups which is between two hydroxyl groups and the effect of the distance of two hydroxyl groups which comprises 3-8 carbon atoms of alkyl chain group when these two groups were compared with biological activity.

Plaunotol analogues Type I (4), Type II (12-16) and Type III (17, 29-33), which were synthesized, can be characterized by spectroscopic techniques. [13-16]

The biological activity of these 3 types of plaunotol analogues were evaluated by testing their ability to inhibit cyclic adenosine 3′, 5′-monophosphate (cAMP) hydrolysis of cyclic adenosine 3′,5′- monophosphate phosphodiesterase (PDE) in order to compare the biological activity with that of plaunotol. [17 - 20]