CHAPTER III

RESULTS AND DISCUSSION

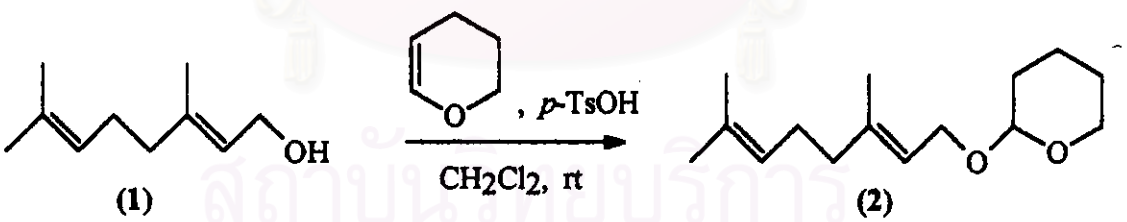
Synthesis of Plaunotol Analogues from geraniol

General Discussion

The synthesis of plaunotol analogues was accomplished in three to five steps starting from commercially available geraniol. The plaunotol analogues were characterized by IR, ^{1}H and ^{13}C-NMR, MS and Elemental Analysis.

Synthesis of 3,7-Dimethyl-2,6-octadienyl tetrahydropyranyl ether (2)

Scheme 7 shows the preparation of 3,7-Dimethyl-2,6-octadienyl tetrahydro pyranyl ether (2) which the hydroxyl group of geraniol was protected by tetrahydropyranyl ether.[22 - 24] The reaction between geraniol (1) (1 equiv) and dihydropyran (2 equiv) which was catalyzed by *p*-toluenesulfonic acid was carried out in CH_2Cl_2 at room temperature for 2 hours to obtain (2) in 96 %yield.



(1) (2)

Scheme 7

The spectroscopic data clearly confirmed the structure of (2). The IR spectrum of (2) is shown in figure 4 and the absorption peaks are assigned in table 2.

Table 2 : The IR absorption band assignment of compound **(2)**

Tentative assignments	Band type	Wavenumber (cm^{-1})
C-H streching vibration of CH_2 , CH_3	s	2937 , 2866
C=C streching vibration	w	1653
C-H bending vibration of CH_2 , CH_3	m	1454 , 1378
O-CH-O streching vibration of acetal group	m	1123
C-O streching vibration	s	1029

The ^1H NMR spectrum of compound **(2)** (Figure 5), clearly showed multiplet signal at 4.56-4.62 ppm which indicated one proton of an acetal group. The signal at 3.41-4.25 ppm represented two methylene groups attached to oxygen atoms. The two olefinic protons and three vinylic methyl groups were observed in the range of 4.99-5.39 ppm and 1.39-1.88 ppm, respectively.

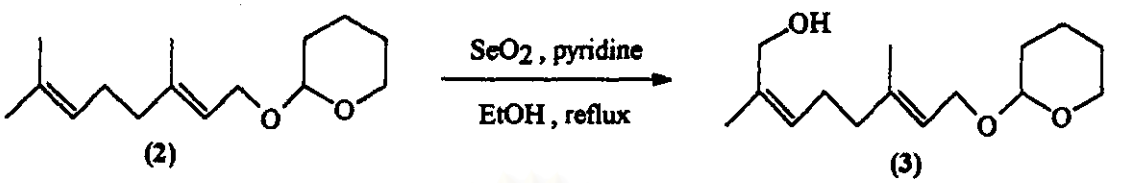
The ^{13}C NMR spectrum and DEPT experiments (Figure 6) revealed the presence of 15 nonequivalent carbons, of which eleven are sp^3 and four are sp^2 hybridized carbons. These four vinyl carbons were consistent with the presence of two double bonds in the molecule which showed signals at 140.2, 131.6, 124.0 and 120.5 ppm, respectively. The signal at 97.7 ppm was assigned to O-CH-O of acetal group and the signals of ether groups (CH_2-O) were at 63.6 and 62.3 ppm.

MS (Figure 7) data gave the fragmentation ion peak at m/z 136 (M^+-102) indicated the elimination of dihydropyran and water. The ion peaks at m/z 85, 69 and 41 were assigned as $C_5H_9O^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

Synthesis of 2,6-Dimethyl-8-(2-tetrahydropyranyloxy)-2,6-octadien-1-ol (3)

Scheme 8 illustrated the preparation of 2,6 - dimethyl- 8 - (2 - tetrahydro pyranyloxy)- 2,6 -octadien- 1-ol **(3)** following experimental of Camps, L. and co-workers [25] by oxidation of an allylic group of compound **(2)** by selenium dioxide. [25-27] The reaction between (2) (2 equiv) and selenium dioxide (1 equiv) in the

presence of pyridine was carried out in the present of solvent (EtOH) under reflux for 4 hours to give product (3) in 48 % yield.



(2) (3)

Scheme 8

The spectroscopic data clearly confirm the structure of (3). The IR spectrum of (3) is shown in figure 8 and the absorption peaks are tabulated in table 3 which showed the presence of a hydroxyl group according to the broad absorption band between 3629-3106 cm^{-1}.

Table 3 : The IR absorption band assignments of compound (3)

Tentative assignments	Band type	Wavenumber (cm^{-1})
O-H streching vibration of alcohol	b	3629 - 3106
C-H streching vibration of CH_2 , CH_3	s	2942 , 2866
C=C streching vibration	w	1658
C-H bending vibration of CH_2 , CH_3	m	1454 , 1383
O-CH-O streching vibration of acetal group	m	1119
C-O streching vibration	s	1024

The ^1H NMR spectrum of compound (3) (Figure 9), clearly showed broad singlet signal at 2.63 ppm which indicated one proton of hydroxyl group. The signal at 4.49-4.56 ppm indicated the multiplet signal of methine proton which attached to two oxygen atoms, and similarly, the signal at 3.33-4.18 ppm represented that the six protons of three methylene groups attached to oxygen atoms. The two olefinic protons and two vinylic methyl groups were observed in the range of 5.18-5.31 ppm and 1.29-1.82 ppm, respectively.

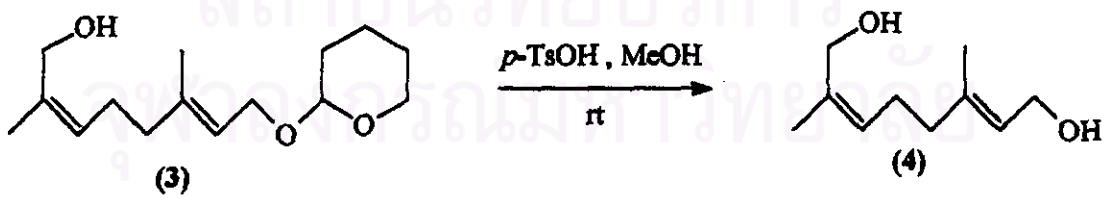
The ^{13}C NMR spectrum and DEPT experiments (Figure 10) revealed the presence of 15 nonequivalent carbons, of which eleven are sp^3 and four are sp^2 hybridized carbons. These four vinyl carbons were consistent with the presence of two double bonds in the molecule which showed signals at 139.8, 135.1, 125.1 and 120.7 ppm, respectively. The signal at 97.6 ppm was assigned to O-CH-O of acetal group and the signals of ether groups (CH_2-O) were at 63.5 and 62.1 ppm. Moreover, the signal at 68.4 ppm was shown to be hydroxymethyl group.

MS (Figure 11) data gave the fragmentation ion peaks at m/z 85, 67 and 43. These ion peaks were assigned as $C_5H_9O^+$, $C_5H_7^+$ and $C_3H_7^+$, respectively.

Comparison of the ^{13}C NMR spectrum and DEPT experiments of this compound with that of compound **(2)** indicated that compound **(3)** differed from compound **(2)** only in having the hydroxymethyl group at 68.4 ppm inplace of one methyl group at 25.7 ppm of compound **(2)** which was at the terminal of geranyl group.

Synthesis of 2,6-Dimethyl-2,6-octadien-1,8-diol (4)

Scheme 9 showed cleavage of the tetrahydropyranyl group in **(3)** with methanol containing *p*-toluenesulfonic acid to give 2,6-dimethyl - 2,6-octadien-1,8-diol **(4)**. [28-29] The reaction between **(3)** (1 equiv) and *p*-toluenesulfonic acid (0.01 equiv) was carried out in MeOH at 0°C for 1 hour and room temperature 3 hours to give **(4)** in 80 % yield.



(3) **(4)**

Scheme 9

The spectroscopic data clearly confirmed the structure of **(4)**. The IR spectrum of **(4)** is shown in figure 12 and the absorption peaks are assigned in table 4.

Table 4 : The IR absorption band assignments of compound **(4)**

Tentative assignments	Band type	Wavenumber (cm^{-1})
O-H streching vibration of alcohol	b	3603 - 3034
C-H streching vibration of CH_2 , CH_3	m	2915 , 2864
C=C streching vibration	w	1658
C-H bending vibration of CH_2 , CH_3	m	1441 , 1380
C-O streching vibration	s	1000

The ^1H NMR spectrum of compound **(4)** (Figure 13), clearly showed broad singlet signal at 3.45 ppm which indicated two protons of hydroxyl groups. The signals at 4.02 and 3.85 ppm showed the doublet and singlet signals of methylene protons, respectively, attached to oxygen atoms of hydroxyl groups. The signal at 5.27 ppm represented the two protons of olefinic groups. The two vinylic methyl groups were observed at 1.57 and 1.55 ppm, respectively.

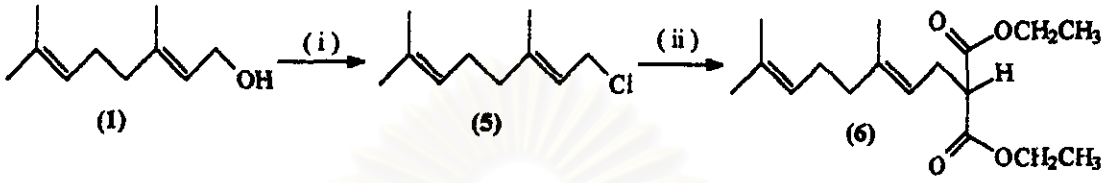
The ^{13}C NMR spectrum and DEPT experiments (Figure 14) revealed the presence of 10 nonequivalent carbons, of which six are sp^3 and four are sp^2 hybridized carbons. These four vinyl carbons were consistent with the presence of two double bonds in the molecule which showed signals at 138.1, 134.9, 124.9 and 123.9 ppm, respectively. The signals at 68.2 and 58.9 ppm were assigned to (CH_2-O) of hydroxymethyl groups.

MS (Figure 15) data gave the fragmentation ion peaks at m/z 83, 70 and 41. These ion peaks were assigned as $C_5H_7O^+$, $C_4H_6O^+$ and $C_3H_5^+$, respectively.

Synthesis of Ethyl-2-ethoxycarbonyl-5,9-dimethyldeca-4,8-dienoate (6)

The two-carbon homologation exploited malonic esterification starting from geraniol **(1)** (scheme 10). Treatment of geraniol with PPh_3-CCl_4 at reflux temperature afforded geranyl chloride.[30-33] Geranyl chloride was used for the following reaction

without further purification. Treatment of geranyl chloride **(5)** (1 equiv) with diethyl malonate (5 equiv) in the presence of NaH (2 equiv) gave the diethyl malonic ester **(6)** in 81 % yield. [34-35]



Scheme 10 : *Reagents and conditions* ;

i, PPh_3 (2 equiv), CCl_4(2 equiv), CH_2Cl_2, reflux, 4 h

ii, NaH (2 equiv), $CH_2(CO_2CH_2CH_3)_2$(5 equiv), THF, reflux, 4h

The IR spectrum of compound **6** (Figure 16) was summarized in table 5.

Table 5 : The IR absorption band assignments of compound **(6)**

Tentative assignments	Band type	Wavenumber (cm^{-1})
C-H streching vibration of CH_2 , CH_3	m	2974 , 2924
C=O streching vibration of ester	s	1733
C-H bending vibration of CH_2 , CH_3	m	1446 , 1380
C-O streching vibration	m	1237 , 1149

The ^1H NMR spectrum of compound **(6)** (Figure 17), clearly showed three singlet signals at 1.66, 1.61 and 1.57 ppm which indicated nine protons of three olefinic methyl groups. The signal at 2.54 ppm indicated the triplet signal of methylene proton at C-3, and similarly, the signal at 1.86-2.10 ppm represented that the four protons of two methylene groups at C-6, C-7. The two olefinic protons were observed in the range of 5.02-5.12 ppm. Moreover, the chemical shift value of one proton at C-2 which attached to two carbonyl carbons appeared as triplet signal at

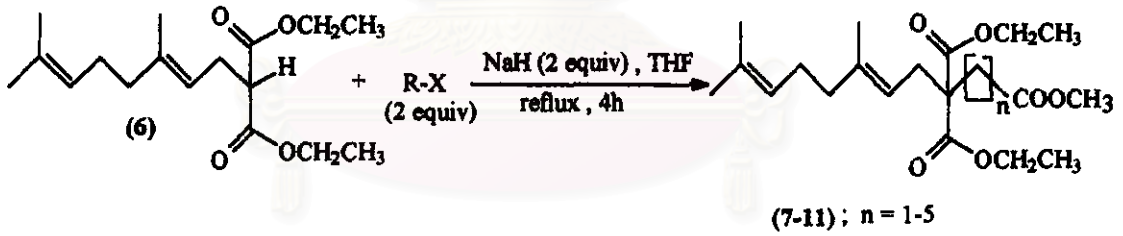
3.31 ppm and the signals at 1.22 and 4.15 ppm represented two methyl and two methylene protons (CH_3 and CH_2) of the diethyl malonate, respectively.

The ^{13}C NMR spectrum and DEPT experiments (Figure 18) showed the olefinic carbons at 138.6, 131.2, 124.1 and 119.3 ppm, respectively. The signals at 169.4, 61.2, 52.1 and 14.2 ppm were assigned to the two carbonyl groups, two methylene carbons attached to oxygen atoms, methine carbon and two methyl carbons of diethyl malonate, respectively. Finally, three methylene carbons and three vinylic methyl carbons signals appeared at 39.8, 27.6, 26.7, 25.6, 17.8 and 16.0 ppm, respectively.

MS (Figure 19) data gave the fragmentation ion peaks at m/z 69 and 41. These ion peaks were assigned as $C_5H_9^+$ and $C_3H_5^+$, respectively.

Synthesis of compound (7)-(11)

The compound (7)-(11) could be synthesized by alkylation of compound (6) with various ω-haloacids methylesters (R-X) (scheme 11).[36-37]



Scheme 11

Treatment of compound (6) (1 equiv) with NaH (2 equiv) at 0-25 °C, followed by ω-haloacids methylesters (R-X) (2 equiv) at reflux temperature for 4 h, gave the corresponding triesters (7)-(11) in good yield. (Table 6)

Table 6 : The Alkylation of compound (6) with various ω-haloacids methylesters (R-X) [a] in the same condition.

entry	Methyl haloester(R-X)	product	%yield
1	$BrCH_2COOCH_3$	compound 7	78
2	$Br(CH_2)_2COOCH_3$	compound 8	73
3	$I(CH_2)_3COOCH_3$	compound 9	68
4	$Br(CH_2)_4COOCH_3$	compound 10	67
5	$Br(CH_2)_5COOCH_3$	compound 11	63

(a) Methyl haloesters (R - X) were obtained via reaction of the acid halides with diazomethane in the presence of diethyl ether which was prepared by following procedure described in the appendex section. Most acid halides used are known and they were purchased from Fluka.

From the table 6 showed that % yield of compound (7)-(11) are decreased respectively when the length of alkyl chain of ω-haloacids methylesters are increased. These results showed that % yield of these compounds depended on two factors; the inductive effect of ester group which was electron withdrawing character and the folding of alkyl chain of ω-haloacids methylesters. When considering the inductive effect of ester group, it was found that when the length of alkyl chain of ω-haloacids methylesters are increased, the inductive effect of ester group will be decreased which affects the strength of CH_2-X bond and will lead to the decreased in % yield of these compounds. Whereas the folding of alkyl chain of ω-haloacids methylesters will be increased when the length of alkyl chain of ω-haloacids methylesters are increased. As a result, the attack of nucleophile will be difficult and % yield of these compounds will be decreased.

The spectroscopic data clearly confirmed the structure of compound (7)-(11). The IR spectrum of (7)-(11) are shown in figure 20-24 and the absorption peaks are assigned in table 7.

Table 7 : The IR absorption band assignments of compound (7)-(11)

Tentative Assignments	Band type	ν (cm^{-1}) cpd.7	ν (cm^{-1}) cpd.8	ν (cm^{-1}) cpd.9	ν (cm^{-1}) cpd.10	ν (cm^{-1}) cpd.11
C-H streching vibration of CH_2,CH_3	m	2975 , 2929	2980 , 2924	2975 , 2929	2955 , 2929	2934 , 2863
C=O streching vibration of ester	s	1736	1730	1730	1736	1736
C-H bending vibration of CH_2,CH_3	m	1433 , 1350	1444 , 1362	1444 , 1367	1439 , 1372	1439 , 1372
C-O streching vibration	m	1172	1177	1172	1178	1178

The ^1H NMR spectrum of compound (7) (Figure 25), clearly showed three singlet signals at 1.61, 1.59 and 1.57 ppm which indicated nine protons of three olefinic methyl groups. The signal at 2.65 ppm indicated the doublet signal of methylene proton at C-4, and similarly, the signal at 1.81-2.02 ppm represented that the four protons of two methylene groups at C-7, C-8. The two olefinic protons were observed in the range of 4.81-5.02 ppm. The signals at 1.19 and 4.08 ppm were assigned to the two methyl and two methylene protons (CH_3 and CH_2) of diethyl malonate. Moreover, the signals at 2.84 and 3.57 ppm represented the methylene and methyl protons of methyl bromoacetate, respectively.

Comparison of ^1H NMR spectrum of compound (8) (Figure 26) with that of compound (7) indicated that compound (8) differed from compound (7) only in having two methylene and methyl protons of methyl 3-bromopropionate at 2.18, 2.23 and 3.59 ppm, respectively.

Comparison of ^1H NMR spectrum of compound (9) (Figure 27) with that of compound (7) demonstrated that compound (9) differed from compound (7) only in

having three methylene and methyl protons of methyl 4-iodobutyrate at 1.31-1.40, 1.67-1.78, 2.14 and 3.52 ppm, respectively.

Comparison of ^{1}H NMR spectrum of compound **(10)** (Figure 28) with that of compound **(7)** indicated that compound **(10)** differed from compound **(7)** only in having four methylene and methyl protons of methyl 5-bromovalerate at 1.03-1.25, 1.42-1.57, 1.72-1.88, 2.15-2.27 and 3.58 (3.66) ppm, respectively.

Comparison of ^{1}H NMR spectrum of compound **(11)** (Figure 29) with that of compound **(7)** demonstrated that compound **(11)** differed from compound **(7)** only in having five methylene and methyl protons of methyl 6-bromocaproate at 1.01-1.39, 1.47-1.58, 1.73-1.84, 2.18-2.27 and 3.59 (3.67) ppm, respectively.

The ^{13}C NMR spectrum and DEPT experiments of compound **(7)** (Figure 30) showed the two carbonyl groups (C=O), two methylene carbons attached to oxygen atoms (O-CH_2), quarternary carbon (C-3) and two methyl carbons (CH_3) of diethyl malonate according to the signals at 169.9, 61.3, 55.7 and 14.2 ppm, respectively. The signals of olefinic carbons appeared at 139.8, 131.4, 123.9 and 117.7 ppm. The signals at 39.7, 31.7 and 26.5 ppm were assigned to the three methylene carbons of geranyl group. The signals of vinylic methyl carbons appeared at 25.6, 17.9 and 16.0 ppm, respectively. Moreover, the signals at 171.1, 51.2 and 36.8 ppm were assigned to C=O, CH_3-O, CH_2 of methyl bromoacetate, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(8)** (Figure 31) with that of compound **(7)** indicated that compound **(8)** differed from compound **(7)** only in having C=O, CH_3-O, 2(CH_2) of methyl 3-bromopropionate at 173.5, 51.9, 31.4 and 27.9 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(9)** (Figure 32) with that of compound **(7)** demonstrated that compound **(9)** differed from compound **(7)** only in having C=O, CH_3-O, 3(CH_2) of methyl 4-iodobutyrate at 173.1, 51.2, 33.9, 31.4 and 19.6 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(10)** (Figure 33) with that of compound **(7)** indicated that compound **(10)** differed

from compound (7) only in having C=O, CH_3-O, 4(CH_2) of methyl 5-bromovalerate at 173.3 (173.7), 51.3 (52.2), 33.7 (34.0), 31.8, 25.1 and 23.6 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound (11) (Figure 34) with that of compound (7) demonstrated that compound (11) differed from compound (7) only in having C=O, CH_3-O, 5(CH_2) of methyl 6-bromocaproate at 173.6 (174.0), 51.4 (52.2), 33.9 (34.2), 31.9, 30.9, 24.7 and 23.7 ppm, respectively.

The mass spectrum of compound (7) (Figure 35) gave the fragmentation ion peaks at m/z 239, 193, 165, 69 and 41. These ion peaks were assigned as $C_{13}H_{19}O_4^+$, $C_{11}H_{13}O_3^+$, $C_{10}H_{13}O_2^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound (8) (Figure 36) gave the fragmentation ion peaks at m/z 246, 173, 69 and 41. These ion peaks were assigned as $C_{16}H_{22}O_2^+$, $C_{13}H_{17}^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

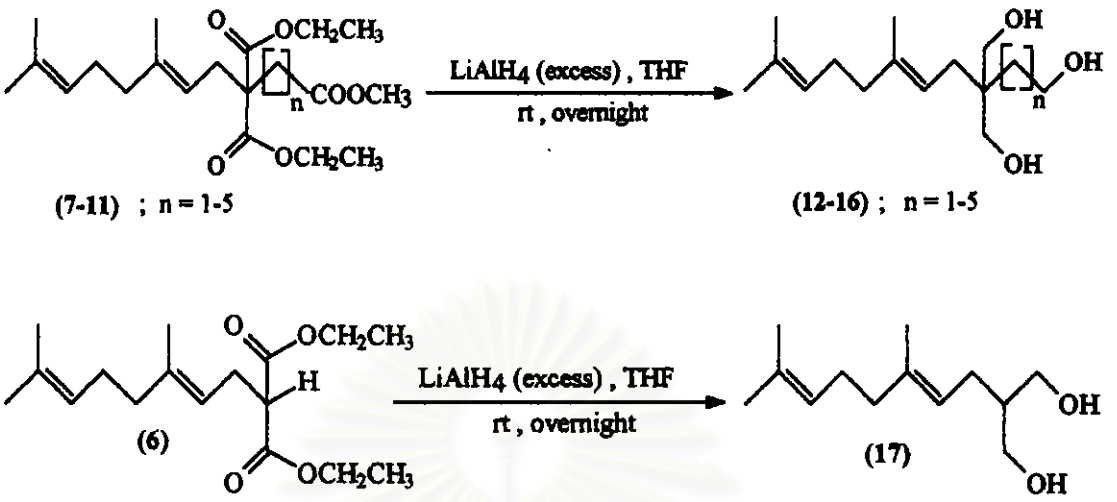
MS data of compound (9) (Figure 37) gave the fragmentation ion peaks at m/e 69 and 41. These ion peaks were assigned as $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound (10) (Figure38) gave the fragmentation ion peaks at m/z 69 and 41. These ion peaks were assigned as $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound (11) (Figure 39) gave the fragmentation ion peaks at m/z 379, 69 and 41. These ion peaks were assigned as $C_{22}H_{35}O_5^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

Synthesis of compound (12)-(17)

The compound (12) - (17) are prepared in good yield by reduction of compound (6)-(11)with $LiAlH_4$ which afforded the primary alcohol.(Scheme12) [38-40]



Scheme 12

Treatment of compound **(6) - (11)** (1 equiv) with Lithium Aluminium Hydride ($LiAlH_4$) (excess) at room temperature overnight gave the corresponding dialcohol **(17)** and trialcohols **(12)-(16)** in good yield. (Table 8).

Table 8 : The reduction of compound **(6)-(11)** with $LiAlH_4$ under the same condition.

entry	substrates	product	%yield
1	compound 6	compound 17	74
2	compound 7	compound 12	75
3	compound 8	compound 13	74
4	compound 9	compound 14	73
5	compound 10	compound 15	71
6	compound 11	compound 16	70

The spectroscopic data clearly confirmed the structure of compound **(12)-(17)**. The IR spectrum of **(12) - (17)** are shown in figure 40-45 and the absorption peaks are assigned in table 9 which showed the presence of a hydroxyl group according to the broad absorption band between 3600 to 3000 cm^{-1}.

Table 9 : The IR absorption band assignments of compound **(12)-(17)**

Tentative Assignments	Band type	ν (cm^{-1}) cpd.12	ν (cm^{-1}) cpd.13	ν (cm^{-1}) cpd.14	ν (cm^{-1}) cpd.15	ν (cm^{-1}) cpd.16	ν (cm^{-1}) cpd.17
O-H streching vibration of alcohol	b	3616 - 3050	3616 - 3041	3615 - 3078	3636 - 3052	3590 - 3078	3683 - 3058
C-H streching vibration of CH_2,CH_3	s	2966 , 2925	2931 , 2872	2929 , 2866	2929 , 2858	2929 , 2858	2924 , 2847
C-H bending vibration of CH_2,CH_3	m	1439 , 1374	1445 , 1380	1444 , 1378	1444 , 1372	1449 , 1378	1441 , 1375
C-O streching vibration	s	1040	1051	1050	1050	1040	1033

The ^1H NMR spectrum of compound **(12)** (Figure 46) was similar to that of compound **(7)** except for the signals at 3.50, 3.68 and 3.76-4.09 ppm. These signals represented two methylene protons of two hydroxymethyl groups attached to C-3, methylene proton at C-1 and three hydroxyl groups, respectively.

The ^1H NMR spectrum of compound **(13)** (Figure 47) was similar to that of compound **(8)** except for the signals at 3.33-3.67 and 3.89-4.25 ppm. These signals represented three methylene protons of three hydroxymethyl groups at C-1 and attached to C-4, and three hydroxyl groups, respectively.

The ^1H NMR spectrum of compound **(14)** (Figure 48) was similar to that of compound **(9)** except for the signals at 3.46 and 3.52 - 4.77 ppm. These signals represented two methylene protons of two hydroxymethyl groups attached to C-5, methylene protons at C-1 and three hydroxyl groups, respectively.

The ^{1}H NMR spectrum of compound **(15)** (Figure 49) was similar to that of compound **(10)** except for the signals at 2.95, 3.47 and 3.51-3.64 ppm. These signals represented one hydroxyl group, two methylene protons of two hydroxymethyl groups attached to C-6, methylene proton at C-1 and two hydroxyl groups, respectively.

The ^{1}H NMR spectrum of compound **(16)** (Figure 50) was similar to that of compound **(11)** except for the signals at 3.16, 3.44 and 3.49-3.68 ppm. These signals represented one hydroxyl group, two methylene protons of two hydroxy methyl groups attached to C-7, methylene proton at C-1 and two hydroxyl groups, respectively.

The ^{1}H NMR spectrum of compound **(17)** (Figure 51) was similar to that of compound **(6)** except for the signals at 3.42-3.58, 3.58-3.70 and 3.89 ppm. These signals represented methylene protons at C-1, methylene protons of hydroxymethyl group attached to C-2, and two hydroxyl groups, respectively.

Furthermore, comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(12)** (Figure 52) with that of compound **(7)** demonstrated that compound **(12)** differed from compound **(7)** only in having two methylene carbons of hydroxy methyl groups attached to C-3 and methylene carbon at C-1 at 67.6 and 58.4 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(13)** (Figure 53) with that of compound **(8)** demonstrated that compound **(13)** differed from compound **(8)** only in having two methylene carbons of hydroxymethyl groups attached to C-4 and methylene carbon at C-1 at 67.9 and 62.9 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(14)** (Figure 54) with that of compound **(9)** demonstrated that compound **(14)** differed from compound **(9)** only in having two methylene carbons of hydroxymethyl groups attached to C-5 and methylene carbon at C-1 at 67.7 and 61.9 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(15)** (Figure 55) with that of compound **(10)** demonstrated that compound **(15)** differed

from compound (10) only in having two methylene carbons of hydroxymethyl groups attached to C-6 and methylene carbon at C-1 at 68.2 and 62.5 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound (16) (Figure 56) with that of compound (11) demonstrated that compound (16) differed from compound (11) only in having two methylene carbons of hydroxymethyl groups attached to C-7 and methylene carbon at C-1 at 68.1 and 62.5 ppm, respectively. .

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound (17) (Figure 57) with that of compound (6) demonstrated that compound (17) differed from compound (6) only in having methylene carbon of hydroxymethyl group which attached to C-2 and methylene carbon at C-1 at 65.0 ppm, respectively.

Moreover, the mass spectrum of compound (12) (Figure 58) gave the fragmentation ion peaks at m/z 69 and 41. These ion peaks were assigned as $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound (13) (Figure 59) gave the fragmentation ion peaks at m/z 69 and 41. These ion peaks were assigned as $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound (14) (Figure 60) gave the fragmentation ion peaks at m/z 81, 69 and 41. These ion peaks were assigned as $C_6H_9^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

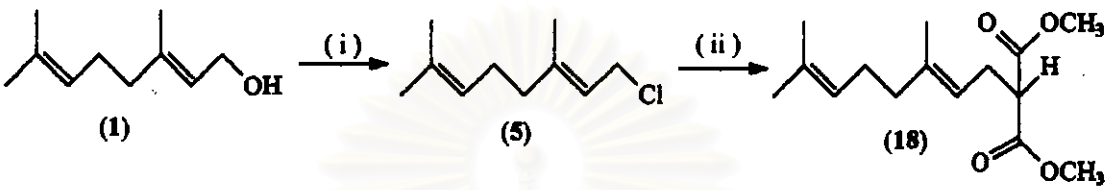
MS data of compound (15) (Figure 61) gave the fragmentation ion peaks at m/z 81, 69 and 41. These ion peaks were assigned as $C_6H_9^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound (16) (Figure 62) gave the fragmentation ion peaks at m/z 81, 69 and 41. These ion peaks were assigned as $C_6H_9^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound (17) (Figure 63) gave the fragmentation ion peaks at m/z 81, 69 and 41. These ion peaks were assigned as $C_6H_9^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

Synthesis of Methyl-2-methoxycarbonyl-5,9-dimethyldeca-4,8-dienoate (18)

By a method similar to that used in the preparation compound (6), compound (18) was obtained from treatment of geranyl chloride (5) (1equiv) with dimethyl malonate (5 equiv) in the pressence of NaH (2 equiv) gave the dimethyl ester (18) in 93 % yield. [30-35] (Scheme 13)



(1) (5) (18)

Scheme 13 : *Reagents and conditions* ;

i, PPh_3 (2 equiv), CCl_4(2 equiv), CH_2Cl_2, reflux, 4 h

ii, NaH (2 equiv), $CH_2(CO_2CH_3)_2$ (5 equiv), THF, reflux, 4h

The IR spectrum of compound 18 (Figure 64) was summarized in table 10.

Table 10 : The IR absorption band assignments of compound (18)

Tentative assignments	Band type	Wavenumber (cm^{-1})
C-H streching vibration of CH_2 , CH_3	m	2955 , 2919
C=O streching vibration of ester	s	1741
C-H bending vibration of CH_2 , CH_3	m	1434 , 1342
C-O streching vibration	m	1239 , 1152

The ^1H NMR spectrum of compound (18) (figure 65), clearly showed three singlet signals at 1.63, 1.59 and 1.55 ppm which indicated nine protons of three olefinic methyl groups. The signal at 2.57 ppm indicated the triplet signal of methylene proton at C-3, and similarly, the signal at 1.85-2.08 ppm represented that the four protons of two methylene groups at C-6, C-7. The two olefinic protons were observed in the range of 4.96-5.12 ppm. Moreover, the resonance signal of one

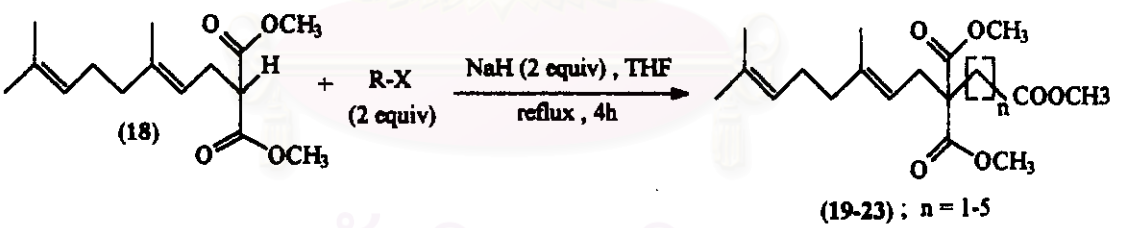
proton at C-2 which attached to two carbonyl carbons appeared as triplet signal at 3.33 ppm and the signal at 3.68 ppm indicated two methyl protons of the dimethyl malonate, respectively.

The ^{13}C NMR spectrum and DEPT experiments (Figure 66) showed the olefinic carbons at 138.7, 131.4, 123.9 and 119.4 ppm, respectively. The signals at 169.6, 52.4 and 51.9 ppm were assigned to the two carbonyl groups, two methyl carbons attached to oxygen atoms and methine carbon of dimethyl malonate, respectively. Finally, three methylene carbons and three vinylic methyl carbons appeared the signals at 39.6, 27.5, 26.5, 25.6, 17.6 and 16.0 ppm, respectively.

MS (Figure 67) data gave the fragmentation ion peaks at m/z 237, 136, 69 and 41. These ion peaks were assigned as $C_{14}H_{21}O_3^+$, $C_{10}H_{16}^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

Synthesis of compound (19)-(23)

The compound **(19)** - **(23)** could be synthesized by alkylation of compound **(18)** with various ω-haloacids methylesters (R-X) (scheme 14).[36-37]



Scheme 14

Treatment of compound **(18)** (1 equiv) with NaH (2 equiv) at 0-25 °C, followed by ω-haloacids methylesters (R-X) (2 equiv) at reflux temperature for 4 h, gave the corresponding triesters **(19)-(23)** in good yield. (Table 11)

Table 11 : The Alkylation of compound **(18)** with various ω-haloacids methylesters (R-X) in the same condition.

entry	Methyl haloester(R-X)	product	%yield
1	$BrCH_2COOCH_3$	compound 19	82
2	$Br(CH_2)_2COOCH_3$	compound 20	78
3	$I(CH_2)_3COOCH_3$	compound 21	74
4	$Br(CH_2)_4COOCH_3$	compound 22	70
5	$Br(CH_2)_5COOCH_3$	compound 23	68

From the table 11 showed that %yield of compound **(19) - (23)** are decreased respectively when the length of alkyl chain of ω-haloacids methylesters are increased. These results are the same as compound **(7)-(11)** and probably had the same explanation.

The spectroscopic data clearly confirmed the structure of compound **(19)-(23)**. The IR spectrum of **(19)-(23)** are shown in figure 68-72 and the absorption peaks are assigned in table 12.

Table 12 : The IR absorption band assignments of compound **(19)-(23)**

Tentative Assignments	Band type	ν (cm^{-1}) cpd.19	ν (cm^{-1}) cpd.20	ν (cm^{-1}) cpd.21	ν (cm^{-1}) cpd.22	ν (cm^{-1}) cpd.23
C-H streching vibration of CH_2,CH_3	m	2950 , 2919	2950 , 2919	2950 , 2919	2950 , 2924	2950 , 2929
C=O streching vibration of ester	s	1736	1731	1731	1731	1731
C-H bending vibration of CH_2,CH_3	m	1439 , 1357	1439 , 1378	1434	1434	1434
C-O streching vibration	m	1291 , 1173	1219 , 1173	1214 , 1173	1214 , 1168	1209 , 1173

The ^{1}H NMR spectrum of **(19)** (Figure 73), clearly showed two singlet signals and multiplet signal at 1.52, 1.55 and 1.59-1.70 ppm which indicated nine protons of three olefinic methyl groups. The signal at 2.71 ppm indicated the doublet signal of methylene proton at C-4, and similarly, the signal at 1.88-2.10 ppm represented that the four protons of two methylene groups at C-7, C-8. The two olefinic protons were observed in the range of 4.81-5.06 ppm. The signal at 3.70 ppm was assigned to the two methyl protons attached to oxygen atoms of dimethyl malonate. Moreover, the signals at 2.91 and 3.62 ppm represented the methylene and methyl protons of methyl bromoacetate, respectively.

Comparison of ^{1}H NMR spectrum of compound **(20)** (Figure 74) with that of compound **(19)** indicated that compound **(20)** differed from compound **(19)** only in having two methylene and methyl protons of methyl 3-bromopropionate at 2.11-2.35 and 3.64 ppm, respectively.

Comparison of ^{1}H NMR spectrum of compound (21) (Figure 75) with that of compound (19) demonstrated that compound (21) differed from compound (19) only in having three methylene and methyl protons of methyl 4-iodobutyrate at 1.32-1.48, 1.68-1.84, 2.20 and 3.55 ppm, respectively.

Comparison of ^{1}H NMR spectrum of compound (22) (Figure 76) with that of compound (19) indicated that compound (22) differed from compound (19) only in having four methylene and methyl protons of methyl 5-bromovalerate at 1.07-1.26, 1.60-1.66, 1.75-1.88, 2.28 and 3.63 ppm, respectively.

Comparison of ^{1}H NMR spectrum of compound (23) (Figure 77) with that of compound (19) demonstrated that compound (23) differed from compound (19) only in having five methylene and methyl protons of methyl 6-bromocaproate at 1.08-1.40, 1.65, 1.78-1.86, 2.26 and 3.63 ppm, respectively.

The ^{13}C NMR spectrum and DEPT experiments of compound (19) (Figure 78) showed the two carbonyl groups (C=O), two methyl carbons attached to oxygen atoms (O-CH_3) and quarternary carbon (C-3) of dimethyl malonate according to the signals at 170.7, 52.7 and 55.6 ppm, respectively. The signals of olefinic carbons appeared at 140.2, 131.6, 123.9 and 117.4 ppm. The signals at 39.9, 31.9 and 26.4 ppm were assigned to the three methylene carbons of geranyl group. The signals of vinylic methyl carbons appeared at 25.6, 17.6 and 15.9 ppm, respectively. Moreover, the signals at 171.1, 51.7 and 36.9 ppm were assigned to C=O, CH_3-O, CH_2 of methyl bromoacetate, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound (20) (Figure 79) with that of compound (19) indicated that compound (20) differed from compound (19) only in having C=O, CH_3-O, 2(CH_2) of methyl 3-bromopropionate at 173.2, 51.7, 31.8 and 27.7 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound (21) (Figure 80) with that of compound (19) demonstrated that compound (21) differed from compound (19) only in having C=O, CH_3-O, 3(CH_2) of methyl 4-iodobutyrate at 173.2, 51.4, 34.0, 31.6 and 19.7 ppm, respectively.

Comparison ^{13}C NMR spectrum and DEPT experiments of compound **(22)** (Figure 81) with that of compound **(19)** indicated that compound **(22)** differed from compound **(19)** only in having C=O, CH_3-O, 4(CH_2) of methyl 5-bromovalerate at 173.8, 51.5, 33.7, 31.9, 25.1 and 23.7 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(23)** (Figure 82) with that of compound **(19)** demonstrated that compound **(23)** differed from compound **(19)** only in having C=O, CH_3-O, 5(CH_2) of methyl 6-bromocaproate at 174.0, 51.4, 33.9, 32.1, 31.1, 24.7 and 23.8 ppm, respectively.

The mass spectrum of compound **(19)** (Figure 83) gave the fragmentation ion peaks at m/z 265, 211, 69 and 41. These ion peaks were assigned as $C_{15}H_{21}O_4^+$, $C_{11}H_{15}O_4^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound **(20)** (Figure 84) gave the fragmentation ion peaks at m/z 69 and 41. These ion peaks were assigned as $C_5H_9^+$ and $C_3H_5^+$, respectively.

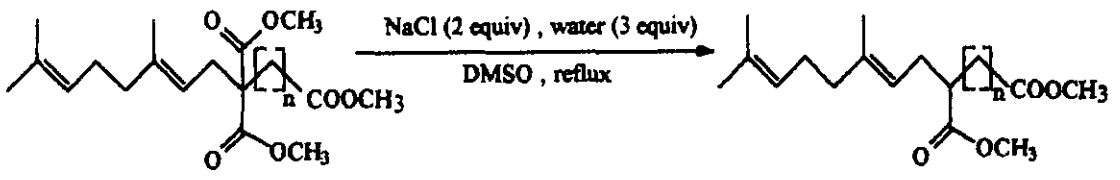
MS data of compound **(21)** (Figure 85) gave the fragmentation ion peaks at m/z 232, 69 and 41. These ion peaks were assigned as $C_{15}H_{20}O_2^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound **(22)** (Figure 86) gave the fragmentation ion peaks at m/z 246, 193, 69 and 41. These ion peaks were assigned as $C_{16}H_{22}O_2^+$, $C_{12}H_{17}O_2^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound **(23)** (Figure 87) gave the fragmentation ion peaks at m/e 69 and 41. These ion peaks were assigned as $C_5H_9^+$ and $C_3H_5^+$, respectively.

Synthesis of compound (24)-(28)

Decarboxylation of the triesters **(19)-(23)** under neutral conditions (NaCl in moist DMSO) afforded diesters **(24)-(28)** in good yield (scheme 15). [41]



(19-23) ; n = 1-5 (24-28) ; n = 1-5

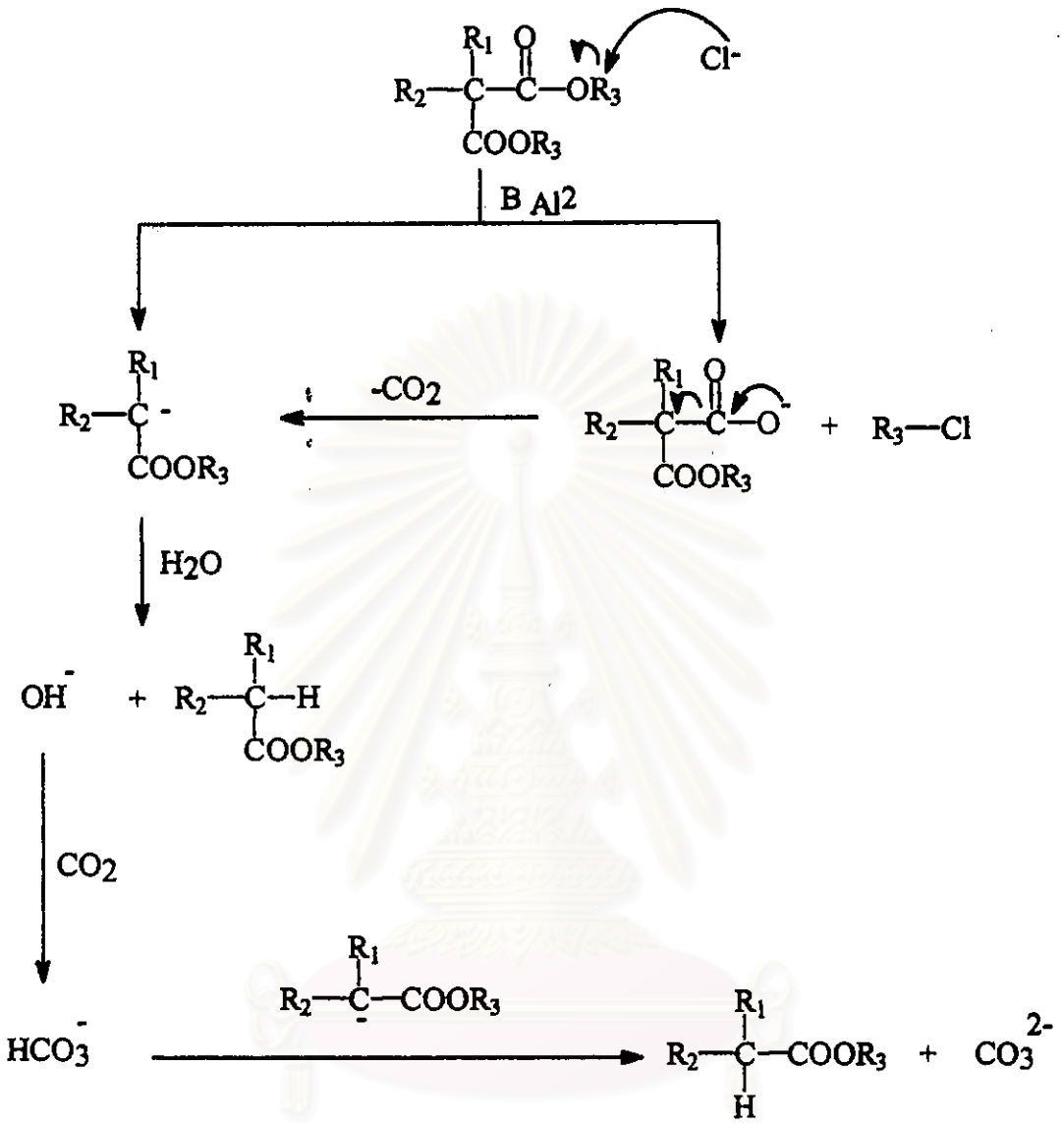
Scheme 15

Treatment of compound **(19)-(23)** (1 equiv) with sodium chloride (2 equiv) and water (3 equiv) in DMSO under reflux for various hours gave the corresponding diesters **(24)-(28)** in good yield. (Table 13)

Table 13 : The decarboxylation of compound **(19)-(23)** under neutral conditions (NaCl in moist DMSO)

entry	substrates	time (hours)	product	%yield
1	compound 19	2	compound 24	74
2	compound 20	2	compound 25	76
3	compound 21	4	compound 26	71
4	compound 22	6	compound 27	73
5	compound 23	6	compound 28	72

The reaction time of decarboxylation are shown in table 13, suggested that the substrate structure, especially at disubstituted malonate esters, had strong effect on the rate of decarboxylation by NaCl in moist DMSO. This probably resulted from steric effect which depended on the substrate structure, for example compound 19 whose less stric hindrance of the reaction is reflected in the short reaction time. Moreover, the mechanistic pathway outlined in scheme 16 appeared to be the dominant mechanistic route for disubstituted malonate ester which has been studied by Krapcho and co-workers. [41]



Scheme 16

The spectroscopic data clearlyed confirm the structure of compound **(24)-(28)**. The IR spectrum of **(24)-(28)** arc shown in figurc 88-92 and thc absorption peaks are assigned in table 14.

Table 14 : The IR absorption band assignments of compound **(24)-(28)**

Tentative Assignments	Band type	ν (cm^{-1}) cpd.24	ν (cm^{-1}) cpd.25	ν (cm^{-1}) cpd.26	ν (cm^{-1}) cpd.27	ν (cm^{-1}) cpd.28
C-H streching vibration of CH_2,CH_3	m	2960, 2858	2955, 2858	2955, 2863	2950, 2858	2929, 2858
C=O streching vibration of ester	s	1741	1736	1736	1736	1736
C-H bending vibration of CH_2,CH_3	m	1439, 1372	1444, 1370	1434, 1368	1439, 1380	1434, 1374
C-O streching vibration	m	1168	1163	1163	1157	1163

The ^{1}H NMR spectrum of compound **(24)** (Figure 93) was similar to that of compound **(19)** except for the signals at 2.15-2.46 and 3.65 ppm. These signals represented one methine proton at C-3 and one methyl proton of methyl ester group attached to C-3, respectively.

The ^{1}H NMR spectrum of compound **(25)** (Figure 94) was similar to that of compound **(20)** except for the signals at 1.78-1.92 and 3.63 ppm. These signals represented one methine proton at C-4 and one methyl proton of methyl ester group attached to C-4, respectively.

The ^{1}H NMR spectrum of compound **(26)** (Figure 95) was similar to that of compound **(21)** except for the signals at 2.12-2.46 and 3.64 ppm. These signals represented one methine proton at C-5 and one methyl proton of methyl ester group attached to C-5, respectively.

The ^{1}H NMR spectrum of compound **(27)** (Figure 96) was similar to that of compound **(22)** except for the signals at 2.11-2.40 and 3.62 ppm. These signals

represented one methine proton at C-6 and one methyl proton of methyl ester group attached to C-6, respectively.

The ^{1}H NMR spectrum of compound **(28)** (Figure 97) was similar to that of compound **(23)** except for the signals at 2.11-2.40 and 3.63 ppm. These ion peaks represented one methine proton at C-7 and one methyl proton of methyl ester group attached to C-7, respectively.

Furthermore, comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(24)** (Figure 98) with that of compound **(19)** indicated that compound **(24)** differed from compound **(19)** only in having one carbonyl group and one methyl carbon of methyl ester group attached to C-3, and methine carbon at C-3 at 172.6, 51.8, 41.4 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(25)** (Figure 99) with that of compound **(20)** indicated that compound **(25)** differed from compound **(20)** only in having onc carbonyl group and one methyl carbon of methyl ester group attached to C-4, and methine carbon at C-4 at 173.4, 51.6, 45.0 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(26)** (Figure 100) with that of compound **(21)** indicated that compound **(26)** differed from compound **(21)** only in having one carbonyl group and one methyl carbon of methyl ester group attached to C-5, and methine carbon at C-5 at 173.8, 51.5, 45.6 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(27)** (Figure 101) with that of compound **(22)** indicated that compound **(27)** differed from compound **(22)** only in having one carbonyl group and one methyl carbon of methyl ester group attached to C-6, and methine carbon at C-6 at 173.9, 51.4, 45.7 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(28)** (Figure 102) with that of compound **(23)** indicated that compound **(28)** differed from compound **(23)** only in having one carbonyl group and one methyl carbon of methyl

ester group attached to C-7, and methine carbon at C-7 at 174.1, 51.4, 45.8 ppm, respectively.

Moreover, the mass spectrum of compound **(24)** (Figure 103) gave the fragmentation ion peaks at m/z 207, 153, 69 and 41. These ion peaks were assigned as $C_{13}H_{19}O_2^+$, $C_9H_{13}O_2^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound **(25)** (Figure 104) gave the fragmentation ion peaks at m/z 167, 135, 69 and 41. These ion peaks were assigned as $C_{10}H_{15}O_2^+$, $C_9H_{11}O^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

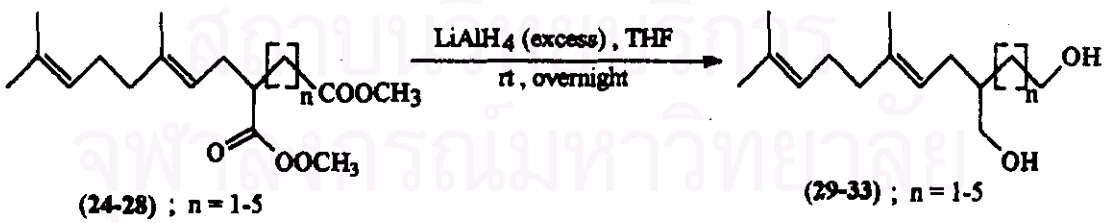
MS data of compound **(26)** (Figure 105) gave the fragmentation ion peaks at m/z 69 and 41. These ion peaks were assigned as $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound **(27)** (Figure 106) gave the fragmentation ion peaks at m/z 69 and 41. These ion peaks were assigned as $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound **(28)** (Figure 107) gave the fragmentation ion peaks at m/z 291, 69 and 41. These ion peaks were assigned as $C_{18}H_{27}O_3^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

Synthesis of compound (29)-(33)

The compound **(29)-(33)** are prepared in good yield by reduction of compound **(24)-(28)**with $LiAlH_4$ to give the primary alcohol (scheme17).[38-40]



Scheme 17

Treatment of compound **(24)-(28)** (1 equiv.) with Lithium Aluminium Hydride ($LiAlH_4$) (excess) at room temperature overnight gave the corresponding dialcohols **(29)-(33)** in good yield. (Table 15)

Table 15 : The reduction of compound **(24)-(28)** with $LiAlH_4$ under the same condition

entry	substrates	products	%yield
1	compound 24	compound 29	86
2	compound 25	compound 30	84
3	compound 26	compound 31	82
4	compound 27	compound 32	83
5	compound 28	compound 33	82

The spectroscopic data clearly confirmed the structure of compound **(29)-(33)**. The IR spectrum of **(29)-(33)** are shown in figure 108-112 and the absorption peaks are assigned in table 16 which showed the pressence of a hydroxyl group according to the broad absorption band between 3600 to 3000 cm^{-1}.

Table 16 : The IR absorption band assignments of **(29)-(33)**

Tentative Assignments	Band type	ν (cm^{-1}) cpd.29	ν (cm^{-1}) cpd.30	ν (cm^{-1}) cpd.31	ν (cm^{-1}) cpd.32	ν (cm^{-1}) cpd.33
O-H streching vibration of alcohol	br	3625-3058	3591-3066	3633-3067	3616-3064	3593-3065
C-H streching vibration of CH_2,CH_3	st	2917, 2875	2923, 2876	2927, 2857	2927, 2857	2927, 2852
C-H bending vibration of CH_2,CH_3	me	1447, 1374	1449, 1374	1445, 1378	1454, 1374	1445, 1374
C-O streching vibration	me	1048	1057	1048	1043	1057

The ^{1}H NMR spectrum of compound **(29)** (Figure 113) was similar to that of compound **(24)** except for the signals at 3.36-3.79 and 3.91 ppm. These signals represented two methylene protons and two hydroxyl groups of two hydroxymethyl groups at C-1 and attached to C-3, respectively.

The ^{1}H NMR spectrum of compound **(30)** (Figure 114) was similar to that of compound **(25)** except for the signal at 3.10-3.65 ppm. This signal represented two methylene protons and two hydroxyl groups of two hydroxymethyl groups at C-1 and attached to C-4, respectively.

The ^{1}H NMR spectrum of compound **(31)** (Figure 115) was similar to that of compound **(26)** except for the signals at 1.88-2.10, 3.49 and 3.60 ppm. These signals represented two hydroxyl groups, methylene proton attached to C-5, and methylene proton at C-1, respectively.

The ^{1}H NMR spectrum of compound **(32)** (Figure 116) was similar to that of compound **(27)** except for the signals at 2.31, 3.45 and 3.57 ppm. These signals represented two hydroxyl groups, methylene proton which attached to C-6, and methylene proton at C-1, respectively.

The ^{1}H NMR spectrum of compound **(33)** (Figure 117) was similar to that of compound **(28)** except for the signals at 2.17, 3.45 and 3.56 ppm. These signals represented two hydroxyl groups, methylene proton which attached to C-7, and methylene proton at C-1, respectively.

Furthermore, comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(29)** (Figure 118) with that of compound **(24)** indicated that compound **(29)** differed from compound **(24)** only in having methylene carbon of hydroxymethyl group attached to C-3 and methylene carbon at C-1 at 66.2 and 61.1 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(30)** (Figure 119) with that of compound **(25)** indicated that compound **(30)** differed from compound **(25)** only in having methylene carbon of hydroxymethyl group attached to C-4 and methylene carbon at C-1 at 65.0 and 62.7 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(31)** (Figure 120) with that of compound **(26)** indicated that compound **(31)** differed from compound **(26)** only in having methylene carbon of hydroxymethyl group attached to C-5 and methylene carbon at C-1 at 65.5 and 62.6 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(32)** (Figure 121) with that of compound **(27)** indicated that compound **(32)** differed from compound **(27)** only in having methylene carbon of hydroxymethyl group attached to C-6 and methylene carbon at C-1 at 65.6 and 62.7 ppm, respectively.

Comparison of ^{13}C NMR spectrum and DEPT experiments of compound **(33)** (Figure 122) with that of compound **(28)** indicated that compound **(33)** differed from compound **(28)** only in having methylene carbon of hydroxymethyl group attached to C-7 and methylene carbon at C-1 at 65.6 and 62.8 ppm, respectively.

Moreover, the mass spectrum of compound **(29)** (Figure 123) gave the fragmentation ion peaks at m/z 69 and 41. These ion peaks were assigned as $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound **(30)** (Figure 124) gave the fragmentation ion peaks at m/z 179, 69 and 41. These ion peaks were assigned as $C_{12}H_{19}O^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound **(31)** (Figure 125) gave the fragmentation ion peaks at m/z 193, 69 and 41. These ion peaks were assigned as $C_{13}H_{21}O^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound **(32)** (Figure 126) gave the fragmentation ion peaks at m/z 207, 69 and 41. These ion peaks were assigned as $C_{14}H_{23}O^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

MS data of compound **(33)** (Figure 127) gave the fragmentation ion peaks at m/z 221, 69 and 41. These ion peaks were assigned as $C_{15}H_{25}O^+$, $C_5H_9^+$ and $C_3H_5^+$, respectively.

Inhibitory Activity of Plaunotol Analogues on cyclic AMP phosphodiesterase.

In order to study and investigate the structure activity relationship, plaunotol analogues compound (4), compound (12)-(17), compound (29)-(33), geraniol and plaunotol were tested for cyclic AMP phosphodiesterase inhibitory activity . The results are summarized in table 17.

Table 17 : Inhibitory Activity of plaunotol analogues, geraniol and plaunotol on cyclic AMP phosphodiesterase.

Sample	%Inhibition Activity (400μg/ml.)
geraniol	20.3
compound 12	29.3
compound 13	34.5
compound 14	32.8
compound 15	32.8
compound 16	17.2
compound 17	27.6
compound 29	43.1
compound 30	44.8
compound 31	25.0
compound 32	8.6
compound 33	0.0
compound 4	23.7
plaunotol	0.0

From Table 17 it showed that plaunotol itself did not show inhibitory activity on cyclic AMP phosphodiesterase. Geraniol and compound (4), which have two hydroxyl groups, have the same inhibitory activity. Therefore, the presence of a hydroxyl group at one side of the chain of compound (4) is not necessary for

inhibitory activity. Compound (33), which has two hydroxyl groups and the distance between the two hydroxyl groups comprising of exactly 8 carbon atoms as the same as plaunotol itsclf, did not show inhibitory activity, too. Compound (17),(29)-(32), which also have two hydroxyl groups but have the distance between the two hydroxyl groups comprising of 3-7 carbon atoms, showed inhibitory activity decreasing when the distance between the two hydroxyl groups was increased. This fact indicated that the distance between the two hydroxyl groups seemed essential for the activity of phosphodiesterase inhibition. Similarly, in the case of type II (compound (12)-(16)), which has three hydroxyl groups, showed inhibitory activity decreasing when the distance between the two hydroxyl groups was increased.

From Figure 128 it showed that type II (compound (12)-(16)), which has the three hydroxyl groups, compound (13) and (14) exhibited the highest inhibitory activity on cyclic AMP phosphodiesterase. Thcsc results indicatde that compounds which have the distance between the two hydroxyl groups comprising of 5,6 carbon atoms exhibited higher activity than the other compounds. Similarly, in the case of type III (compound (17), (29)-(33)), which has two hydroxyl groups, compound (29) and (30) exhibited the highest inhibitory activity. This result indicated that compounds, which have the distance between the two hydroxyl groups comprising of 4,5 carbon atoms, exhibited higher activity than the other compounds.

Table 18 : Inhibitory Activity of plaunotol analogues (compound (13), (14), (29) and (30)) on cyclic AMP phosphodiesterase

Sample	IC_{50} (μg/ml.)	IC_{50}(mM.)
compound 13	899	3.33
compound 14	848	2.99
compound 29	1000	4.42
compound 30	954	3.98
caffeine	–	0.28

IC_{50} is the concentration of compound required to give 50% inhibition of phosphodiesterase activity.

Table 18 and Figure 129 indicated that compound **(13)**, **(14)**, **(29)** and **(30)**, which exhibited high inhibitory activity against cAMP phosphodiesterase, showed IC_{50} of 3.33, 2.99, 4.42 and 3.98 mM, respectively. These results indicated that compound **(13)**, **(14)**, **(29)** and **(30)** can stimulate central nervous system (CNS) activities the same way caffeine did; but, these compounds have higher IC_{50} values than caffeine, which has a IC_{50} value of 0.28 mM. So, that the activity of these compound will be exhibited when the dose of these compounds has a high quantity.

Finally, the majority of plaunotol analogues showed inhibitory activity on cyclic AMP phosphodiesterase, so that, these compounds can stimulate central nervous system (CNS) activities except compound **(33)**. Compound **(33)** has two hydroxyl groups, the distance between the two hydroxyl groups comprising of exactly 8 carbon atoms, and did not show inhibitory activity as the same as plaunotol. Therefore, compound **(33)** is a very interesting compound and may be able to test for inhibitory activity against acute gastric ulcers.

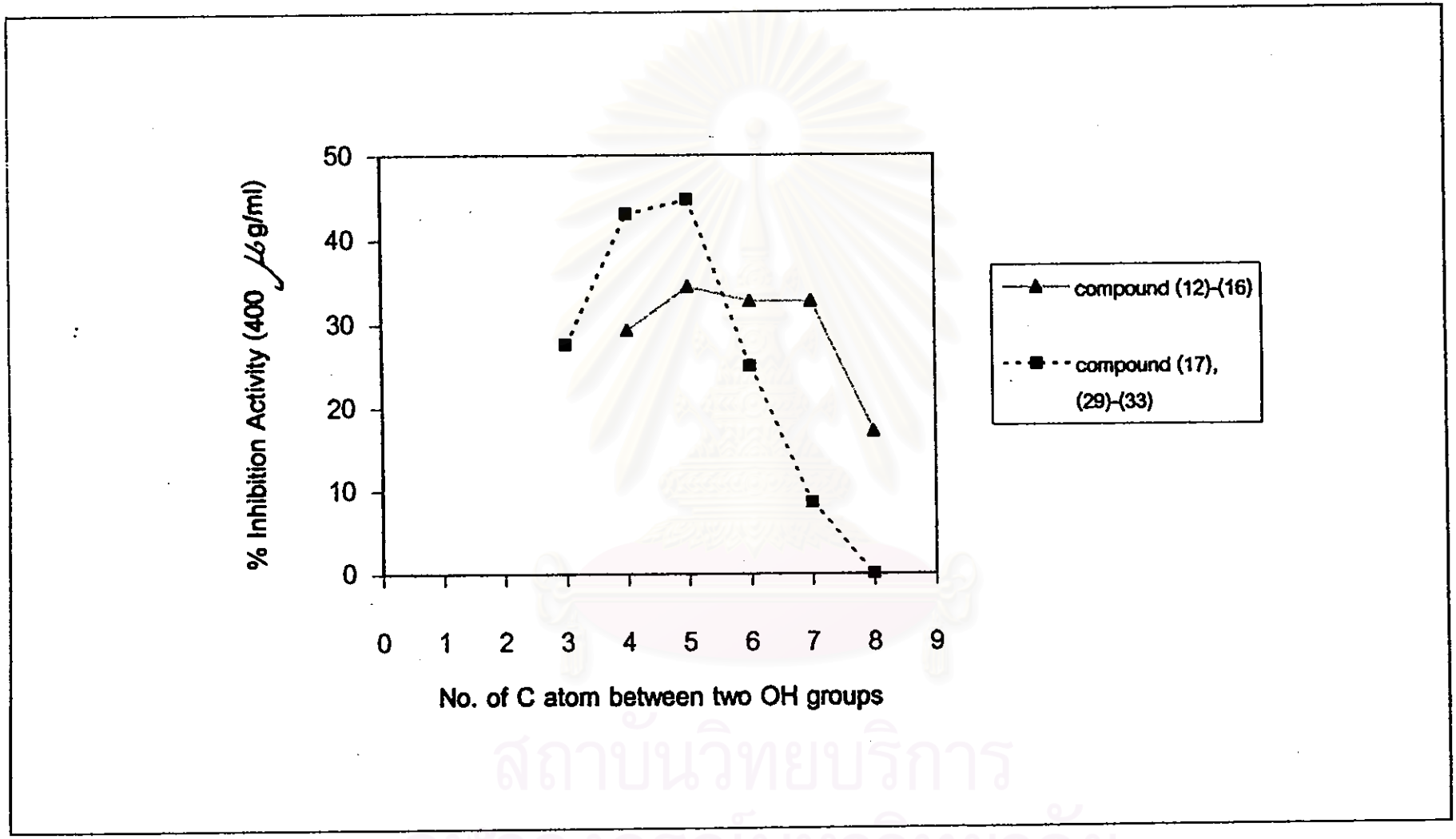


Figure 128 : Inhibitory Activity of Plaunotol Analogues on cyclic AMP Phosphodiesterase.

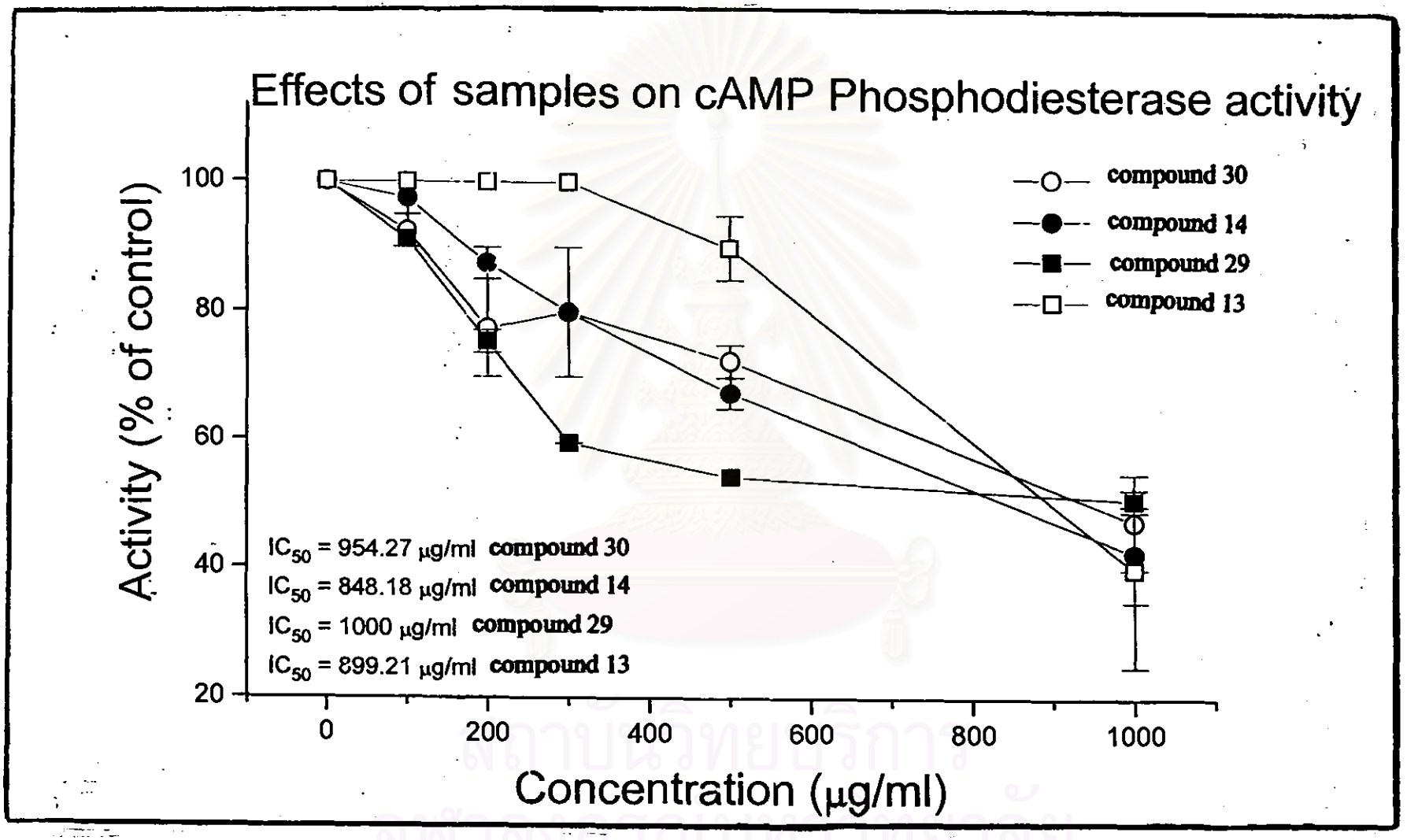


Figure 129 : Effects of Plaunotol Analogues cpmpound (13) , (14) , (29) and (30) on cyclc AMP Phosphodiesterase.