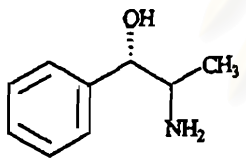
CHAPTER 2
HISTORICAL

1. Bioactive compounds of the Celastraceae

Several Celastraceous plants have been used in traditional medicine. One of the most well-known species is *Catha edulis* Forsk. Its fresh leaves are the main constituent of Khat (Kat) or Abyssinian tea which is widely employed in African and Arab countries to alleviate depression and the sensations of hunger and fatigue. (+)-Norpseudoephedrine (cathine) (3) and (-)-α-aminopropiophenone (cathinone) (4) are isolated and proved to possess pharmacological properties analogous to those of (+)-amphetamine (5) [18].



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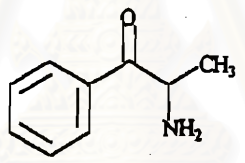

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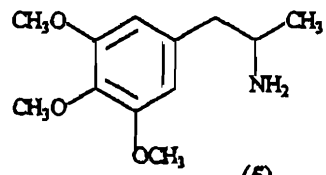


(5)

In recent decade, the Celastraceae is an important source for the discovery of several biologically active compounds, in particular cytotoxic agents. Compounds from this family possessing cytotoxicity are, for example

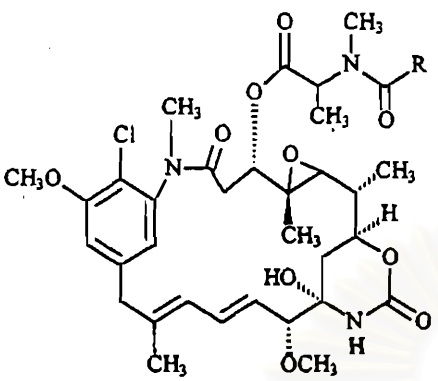
i) maytansinoids or ansamacrolides : maytansine (6), maytanprine (7) and maytanbutine (8) [19-21];

ii) sesquiterpene pyridine alkaloids : emaginatine A (9), emaginatine B (10) [22-23] and hippocrateine I (11) [24];

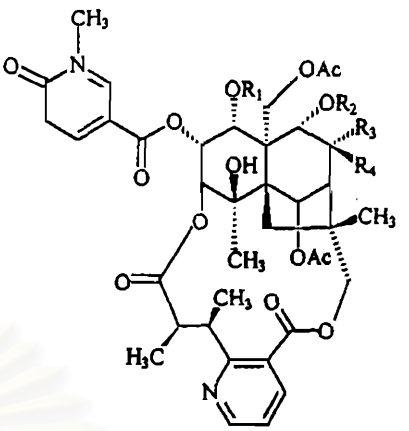
iii) triterpenes : 3-oxo-lup-20(29)-en-30,21α-olide (12) [25], elabunin (13) [26] and maytenfoliol (14) [27];

iv) quinone-methide triterpenes : tingenone (15), 22β-hydroxy-tingenone (1), celastrol (16) and pristimerin (17) [13,15-16,28];

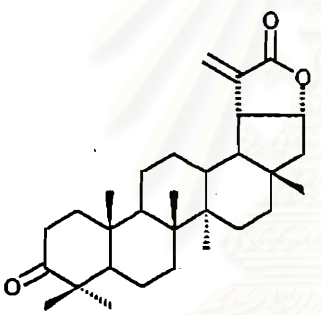
v) diterpenes : triptolide (18) and tripdiolide (triptilide) (19) [29-30].



(6) R = CH_3
(7) R = CH_2CH_3
(8) R = $CH_2CH(CH_3)_2$



	R_1	R_2	R_3	R_4
(9)	Ac	Ac	OAc	H
(10)	Ac	COPh	H	OAc
(11)	COPh	Ac	OAc	H



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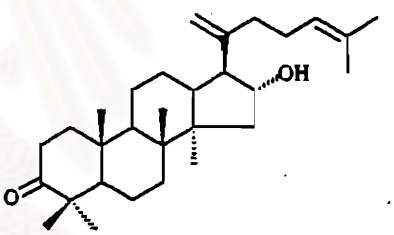

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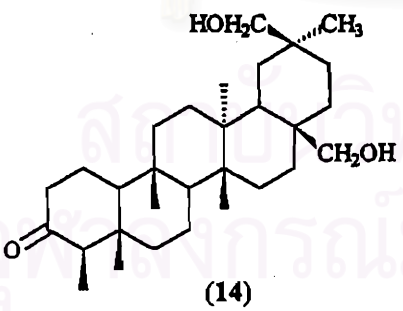

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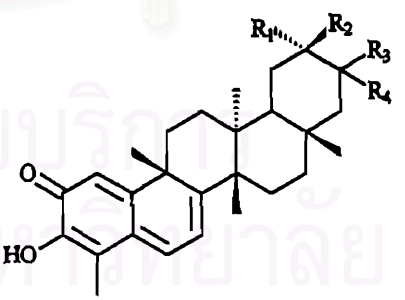
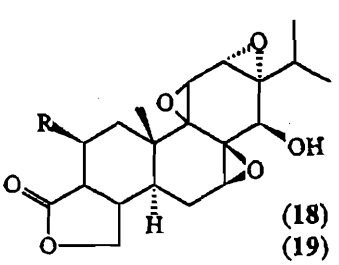


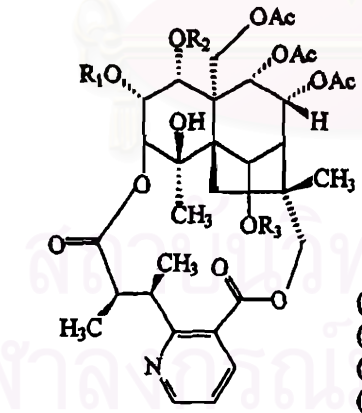
	R_1	R_2	R_3	R_4
(15)	H	CH_3	=O	
(16)	COOH	CH_3	H	H
(17)	$COOCH_3$	CH_3	H	H



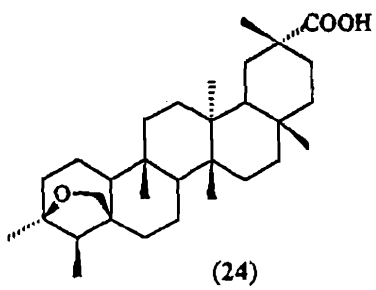
(18) R = H
(19) R = OH

Some of them are now being clinically developed as anticancer drugs. The most famous one is maytansine (**6**), a very strong antitumour compound from several species of *Maytenus* [21]. Although drug development of this compound was unsuccessful [20], its analogues are still of interest [31]. The next two compounds possessing high potential are triptolide (**18**) and tripdiolide (**19**) from root of *Tripterygium wilfordii* Hook. f., a traditional Chinese medicine. They are now being investigated in clinical trial [31]. The only compound clinically used is tingenone. In Brazil, it is indicated to the treatment of skin cancer [32].

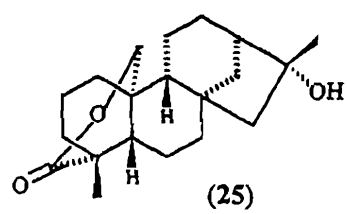
Compounds with other biological activities are also interested. Some quinone-methide triterpenes have been reported for their antimicrobial activity [33-38]. The sesquiterpene pyridine alkaloids emaginatine A (**9**), emaginatine C (**20**), emaginatine I (**21**), emaginatine L (**22**) and emaginatine M (**23**), all displayed antifeedant activity [39], while the friedelane triterpene salaspermic acid (**24**) and the kaurane diterpene tripterifordin (**25**) were reported as inbibitors of HIV replication [40-41].



	R_1	R_2	R_3
(20)	H	COPh	COPh
(21)	Ac	nicotinoyl	Ac
(22)	H	nicotinoyl	COPh
(23)	H	nicotinoyl	Ac



(24)



(25)

2. Quinone-methide triterpenes

Quinone-methide triterpenes are the characteristic orange-red pigments of the Celastraceae and Hippocrateaceae. The earliest one discover in 1936 was tripterin (**16**) from *Tripterygium wilfordii* Hook. f. [42]. In 1939, this compound was also isolated from *Celastrus scandens* Linn., but was named celastrol [43]. In 1951, pristimerin (**17**), another quinone-methide triterpene, the methyl ester derivative of the first one was isolated from *Pristimera indica* (Willd.) A.C.Smith [44]. Both compounds took 30 years for their complete structure determination [48-49]. Their main skeleton is 24-nor-D:A-*friedo*oleanane triterpene with quinone-methide chromophore on ring A/B and a hydroxyl group at C-3 position (Figure 1). Up to Dec, 1996, 74 quinone-methide triterpenes have been found from natural sources, some of which have been biologically investigated. This group of compounds may be called celastroloids after the name of the first isolated one [50].

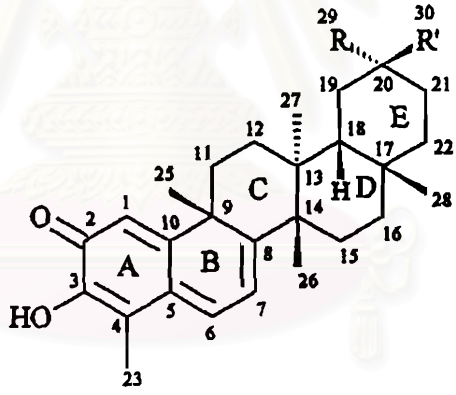


Figure 2. Main skeleton of quinone-methide triterpenes

2.1) Classification of quinone-methide triterpenes

Based on ring A/B chromophores, quinone-methide triterpenes may be divided into 3 main classes and several subclasses as shown in Table 1.

Table 1. Classification of quinone-methide triterpenes based on ring A/B chromophores.

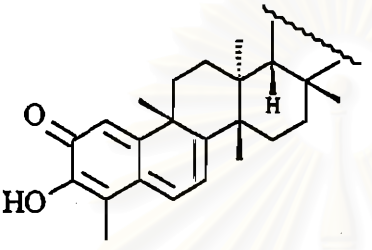
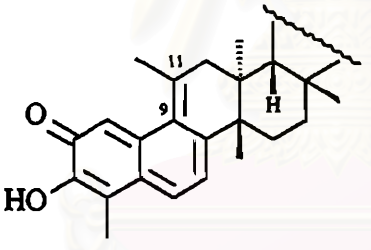
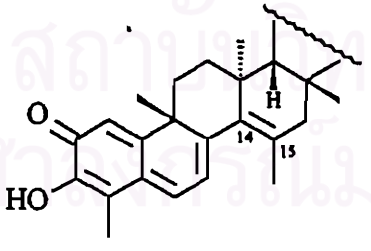
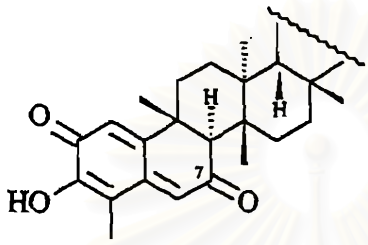
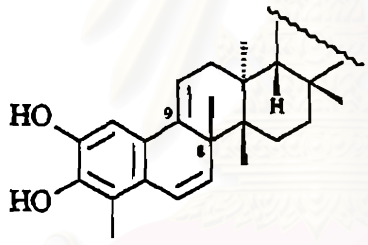
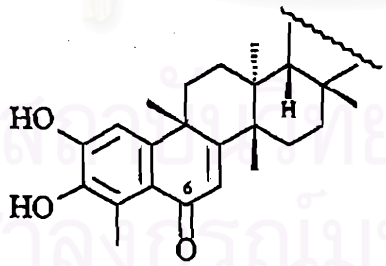
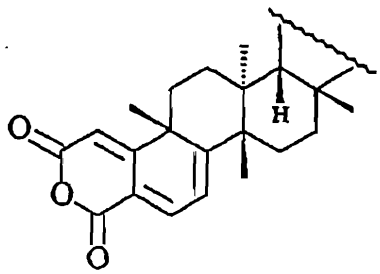
Class / Main skeleton	Approximated UV absorption λ_{max} (solvent)	Ref.
Class 1 Typical quinone-methide triterpenes		
Subclass 1.1 Simple quinone-methide triterpenes 	421 (MeOH)	13,48
Subclass 1.2 Ene-quinone-methide triterpenes		
1.2.1) 9(11)-Ene-(9→11)-quinone-methide triterpenes 	446 (MeOH)	48
1.2.2) 14(15)-Ene-(14→15)-quinone-methide triterpenes 	444 (EtOH)	49

Table 1. (Continued)

Class / Main skeleton	Approximated UV absorption λ_{max} (solvent)	Ref.
Subclass 1.3 7-Oxo-quinone-methide triterpenes	321, 328, 409 (EtOH)	50
		
Class 2 Phenolic-D:A-*friedo*-24-noroleananes		
Subclass 2.1 Phenolic-(9→8)-D:A-*friedo*-24-noroleananes	305, 376 (EtOH)	51
		
	307 (MeOH)	15
Subclass 2.2 6-Oxo-phenolic-D:A-*friedo*-24-noroleananes		
		
Class 3 Anhydride quinone-methide triterpenes	392 (EtOH)	52
		

Most natural quinone-methide triterpenes are monomers. Considering their ring E substitutions and chromophore characterizations, eight compound types can be arranged : pristimerin, excelsine, tingenone, iguesterin, netzahualcoyone, *Salacia* quinone-methide, balaenol and celastranhydride types. The rest being dimeric compounds of monomers in the pristimerin, tingenone or netzahualcoyone types. Two kinds of linkages either one or two ether-linkages were detected. All of these naturally occurring quinone-methide triterpenes are summarized in Tables 2 and 3.

Table 2. Naturally occurring monomeric quinone-methide triterpenes

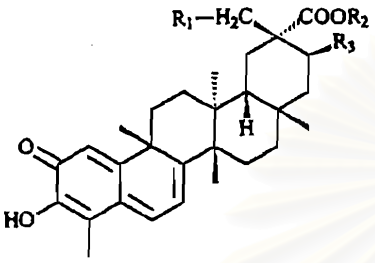
Compound / Structure	Plant source		Reference
1.Pristimerin type			
Pristimerin  ($R_1 = R_3 = H$, $R_2 = CH_3$)	*Acanthothamnus aphyllus* T.S.Brandegee	root	53
	Austroplenckia populnea (Reiss.) Lundell	root bark	54
	Cassine balae Kostermans	outer root-bark	49,55
	Catha edulis Forsk	root bark	56-57
	Celastrus paniculatus Willd.	root bark	58
		outer root-bark	52
	Crossopetalum uragoga O Ktze	root	59
	Gymnosporia emarginata (Willd.) Hook. f. ex Thw.	root	60
	Gymnosporia montana (Roth) Benth.	root bark, and stem bark	61
	Hippocratea excelsa H.B. et K.	stem bark and root bark	62
	Kokoona reflexa Thw.	outer root-bark	52
	Kokoona zeylanica Thw.	outer stem-bark	63-65
		root bark	64
	Maytenus boaria Molina	root	66
	Maytenus canariensis (Loes) Kunkel et Sunding	root bark	65,69
		root bark	37,66
	Maytenus chuchuhuasca R. Hamet et Colas	stem bark	15,70

Table 2.(continued)

Compound / Structure	Plant source		Reference
Pristimerin (continued)	*Maytenus chuchuhuasca* R. Hamet et Colas	bark	71
	Maytenus disperma (F. Muell.) Loes.	outer root-bark	73
	Maytenus horrida Reiss.		33-34
	Maytenus ilicifolia Mart. ex Reiss.	root bark	51
		root cortex	74
	Maytenus obtusifolia Mart.	root	66
	Maytenus scutioides (Griseb.) Lourteig et O'Donell	root bark	38
	Maytenus umbellata (R.Br.) Mabberley	root	75
	Pachystigma canbyi A. Grey	root bark	76
	Plenckia polpunea Reiss.	root	77
	Pleurostylia opposita (Wall.ex Carey) Alston	stem bark	78
	Prionostemma aspera Miers	root bark	48
	Reissantia indica (Halle) Ding Hou.	root	44,79
		root bark	80
	Rzedowskia tolantoguensis F. Gonzalez-Medrano	root	33,81
	Salacia beddomei Gamble	stem bark	82
	Salacia crassifolia G. Don		83
	Salacia macrosperma Wight	root bark	84-85
	Salacia reticulata Wight var. *β-diandra*	bark	86
		outer stem-bark	87
		outer root-bark	88

Table 2.(continued)

Compound / Structure	Plant source		Reference
Pristimerin (continued)	*Salacia* sp.	root	89
		root bark	48
	Schaefferia cuneifolia A.Gray	root	90
	Schaefferia cuneifolia Standley		34
	Zinowiewia costarricensis Lundell	root bark	91
	Zinowiewia integerrima Turcs.	root bark	92
Celastrol (tripterin) ($R_1 = R_2 = R_3 = H$)	*Catha edulis* Forsk	root bark	56-57
	Celastrus paniculatus Willd.	outer root-bark	52
		fresh aril	93
	Celastrus scandens Linn.	root bark	43
	Celastrus strigillosus Nakai	root	45
	Hippocratea excelsa H.B. et K.	stem bark and root bark	62
	Kokoona ochracea (Elm.) Mirrill	stem bark	16
	Kokoona zeylanica Thw.	outer stem-bark	64-65
		root bark	64
		soap cake	65
	Maytenus canariensis (Loes.) Kunkel et Sunding	root bark	66
	Maytenus horrida Reiss.		34
	Maytenus scutioides (Griseb.) Lourteig et O'Donell	root bark	38
	Maytenus umbellata (R.Br.) Mabberley	root	75
	Mortonia greggi A. Gray	root	94

Table 2.(continued)

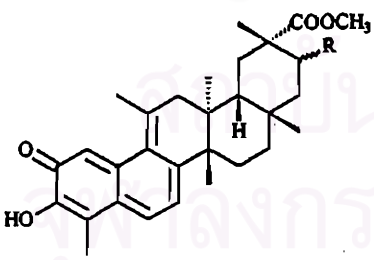
Compound / Structure	Plant source		Reference
Celastrol (continued)	*Orthosphenia mexicana* Standley	root bark	95
	Salacia reticulata Wight var. *β-diandra*	outer root-bark	88
	Schaefferia cuneifolia Standley		34
	Tripterygium wilfordii Hook. f.	root	42,96
		tissue culture	97-100
		crude drug	102
		root bark	103
	Tripterygium hypoglaucum Hutchinson	root	102
	Tripterygium regelii Sprague et Takeda	root	45,104
21-Hydroxypristimerin (R_1 = H, R_2 = CH_3, R_3 = OH)	*Salacia* sp.	root bark	48
30-Hydroxy-pristimerin (R_1 = OH, R_2 = CH_3, R_3 = H)	*Salacia reticulata* Wight var. *β-diandra*	outer root-bark	88
Pristimerinene	*Prionostemma aspera* Miers	root bark	48
 (R = H)			
21-Hydroxypristimerinene (R = OH)	*Salacia* sp.	root bark	48

Table 2.(continued)

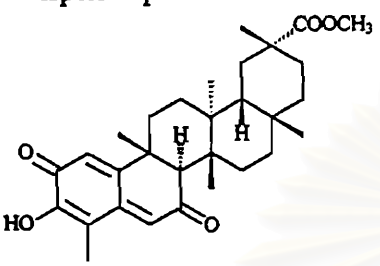
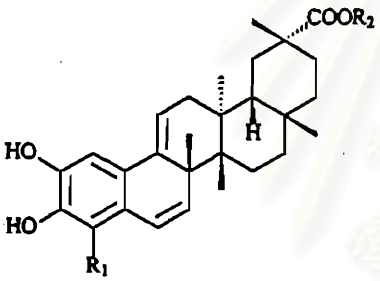
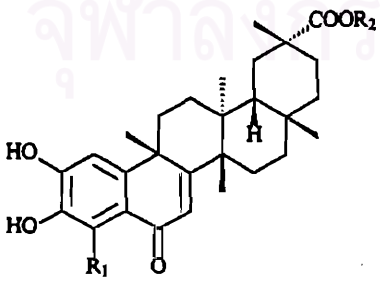
Compound / Structure	Plant source		Reference
Dispermoquinone 	*Austroplenckia populnea* (Reiss.) Lundell	root bark	54
	Austroplenckia populnea (Reiss.) Lundell var. *ovata*	bark wood	105
	Maytenus disperma (F. Muell.) Loes.	outer root-bark	106
Isopristimerin III  ($R_1 = R_2 = CH_3$)	*Maytenus ebenifolia* Reiss.		107
	Maytenus ilicifolia Mart. ex Reiss.	root bark	51
23-Oxoisopristimerin III (R_1 = CHO, $R_2 = CH_3$)	*Kokoona zeylanica* Thw.	outer stem-bark	64-65
		root bark	64
		inner bark	108
		soap cake	65
Wilforol B ($R_1 = CH_3$, R_2 = H)	*Tripterygium wilfordii* Hook. f.	root bark	103
Zeylasterone  (R_1 = COOH, $R_2 = CH_3$)	*Celastrus paniculatus* Willd.	outer root-bark	52
	Kokoona reflexa Thw.	outer root-bark	52
	Kokoona zeylanica Thw.	outer stem-bark	63-65
		root bark	64
		inner bark	109

Table 2.(continued)

Compound / Structure	Plant source		Reference
Zeylasteral (R_1 = CHO, R_2 = CH_3)	*Celastrus paniculatus* Willd.	outer root-bark	52
	Kokoona reflexa Thw.	outer root-bark	52
	Kokoona zeylanica Thw.	outer stem-bark	64-65,110
		root bark	64
		soap cake	65
Desmethylzeylasterone (R_1 = COOH, R_2 = H)	*Kokoona zeylanica* Thw.	outer stem-bark	64-65,110
		root bark	64
	Tripterygium wilfordii Hook. f.	root bark	103
Desmethylzeylasteral (R_1 = CHO, R_2 = H)	*Kokoona zeylanica* Thw.	outer stem-bark and root bark	64
		outer root-bark	65,111
	Tripterygium wilfordii Hook. f.	root bark	103
Wilforol A (R_1 = CH_3, R_2 = H)	*Tripterygium wilfordii* Hook. f.	root bark	103
6-Oxopristimerol (R_1 = R_2 = CH_3)	*Maytenus canariensis* (Loes) Kunkel et Sunding	root bark	37
	Maytenus chuchuhuasca R. Hamet et Colas	stem bark	15
23-Nor-6-oxopristimerol (R_1 = H, R_2 = CH_3)	*Kokoona zeylanica* Thw.	outer root-bark	111
23-Nor-6-oxodesmethyl-pristimerol (R_1 = R_2 = H)	*Kokoona zeylanica* Thw.	outer stem-bark	64
		root bark	64
		outer root-bark	111
	Trypterygium wilfordii Hook. f.	root bark	103

Table 2.(continued)

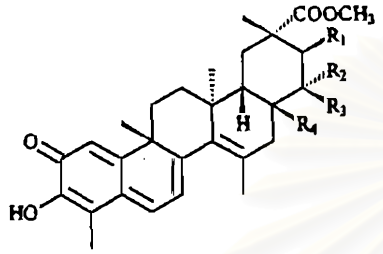
Compound / Structure	Plant source		Reference
2. Natzahualcoyone type			
Netzahualcoyone  (R_1 = OH, R_2R_3 = O, R_4 = CH_3)	*Maytenus horrida* Reiss.		33-34
	Orthosphenia mexicana Standley		112
		root bark	113
	Rzedowskia tolantoguensis F. Gonzalez-Medrano	root	81
			33
	Schaefferia cuneifolia Standley		34
Netzahualcoyondiol (R_1 = OH, R_2 = H, R_3 = OH, R_4 = CH_3)	*Maytenus horrida* Reiss.		33
	Orthosphenia mexicana Standley		112
	Rzedowskia tolantoguensis F. Gonzalez-Medrano	root	81
			33
Netzahualcoyonol (R_1 = OH, R_2 = R_3 = H, R_4 = CH_3)	*Maytenus horrida* Reiss.		33-34
	Orthosphenia mexicana Standley		112
	Rzedowskia tolantoguensis F. Gonzalez-Medrano	root	81
			33
	Schaefferia cuneifolia Standley		34
Netzahualcoyene (R_1 = R_2 = R_3 = H, R_4 = CH_3)	*Maytenus horrida* Reiss.		33-34,112
	Maytenus scutioides (Griseb.) Lourteig et O'Donell	root bark	38
	Rzedowskia tolantoguensis F. Gonzalez-Medrano		33
	Salacia reticulata Wight var. *β-diandra*	outer root-bark	88
	Schaefferia cuneifolia Standley		34

Table 2.(continued)

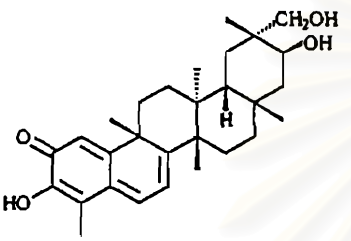
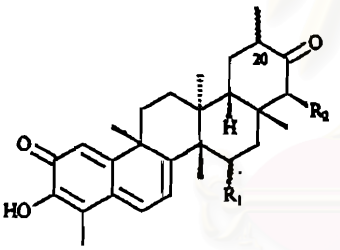
Compound / Structure	Plant source		Reference
Netzahualcoyol (R_1 = OH, R_2 = R_3 = H, R_4 = $COOCH_3$)	*Orthosphenia mexicana* Standley		112
3. Excelsine type			
Excelsine 	*Hippocratea excelsa* H.B. et K.	stem bark and root bark	62
4. Tingenone type			
Tingenone (tingenin A, maitenin,)  (20β-CH_3, R_1 = R_2 = H)	*Acanthothamnus aphyllus* T.S.Brandegee	root	53
	Cassine balae Kostermans	outer root-bark	49,55
	Cassine papillosa (Hochst.) Kuntze	stem bark	114
	Maytenus canariensis (Loes.) Kunkel et Sunding	root bark	66
	Catha edulis Forsk	root	56
		root bark	57
	Crossopetalum uragoga O Ktze	root bark and root medulla	59
	Euonymus tingens Wall.	stem bark	115
		bark	116
	Gymnosporia emarginata (Willd.) Hook. f. ex Thw.	root	60
	Gymnosporia montana (Roth) Benth.	stem bark and root bark	61,117

Table 2.(continued)

Compound / Structure	Plant source		Reference
Tingenone (continued)	*Hippocratea excelsa* H.B. et K.	stem bark and root bark	62
	Kokoona ochracea (Elm.) Mirrill	stem bark	16
	Maytenus buchananii (Loes.) R. Wilczek	tissue culture	28
	Maytenus canariensis (Loes) Kunkel et Sunding	root bark	37
	Maytenus canariensis (Loes) Kunkel et Sunding	root bark	69
	Maytenus chuchuhuasca R. Hamet et Colas	stem bark	15,70
	Maytenus chuchuhuasca R. Hamet et Colas	bark	71
	Maytenus horrida Reiss.		33-34
	Maytenus ilicifolia Mart. ex Reiss.		118
		root cortex	74
		bark	119
	Maytenus laevis Reiss.	root bark	120
	Maytenus obtusifolia Mart.	root	66
	Maytenus scutioides (Griseb.) Lourteig et O'Donell	root bark	38
	Maytenus sp.		121
	Maytenus umbellata (R.Br.) Mabberley	root	75
	Maytenus wallichiana (Spreng ex Wight et Arn.) Raju et Babu	tissue culture	122-123
	Plenckia polpunea Reiss.	root	77

Table 2.(continued)

Compound / Structure	Plant source		Reference
Tingenone (continued)	*Prionostemma aspera* Miers	root bark	48
	Reissantia indica (Halle) Ding Hou.	root bark	80
	Rzedowskia tolantoguensis F. Gonzalez-Medrano	root	81
	Rzedowskia tolantoguensis F. Gonzalez-Medrano		33
	Salacia macrosperma Wight	root bark	84-85
	Salacia reticulata Wight var. *β-diandra*	outer root-bark	88
	Salacia sp.	root bark	48
		root	89
	Schaefferia cuneifolia A.Gray	root	90
	Schaefferia cuneifolia Standley		34
	Tripterygium wilfordii Hook. f.	tissue culture	98-100
	Zinowiewia costarricensis Lundell.	root bark	91
Tingenin B (22β-hydroxy-tingenone) (20β-CH_3, R_1 = H, R_2 = OH)	*Acanthothamnus aphyllus* T.S.Brandegee	root	53
	Cassine balae Kostermans	outer root-bark	49,55
	Cassine papillosa (Hochst.) Kuntze	stem bark	114
	Catha edulis Forsk	root bark	56-57
	Euonymus tingens Wall.	stem bark	115
	Glyptopetalum sclerocarpum Laws.	stem bark	13

Table 2.(continued)

Compound / Structure	Plant source		Reference
Tingenin B (continued)	*Maytenus buchananii* (Loes.) R. Wilczek	tissue culture	28
	Maytenus canariensis (Loes) Kunkel et Sunding	root bark	37
	Maytenus chuchuhuasca R. Hamet et Colas	stem bark	15
	Maytenus chuchuhuasca R. Hamet et Colas	bark	71
	Maytenus laevis Reiss.	root bark	120
	Maytenus obtusifolia Mart.	root	66
	Maytenus sp.		121
	Salacia reticulata Wight var. *β–diandra*	outer root-bark	88
	Tripterygium wilfordii Hook. f.	tissue culture	100
15α,22β-Dihydroxytingenone (20β-CH_3, $R_1 = R_2 = OH$)	*Cassine balae* Kostermans	outer root-bark	55
20-Hydroxy-20-epi-tingenone (20α-CH_3, 20β-OH, $R_1 = R_2 = H$)	*Austroplenckia populnea* (Reiss.) Lundell	root bark	54
	Cassine balae Kostermans	outer root-bark	49-55
	Euonymus tingens Wall.	bark	116
	Glyptopetalum sclerocarpum Laws.	stem bark	14
	Kokoona ochracea (Elm.) Mirrill	stem bark	16
	Rzedowskia tolantoguensis F. Gonzalez-Medrano	root	81
	Salacia macrosperma Wight	root bark	84 -85

Table 2.(continued)

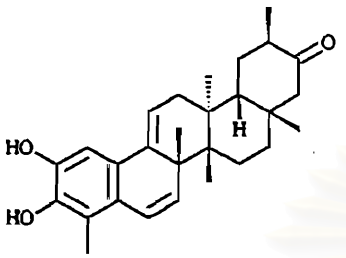
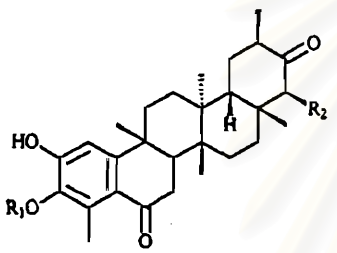
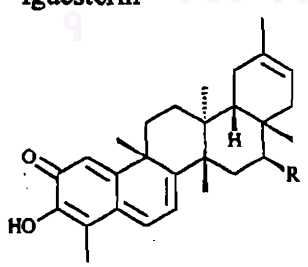
Compound / Structure	Plant source		Reference
Isotingenone III	*Maytenus ebenifolia* Reiss.		107
	*Maytenus ilicifolia* Mart. ex Reiss.	root bark	51
6-Oxotingenol	*Maytenus ilicifolia* Mart. ex Reiss.	root bark	15
	*Maytenus canariensis* (Loes) Kunkel et Sunding	root bark	37
(R = R_2 = H)			
3-Methyl-6-oxotingenol (R_1 = CH_3, R_2 = H)	*Maytenus canariensis* (Loes) Kunkel et Sunding	root bark	37
	Maytenus chuchuhuasca R. Hamet et Colas		107
		stem bark	15
3-Methyl-22β,23-dihydroxy-6-oxotingenol (R_1 = CH_3, R_2 = OH)	*Maytenus chuchuhuasca* R. Hamet et Colas	stem bark	15
5. Iguesterin type			
Iguesterin	*Maytenus canariensis* (Loes.) Kunkel et Sunding	root bark	65-66
	*Catha edulis* Forsk	root bark	56-57
	Gymnosporia emarginata (Willd.) Hook. f. ex Thw.	root	60
(R = H)			
	Gymnosporia montana (Roth) Benth.	stem bark and root bark	61

Table 2. (continued)

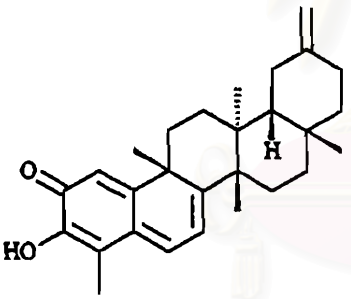
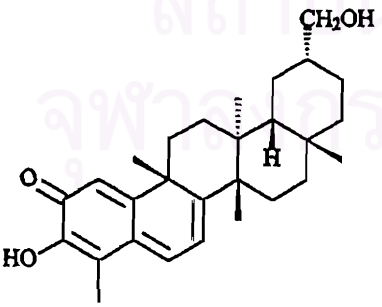
Compound / Structure	Plant source		Reference
Iguesterin (continued)	*Maytenus canariensis* (Loes) Kunkel et Sunding	root bark	37,69
	Maytenus horrida Reiss.		33
	Maytenus umbellata (R.Br.) Mabberley	root	75
	Rzedowskia tolantoguensis F. Gonzalez-Medrano		33
	Salacia reticulata Wight var. *β–diandra*	bark	86
16β-Hydroxyiguesterin (R = OH)	*Maytenus canariensis* (Loes) Kunkel et Sunding	root bark	124
Isoiquesterin	*Salacia madagascariensis* DC.	root	125
 (R = CH_3)	*Salacia reticulata* Wight var. *β-diandra*	root bark outer root-bark	50 88
Isoiguesterinol	*Salacia reticulata* Wight var. *β-diandra*	outer root-bark	88
 (R = CH_2OH)			

Table 2.(continued)

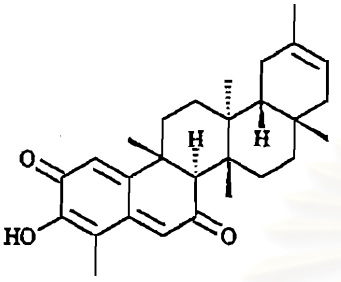
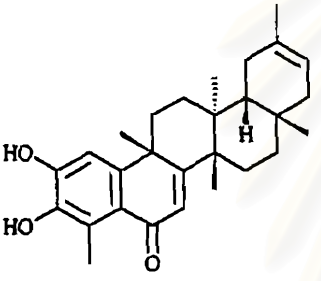
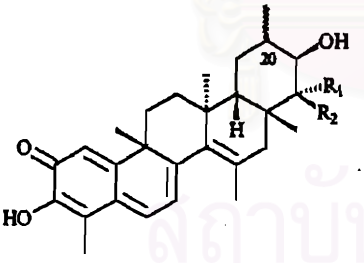
Compound / Structure	Plant source		Reference
Salaciquinone 	*Salacia reticulata* Wight var. *β-diandra*	root bark outer root-bark	50 88
6-Oxo-iguesterol 	*Maytenus canariensis* (Loes) Kunkel et Sunding	root bark	37
6. Balaenol type			
Balaenol  (20β-CH_3, $R_1 = R_2 = H$)	*Cassine balae* Kostermans	outer root-bark	49,55,126
Balaenonol (20β-CH_3, $R_1R_2 = O$)	*Cassine balae* Kostermans	outer root-bark	49,55,126
Isobalaenol (20α-CH_3, $R_1 = R_2 = H$)	*Cassine balae* Kostermans	outer root-bark	55
Isobalaendiol (20α-CH_3, $R_1 = H$, $R_2 = OH$)	*Cassine balae* Kostermans	outer root-bark	49,55

Table 2.(continued)

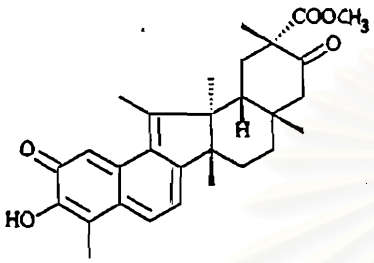
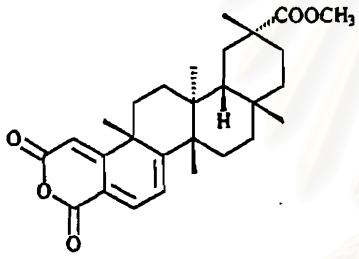
Compound / Structure	Plant source		Reference
7. Salacia quinonemethide			
Salacia quinonemethide 	*Salacia macrosperma* Wight	root bark	84-85
8. Celastrananhydride type			
Celastranhydride 	*Cassine balae* Kostermans		52
	Kokoona reflexa Thw.		52
	Kokoona zeylanica Thw.	outer root-bark	52
	Reissantia indica (Halle) Ding Hou.		52

Table 3. Naturally occurring dimeric quinone-methide triterpenes.

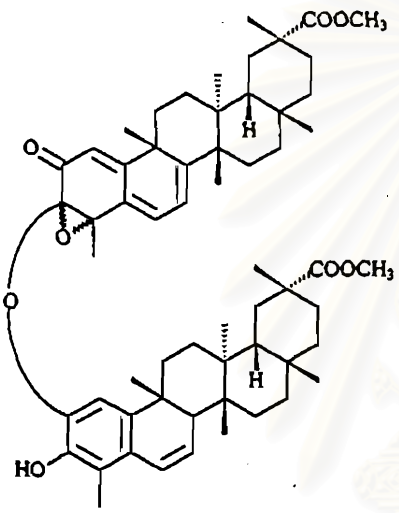
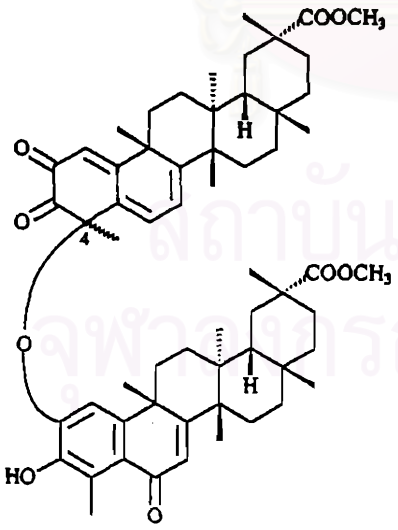
Compound / Structure	Plant source		Reference
1. One-ether linkage dimers			
1.1) Pristimerin-pristimerin type			
Magellanin 	*Maytenus magellanica* Hook. f.		127
Rzedowskia bistriterpenoid 	*Rzedowskia tolantoguensis* F. Gonzalez-Medrano	root	128
(4α-CH_3)			
4-Epimeric Rzedowskia bistriterpenoid (4β-CH_3)	*Rzedowskia tolantoguensis* F. Gonzalez-Medrano	root	128

Table 3. (continued)

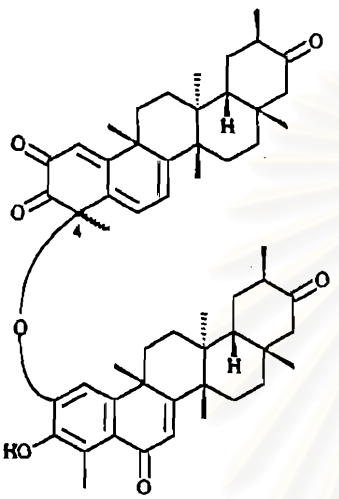
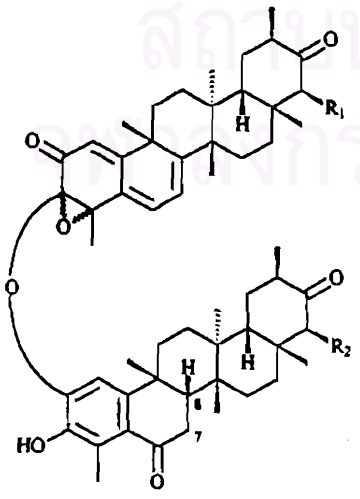
Compound / Structure	Plant source		Reference
1.2) Tingenone-tingenone type			
Umbellatin α  (4α-CH_3)	*Maytenus umbellata* (R.Br.) Mabberley	root	36
Umbellatin β (4β-CH_3)	*Maytenus umbellata* (R.Br.) Mabberley	root	36
D:A-*Friedo*-24,30-dinor-oleana-1(10),5,7-triene-2,21-dione, 3,4-epoxy-3-[[(8β,20β) -3-hydroxy-6,21-dioxo-D:A-*friedo*-24,30-dinoroleana-1,3, 5(10)-trien-2-yl]oxy](4ξ,20β)  (R_1 = R_2 = H)	*Maytenus chuchuhuasca* R. Hamet et Colas		107

Table 3. (continued)

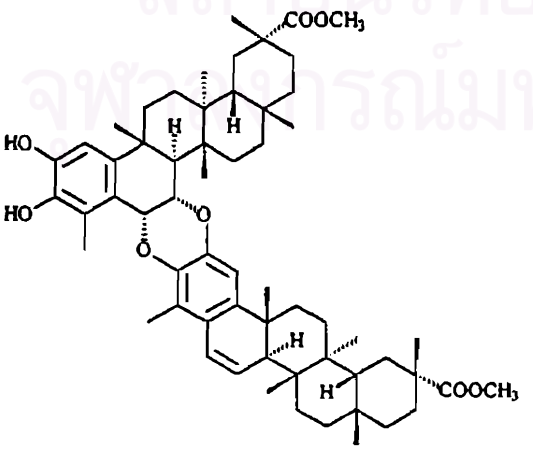
Compound / Structure	Plant source	Reference
D:A-*Friedo*-24,30-dinor-oleana-1,3,5 (10),7-tetraene-6,21-dione, 2-[[(4ξ,20β)-3,4-epoxy-2,21-dioxo-D:A-*friedo*-24,30-dinoroleana-1(10),5,7-trien-3-yl]oxy]-3-hydroxy (20β) ($R_1 = R_2 = H$, 7,8-dehydro)	*Maytenus chuchuhuasca* R. Hamet et Colas	107
D:A-*Friedo*-24,30-dinor-oleana-1,3,5 (10),7-tetraene-6,21-dione, 2-[[(4ξ, 20β, 22β)-3,4-epoxy-22-hydroxy-2,21-dioxo-D:A-*friedo*-24,30-dinoroleana-1(10),5,7-trien-3-yl]oxy]-3,22-dihydroxy (20β,22β) ($R_1 = H$, $R_2 = OH$, 7,8-dehydro)	*Maytenus chuchuhuasca* R. Hamet et Colas	107
D:A-*Friedo*-24,30-dinor-oleana-1,3,5 (10),7-tetraene-6,21-dione, 2-[[(4ξ,20β, 22β)- 3,4-epoxy-22-hydroxy-2,21-dioxo-D:A-*friedo*-24,30-dinoroleana-1(10),5,7-trien-3-yl]oxy]-3-hydroxy (20β) ($R_1 = R_2 = OH$, 7,8-dehydro)	*Maytenus chuchuhuasca* R. Hamet et Colas	107
2. Two-ether linkage dimers		
2.1) Pristimerin-pristimerin type		
Cangorosin A 	*Maytenus ilicifolia* Mart. ex Reiss. root	107, 129-130

Table 3. (continued)

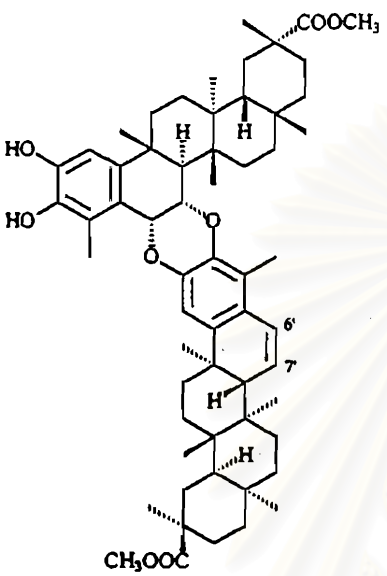
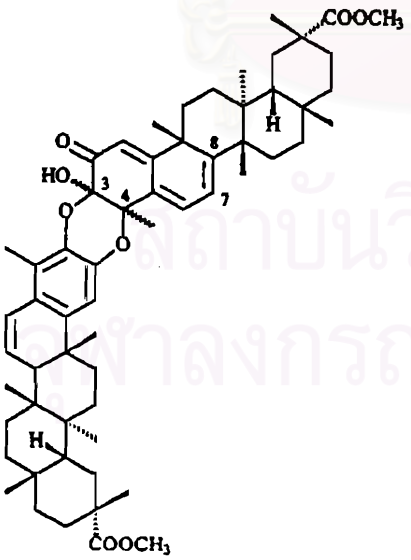
Compound / Structure	Plant source		Reference
Isocangorosin A 	*Maytenus ilicifolia* Mart. ex Reiss.	root	107,129-130
6',7'-Dihydroisocangorosin A (6',7'-dihydro)	*Maytenus ilicifolia* Mart. ex Reiss.	root	107,129-130
Scutionin αA  (3β-OH, 4β-CH_3)	*Maytenus scutioides* (Griseb.) Lourteig et O'Donell	root bark	38
7,8-Dihydro-scutionin αA (3β-OH, 4β-CH_3, 7,8-dihydro)	*Maytenus scutioides* (Griseb.) Lourteig et O'Donell	root bark	38
7,8-Dihydro-scutionin βA (3α-OH, 4α-CH_3, 7,8-dihydro)	*Maytenus scutioides* (Griseb.) Lourteig et O'Donell	root bark	38

Table 3. (continued)

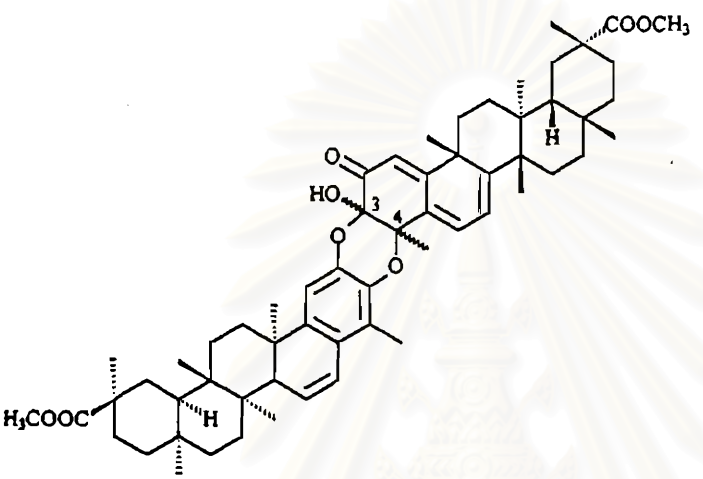
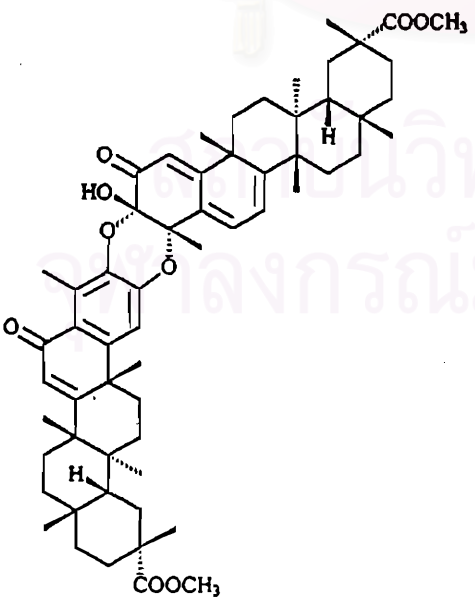
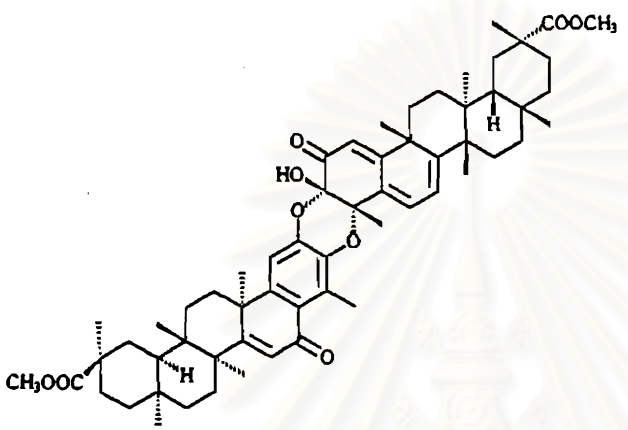
Compound / Structure	Plant source		Reference
7,8-Dihydro-scutionin αB	*Maytenus scutioides* (Griseb.) Lourteig et O'Donell	root bark	38
 (3β-OH, 4β-CH_3)			
7,8-Dihydro-scutionin βB (3α-OH, 4α-CH_3)	*Maytenus scutioides* (Griseb.) Lourteig et O'Donell	root bark	38
Scutidin αA 	*Maytenus scutioides* (Griseb.) Lourteig et O'Donell	root bark	38

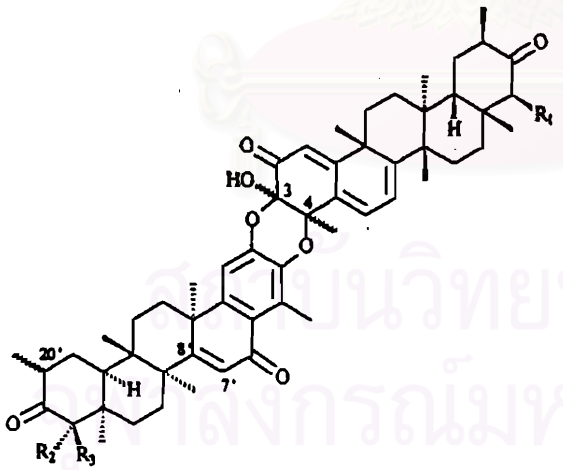
Table 3. (continued)

Compound / Structure	Plant source		Reference
7,8-Dihydro-scutidin αB	*Maytenus scutioides* (Griseb.) Lourteig et O'Donell	root bark	38



2.2) Tingenone-tingenone type

Xuxuarine Aα	*Maytenus chuchuhuasca* R. Hamet et Colas	bark	71

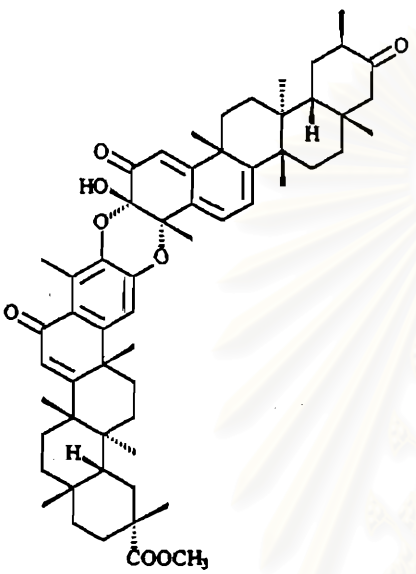
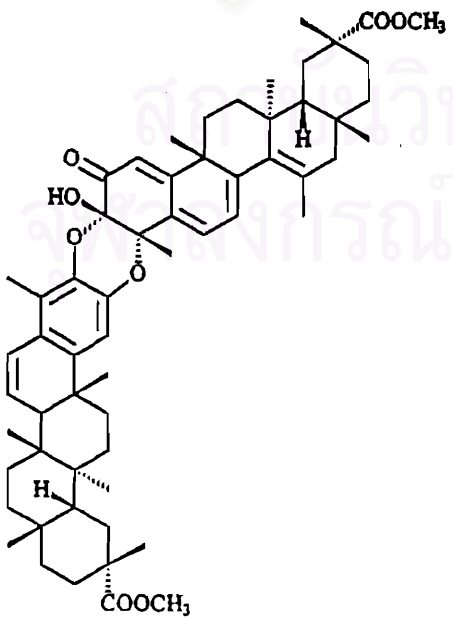


(3β-OH, 4β-CH_3, 20'α-CH_3,
$R_1 = R_2 = R_3 = H$)

Table 3. (continued)

Compound / Structure	Plant source		Reference
Xuxuarine Aβ (3α-OH, 4α-CH_3, 20'α-CH_3, $R_1 = R_2 = R_3 = H$)	*Maytenus chuchuhuasca* R. Hamet et Colas	bark	71
Xuxuarine Bα (3β-OH, 4β-CH_3, 20'α-CH_3, $R_1 = R_3 = OH$, $R_2 = H$)	*Maytenus chuchuhuasca* R. Hamet et Colas	bark	71
Xuxuarine Bβ (3α-OH, 4α-CH_3, 20'α-CH_3, $R_1 = R_3 = OH$, $R_2 = H$)	*Maytenus chuchuhuasca* R. Hamet et Colas	bark	71
Xuxuarine Cα (3β-OH, 4β-CH_3, 20'α-CH_3, $R_1 = OH$, $R_2 = R_3 = H$)	*Maytenus chuchuhuasca* R. Hamet et Colas	bark	71
Xuxuarine Cβ (3α-OH, 4α-CH_3, 20'α-CH_3, $R_1 = OH$, $R_2 = R_3 = H$)	*Maytenus chuchuhuasca* R. Hamet et Colas	bark	71
Xuxuarine Dα (3β-OH, 4β-CH_3, 20'α-CH_3, $R_1 = R_3 = H$, $R_2 = OH$)	*Maytenus chuchuhuasca* R. Hamet et Colas	bark	71
Xuxuarine Dβ (3α-OH, 4α-CH_3, 20'α-CH_3, $R_1 = R_3 = H$, $R_2 = OH$)	*Maytenus chuchuhuasca* R. Hamet et Colas	bark	71
7',8'-Dihydroxuxuarine Aβ (3α-OH, 4α-CH_3, 20'α-CH_3, 7',8'-dihydro, $R_1 = R_2 = R_3 = H$)	*Maytenus chuchuhuasca* R. Hamet et Colas	bark	71

Table 3. (continued)

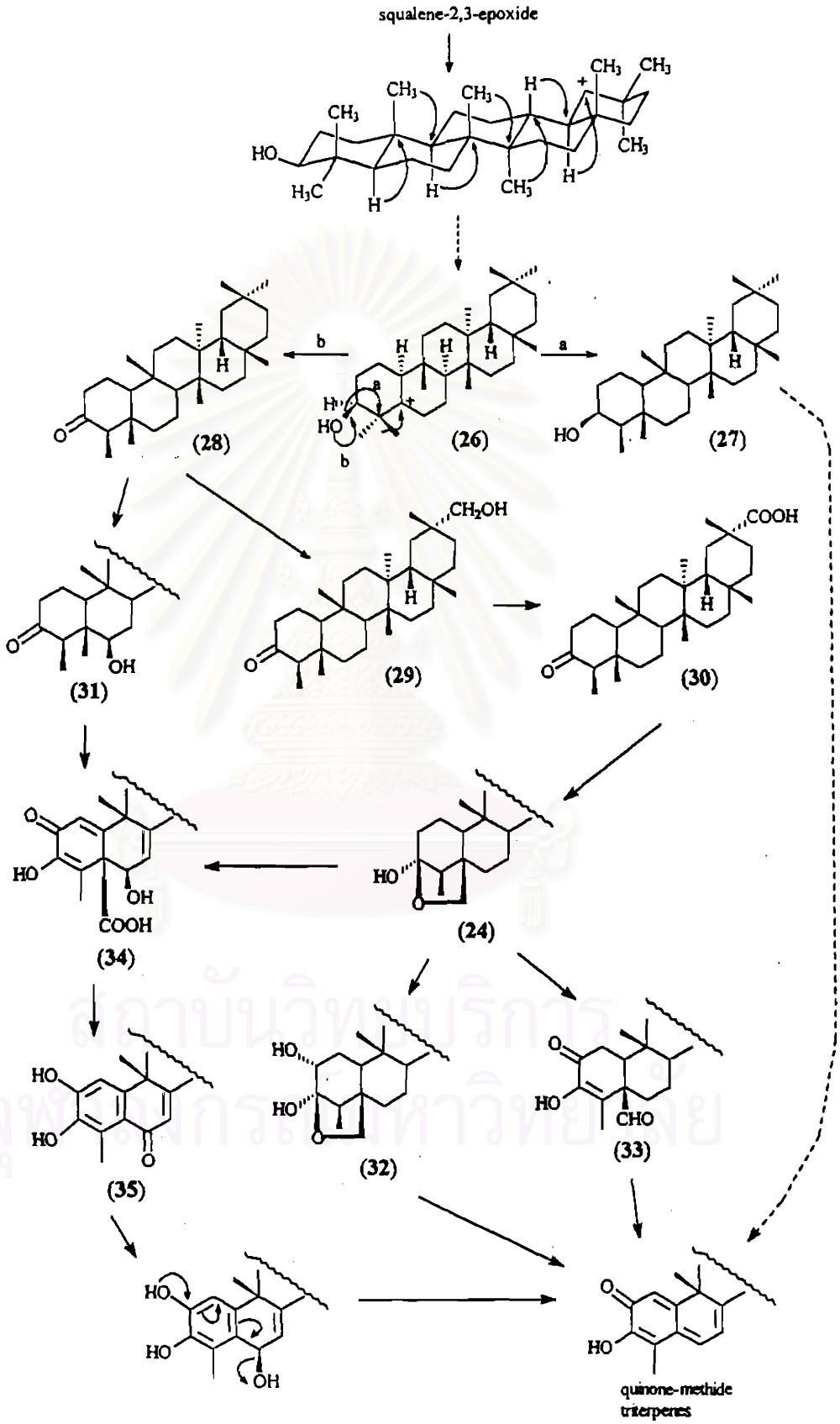
Compound / Structure	Plant source		Reference
2.3) Pristimerin-tingenone type			
Cangorosin B 	*Maytenus ilicifolia* Mart. ex Reiss.		107,130
2.4)Pristimerin-netzahualcoyone type			
Netzascutionin αA 	*Maytenus scutioides* (Griseb.) Lourteig et O'Donell	root bark	38

2.2) Biogenesis of quinone-methide triterpenes

No experimental proof has been provided for the biosynthetic origin of quinone-methide triterpenes. Only postulated biogenetic pathways between each compound type, summarized as followed, were suggested according to their co-occurrence in some plant species.

2.2.1) Origin of quinone-methide triterpenes

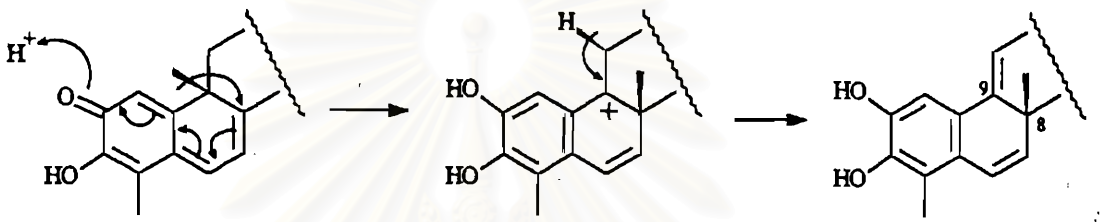
The cation pentacyclic triterpene intermediate formed from squalene-2,3-epoxide in a chair-chair-chair-chair-chair conformation could rearrange under a series of 1,2-shifts to give the carbocation precursor (**26**) of D:A-*friedo*oleananes. Canophyllol (**27**), a D:A-*friedo*oleanane derived from 1,2-shift of 4β-CH_3 of this precursor, was suggested as an intermediate of biosynthesis of quinone-methide triterpenes [75]. However, friedelin (**28**) fitted better in this role. Subsequently, biogenetic pathways involving the oxidation of ring A and B, concurrent with demethylation at C-5 to quinone-methide triterpenes, were proposed *via* two routes : (i) *via* D:A-*friedo*oleanan-29-ol-3-one (**29**), polpunonic acid (**30**) and salaspermic acid (**24**)[28,51,63,95] and (ii) *via* zeylanone (**31**) [63]. In the first route, a number of different intermediates were postulated according to their co-occurrence with precursor compounds for each plant species. Orthosphenic acid (**32**) and cangoronine (**33**) were proposed for *Orthosphenia mexicana* Standley [95] and *Maytenus ilicifolia* Mart.ex Reiss.[51], respectively, while an unnaturally occurring compound (**34**) was proposed for *Kokoona zeylanica* Thw. [63]. The second route also proposed for *Kokoona zeylanica* Thw., was postulated according to the co-occurrence of quinone-methide triterpenes with its derivatives, 6-oxo-phenolic-D:A-*friedo*-24-noroleananes [63].



Scheme 1. Biogenetic origin of quinone-methide triterpenes from squalene-2,3-epoxide.

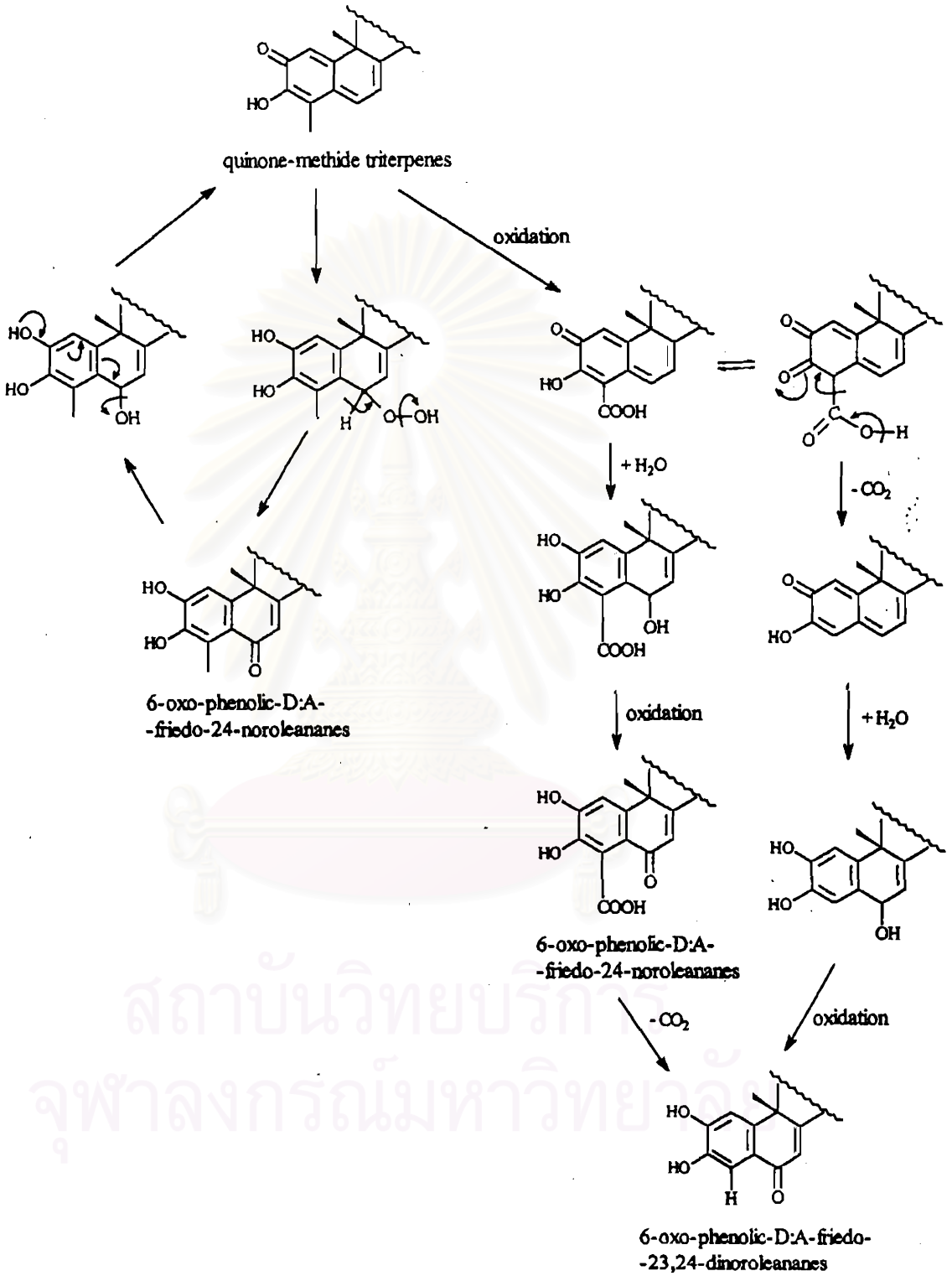
2.2.2) Rearrangement of quinone-methide triterpenes to phenolic-D:A-*friedo*-24-noroleananes

Phenolic (9→8)-D:A-*friedo*-24-noroleananes could arise from typical quinone-methide triterpenes by an acid-catalyzed rearrangement as shown in Scheme 2[65]. *In vitro* acidic reactions of quinone-methide triterpenes also yield these phenolic derivatives [48,121,131-132].



Scheme 2. Rearrangement mechanism of quinone-methide triterpenes to phenolic (9→8)-D:A-*friedo*-24-noroleananes.

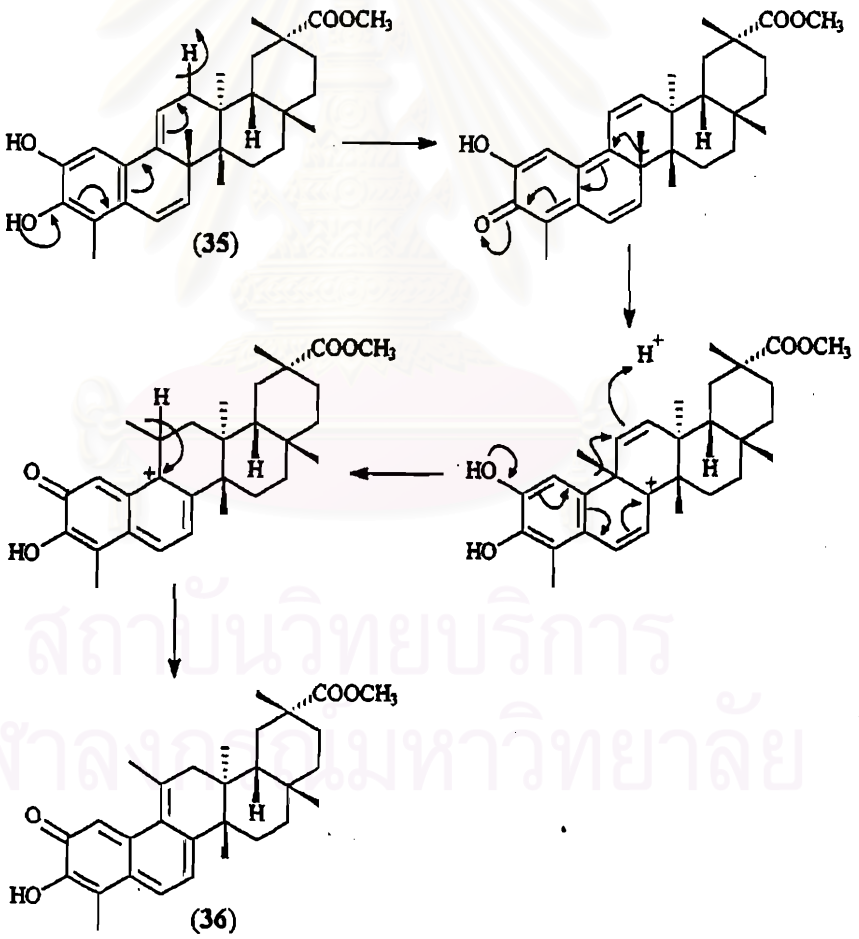
The other phenolic derivatives, 6-oxo-phenolic-D:A-*friedo*-24-noroleananes have been stated as intermediates in quinone-methide triterpenes biogenesis as previously mentioned [63]. On the other hand, quinone-methide triterpenes could also be the precursor of 6-oxo-phenolic-D:A-*friedo*-24-noroleananes as suggested in Scheme 3 [63,111], whereas its 23,24-dinor analogues could be achieved either by oxidation and decarboxylation directly at C-23 or prior to the rearrangement of quinone-methide triterpenes to 6-oxo-phenolic-D:A-*friedo*-24-noroleanane skeleton [111].



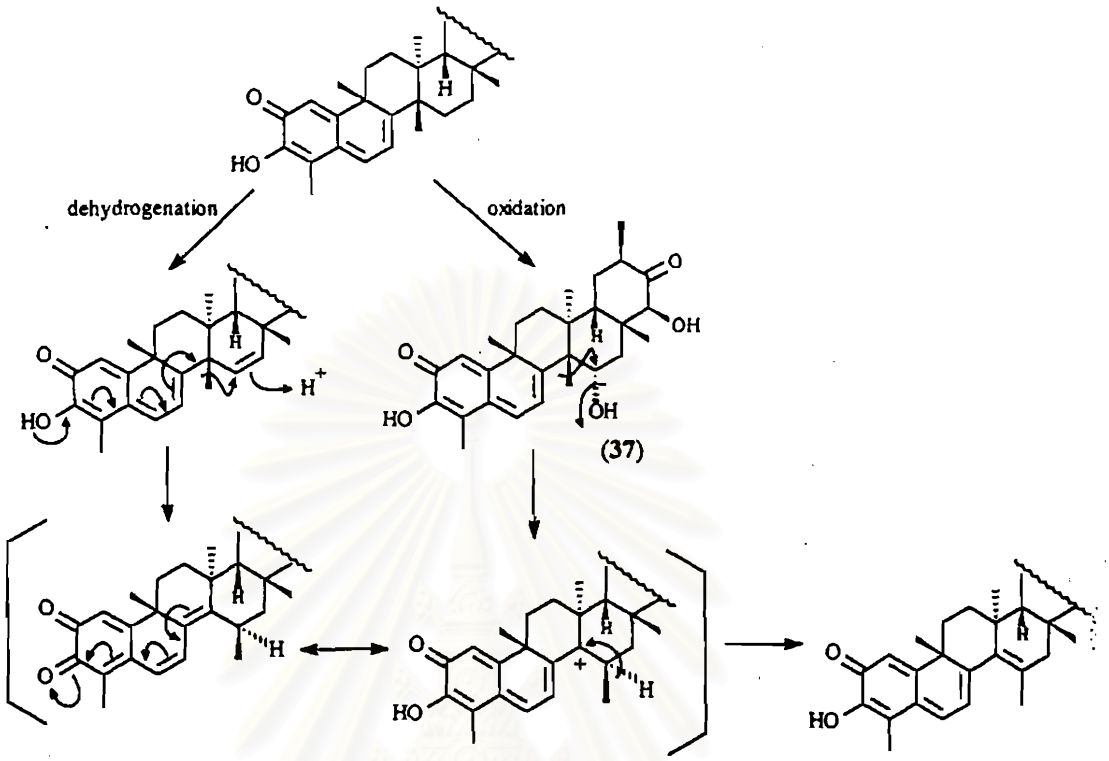
Scheme 3. Biogenetic relationships among quinone-methide triterpenes, 24-nor and 23,24-dinor derivatives of 6-oxo-phenolic-D:A-*friedo*oleananes

2.2.3) Biogenesis of ene-quinone-methide triterpenes

Isopristimerin III (**35**), a phenolic-D:A-*friedo*-24-noroleanane, might be a feasible biosynthetic precursor of pristimerinene (**36**), one of the 9(11)-ene-(9→11)-quinone-methide triterpenes, as shown in Scheme 4, judging from their co-occurrence in *Kokoona zeylanica* Thw. [65,108]. In addition, 14(15)-ene-(14→15)-quinone-methide triterpenes could arise from the corresponding quinone-methide triterpenes *via* dehydrogenation or oxidation at C-15, followed by a series of rearrangements (Scheme 5) [49,126]. The natural occurrence of a 15α-hydroxy-quinone-methide derivative, 15α,22β-dihydroxy-tingenone (**37**), also supports this hypothesis [52].



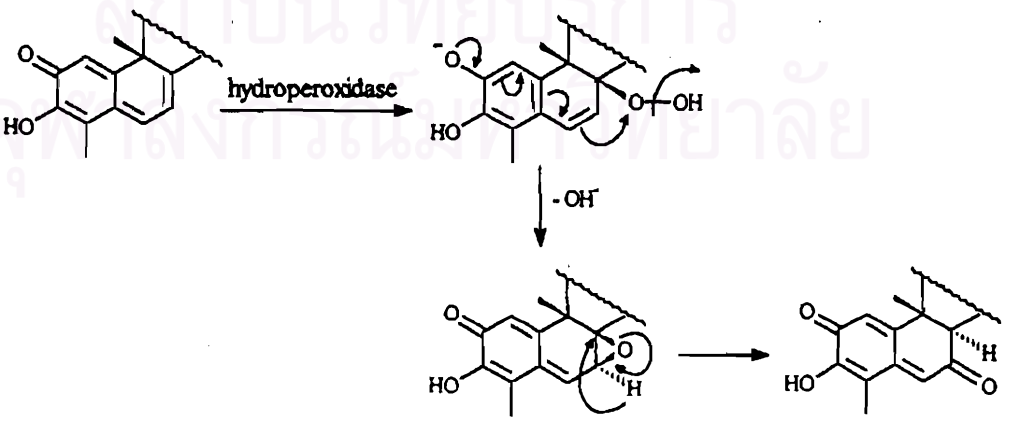
Scheme 4. Biogenetic pathway of pristimerinene (**36**).



Scheme 5. Biogenetic pathway of 14(15)-ene-(14→15)-quinone-methide triterpenes.

2.2.4) Biogenesis of 7-oxo-quinone-methide triterpenes

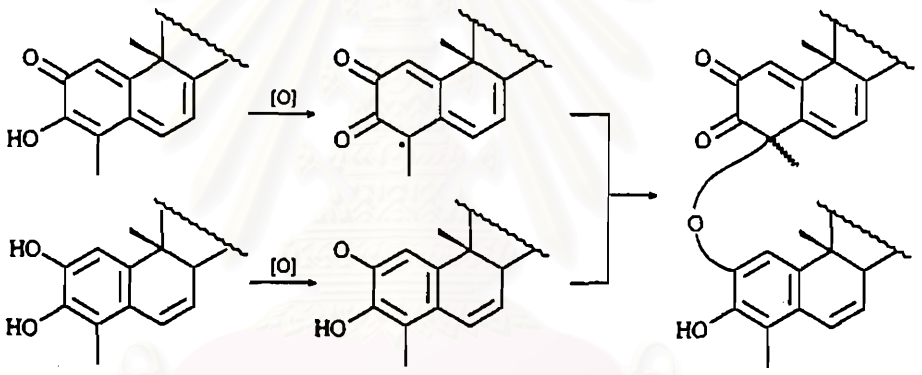
Compounds with 7-oxo-quinone-methide triterpene skeleton were suggested to be derived from their corresponding quinone-methide triterpenes *via* a peroxide and an epoxide intermediates [28,50].



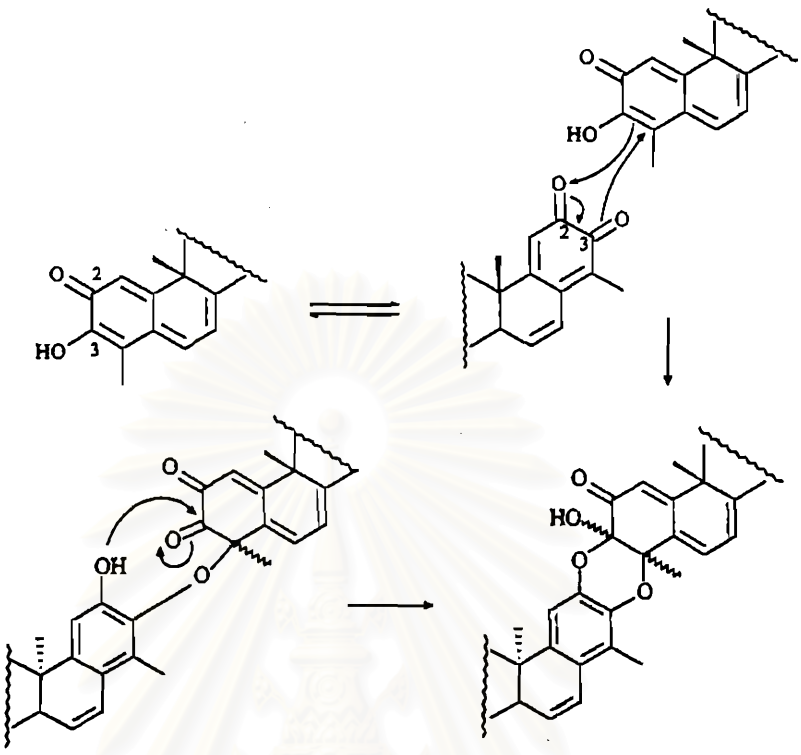
Scheme 6. Biogenetic pathway of 7-oxo-quinone-methide triterpenes.

2.2.5) Biogenesis of dimeric quinone-methide triterpenes

A 2,3-diketone type triterpene, being oxidative state of its quinoid, was suggested as an intermediate that could couple with another oxidative phenolic monomer molecule to give the one ether-linkage dimeric skeletons (Scheme 7) [72], whereas the two ether-linkage dimeric quinone-methide triterpenes were proposed to arise by an *ortho*-quinone Diel-Alder reaction between a quinoid type molecule and its equilibrium state, 2,3-diketone structure, with particular stereochemistry [38,71,72]. These dimers were also postulated to subsequently form from their corresponding one ether-linkage compounds [72] (Scheme 8).



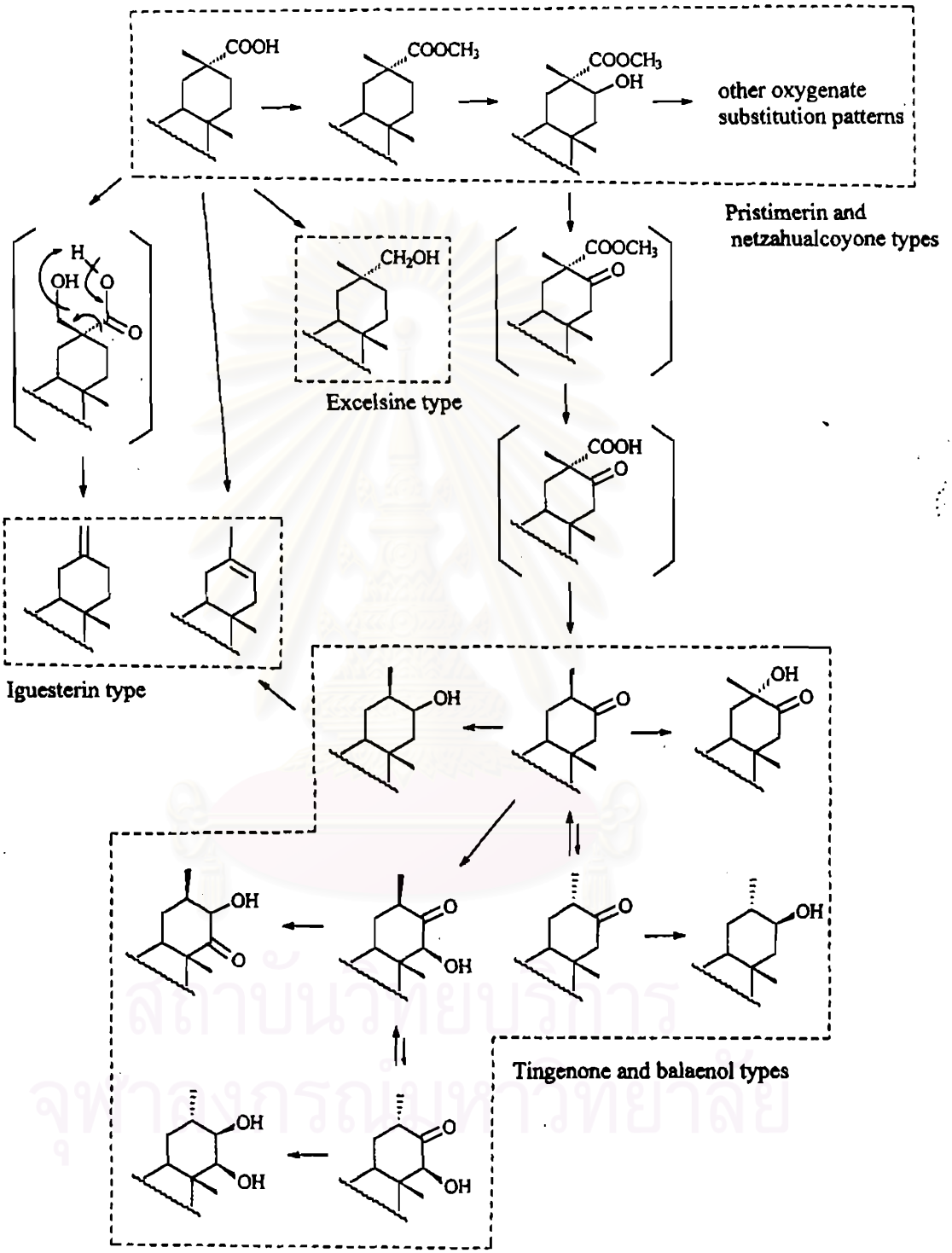
Scheme 7. Biogenetic route of one ether-linkage dimeric quinone-methide triterpenes.



Scheme 8. Biogenetic routes of two ether-linkage dimeric quinone-methide triterpenes.

2.2.6) Rearrangement of functional substituents on ring E

Quinone-methide triterpenes in each type mostly differ only in their ring E substitution patterns. The α-oriented C-20 substitution, always a carboxyl functionality, corresponded to their D:A-*friedo*oleanane precursors and could be further derived into a methyl ester or a hydroxymethylene, with or without additional oxidation at other positions on ring E to give compounds of the pristimerin, netzahualcoyone [28,48] and excelsine types [62]. Furthermore, the carboxylic functionality could be lost either before [28] or after [48] the oxidation on ring E to give compounds of the tingenone and balaenol types [28,48-49], whereas decarboxylation would lead to iguesterin type [28,88]. The latter might also be produced from another pathway involving dehydration of the 21-hydroxy-decarboxylated derivatives [48].



Scheme 9. Proposed correlation of rearranged substitutents on ring E of quinone-methide triterpenes.

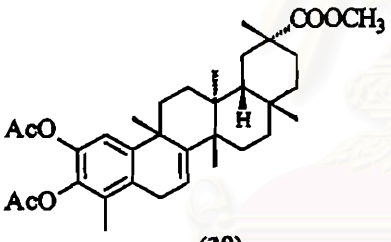
2.3).Biological activities of quinone-methide triterpenes

Several quinone-methide triterpenes have shown interesting biological activities, particularly on cytotoxic and antimicrobial properties. An overview of their bioactivities are as follows :

2.3.1) Cytotoxic activity

Several quinone-methide triterpenes exhibited broadly strong cytotoxic activity [13,15-16,51]. Relationships between the structure and their cytotoxic activity were follows :

- In general, compounds with ring A/B quinone-methide chromophore are more active than those with ring A phenolic system [15,33,51], except for the diacetyl-dihydro synthetic derivatives of pristimerin, tingenone and iguesterin (**38**)-(**40**) which seem to be more active, through not very significantly, than their original compounds [33,69].



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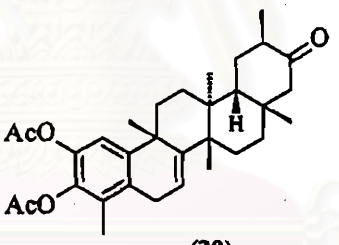

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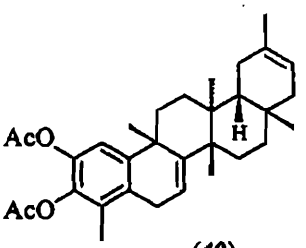
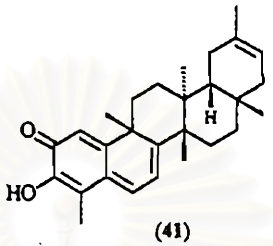


(40)

- Oxygenated substituents on ring E appear to promote the activity [33].

- In two ether-linkage dimers, compounds with the α-linkage between the monomers are more active than those with β-linkage [71].

As for their mechanism of action, pristimerin (**17**), tingenone (**15**) and iguesterin (**41**) were shown to inhibit DNA, RNA and protein syntheses [69,133]. Tingenone (**15**) can form hydrogen bond between its hydroxyl group and the phosphate group of DNA owing to its suitable ring A/B structure [119].

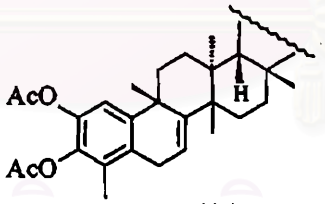


(41)

2.3.2) Antimicrobial activity

Quinone-methide triterpenes exhibit antimicrobial activity with the spectrum to gram-positive bacteria, yeasts, mycobacterium, *Gibberella*, pneumococcus and pyrogenes [34-35,44,74,79,133]. The relationships between structure and antibacterial activity are summarized as follows :

- Antimicrobial activity does not differ between compounds with quinone-methide chromophore and their diacetyl-dihydro synthetic derivatives (**42**) [34].



(42)

- Free hydroxyl groups on ring A of 6-oxo-phenolic-D:A-*friedo*-24-noroleananes are necessary [37].

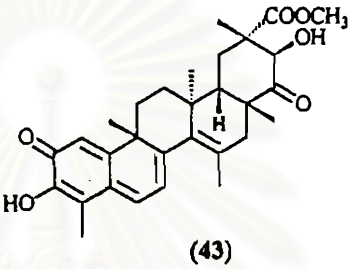
- Double-bond between C-14 and C-15, found in natzahualcoyone series, does not affect the activity [34]. However, in dimeric compounds, it is important [38].

- Functional groups on ring E are associated with potency. Compounds with oxygenated functional groups, such as hydroxyl or ketone groups, are more active than those without [33-34].

- Quinone-methide triterpenes with a carboxyl group at C-20 give the best efficacy. If this group was methylated, the activity would be decreased [34].

- The dimeric quinone-methide triterpenes are less active than the monomers [36].

There were a few studies on antimicrobial mechanism of netzahualcoyone (**43**), a highly potent compound. It displayed inhibitory effect on the cellular respiration of gram-positive bacteria and yeasts. For gram-negative bacteria, this effect was observed only in the sonically disrupted cells, suggesting that the outer membrane of gram-negative bacteria may be a permeability barrier prohibiting the sensitivity of these bacteria to this compound [35,136].



(43)

2.3.3) Antiparasitic activity

Tingenone (**15**) was effective against *Trypanosoma cruzi*, a flagellate protozoon causing Chagas' disease, by inhibiting its macromolecule biosynthesis [137-138]. Another compound, pristimerin (**17**), possessed antimalarial activity against *Plasmodium falciparum*, but with less potency than the commercial drugs [58].

2.3.4) Anti-inflammation in rheumatoid arthritis

Quinone-methide triterpenes were suggested as drugs for the treatment of rheumatoid disorders [139]. Celastrol (**16**) was found to inhibit the lipid-peroxidation of mitochondrial membrane [140] by directly scavenging radicals with the quinone-methide structure moiety, while the anion carboxyl group donating the negative surface charge on the membrane to prevent the attack of oxygen radicals [141]. Moreover, celastrol (**16**) was shown to be an immunosuppressor [104]. It inhibited antibody response [142-143], decreased the production and release of IL-1, IL-2 and PGE-2 [144-145] and also inhibited the proliferation of splenic and lymph node cells [96,145-146].

2.3.5) Effect on mitochondria

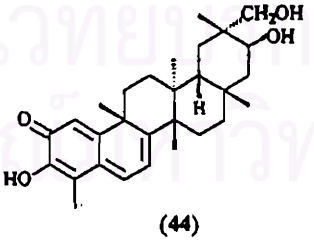
22β-Hydroxy-tingenone (1) showed uncoupling effect on mitochondrial oxidative phosphorylation, and also increased the activity of enzyme ATPase, resulting in the decrease in ATP level. Accumulated in mitochondria, the compound could block the process in electron transport [17].

2.3.6) Toxicity

Tingenone (15) and netzahualcoyone (43) were studied for their toxicity. Their LD_{50} were 19.39 and 100 mg/kg by intraperitoneal route in mice [147-148], respectively. Pristimerin (17) was also proved to be toxic to mice. However, when the compound was orally administered, no toxic symptom was observed even in the dose of 0.5 g/kg daily for 28 days [44].

2.3.7) Other activities

Several other bioactivities of quinone-methide triterpenes have been studied. Celastrol (16) exhibited reversible inhibitory effect on spermatozoal functions and, hence, it was considered as a novel non-steroidal male contraceptive agent [100-101]. Both tingenone (15) and pristimerin (17) were allelochemicals inhibiting the germination of lentil seeds [90]. Tingenone (15) also displayed moderate activity in the brine-shrimp lethality assay although pristimerin (17) and other two compounds, celastrol (16) and excelsine (44), showed negative results [62].



(44)

Negative biological results have also been reported. Tingenone (15) produced no anti-inflammation effect in rats, no effects on erythrocytes, leukocytes, isolated guinea pig ileum, *in situ* toad heart; and had no significant effect on blood pressure and respiration in anesthetized rats [147]. 22β–hydroxy-tingenone (1) was inactive against HIV-1 and HIV-2 reverse transcriptase [149-150]; and netzahualcoyone (43) had no effect on isolated rat uterus [148].