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Labdane Diterpenes with Highly Functionalized B Rings

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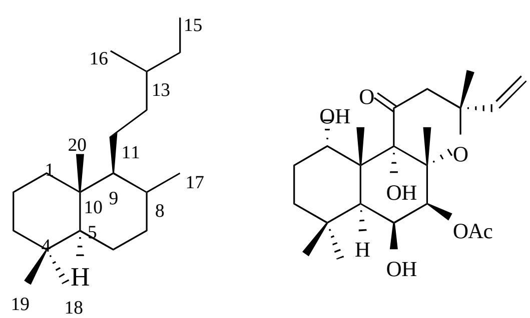
Abstract: In this review, the natural source, structure, biological activities and the synthesis of labdanes diterpenes with highly functionalized B rings, described to date are shown. The structures for these compounds have been classified taking into account the number of oxygenated positions of the B ring. In this manner the classification has 7 groups of deoxygenated labdanes, 6 of trioxygenated and one group of the tetraoxygenated ones.

Keywords: Bioactivities, diterpenes, forskolin, labdanes, synthesis, terpenes.

1. INTRODUCTION

Compounds with labdane skeleton are among the natural products, more abundant and widely distributed in nature. Forskolin, a labdane with a manoil oxide structure and a highly functionalized B ring [1], is perhaps the most interesting labdane because of its biological activities. Forskolin isolated in 1977 from the roots of *Coleus forskohlii* has shown to have therapeutic potential against glaucoma, congestive heart failure and bronchial asthmas. In addition, forskolin, together with a few other congeners, is a unique and potent stimulator of enzyme adenylate cyclase in various tissues. For example, it has been shown to be effective for lowering blood pressure, inhibiting platelet aggregation, improving heart function, and possibly increasing nitric oxide levels [2].



labdane **forskolin**

Within the labdane skeleton compounds with important biological activities are known, but there are a wide number of labdanes with unknown or even no tested.

In this review, the known labdanes diterpenes with more than one oxygenated functionality in the B ring have been collected, because they constitute an interesting class of natural products some of them with important bioactivity [1].

For each compound is presented:

1) From where the structure and the nature source have been isolated.
2) The biological activity if known.
3) The described syntheses until date for these compounds.

Table **1** shows the natural sources from where all the compounds of this review have been isolated.

Table 1. Highly Functionalized B Ring Labdanes Isolation Sources

Family	Gener	Specimen
Asteraceae	*Amphiachyris*	*Amphiachyris amoena*
	Austroeupatorium	*Austroeupatorium inulaefolium*
	Blepharizonia	*Blepharizonia plumosa*
	Chrysothamnus	*Chrysothamnus paniculatus*
	Erigeron	*Erigeron philadelphicus*
	Grindelia	*Grindelia camporum*
		G. humilis
		G. robusta
	Gutierrezia	*Gutierrezia spathulata*
	Gymnosperma	*Gymnosperma glutinosa*
	Haplopappus	*Haplopappus parvifolius*
	Helichrysum	*Helichrysum ambiguum*
	Koanophyllon	*Koanophyllon conglobatum*
	Stevia	*Stevia aristata*
		S. berlandiera
		S. rebaudiana
		S. monardaefolia
		S. subpubescens
	Waitzia	*Waitzia acuminata*
Lamiaceae	*Ballota*	*Ballota aucheri*
		B. acetobulosa
		B. lanata
		B. nigra
		B. rupestris
		B. undulata
	Coleus	*Coleus forskohlii*
	Galeopsis	*Galeopsis angustifolia*
	Hyptis	*Hyptis fasciculate*
	Leucas	*Leucas cephalotes*
		L. neufliseana
	Leonotis	*Leonotis ocymifolia*
		L. dubia
		L. leonitis
		L. leonurus
		L. nepetaefolia
	Leonorus	*Leonorus cardiaca*
		L. heterophyllus
		L. japonicus

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Table 1. contd…..

Family	Gener	Specimen
Lamiaceae		*L. persicus*
		L. reuteri
		L. sibiricus
	Marrubium	*Marrubium alysson*
		M. anisodon
		M. astracanicum
		M. cylleneum
		M. globosum
		M. incanum
		M. peregrinum
		M. polydon
		M. sericeum
		M. supinum
		M. thessalum
		M. trachyticum
		M. velutinum
		M. vulgare
	Otostegia	*Otostegia fructicosa*
	Roylea	*Roylea calycina*
	Salvia	*Salvia moorcraftiana*
	Sideritis	*Sideritis arborescens*
		S. argyrea
		S. foetens
		S. mugronensis
	Solidago	*Solidago canadiensis*
		S. chilensis
	Vitex	*Vitex agnus-castus*
		V. cannabifolia
		V. rotundifolia
		V. trifolia
Trimusculidae	*Trimusculus*	*Trimusculus conica*
		T. costatus
		T. peruvianus
		T. reticulatus
Zingiberaceae	*Afromomum*	*Afromomum sceptrum*
	Hedychium	*Hedychium spicatum*
Cistaceae	*Cistus*	*Cistus ladaniferus*
		C. laurifolius
		C. psilosepalus
Sapindaceae	*Dodonaea*	*Dodonaea lobulata*
Lejeuneaceae	*Ptychanthus*	*Ptychanthus striatus*
Rhizophoraceae	*Rhizophora*	*Rhizophora mucronata*
Euphorbiaceae	*Croton*	*Croton macrostachys*
	Excoecoria	*Excoecoria agallocha*
		E. cochinchinensis
Carcharhinidae		*Carcharhinus leucas*
Porellaceae	*Porella*	*Porella perrottetiana*

Table 1. contd…..

Family	Gener	Specimen
Jubaladae	*Frullania*	*Frullania hamachiloba*
Pseudolepicolea ceae	*Blefarostoma*	*Blefarostoma trichophyllum*
Ranunculaceae	*Trollius*	*Trollius lebedouri*
Sclerotiniaceae	*Sclerotinia*	*Sclerotinia homoeocarpa*
Solanaceae	*Nicotiana*	*Nicotiana tabacum (Greek tobacco)*

Plants corresponding to 16 families, standing out the Asteraceas and Lamiaceas have been studied, from which plants corresponding to 13 and 14 geners respectively have been studied and some of them appear with 14 different specimens, as in the case of the *Marrubium*.

Also some compounds have been isolated from marine organisms of the Trimusculidae and Carcharhinidae geners.

In the Table **2** the classification followed with these compounds according to the number of oxygenated functionalities appear on the B ring, classified in increasing order of oxygenated functionalities, and the number of compounds of each type. The classification has 7 groups of deoxygenated labdanes, 6 of trioxygenated and one group of the tetraoxygenated ones.

Table 2. Clasification of Di, Tri and Tetraoxygenated B Ring Labdanes

Compounds	Oxygenated Positions on Ring B	Groups	Number of Known Compounds
Dioxygenated	5, 8	I	1
	6, 7	II	30
	6, 8	III	19
	6, 9	IV	94
	7, 8	V	38
	7, 9	VI	11
	8, 9	VII	4
Trioxygenated	5, 6, 9	VIII	1
	5, 8, 9	IX	1
	6, 7, 8	X	40
	6, 7, 9	XI	40
	6, 8, 9	XII	14
	7, 8, 9	XIII	22
Tetraoxygenated	6, 7, 8, 9	XIV	19

The structures of the mentioned compounds are shown below and are classified by groups (I-XIV) according to the functionalization on the B ring. Each group has been arranged considering the functionalization from minor to major complexity of the ring system and the side chain. Each compound has a number that appears in the table next to each group together with the natural source from where it has been isolated and the corresponding reference. If the compound has been named, the name is included, and if has been synthesized is marked with an asterisk. Besides in the table appears the known until date biological activity of these compounds.

HIGHLY OXYGENATED B-RING LABDANES

Group I: 5,8-Dioxygenated Labdanes

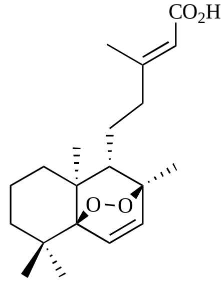

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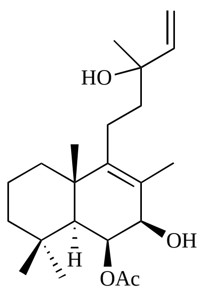
Table 3. 5,8-Dioxygenated Labdanes

5,8-Dioxygenated Labdanes	Isolated From	Reference
1	*Gutierrezia spathulata*	[3]

Group II: 6,7-Dioxygenated Labdanes



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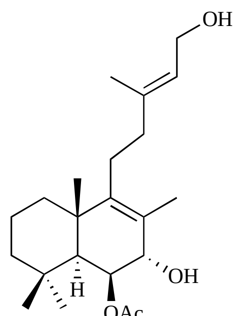

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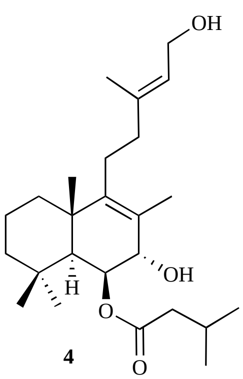

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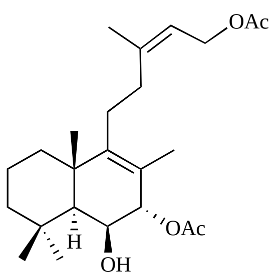

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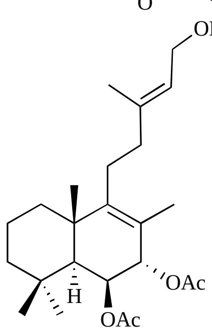

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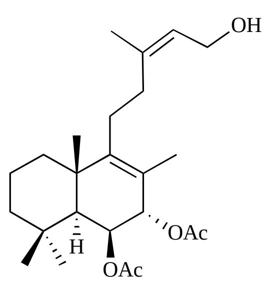

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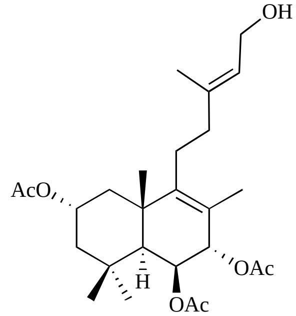

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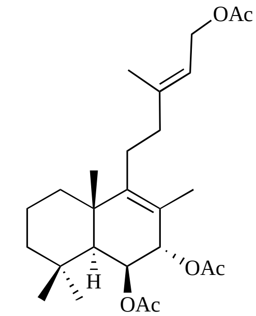

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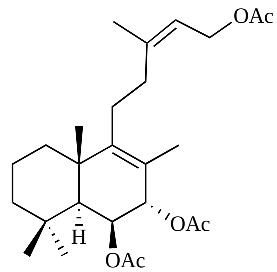

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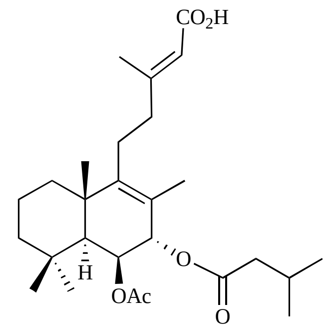

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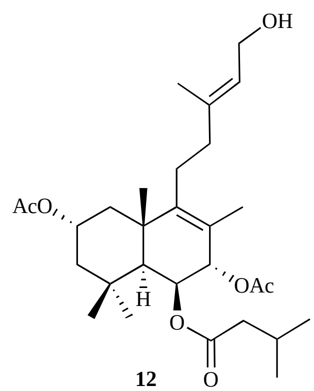

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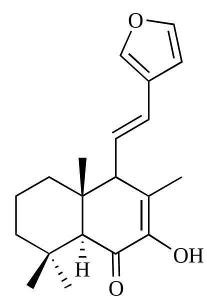

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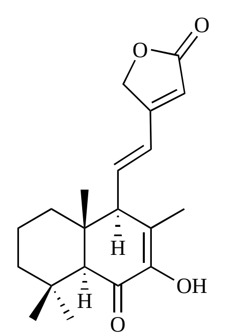

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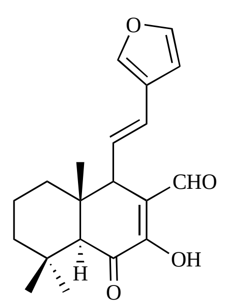

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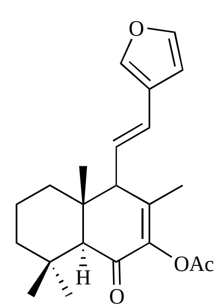

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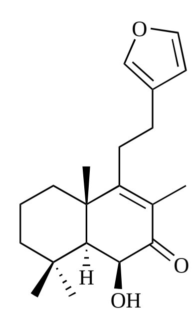

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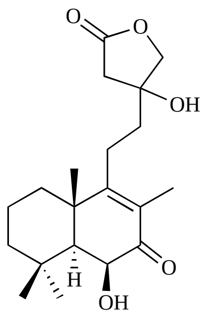

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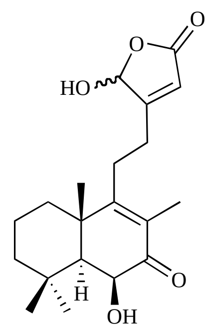

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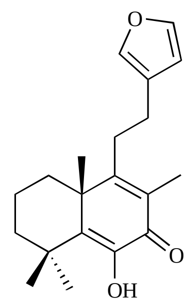

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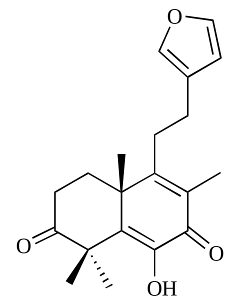

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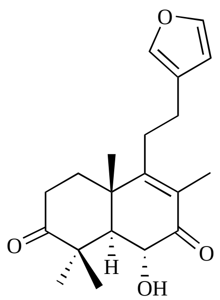

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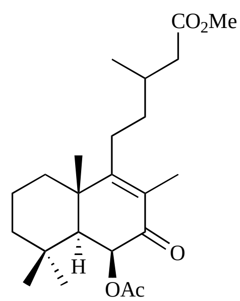

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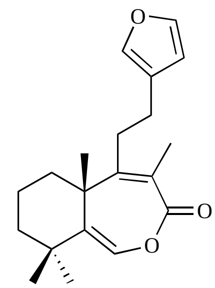

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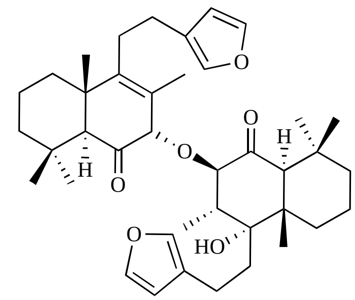

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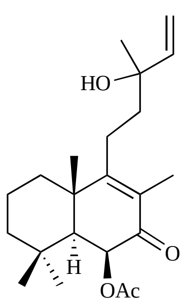

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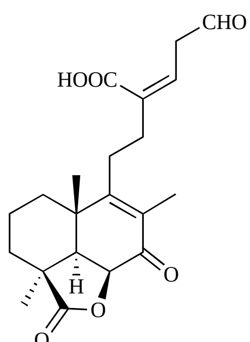

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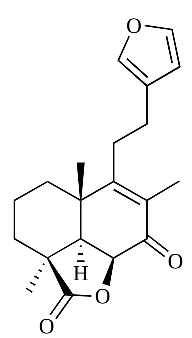

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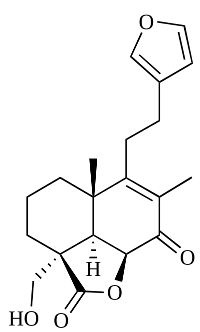

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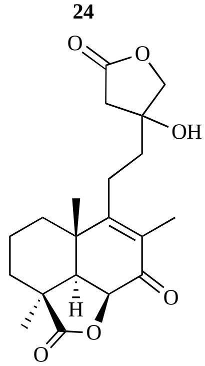

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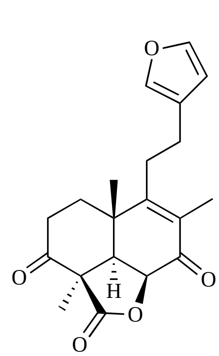

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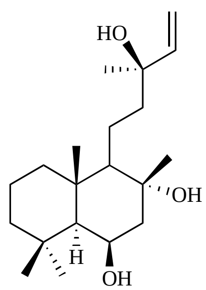
Table 4. 6,7-Dioxygenated Labdanes

6,7-Dioxygenated Labdanes	Isolated From	Activity and References
2*	*Haplopappus parvifolius*	[4]
3	*Trimusculus peruvianus*	[5]
4*	*Trimusculus reticulatus*	Repellent, [6]
5	*Trimusculus peruvianus*	[7]
6	*Trimusculus costatus*	Anticancer, [8]
7	*Trimusculus peruvianus, Trimusculus costatus*	[7, 9]
8	*Trimusculus costatus*	Anticancer, [8, 9]
9*	*Trimusculus costatus*	[8]
10*	*Trimusculus peruvianus*	[7]
11	*Trimusculus conica*	[10]
12	*Trimusculus reticulatus*	Repellent, [6]
7-hydroxyhedychenone, 13	*Hedychium spicatum*	[11, 12]
14	*Hedychium spicatum*	Cytotoxic, [13]
7-hydroxyhydichinal, 15	*Hedychium spicatum*	Anticancer, [14]
7-acetoxyhedychenone, 16	*Hedychium spicatum*	[11, 12]
17	*Ballota aucheri*	[15]
leopersin L, 18	*Leonurus persicus*	[16]
sibiricinone B, 19*	*Leonurus sibiricus*	[17]

Table 4. contd…..

6,7-Dioxygenated Labdanes	Isolated from	Activity and References
heteroneone A, 20	*Leonurus heterophyllus*	[18]
21	*Cistus ladaniferus*	[19]
22	*Haplopappus parvifolius*	[4]
rupestralic acid, 23	*Ballota rupestris*	[20]
ballonigrin, 24	*Ballota rupestres, Ballota lanata, Otostegia fructicosa, Ballota undulata*	[21, 22, 23, 24]
18-hydroxyballonigrin, 25	*Ballota acetobulosa*	[25]
13-hydroxyballonigrinolide, 26	*Ballota lanata, Leonurus persicus*	[22, 16]
ballonigrinone, 27	*Ballota rupestres, Ballota undulata*	[21, 24]
leojaponin, 28	*Leonurus japonicus*	[26]
heteronone B, 29	*Leonurus heterophyllus*	[18]
balloaucherolide, 30	*Ballota aucheri*	[27]
persianone, 31	*Ballota aucheri*	[15]

Group III: 6,8-Dioxygenated Labdanes



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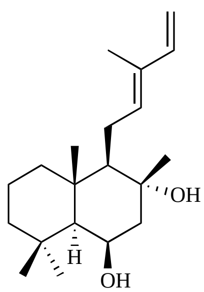

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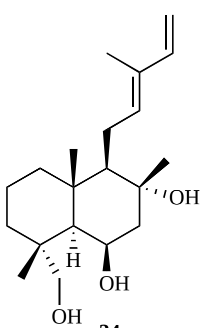

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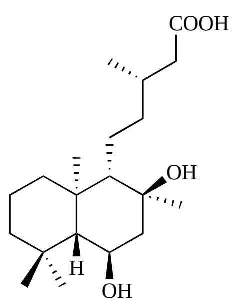

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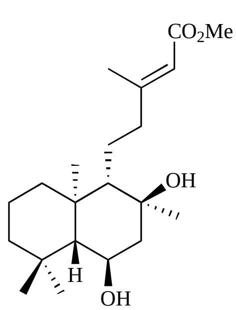

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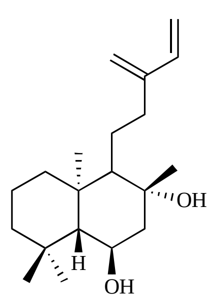

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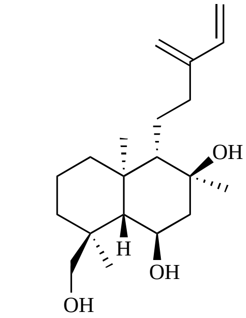

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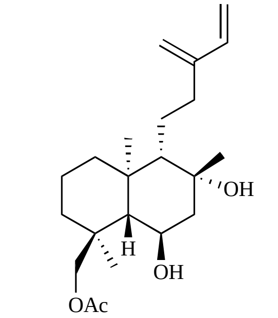

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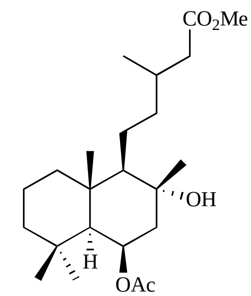

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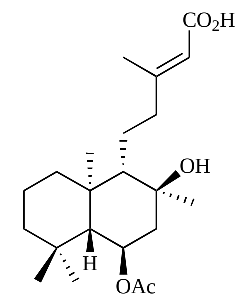

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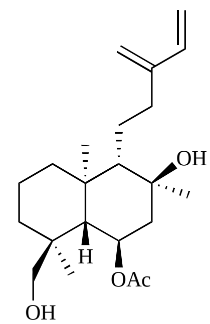

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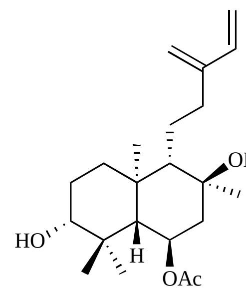

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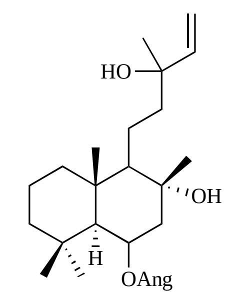

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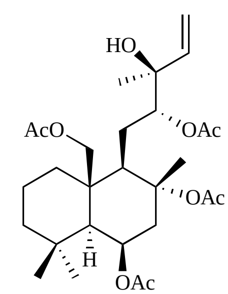

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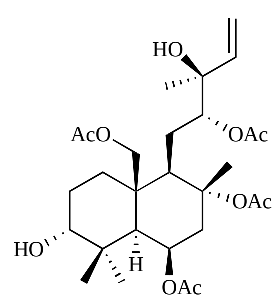

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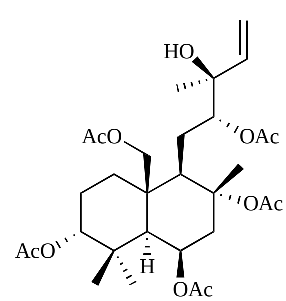

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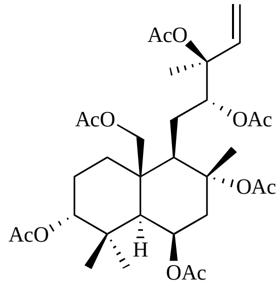

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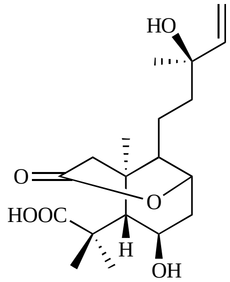

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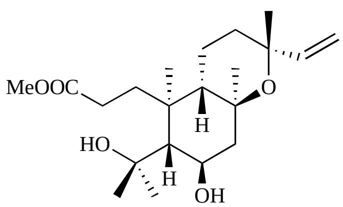
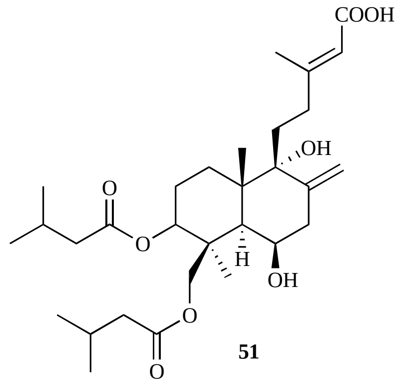


50

Table 5. 6,8-Dioxygenated Labdanes

6,8-Dioxygenated Labdanes	Isolated From	Activity and References
6β-hydroxysclareol, 32	*Salvia moorcraftiana*	[28]
33	*Koanophyllon conglobatum*	[29]
34	*Koanophyllon conglobatum*	[29]
35	*Dodonaea lobulata*	[30]
laurifolic acid, 36	*Cistus laurifolius*	[31]
37	*Sideritis argyrea*	[32]
andalusol, 38	*Sideritis foetens, Sideritis arborescens* Salzm.	[33, 34]
39	*Sideritis foetens*	[33]
40	*Cistus psilosepalus*	[35]
acetyl-laurifolic acid, 41	*Cistus laurifolius L.*	[36]
42	*Sideritis foetens*	[33]
43	*Sideritis foetens*	[33]
6α-angeloyloxy sclareol, 44	*Stevia monardaefolia*	[37]
ptychantin I, 45	*Ptychanthus striatus*	[38]
ptychantin H, 46	*Ptychanthus striatus*	[38]
ptychantin F, 47	*Ptychanthus striatus*	[38]
ptychantin G, 48	*Ptychanthus striatus*	[38]
rhyzophorin A, 49	*Rhizophora mucronata*	[39]
agallochin M, 50	*Excoecaria agallocha* L.	[40]

Group IV: 6,9-Dioxygenated Labdanes



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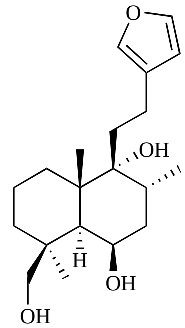

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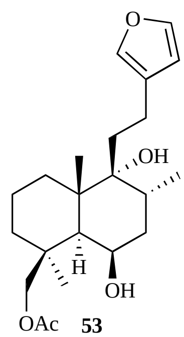

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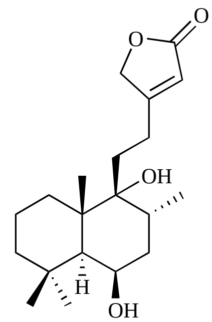

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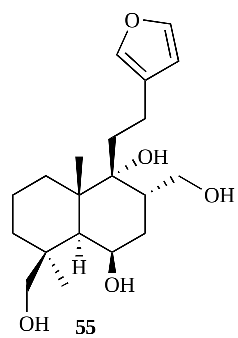

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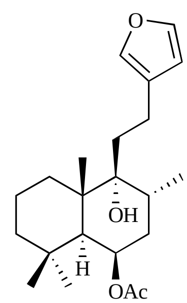

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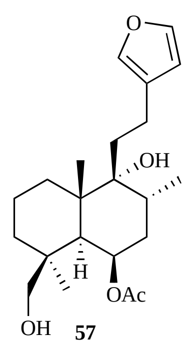

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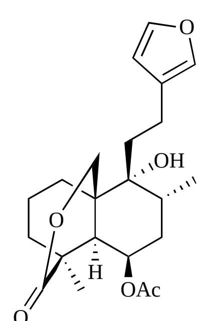

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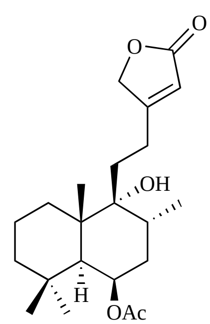

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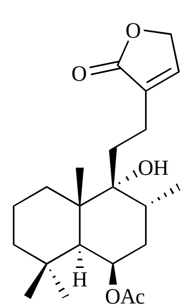

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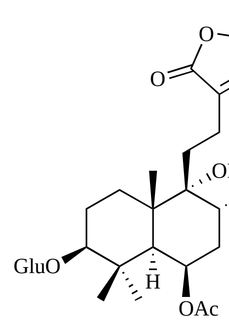

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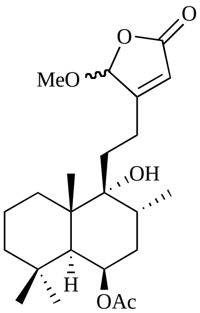

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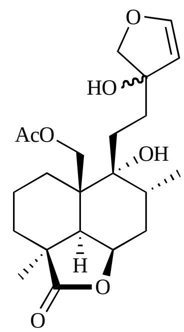

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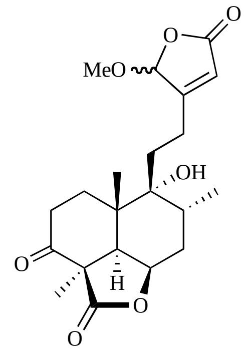

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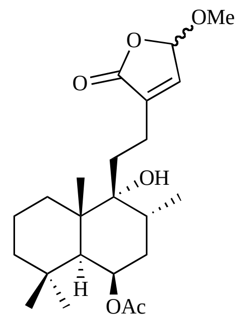

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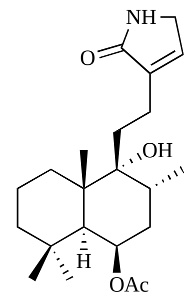

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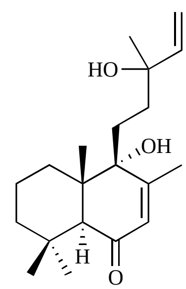

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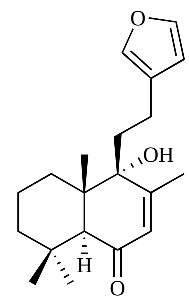

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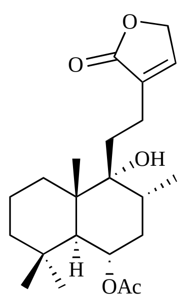

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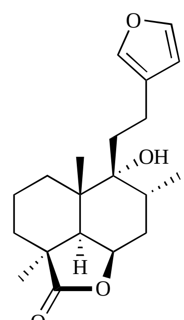

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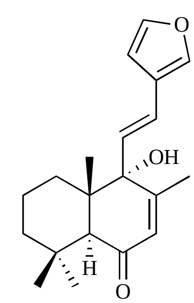

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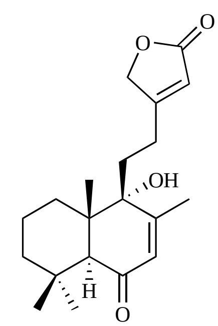

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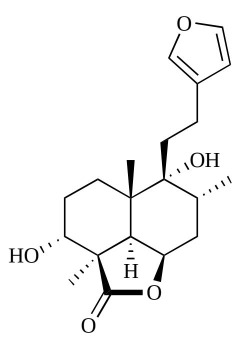

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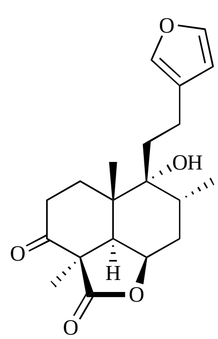

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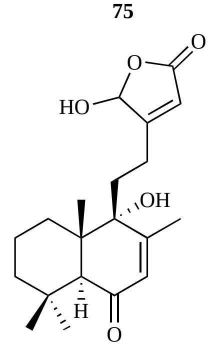

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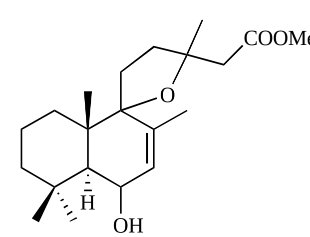

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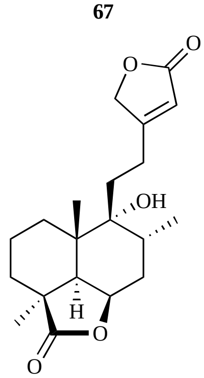

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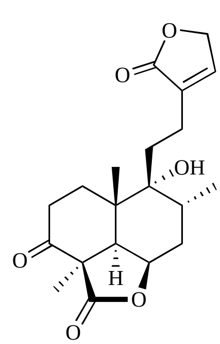

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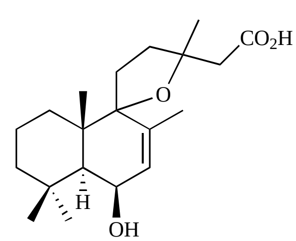

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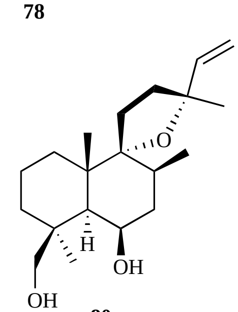

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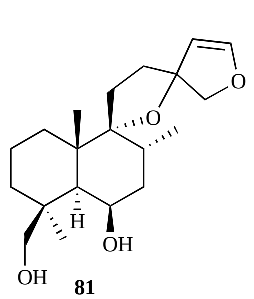

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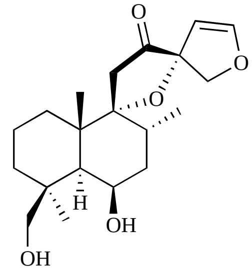

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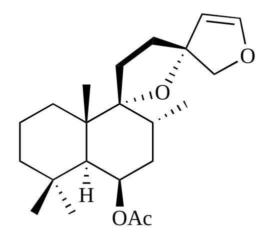

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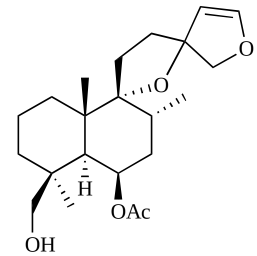

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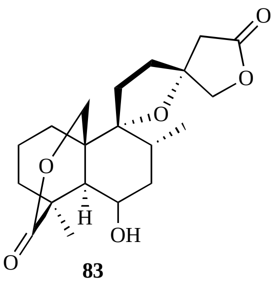

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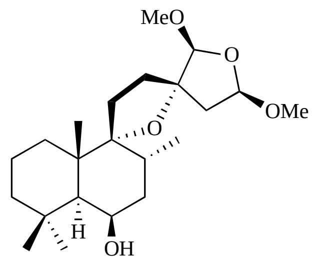

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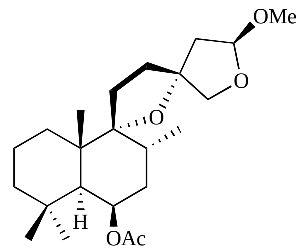

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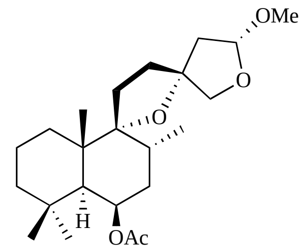

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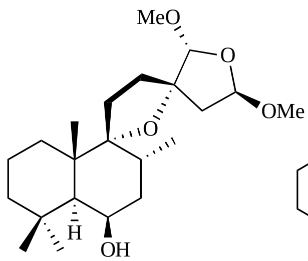

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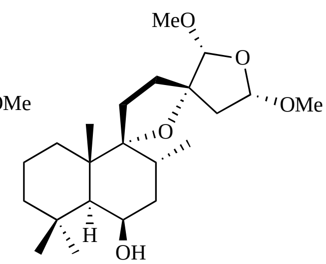

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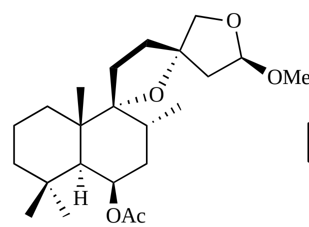

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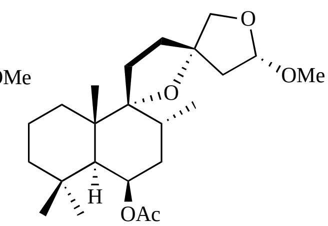

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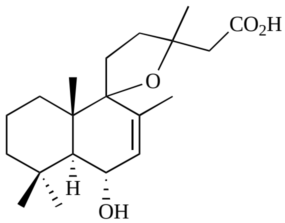

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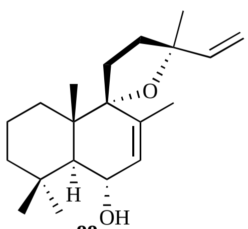

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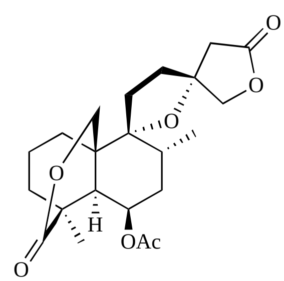

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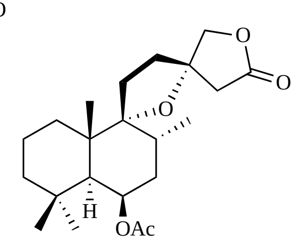

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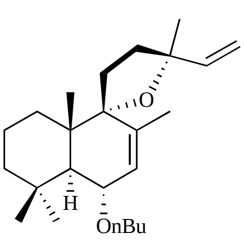

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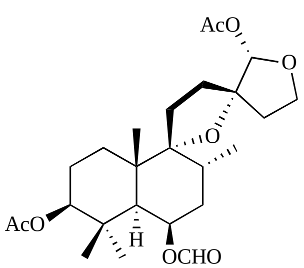

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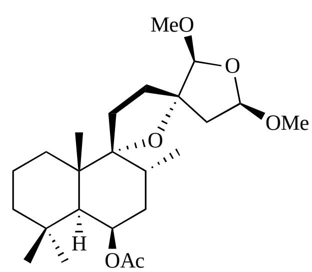

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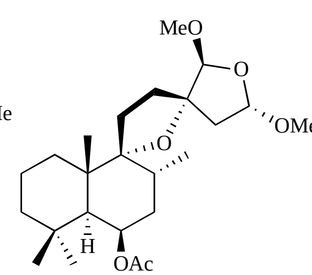

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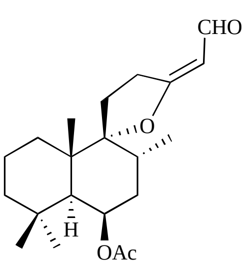

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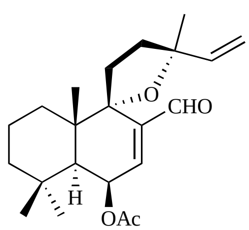

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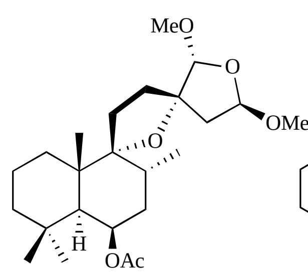

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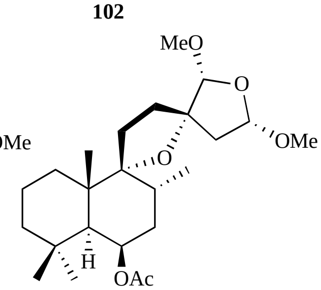

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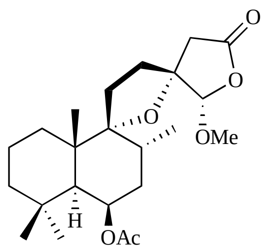

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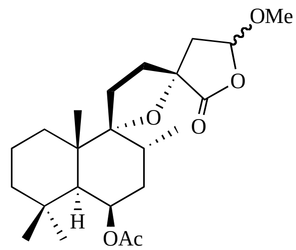

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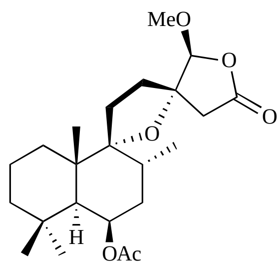

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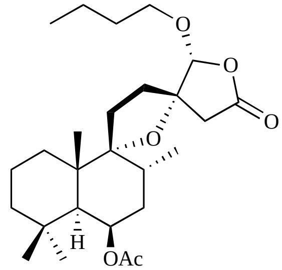

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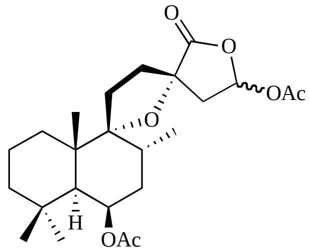

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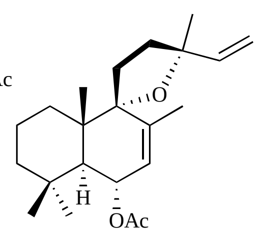

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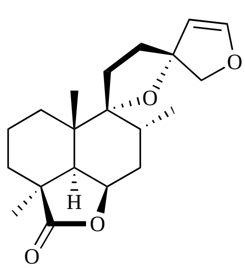

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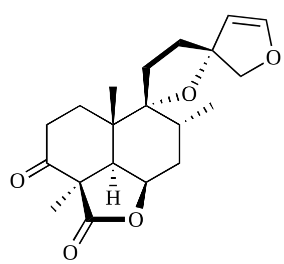

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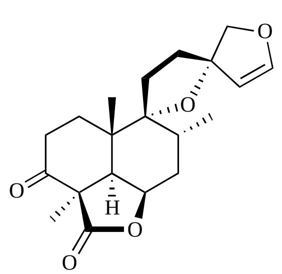

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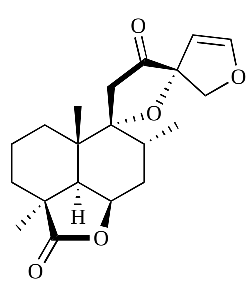

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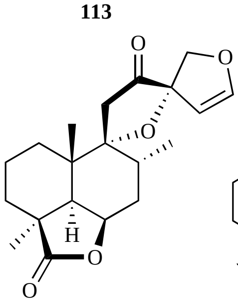

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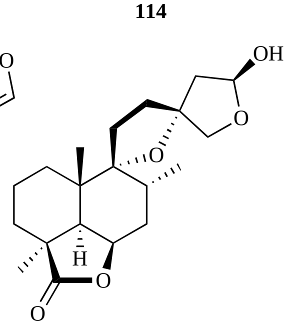

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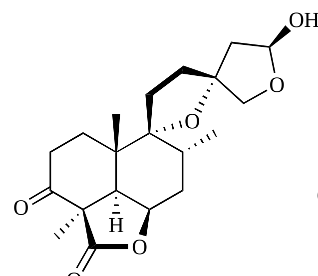

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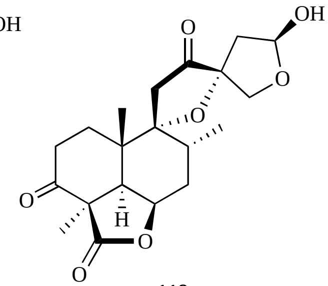

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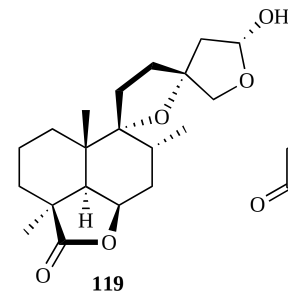

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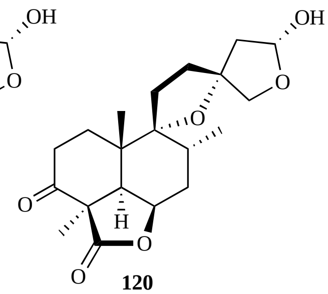

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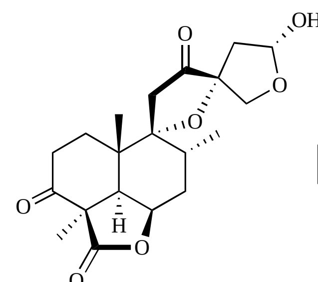

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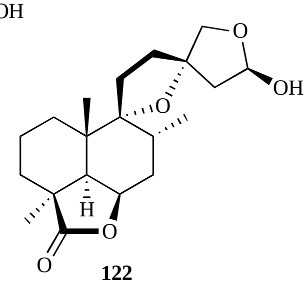

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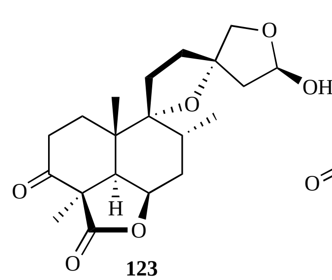

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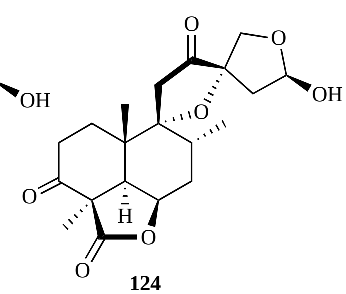

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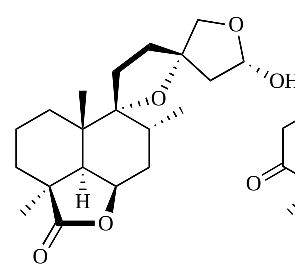

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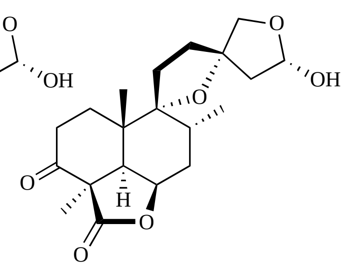

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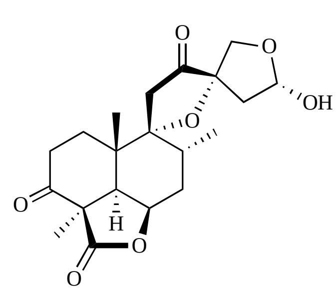

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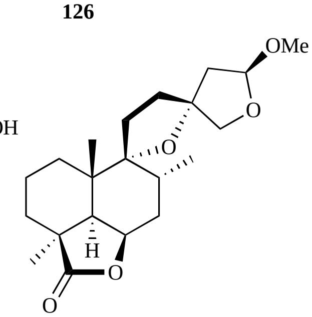

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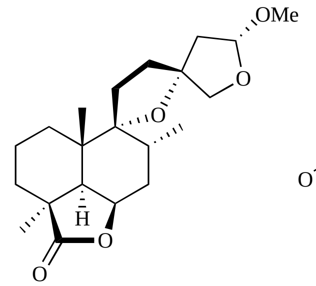

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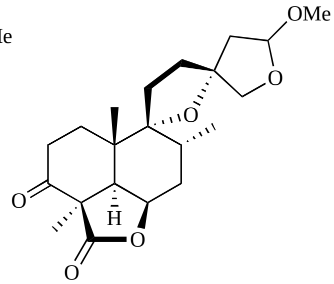

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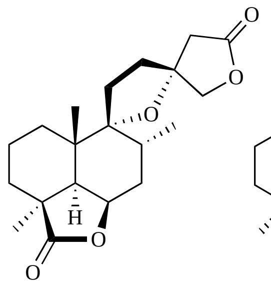

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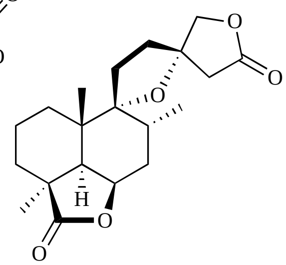

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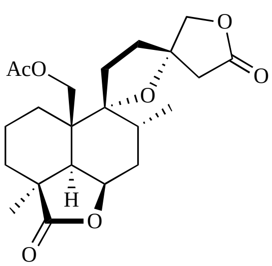

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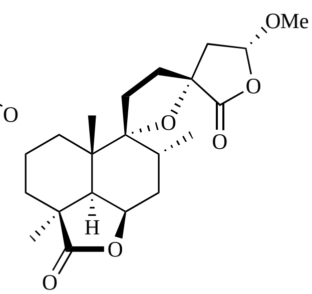

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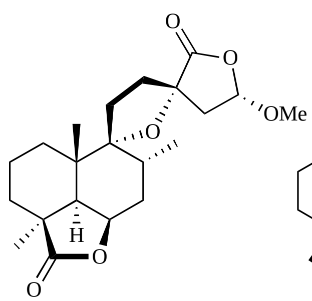

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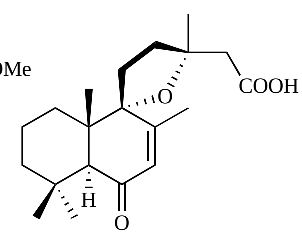

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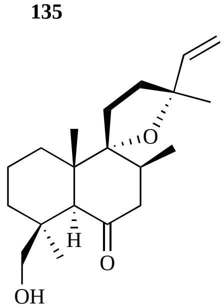

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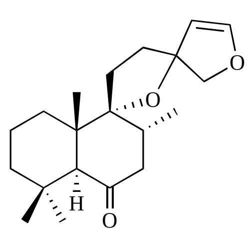

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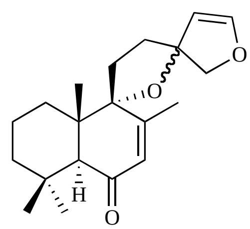

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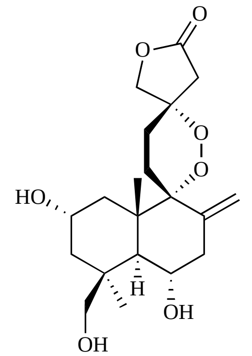

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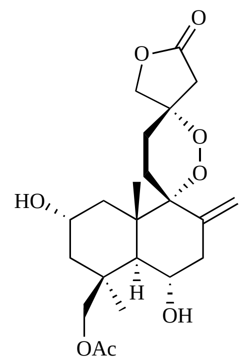

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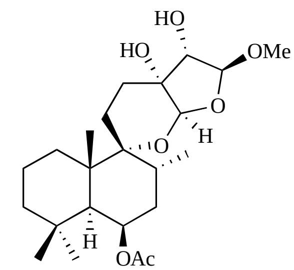

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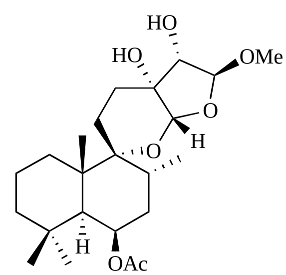

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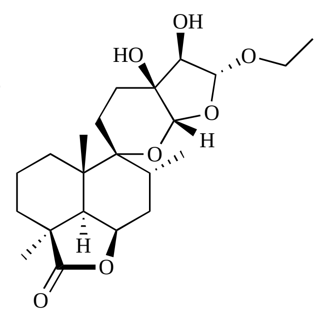

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Table 6. 6,9-Dioxygenated Labdanes

6,9-Dioxygenated Labdanes	Isolated From	Activity and References
51	*Trimusculus peruvianus*	[41]
marrubenol, 52	*Marrubium sericeum,*	[42, 43]
19-acetylmarrubenol, 53	*Marrubium sericeum,*	[43]
deacetylvitexilactone, 54	*Marrubium globosum* ssp. *Libanoticum*	[44, 45]
55	*Leonotis nepetaefolia*	[46]
rotundifuran, 56	*Vitex rotundifolia* L.	[47]
6-acetylmarrubenol, 57	*Marrubium sericeum,*	[43]
dubiin, 58	*Leonotis dubia*	[48]
vitexilactone, 59	*Vitex cannabifolia, Vitex rotundifolia L, Vitex trifolia L.*	[49, 50, 51, 52]

Table 6. contd…..

6,9-Dioxygenated Labdanes	Isolated From	Activity and References
60	*Vitex rotundifolia*	[51]
viteoside A, 61	*Vitex rotundifolia*	[53]
viteagnusin H, 62	*Vitex agnus-castus*	[54]
63	*Vitex rotundifolia*	[51]
vitexlactam A, 64	*Vitex agnus-castus*	[55]
65	*Vitex rotundifolia, Vitex trifolia L.*	[51, 52]
marrubiin, 66	*Marrubium cylleneum, Marrubium trachyticum* Boiss, *Ballota nigra* sub. *Foetida, Marrubium sericeum, Marrubium supinum, Marrubium alysson, Marrubium incanum, Leonotis leonurus, Marrubium vulgare, Marrubium globosum* ssp. *Globosum*	[52, 56, 57, 58, 43, 59, 60, 61, 62, 63]
67	*Marrubium thesasalum*	[64]
peregrinine, 68	*Marrubium incanum, Marrubium thessalum, Marrubium velutinum, Leucas neufliseana*	[60, 64, 59, 65, 63]
69	*Marrubium globosum* ssp. *Libanoticum*	Anti-inflammatory [45, 66]
velutine C, 70	*Marrubium velutinum*	[59]
71	*Leonotis ocymifolia* var. *Raineriana*	[67]
72	*Marrubium thesasalum*	[64]
73	*Haplopappus parvifolius*	[4]
solidagenone, 74	*Solidago canadensis* L., *Solidago chilensis*	[68, 69]
75	*Hedychium spicatum*	Cytotoxic, [13]
76	*Solidago chilensis*	[69]
solicanolide, 77	*Solidago canadensis*	Cytotoxic, [70]
78	*Grindelia camporum, Chrysothamnus paniculatus*	[71]
79	*Grindelia humilis*	[72]
80	*Stevia subpubescens*	[73]
premarrubenol, 81	*Marrubium supinum*	[43]
marrubiglobosin, 82	*Marrubium globosum* ssp. *globosum*	[63]
nepetaefolinol, 83	*Leonotis nepetaefolia*	[46, 74]
84	*Vitex rotundifolia*	[51]
85	*Vitex rotundifolia*	[51]
86	*Vitex rotundifolia*	[51]
87	*Grindelia humilis*	[72]

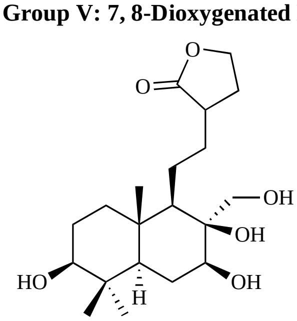
Table 6. contd…..

6,9-Dioxygenated Labdanes	Isolated From	Activity and References
88	*Haplopappus parvifolius*	[4]
89	*Haplopappus parvifolius*	[4]
leucasdin, 90	*Leucas cephalotes Spreng*	[75]
91	*Vitex trifolia*	Trypanocydal activity, [52]
92	*Haplopappus parvifolius*	[4]
prerotundifuran, 93	*Vitex rotundifolia* L.	[47]
6-acetylpremarrubenol, 94	*Marrubium supinum*	[43]
95	*Vitex rotundifolia, Vitex agnus-castus*	[76, 54]
96	*Vitex rotundifolia, Vitex agnus-castus*	[76, 54]
97	*Vitex rotundifolia, Vitex agnus-castus*	[76, 54]
98	*Vitex rotundifolia, Vitex agnus-castus*	[76, 54]
99	*Leonotis ocymifolia* var. *Raineriana*	[67]
previtexilactone, 100	*Vitex rotundifolia L.,Vitex trifolia L.*	[50, 52]
101	*Vitex rotundifolia*	[76]
102	*Vitex rotundifolia*	[76]
103	*Vitex rotundifolia*	[76]
104	*Vitex rotundifolia*	[76]
105	*Vitex rotundifolia*	[51]
106	*Vitex agnus castus L., Vitex rotundifolia*	[77, 51]
107	*Vitex rotundifolia*	[51]
viteagnusin E, 108	*Vitex agnus cactus L*	[77]
109	*Vitex rotundifolia*	[51]
110	*Haplopappus parvifolius*	[4]
premarrubiin, 111	*Marrubium vulgare* L.	[62]
112	*Marrubium thessalum*	[64]
113	*Marrubium thessalum*	[64]
marrubinone B, polyodonine, 114	*Marrubium astracanicum, Marrubium velutinum/Marrubium polydon, Marrubium globosum* ssp. *Globosum*	[78, 52, 59, 79, 63]
marrubinone A, 115	*Marrubium astracanicum*	[78]
15-epi-cyllenin A, 116	*Marrumium vulgare L., Marrubium cylleneneum, Marrubium globosum, Marrubium peregrinum L.*	[80, 59, 44, 81, 45]
15-epi-velutine A, 117	*Leucas neufliseana, Marrubium thessalum, Marrubium velutinum*	[64, 52, 65, 59]

Table 6. contd…..

6,9-Dioxygenated Labdanes	Isolated From	Activity and References
15-epi-velutine B, 118	*Marrubium velutinum*	[59]
cyllenin A, 119	*Marrumium vulgare L., Marrubium cylleneneun, Marrubium globosum, Marrubium peregrinum L.*	[80, 59, 44, 81, 45]
velutine A, 120	*Leucas neufliseana, Marrubium thessalum, Marrubium velutinum*	[64, 52, 65, 59]
velutine B, 121	*Marrubium velutinum*	[59]
13,15-diepicyllenin A, 122	*Marrubium globosum* ssp. *Libanoticum*	[45]
123	*Marrubium velutinum*	[52, 59]
15-epi-velutine B, 124	*Marrubium velutinum*	[52]
13-epicyllenin A, 125	*Marrubium globosum* ssp. *libanoticum*	[45]
126	*Marrubium velutinum*	[52, 59]
velutine B, 127	*Marrubium velutinum*	[52]
128	*Marrubium cylleneum*	[82]
129	*Marrubium cylleneum*	[82]
130	*Marrubium thesasalum*	[64]
131	*Marrubium globosum* ssp. *libanoticum*	[44, 45]
132	*Marrubium globosum* ssp. *libanoticum*	[44, 45]
leonitin, 133	*L. leonitis, Leonotis ocymifolia* var. *raineriana*	[83, 67]
marrusidin A, 134	*Marrubium anisodon*	[84]
marrusidin B, 135	*Marrubium anisodon*	[84]
6-oxogrindelic acid, 136	*Chrysothamnus paniculatus*	[85]
137	*Stevia subpubescens*	[73]
138	*Solidago candensis* L.	[86]
139	*Solidago canadensis* L.	[68]
amoenolide K, 140	*Amphiachyris amoena*	[87]
amoenolide K 19-acetate, 141	*Amphiachyris amoena*	[87]
viteagnusin F, 142	*Vitex agnus-castus*	[54]
viteagnusin G, 143	*Vitex agnus-castus*	[54]
marrulibacetal, 144	*Marrubium globosum* ssp. *libanoticum*	Antispasmodic, [45]

Group V: 7, 8-Dioxygenated Labdanes



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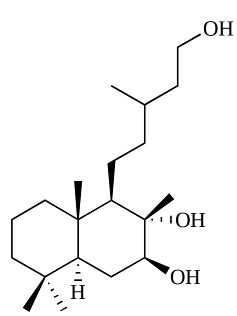

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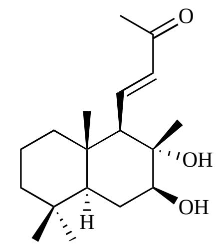

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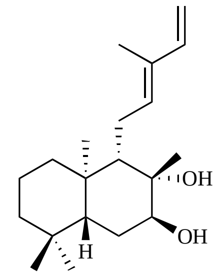

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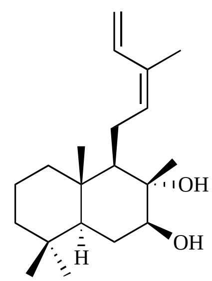

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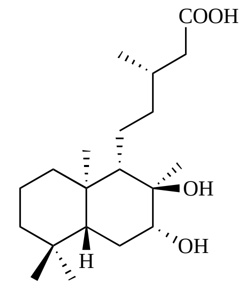

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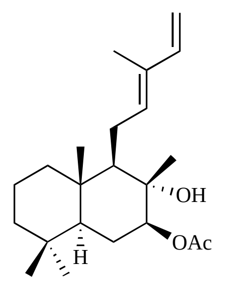

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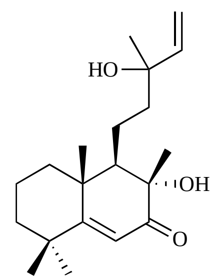

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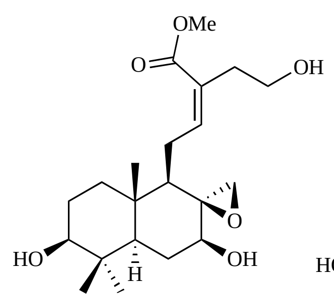

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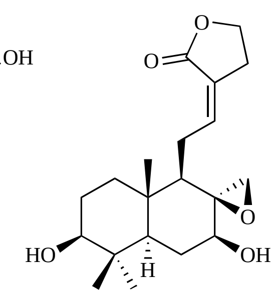

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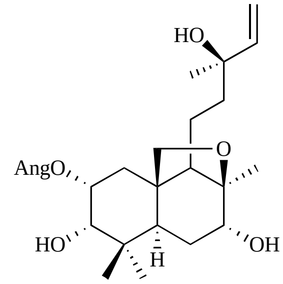

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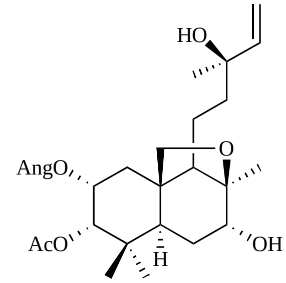

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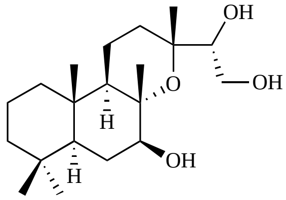

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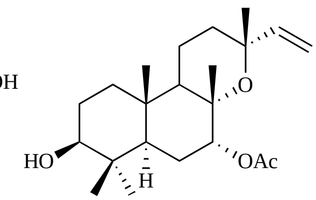

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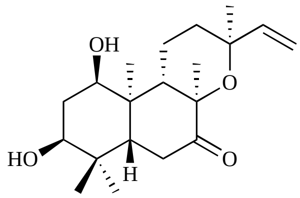

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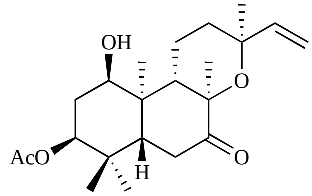

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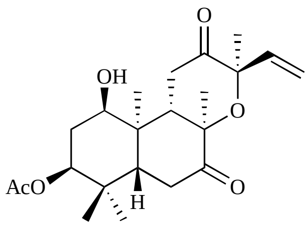

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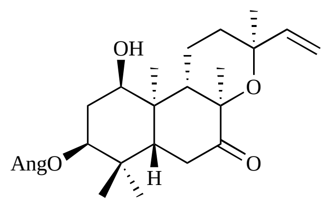

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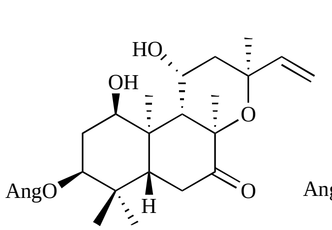

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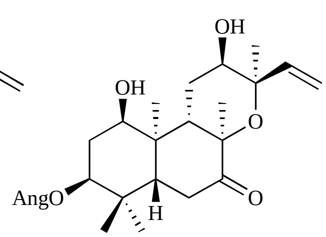

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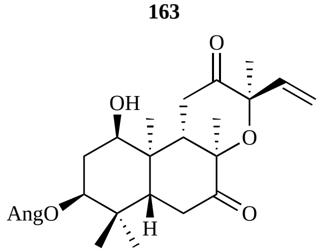

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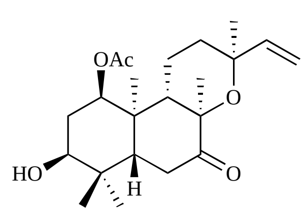

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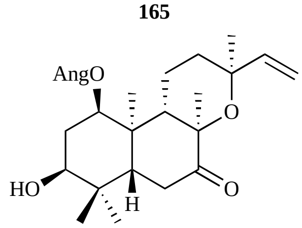

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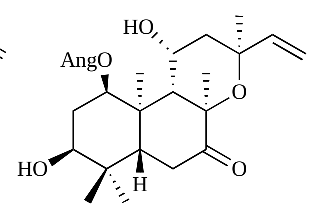

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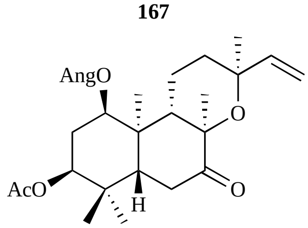

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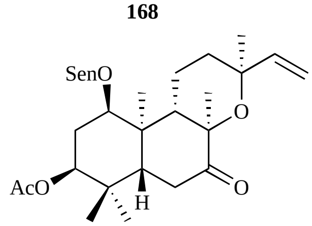

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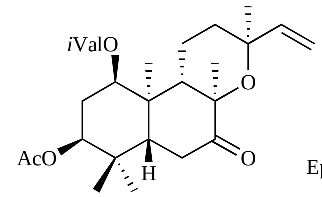

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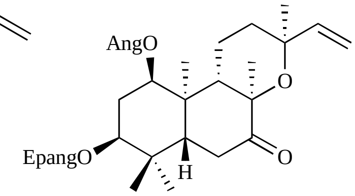

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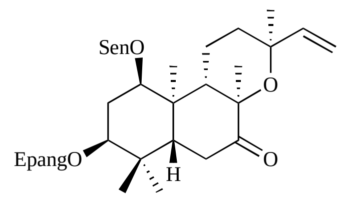

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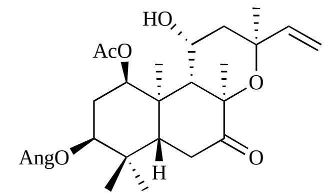

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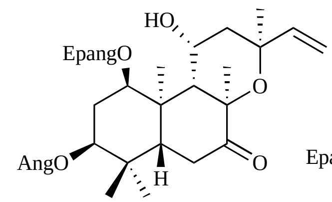

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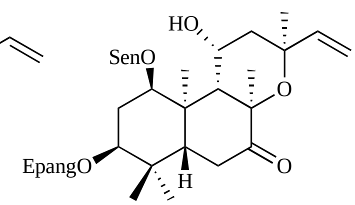

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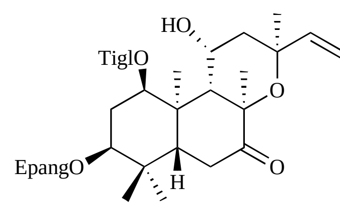

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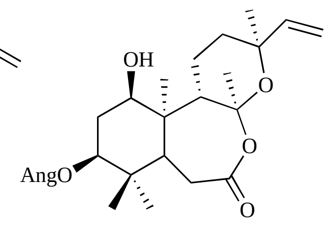

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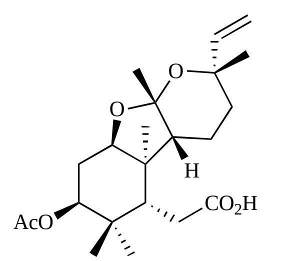

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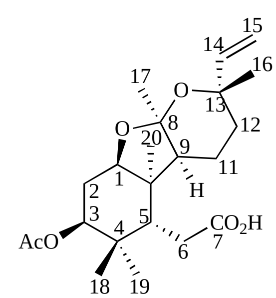

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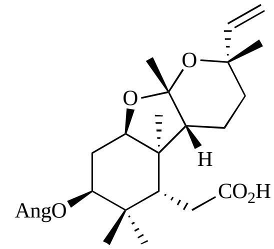

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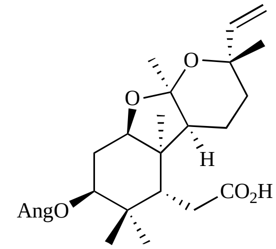

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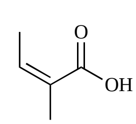
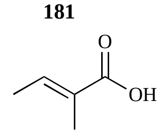
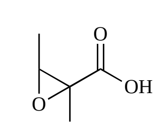


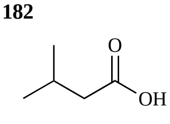
angelic acid (Ang-)



tiglic acid (Tigl-)



epoxyangelic acid (Epang-)

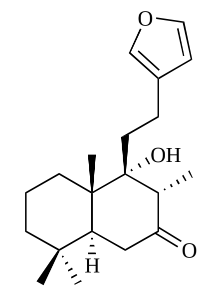


i-valerianic acid (i-Val-)

Table 7. 7, 8-Dioxygenated Labdanes

7,8-Dioxygenated Labdanes	Isolated From	Activity and References
145	*Aframomum sceptrum*	[88]
gymnospermin, 146	*Gymnosperma glutinosa*	[89]
sterebin D, 147	*Stevia rebaudiana*	[90]
148	*Porella perrottetiana*	[91]
149	*Nicotiana tabacum*	[92]
150	*Dodonaea lobulata*	[30]
151	*Koanophyllon conglobatum*	[29]
152	*Haplopappus parvifolius*	[4]
153	*Aframomum sceptrum*	[88]
154	*Aframomum sceptrum*	Trypanocydal activity, [88]
155	*Waitziz acuminata* Steetz	[93]
156	*Waitziz acuminata* Steetz	[93]
borjatriol, 157*	*Sideritis mugronensis*	[94, 95]
hamachilobene E, 158	*Frullania hamachiloba*	[96]
159	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
160	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
161	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
162	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
163	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
164	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
165	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
166	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
167	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
168	*Helichrysum ambiguum* Turcz. subsp. *Ambiguum*	[97]
169	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
170	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
171	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
172	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
173	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
174	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
175	*Helichrysum ambiguum Turcz. subsp. ambiguum*	[97]
176	*Helichrysum ambiguum Turcz. subsp. ambiguum*	[97]
177	*Helichrysum ambiguum Turcz. subsp. ambiguum*	[97]
178	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
179	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
180	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
181	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]
182	*Helichrysum ambiguum* Turcz. subsp. *ambiguum*	[97]

Group VI: 7, 9-Dioxygenated Labdanes



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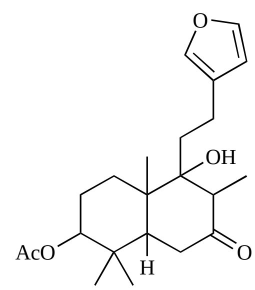

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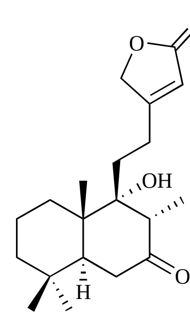

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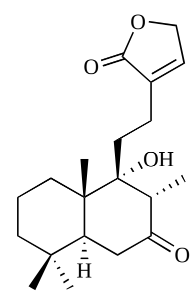

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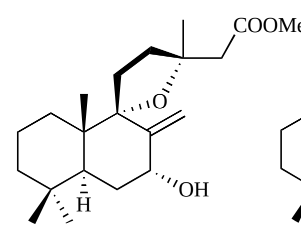

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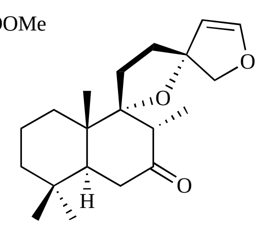

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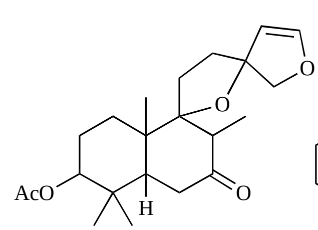

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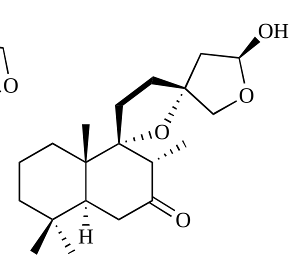

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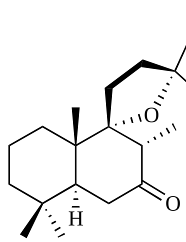

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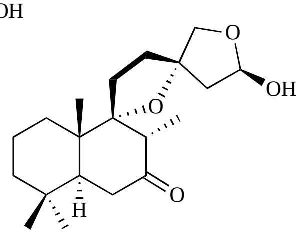

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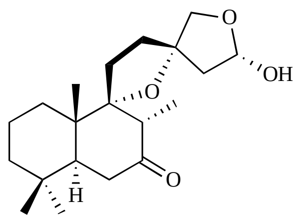
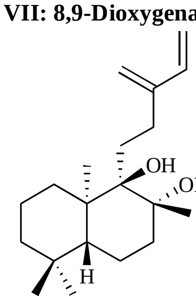


193

Table 8. 7,9-Dioxygenated Labdanes

7,9-Dioxygenated Labdanes	Isolated From	Activity and References
hispanolone, 183*	*Leonurus heterophyllus, Galeopsis angustifolia*	[98, 99]
calyone, 184	*Roylea calycina*	[100]
leopersin G, 185	*Leonurus persicus, Leonurus heterophyllus Sw*	[16, 101]
leoheteronin E, 186	*Leonurus heterophyllus Sw.*	[101]
187	*Grindelia camporum, Chrysothamnus paniculatus*	[71]
prehispanolone, 188*	*Leonurus heterophyllus*	Platelet activating factor (PAF) receptor antagonist, [98]
precalyone, 189	*Roylea calycina*	Antitumoural, [100]
leoheteronone B, 190	*Leonurus heterophyllus Sw*	[102]
15-epileoheteronone B, 191	*Leonurus heterophyllus Sw*	[102]
leoheteronone D, 192	*Leonurus heterophyllus Sw*	[102]
15-epileoheteronone D, 193	*Leonurus heterophyllus Sw*	[102]

Group VII: 8,9-Dioxygenated Labdanes



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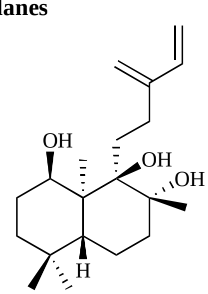

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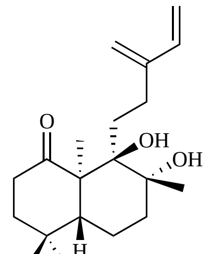

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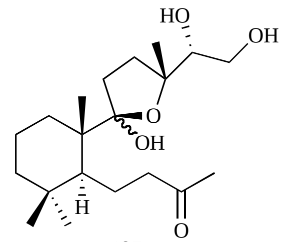
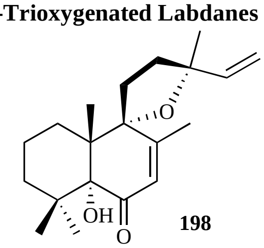


197

Table 9. 8,9-Dioxygenated Labdanes

8,9-Dioxygenated Labdanes	Isolated From	Activity and References
194	*Blepharostoma trichophyllum*	[103]
195	*Blepharostoma trichophyllum*	[103]
196	*Blepharostoma trichophyllum*	[103]
blepharizone, 197	*Blepharizonia plumosa*	[104]

Group VIII: 5,6,9-Trioxygenated Labdanes

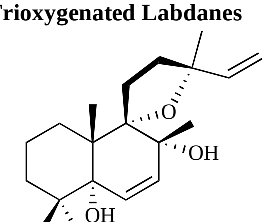


198

Table 10. 5,6,9-Trioxygenated Labdanes

5,6,9-Trioxygenated Labdanes	Isolated From	Reference
198	*Haplopappus parvifolius*	[4]

Group IX: 5,8,9-Trioxygenated Labdanes

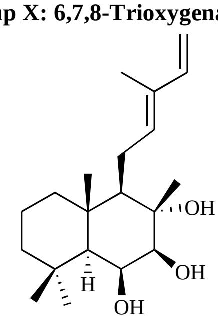


199

Table 11. 5,8,9-Trioxygenated Labdanes

5,8,9-Trioxygenated Labdanes	Isolated From	Reference
199	*Haplopappus parvifolius*	[4]

Group X: 6,7,8-Trioxygenated Labdanes



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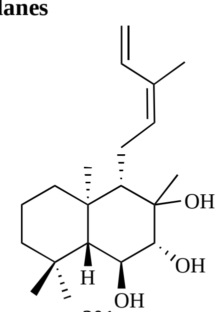

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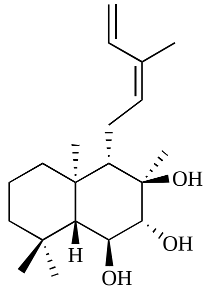

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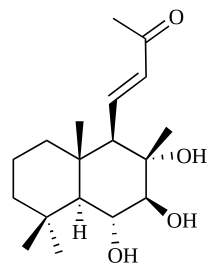

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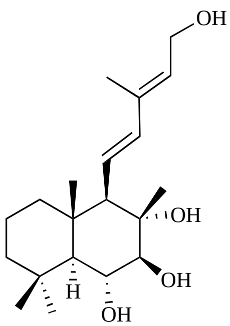

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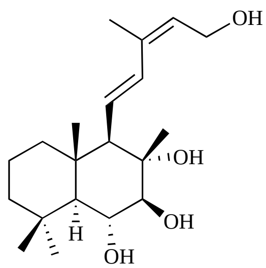

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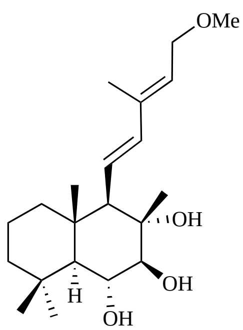

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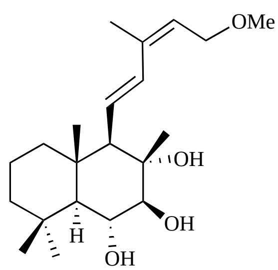

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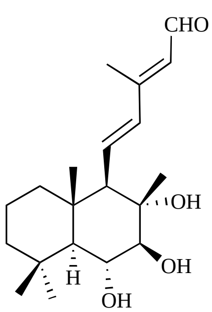

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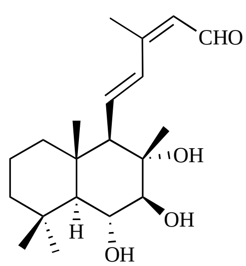

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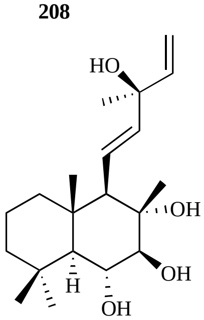

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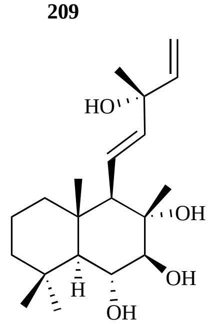

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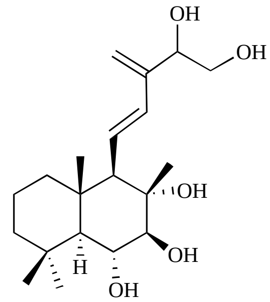

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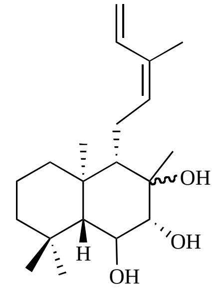

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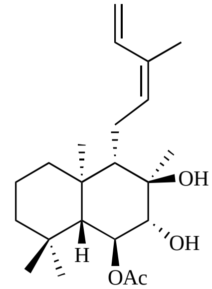

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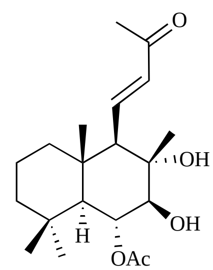

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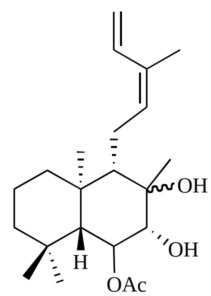

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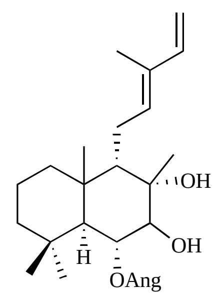

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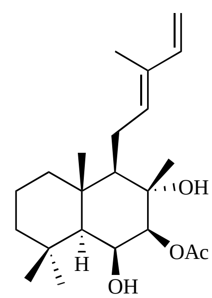

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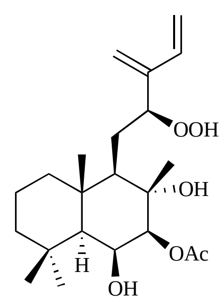

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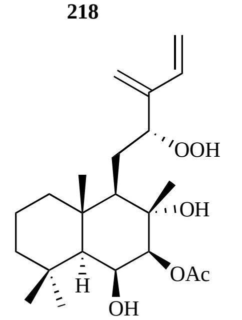

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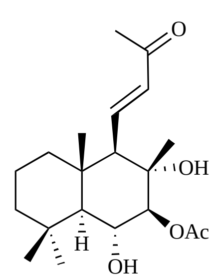

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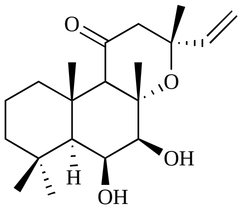
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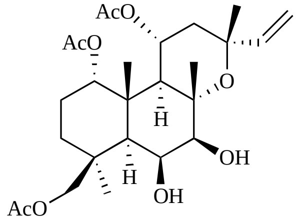
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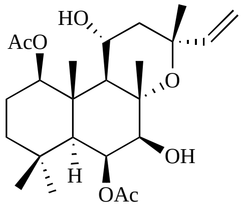
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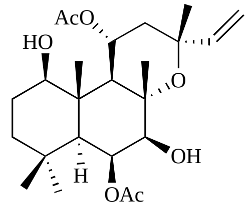
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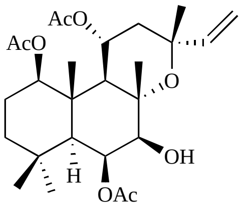
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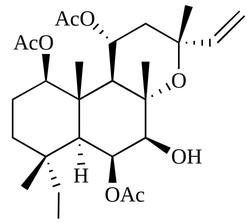
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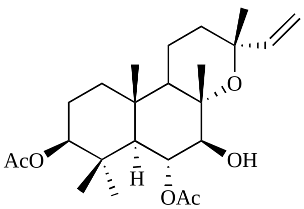
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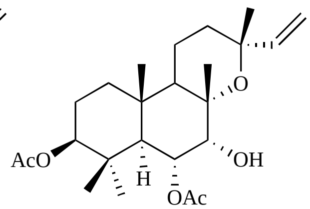
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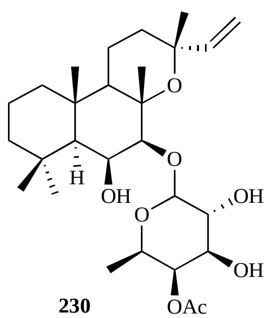
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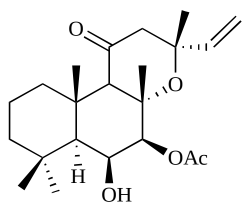
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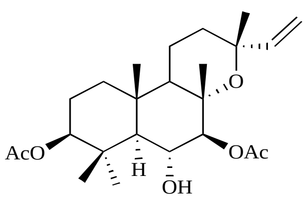
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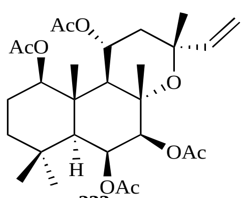
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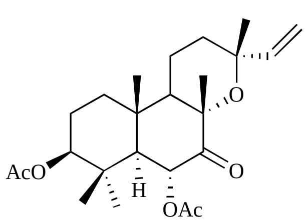
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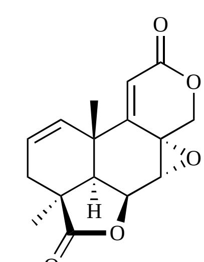
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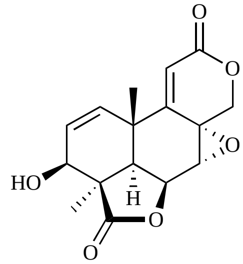
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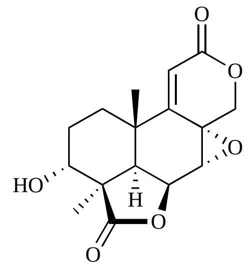
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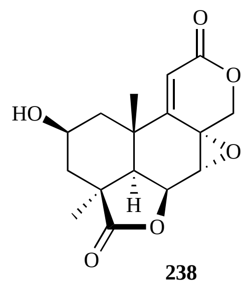
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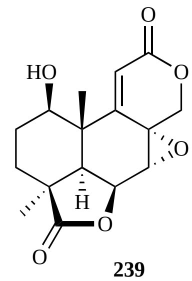
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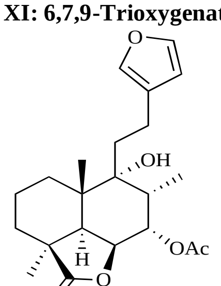
Table 12. 6,7,8-Trioxygenated Labdanes

6,7,8-Trioxygenated Labdanes	Isolated From	Activity and References
crotomachlin, 200*	*Koanophyllon conglobatum, Croton macrostachys*	Antilipoxygenase, [29, 105]
austroinulin, 201	*Austroeupatorium inulaefolium, Stevia rebaudiana*	[106, 107]
202	*Stevia aristata*	[108]
sterebin A, 203	*Stevia rebaudiana*	[90]
sterebin E, 204	*Stevia rebaudiana*	[109]
sterebin F, 205	*Stevia rebaudiana*	[109]
sterebin K, 206	*Stevia rebaudiana*	[109]
sterebin L, 207	*Stevia rebaudiana*	[110]
sterebin I, 208	*Stevia rebaudiana*	[110]
sterebin J, 209	*Stevia rebaudiana*	[110]
sterebin M, 210	*Stevia rebaudiana*	[110]
sterebin N, 211	*Stevia rebaudiana*	[110]
sterebin G/H, 212	*Stevia rebaudiana*	[109]
austroinulin, 213	*Austroeupatorium inlaefolium, Stevia rebaudiana*	[107]
austroinulin 7-O-acetate, 214	*Stevia berlandiera, Stevia aristata*	[108]
sterebin B, 215	*Stevia rebaudiana*	[90]
216	*Stevia rebaudiana*	[107]
6α-angeloyloxy nidorellol, 217	*Stevia monardaefolia*	[111]
218	*Koanophyllon conglobatum*	[29]
219	*Koanophyllon conglobatum*	[29]

Table 12. contd…..

6,7,8-Trioxygenated Labdanes	Isolated From	Activity and References
220	*Koanophyllon conglobatum*	[29]
sterebin C, 221	*Stevia rebaudiana*	[90]
222	*Coleus forskohlii*	[112]
ptychantin J, 223	*Ptychanthus striatus*	[113]
ptychantin E, 224	*Ptychanthus striatus*	[114]
ptychantin C, 225	*Ptychanthus striatus*	[114]
ptychantin A, 226	*Ptychanthus striatus*	[114]
ptychantin D, 227	*Ptychanthus striatus*	[114]
hamachilobene C, 228	*Frullania hamachiloba*	[96]
229	*Frullania hamachiloba*	[96]
ledebourene, 230	*Trollius ledebouri*	[115]
231*	*Coleus forskohlii*	Inhibit glucose transport in rat adipocites, [112]
hamachilobene D, 232	*Frullania hamachiloba*	[96]
ptychantin B, 233	*Ptychanthus striatus*	[114]
234	*Frullania hamachiloba*	[96]
235	*Sclerotinia homoeocarpa*	Herbicide, [116]
236	*Sclerotinia homoeocarpa*	Herbicide, [116]
237	*Sclerotinia homoeocarpa*	Herbicide, [116]
238	*Sclerotinia homoeocarpa*	Herbicide, [116]
239	*Sclerotinia homoeocarpa*	Herbicide, [116]

Group XI: 6,7,9-Trioxygenated Labdanes



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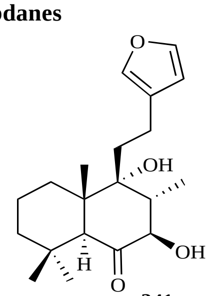

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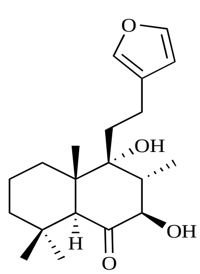

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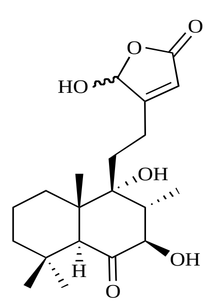

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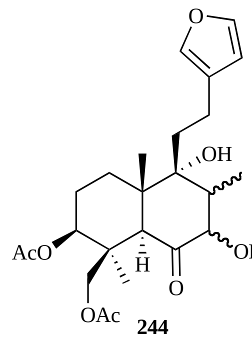

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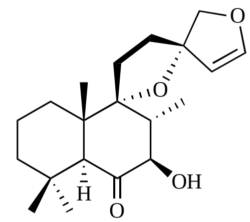

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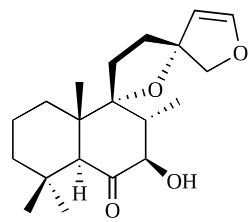

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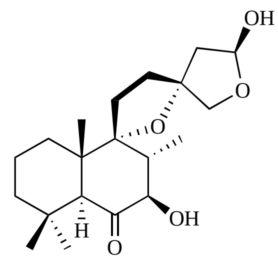

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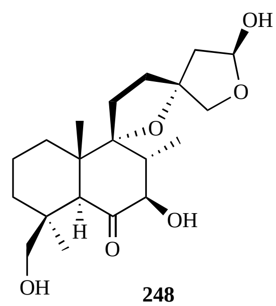

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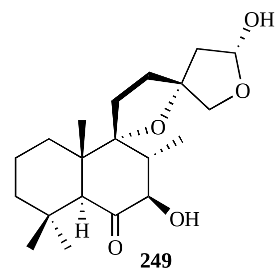

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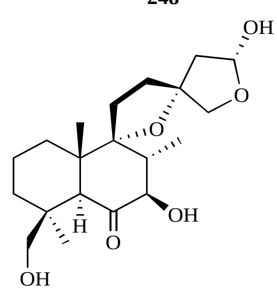

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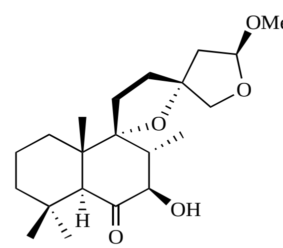

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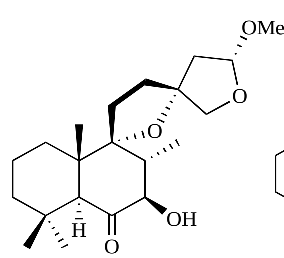

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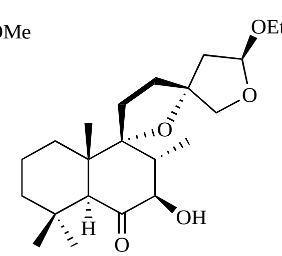

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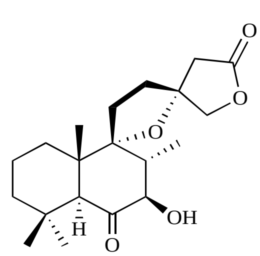

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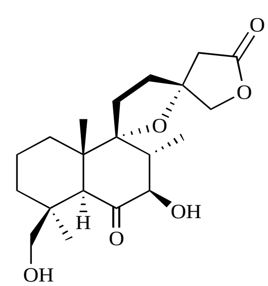

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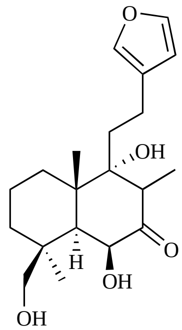
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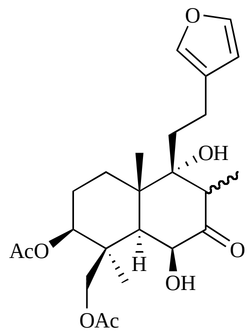
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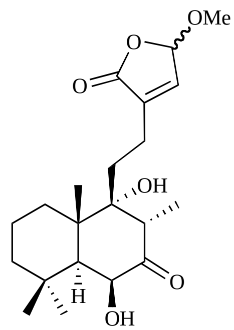
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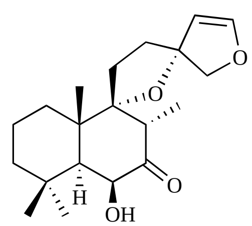
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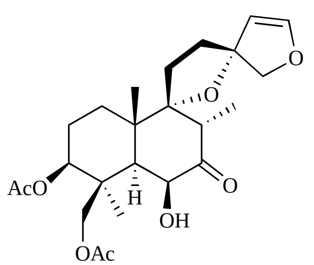
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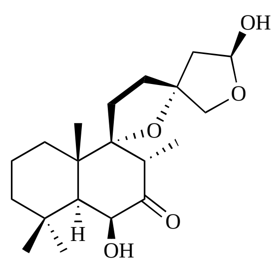
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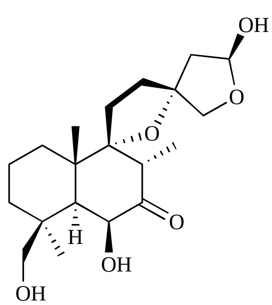
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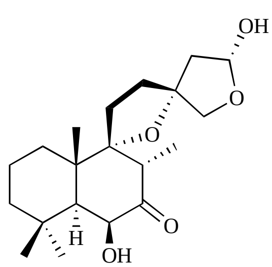
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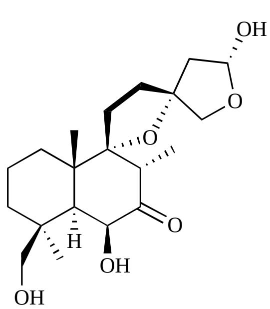
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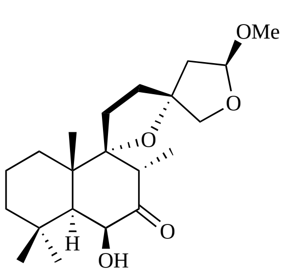
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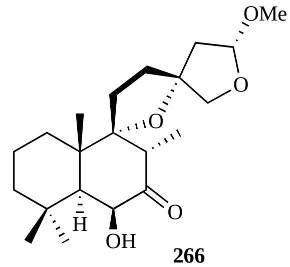
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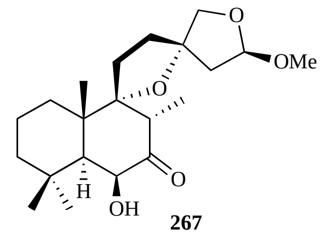
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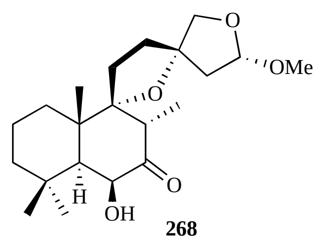
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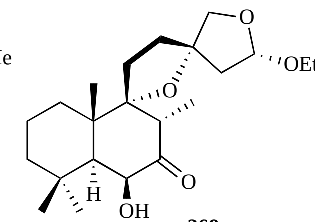
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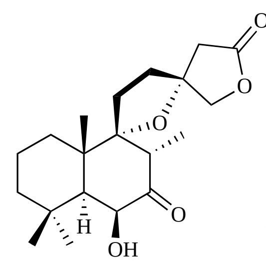
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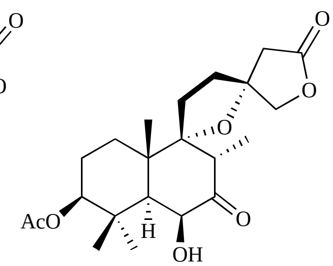
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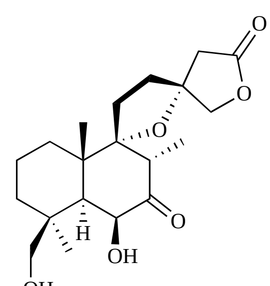
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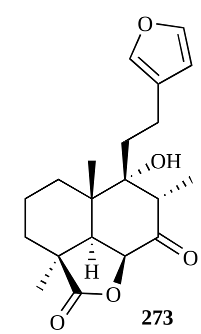
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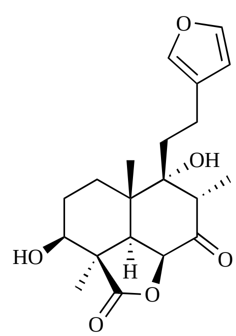
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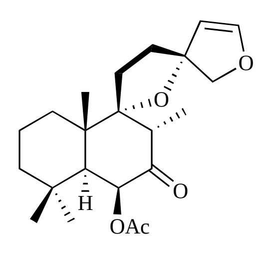
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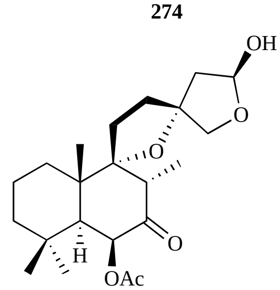
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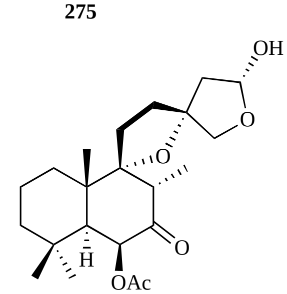
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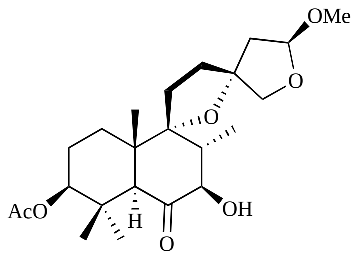

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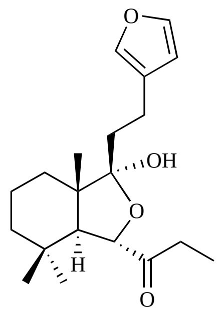

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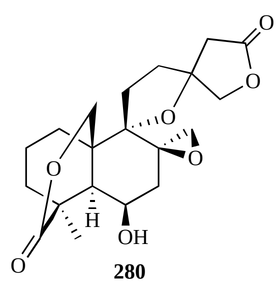
Table 13. 6,7,9-Trioxygenated Labdanes

6,7,9-Trioxygenated Labdanes	Isolated From	Activity and References
7α-acetoxymarrubin, 240	*Ballota nigra*	[21]
leoheterin, 241*	*Leonurus heterophyllus, Otostegia fructicosa*	[117, 101, 23]
242	*Ballota aucheri*	[27]
sibiricinone A, 243*	*Leonurus sibiricus*	[17]
isoleosibirin, 244	*Leonurus sibiricus*	[118]
epi-preleoheterin, 245	*Ballota aucheri, Leonurus japonicus*	[27, 26]
preleoheterin, 246	*Leonurus heterophyllus, Otostegia fructicosa*	Platelet activating factor (PAF) receptor antagonist, [117, 23]
leopersin C, 247	*Leonurus persicus, Otostegia fructicosa, Leonurus heterophyllus Sw.*	[119, 23, 120]
leopersin O, 248	*Leonurus persicus*	[121]
15-epi-leopersin C, 249	*Leonurus persicus, Otostegia fructicosa, Leonurus heterophyllus Sw.*	[119, 120, 23]
15-epi-leopersin O, 250	*Leonurus persicus*	[121]
15-O-methylleopersin C, 251	*Leonurus cardiaca*	Antiplasmodic, [122]
15-epi-O-methylleopersin C, 252	*Leonurus cardiaca*	Antiplasmodic, [122]
15-O-etillopersin C, 253	*Leonurus cardiaca*	Antiplasmodic, [122]
leopersin D, 254*	*Leonurus persicus*	[119]
leopersin P, 255	*Leonurus persicus*	[121]
ballotenol, 256	*Ballota nigra, Leonurus persicus*	[123, 16]
leosibirin, 257	*Leonurus sibiricus*	[118]
sibiricinone C, 258	*Leonurus sibiricus*	[17]
iso-preleoheterin, 259	*Leonurus japonicus*	[26]
preleosibirin, 260	*Ballota nigra*	[124]
leopersin J, 261	*Leonurus persicus*	[16]
leopersin Q, 262	*Leonurus persicus*	[121]
15-epi-leopersin J, 263	*Leonurus persicus*	[16]
15-epi-leopersin Q, 264	*Leonurus persicus*	[121]
15-epi-sibiricinone D, 265	*Leonurus sibiricus*	[17]
sibiricinone D, 266	*Leonurus sibiricus*	[17]
15-epi-sibiricinone E, 267	*Leonurus sibiricus, Ballota aucheri*	[17, 27]
sibiricinone E, 268	*Leonurus sibiricus, Ballota aucheri*	[17, 27]
269	*Ballota aucheri*	[27]
leopersin K, 270	*Leonurus persicus*	[16]
leopersin M, 271	*Leonurus persicus*	[121]
leopersin H, 272	*Leonurus persicus*	[16]
ballotinone, 273	*Ballota nigra, Ballota aucheri, Ballota undulata*	[124, 27, 24]
3β-hydroxyballotinone, 274	*Ballota undulata*	[24]
otostegin A, 275	*Otostegia fructicosa*	[23]
15-epi-otostegin B, 276	*Otostegia fructicosa*	[23]
otostegin B, 277	*Otostegia fructicosa*	[23]
278	*Leonurus japonicus*	[125]
279	*Ballota aucheri*	[15]

Group XII: 6,8,9-Trioxygenated Labdanes



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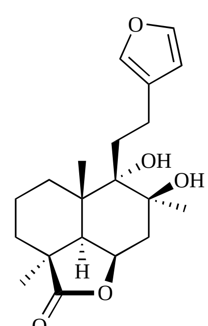

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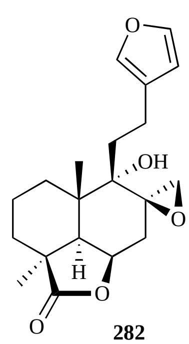

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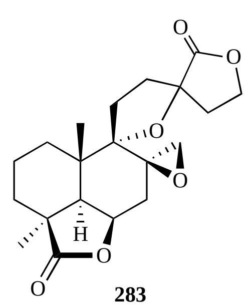

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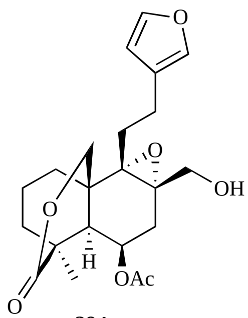

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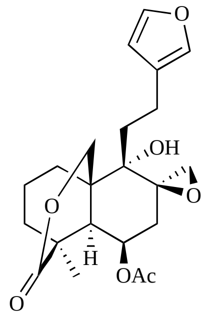

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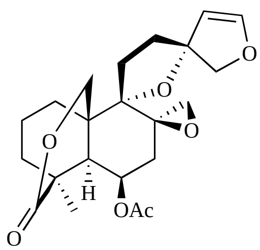

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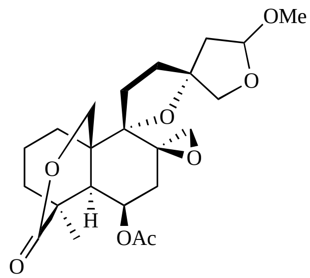

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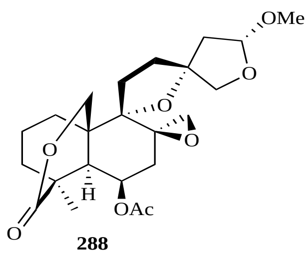

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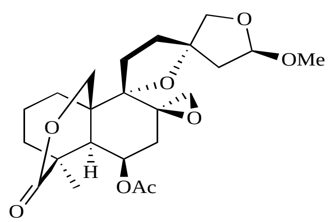

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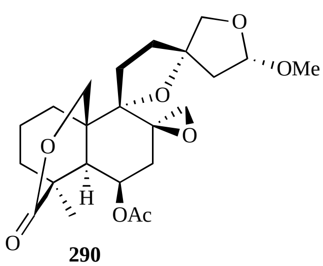

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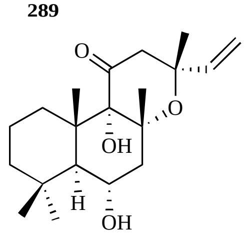

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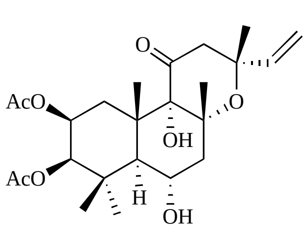

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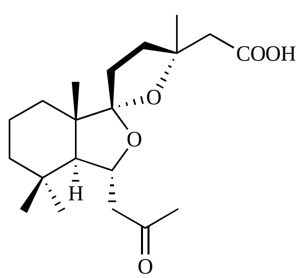
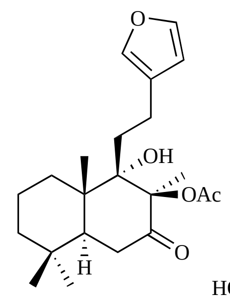


293

Table 14. 6,8,9-Trioxygenated Labdanes

6,8,9-Trioxygenated Labdanes	Isolated From	Reference
nepetaefolinol, 280	*Leonotis nepetaefolia*	[74]
leonotin, 281	*Leonotis nepetaefolia*	[126]
leotiinin, 282	*Leonotis nepetaefolia*	[74]
283	*Leonotis nepetaefolia*	[74]
284	*Leonotis nepetaefolia*	[127]
nepetaefuran, 285	*Leonotis nepetaefolia*	[127]
nepetaefolin, 286	*Leonotis nepetaefolia*	[127]
methoxynepetaefolin, 287	*Leonotis nepetaefolia*	[128]
methoxynepetaefolin, 288	*Hyptis fasciculote*	[128, 129]
15β-methoxyfaciculatin, 289	*Hyptis fasciculate*	[129]
15α-methoxyfaciculatin B, 290	*Hyptis fasciculate*	[129]
coleosol, 291	*Coleus forskohlii*	[130]
excolabdone A, 292	*Excoecaria cochinchinensis*	[131]
chrysothame, 293	*Chrysothamnus paniculatus*	[85]

Group XIII: 7,8,9-Trioxygenated Labdanes



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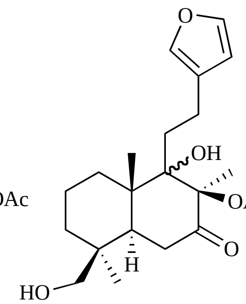

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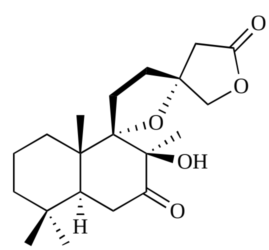

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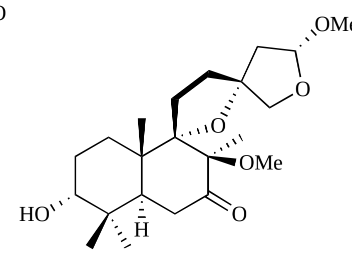

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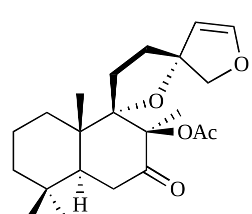

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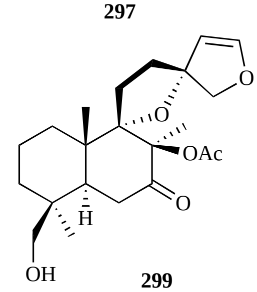

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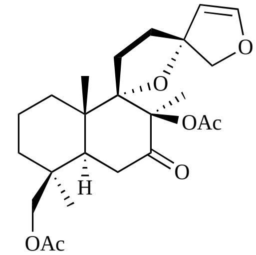

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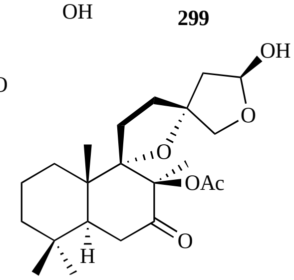

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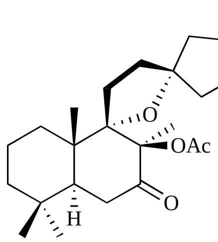

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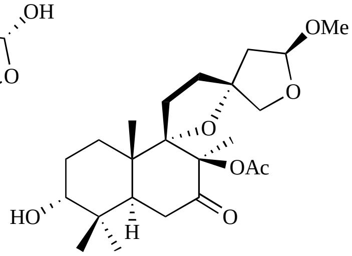

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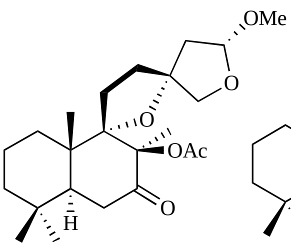

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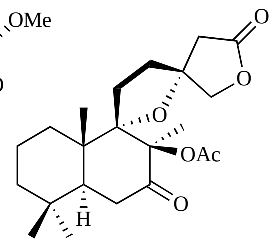

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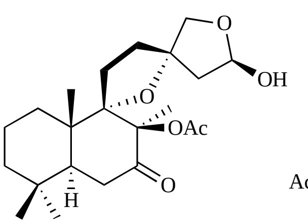

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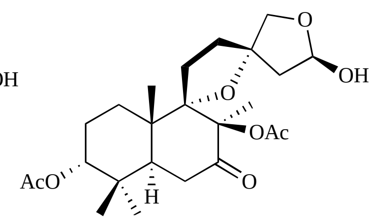

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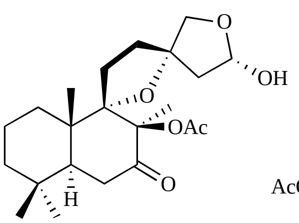

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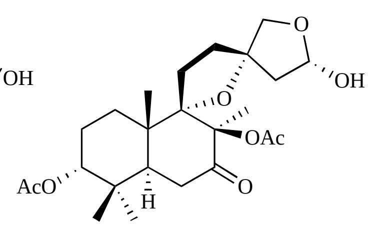

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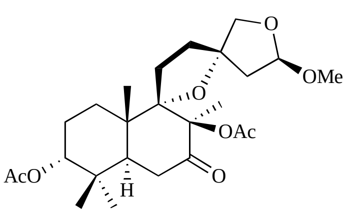

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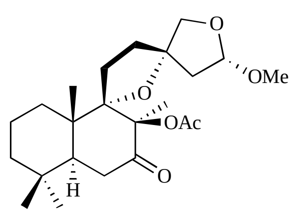

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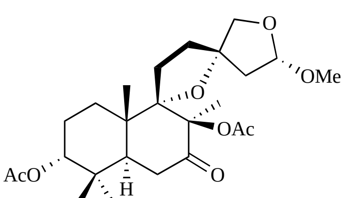

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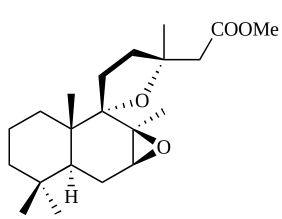

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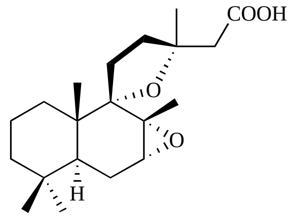

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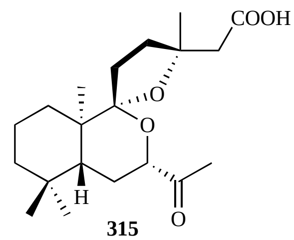
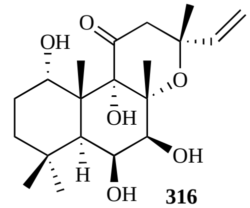


315

Table 15. 7,8,9-Trioxygenated Labdanes

7,8,9-Trioxygenated Labdanes	Isolated From	Refs.
galeopsin, 294	*Galeopsis angustifolia, Leonurus heterophyllus, Leonurus persicus*	[99, 98, 132, 102]
19-hydroxygaleopsin, 295	*Leonurus persicus, Leonurus cardiaca*	[42, 133]
8-deacetoxyleopersin A, 296	*Leonurus persicus*	[132]
3α-hydroxyleoheteronone A, 297	*Leonurus sibiricus*	[134]
pregaleopsin, 298	*Galeopsis angustifolia, Leonurus persicus*	[99, 132]
4β-hydroxymethylpregaleopsin, 299	*Leonurus persicus*	[132]
19-acetoxypregaleopsin, 300	*Leonurus cardiaca*	[135]
leopersin B, 301	*Leonurus persicus, Leonurus heterophyllus Sw.*	[132, 102]
15-epi-leopersin B, 302	*Leonurus persicus, Leonurus heterophyllus Sw.*	[132, 102]
leosibirinone B, 303	*Leonurus sibiricus*	[134]
leoheteronone A, 304	*Leonurus heterophyllus Sw*	[102]
leopersin A, 305	*Leonurus persicus*	[132]
leoheteronone E, 306	*Leonurus heterophyllus Sw*	[102]
3α-acetoxyleoheteronone E, 307	*Leonurus sibiricus*	[134]
15-epileoheteronone E, 308	*Leonurus heterophyllus Sw*	[102]
3α-acetoxy-15-epileoheteronone E, 309	*Leonurus sibiricus*	[134]
leosibirinone A, 310	*Leonurus sibiricus, Leonurus japonicus*	[134, 125]
leoheteronone C, 311	*Leonurus heterophyllus Sw*	[102]
3α-acetoxyleoheteronone C, 312	*Leonurus sibiricus*	[134]
313	*Grindelia camporum, Chrysothamnus paniculatus*	[71]
314	*Grindelia robusta*	[136]
camporic acid, 315	*Grindelia camporum*	[137]

Group XIV: 6,7,8,9-Tetraoxygenated Labdanes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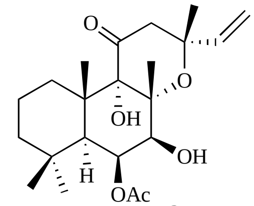
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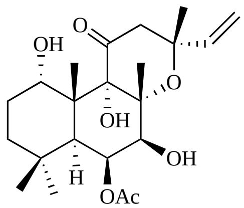
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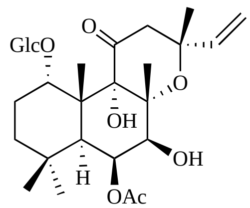
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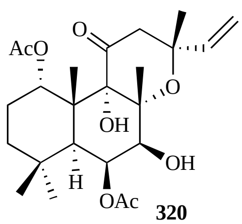
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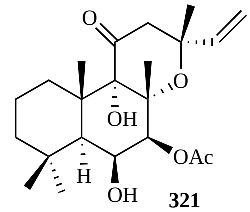
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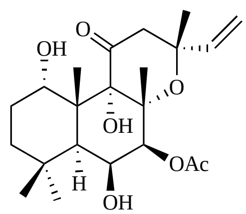
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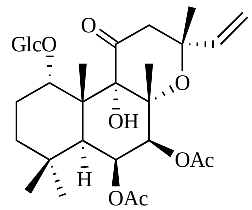
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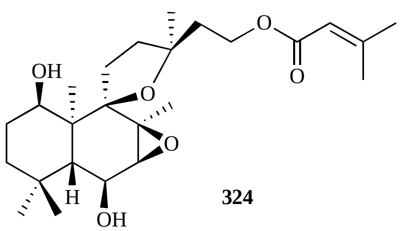
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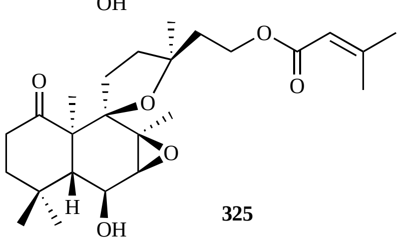
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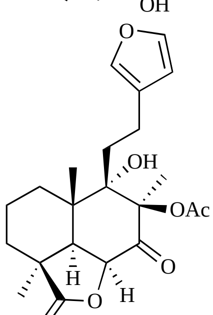
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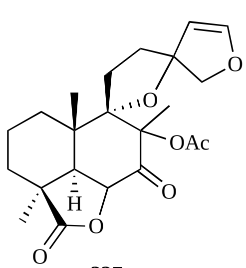
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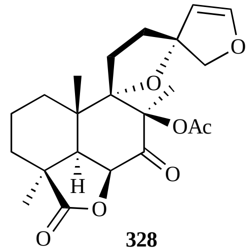
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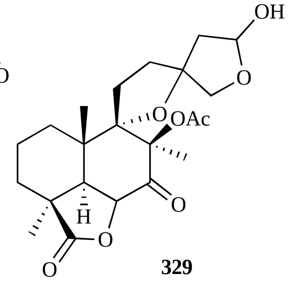
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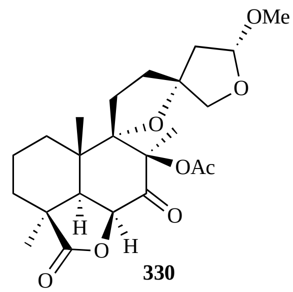
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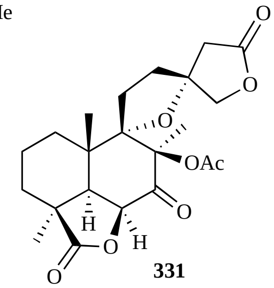
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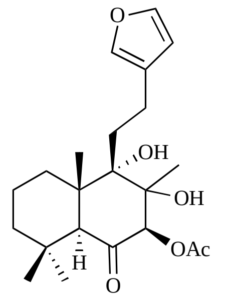
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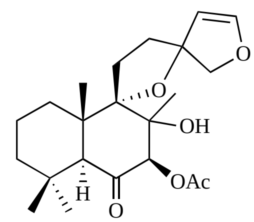
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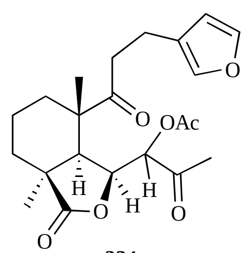

334

Table 16. 6,7,8,9-Tetraoxygenated Labdanes

6,7,8,9-Tetraoxygenated Labdanes	Isolated From	Activity and References
316	*Coleus forskohlii*	[112]
coleonol F, 317	*Coleus forskohlii*	[138]
isoforskolin o excolabdane C, 318	*Coleus forskohlii, Excoecaria cochinchinensis*	[112, 131]
forskoditerpenoxide A, 319	*Coleus forskohlii*	Relaxative effect, [139]
excolabdone B, 320	*Excoecaria cochinchinensis*	[131]
1-deoxyforskolin, 321	*Coleus forskohlii*	[140]
forskolin, 322*	*Coleus forskohlii*	Cardioactive, hypotensive, broncospasmolitic and adenilate ciclase stimulant, [112]

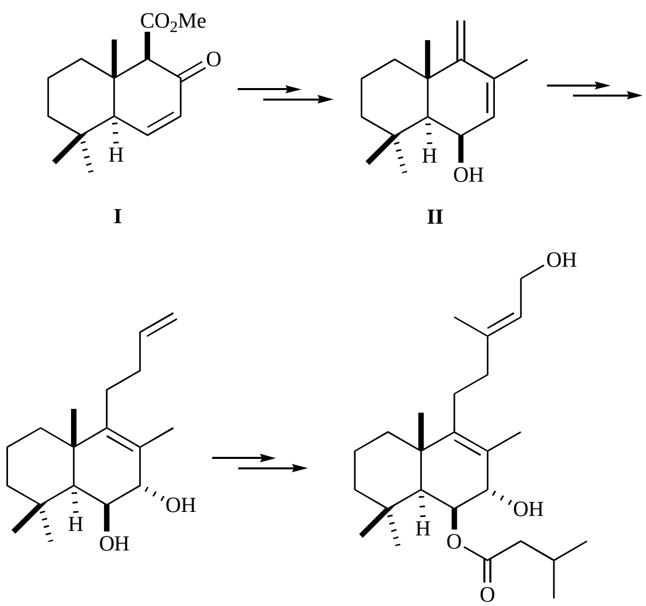
Table 16. contd…..

6,7,8,9-Tetraoxygenated Labdanes	Isolated From	Activity and References
forskoditerpenoxide B, 323	*Coleus forskohlii*	Relaxative effect, [139]
erigerol, 324*	*Erigeron philadelphicus*	[141]
phyladelphinone, 325	*Erigeron philadelphicus*	[142]
leopersin E, 326	*Leonurus persicus*	[119]
leosibiricin, 327	*Leonurus sibiricus, Otostegia fructicosa, Leonurus heterophyllus Sw.*	[118]
328	*Leonurus persicus*	[132]
leocardicin, 329	*Leonurus cardiaca*	[143]
leopersin N, 330	*Leonurus persicus*	[121]
leopersin I, 331	*Leonurus persicus*	[16]
galeuterone, 332	*Galeopsi reuteri*	[144]
pregaleuterone, 333	*Galeopsi reuteri*	[144]
leopersin F/epi-leopersin F, 334	*Leonurus persicus*	[119]

Finally the synthesis carried out until now, for the compounds shown in the previous classification ar described.

Synthesis of 4

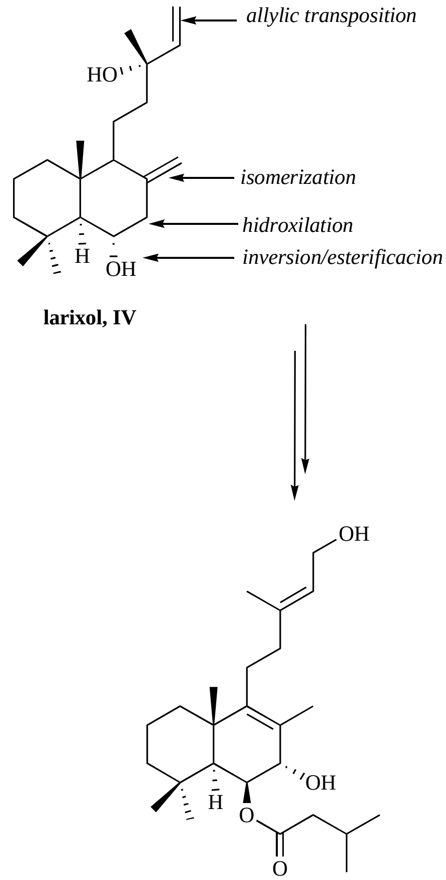
The first synthesis of **(±)-4** was carried out by Gao *et al*. [145] (Scheme **1**) starting from β-ionone, using as key intermediate enone **I**, and with standard transformations was elaborated the hydroxyderivative **II**. Transformation of **II** into **III** that has the required two oxygenated functionalities on the B ring was done by treatment with NBS in AcOH, followed by methanolysis and reaction with allyl cuprate. The side chain was completed by Wacker oxidation followed by HWE olefination. Finally, by protection, esterification and deprotection **(±)-4** was achieved.



III **(±)-4**

Scheme 1. Synthesis of (±)-4 by Gao *et al.*

C. Morin *et al*. [146] achieved the first synthesis of the natural product **(+)-4** establishing the absolute configuration. The synthesis has 7 steps using as starting material (+)-larixol and as key steps the shown in Scheme **2**. The annular double bond isomerization was done by amide treatment. Inversion at C-6 was carried out by oxidation-reduction and the esterification was done in the first steps using isovalerianic acid chloride. The allylic oxidation with SeO_2 took place in a stereoselective manner. The diester was submitted to Pd(II)-catalyzed rearrangement and ulterior hydrolysis gave (+)-4.



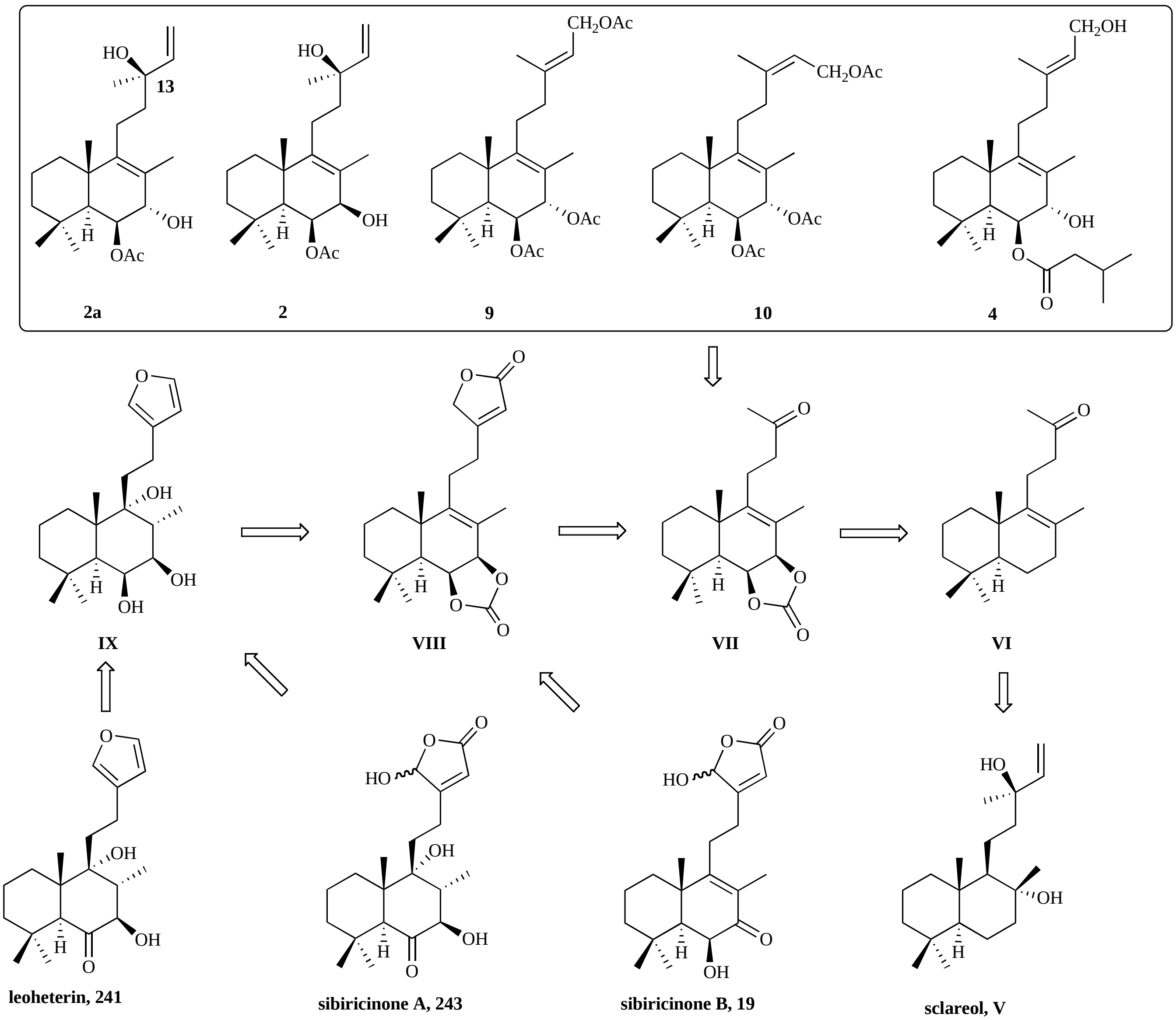
(+)-4

Scheme 2. Synthesis of (+)-4 by Morin *et al.*

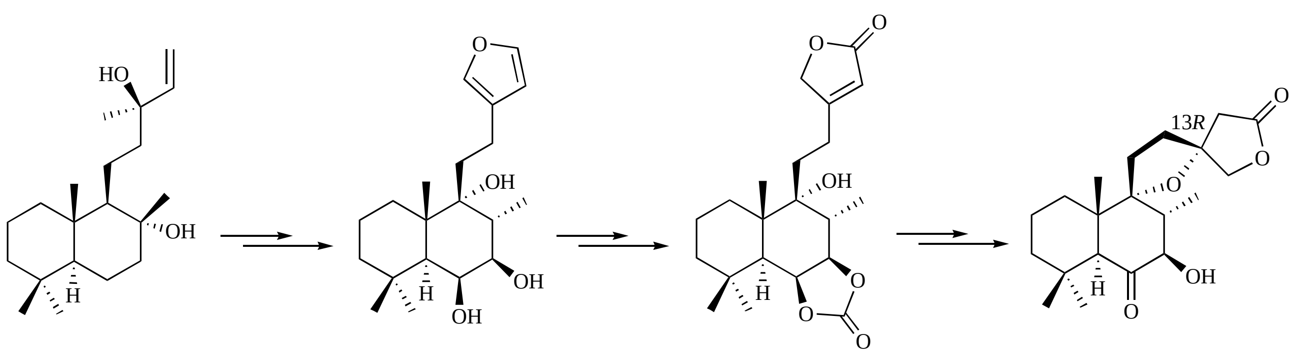
Synthesis of 2, 4, 9, 10, 19, 242 and 243

The synthesis of **2**, **4**, **9** and **10**, and **2** epimer, **2a**, was carried out according to the retrosynthetic Scheme **3**, using sclareol as starting material [147, 148]. The key intermediate is ketone **VII** that has oxygenated functionalities on C-6 and C-7 and comes from ketone **VI** widely used in sclareol chemistry [149]. The side chain was completed from **VII** having control of C-13 configuration by Sharpless reaction and finally by selective esterification was obtained **2**. In this manner was checked that the structure of the natural product isolated from *Haplopappus parvifolius* was not **2**, because of the natural product properties were identical to **2a**, the epimer of **2** in C-7. The stereochemistry in C-13 of **2a** was stablished by asymmetric addition of vinylbromide in presence of (+) and (-)-TADDOL [147].

The syntheses of **4**, **9** and **10** from **VII** need to complete the side chains with *E* or *Z* double bonds, that was achieved by Wittig or HWE methodology and the adequate esterification of the different hydroxy groups [147]. From compound **VII** it was synthesize lactone **VIII** and furane **IX** to achieve the synthesis of **19**, **241** and **243** [148]. The oxidation of **VII** with lead tetracetate and $BF_3{\cdot}Et_2O$ was functionalized C-16, needed for the synthesis of **VIII**. The lactone ring was prepared by Bestmann ketene addition to the corresponding hydroxyketone. Following Faulkner



Scheme 3. Retrosynthesis of 2, 2a, 4, 9, 10, 19, 242 and 243 by Marcos *et al*.



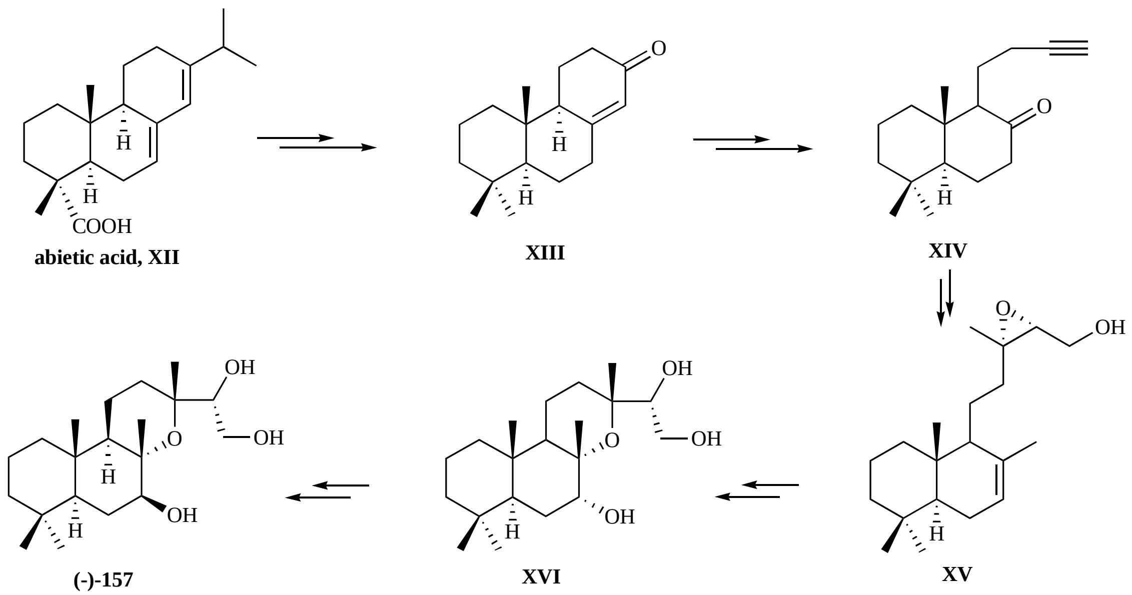
sclareol, V X XI (+)-254

Scheme 4. Synthesis of leopersin D by Marcos *et al*.

methodology by deprotection, MnO_2 and $^1O_2$ oxidation led to the γ-hidroxibutenolide sibiricinone B **19**. Epoxidation of **VIII** permits after reduction the furane **IX**, that already have and hydroxyl at C-9. Standard reactivity gave the final products (+)-leoheterin **241** and (+)-sibiricinone A **243**.

Synthesis of leopersin D, 254

The synthesis of leopersin D **254** (Scheme **4**) has as a key intermediate triol **X**, used among others in sibiricinone A synthesis [150]. This intermediate by standard modifications permits to obtain butenolide **XI** that by cyclization with acids or bases gave



Scheme 5. Synthesis of borjatriol, (-)-**157**, by Abad *et al*.

the dioxospirane present in the natural product. Deprotection, selective esterification and oxidation led to (+)-leopersin D **254**, establishing in this way the absolute configuration of the natural compound.

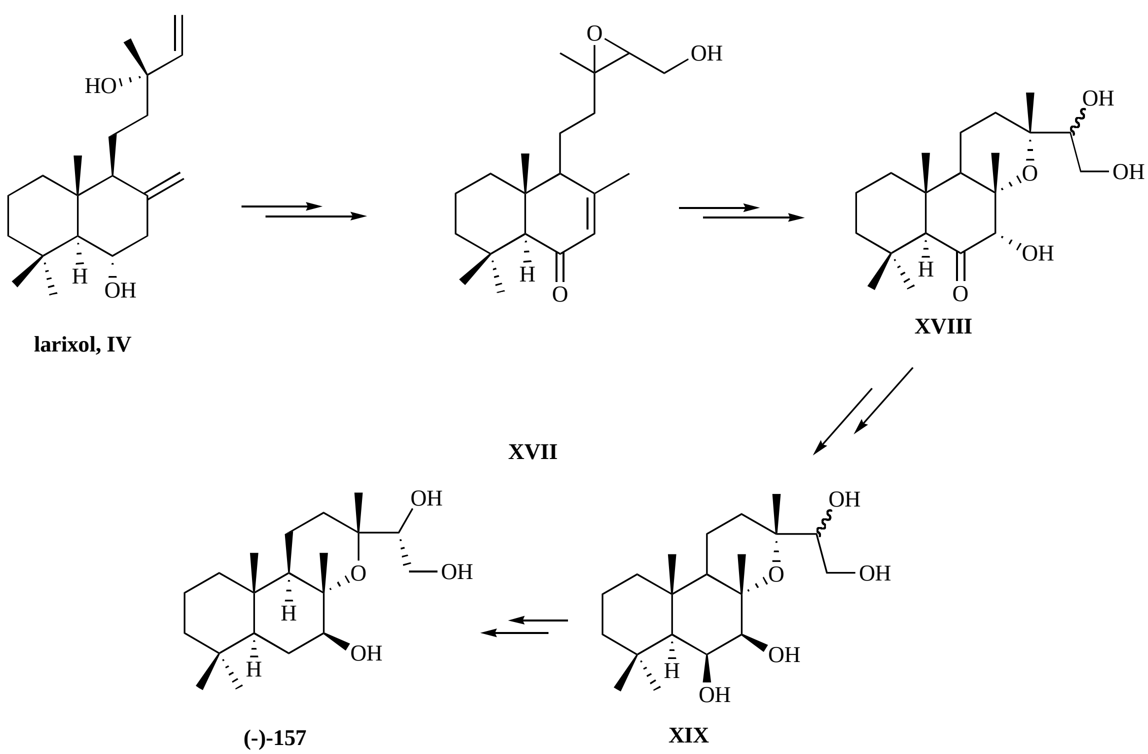
Synthesis of borjatriol, 157

Abad and col synthesized borjatriol (Scheme **5**) from enone **XIII**, obtained from abietic acid [151]. The transformation of the tricyclic system into ketone **XIV** was achieved by Eschenmoser fragmentation of the epoxy-ketone resulting of the treatment of **XIII** $TsNHNH_2$. The side chain was completed by methoxycarbonylation followed by lithium dimethycluprate addittion and the configuration control was done by Sharpless asymmetric epoxidation. The cyclization to obtain ring C was done by regioselective intramolecular epoxide ring opening. The inversion at C-7 by an oxidation-reduction process after a properly chain protection, and followed by deprotection, gave borjatriol (-)-**157.**

For the synthesis of borjatriol (Scheme **6**), Herlem *et al.* used starting material larixol, **IV** [152]. The required epoxide in the side chain needed for the synthesis of the pyran ring was achieved by Payne rearrangement obtaining **XVII**. Later the oxygenated functionalities of C-7 and C-8 positions were introduced and by cyclization in acidic media intermediate **XVIII** was obtained. From this later intermediate was elaborated the adequate functionalization at C-7 and C-14 with the required configuration.

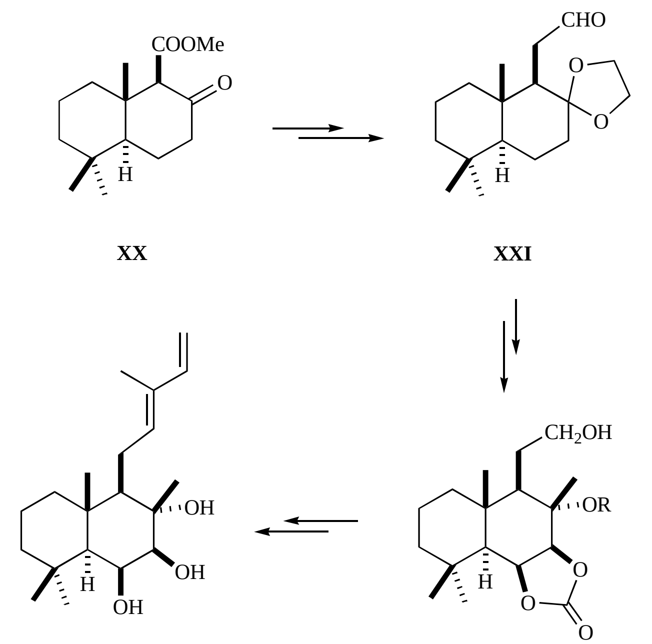
Synthesis of crotomachlin, 200

Herlem *et al.* use ketone **XX** obtained from β-ionone or geraniol for the synthesis of crotomachlin **(±)-200** (Scheme **7**)



Scheme 6. Synthesis of borjatriol, **(-)-157**, by Herlem *et al*.

[153]. Standard transformations, that include cyanide addition to α,β-unsaturated carbonyl, reduction of the nitrile and protection gave intermediate **XXI**. From this intermediate, an enone was elaborated, compound that is adequate to introduce the required oxygenated functionalities in ring B, obtaining in this way intermediate **XXII**. Finally was elaborated the diene of the side chain by Wittig olefinations, achieving in this manner **(±)-200** establishing the structure of cromachlin and its C-8 configuration.



Scheme 7. Synthesis of crotomachlin, **200**, by Herlem *et al*.

Synthesis of forskolin, 322

Until now, there are four total synthesis of forskolin [154] and many advanced intermediates and synthetic approaches. For an excellent review of the synthesis of forskolin, see reference 154.

The first complete synthesis was reported by Ziegler *et al*. [155], Scheme **8**, using lactone **XXIV** as intermediate that was obtained by Diels-Alder of diene **XXIII**. Transformation of **XXIV** into dihydropirane **XXVII** requires reduction of lactone **XXIV**, selective acetylation, stereoselective dihydrohydroxylation, to install the rest of the oxygenated functionalities in the B ring of the intermediate **XXV**. Protection deprotection, followed by C-11 oxidation and 1-litiopropine addition, oxidation and deprotection gave intermediate **XXVI**, which was cyclized in basic conditions to give **XXVII**. Transformation of **XXVII** into forskolin requires addition of higher-order vinyl cuprate in the presence of a large excess of boron trifluoride. Finally, after several manipulations of the functional groups **(±)-322** was obtained.

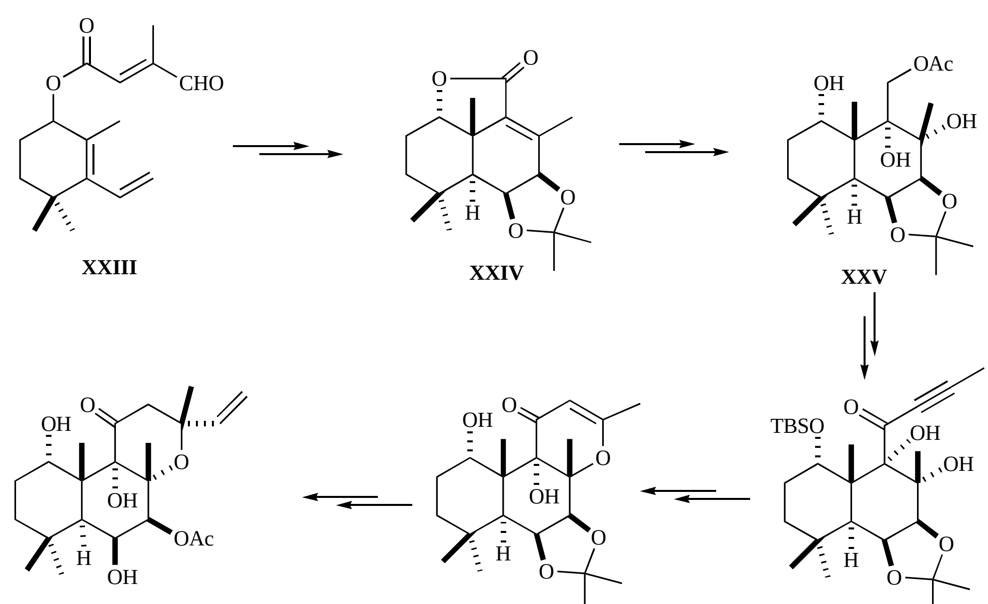
Ikegama *et al.* [156], Scheme **9**, utilized as key intermediate Ziegler lactone **XXIV**, but in this case, the Diels-Alder reaction gave simultaneously both A and B rings of the natural product. The synthesis started with a 2,2-dimethylglutarate derivative that is transformed into lactone **XXVIII** by routine transformations. Cis-dihydroxylation of **XXIX** took place by the α side, so it was necessary to invert the configuration at C-6 and C-7 by a oxidation-reduction of the corresponding 6,7-diketone. Next was completed the **XXIV** formation. The pyran ring was obtained in this case by organoselenium chemistry.

In Corey *et al.* synthesis [157, 158], Scheme **10**, the key step is a Diels-Alder reaction as well. In this case, a cyclocitral derivative was used, that finally rendered Ziegler lactone, **XXIV**, using the endoperoxide **XXXIII**, as intermediate. The Corey´s strategy for the elaboration of the C ring is quite different as endoperoxide **XXXIV** was used as intermediate to obtain **XXXV.** In this process it was necessary the stereoselective addition of a methyl at C-13 by the adequate organometallic. Finally, by adequate tuning of the functional groups forskolin **332** was obtained.

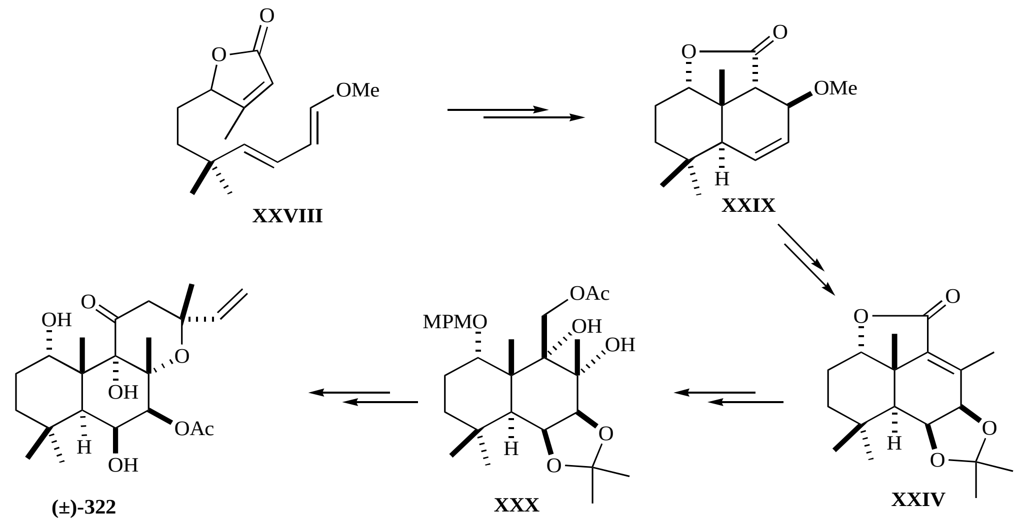
Lett *et al*. Synthesis [159-161], Scheme **11**, made use of the key intermediate aldehyde **XXXIX**. The bicyclic system required a Diels-Alder reaction that led to diene **XXXVII**, from which **XXXVIII** obtained. The C ring was achieved using an intramolecular Michael reaction in a propargylic derivative of **XXXIX**. The addition of the vinylcuprate to intermediate **XXXIX** completed the carbon skeleton and after adequation of the functional groups, forskolin **(±)-322** was obtained.

Synthesis of 231 and forskolin, 322

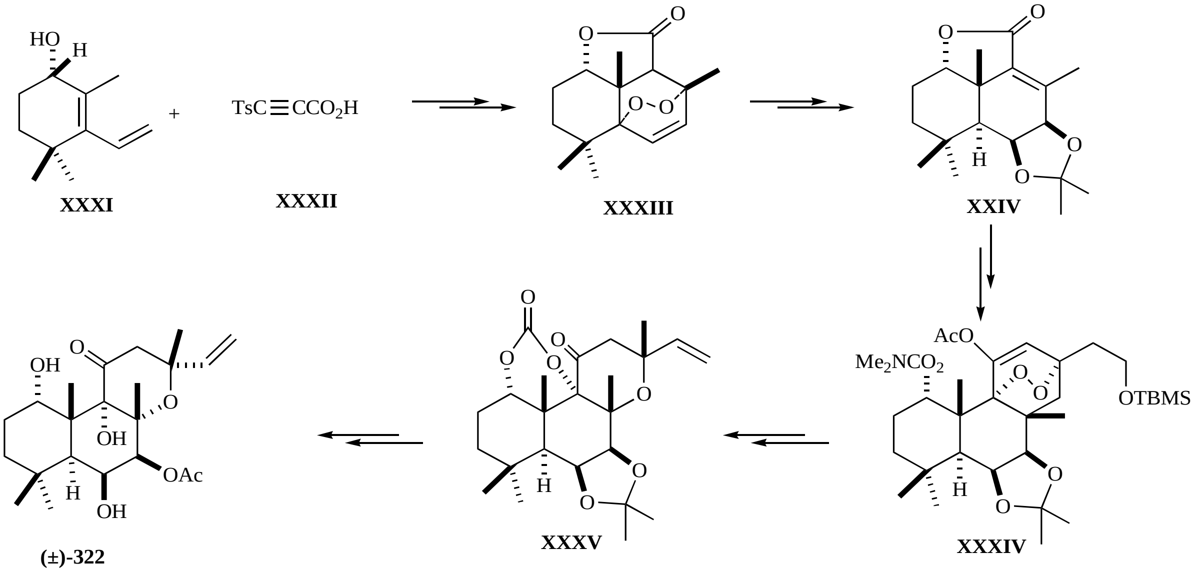
Recently Hagiwara *et al.* [162] Scheme **12** were able to synthesize forskolin **322** in 12 steps and 12% overall yield from the



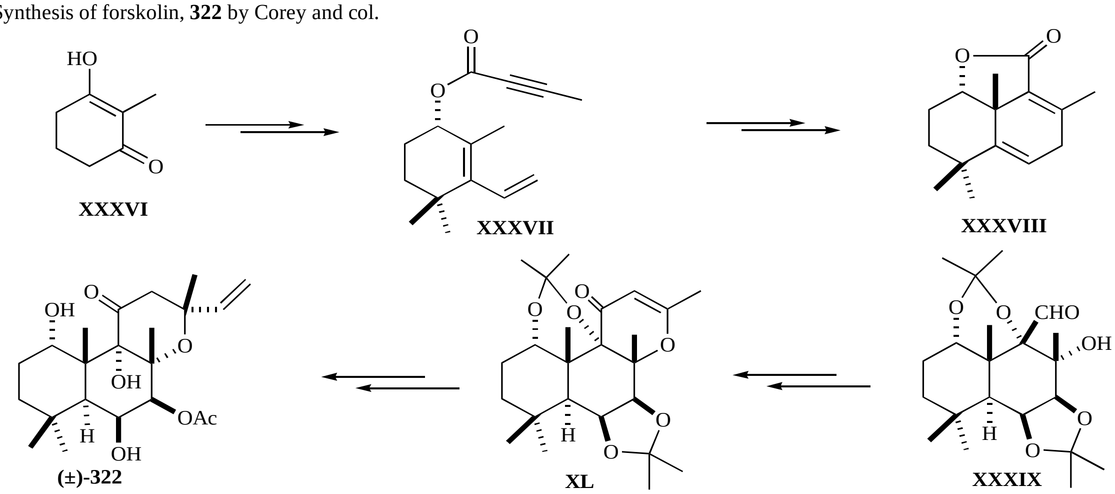
Scheme 8. Synthesis of forskolin, **322** by Ziegler *et al*.



Scheme 9. Synthesis of forskolin, **322** by Ikegami and col.



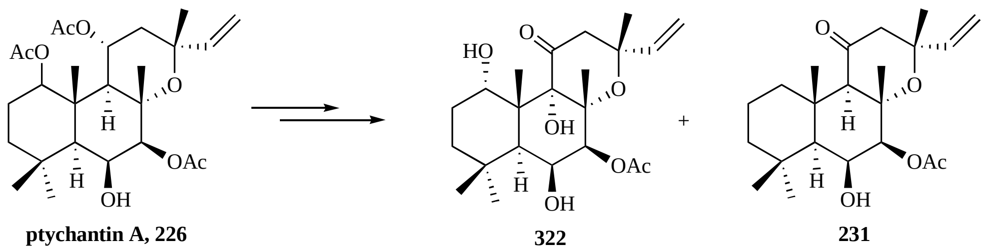
Scheme 10. Synthesis of forskolin, **322** by Corey and col.



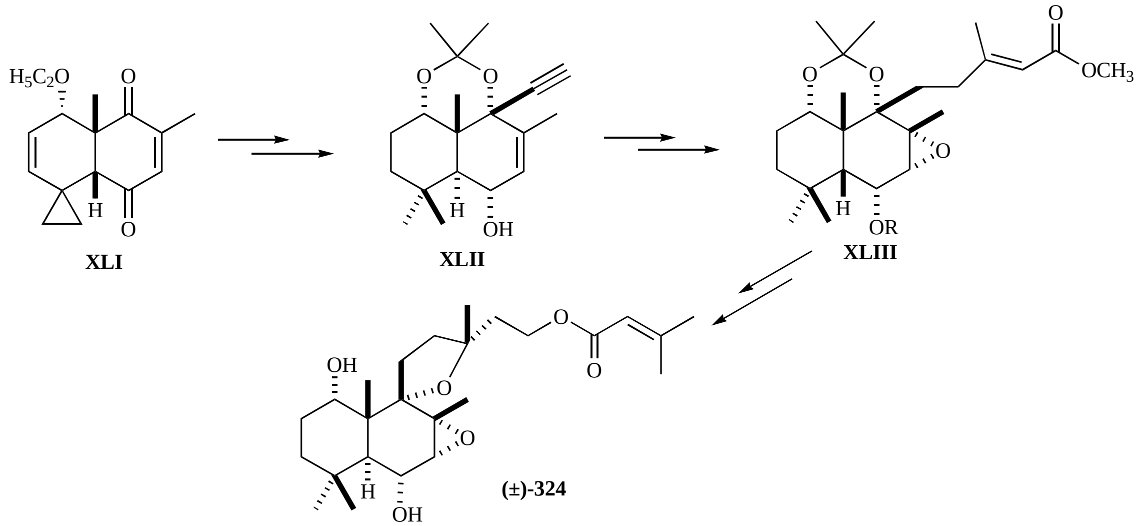
Scheme 11. Synthesis of forskolin, **322** by Lett *et al*.

natural product ptychantin A **226**. The 1α-hydroxy group was furnished by stereoselective reduction of corresponding carbonyl group. The 9α-hydroxy group was introduced stereoselectively by epoxidation of $\Delta^{9,11}$-enolether.

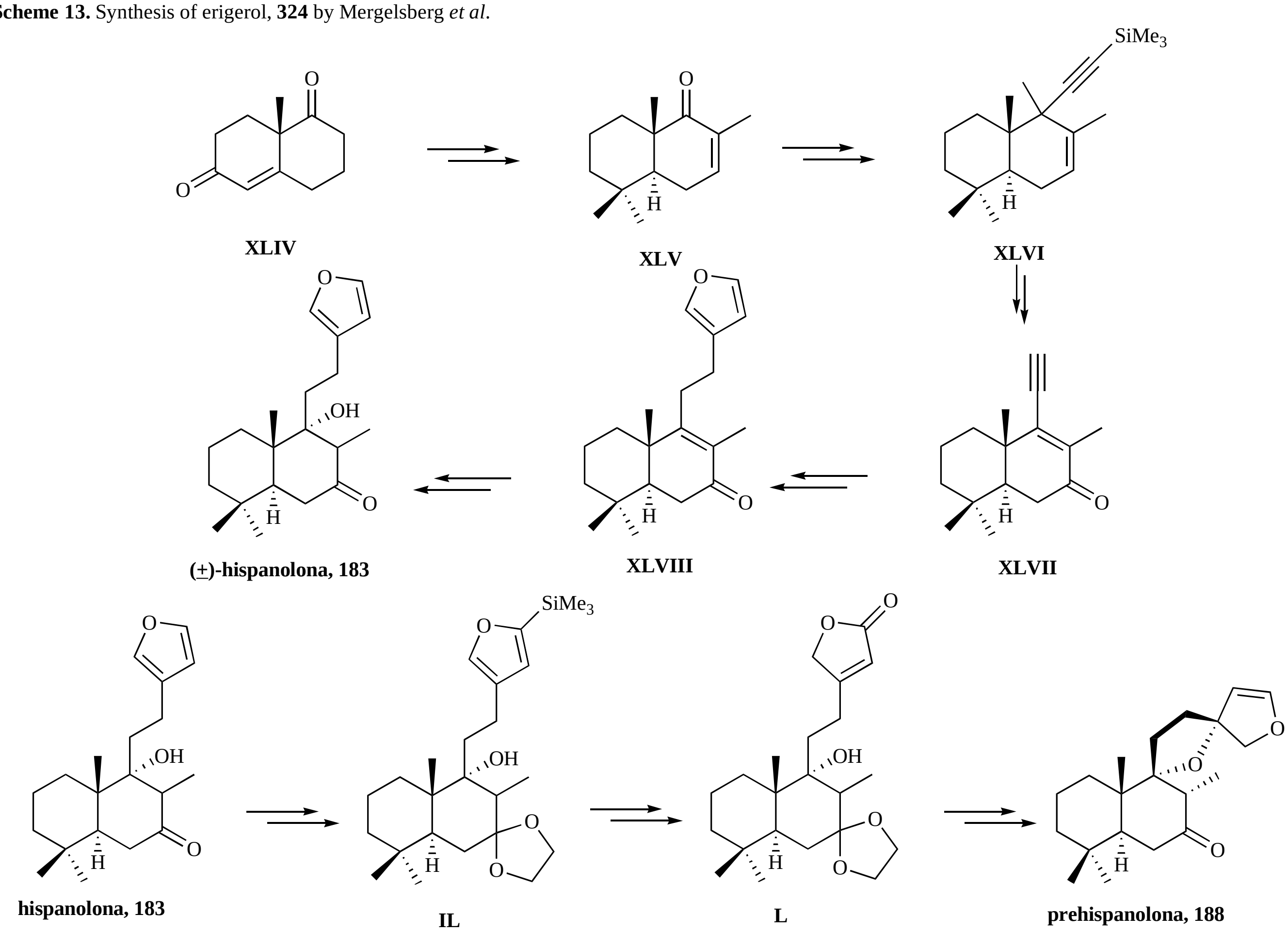
1,9-dideoxyforskolin **231**, has been synthesized in 8 steps and 33% overall yield. The hydroxy group at C-1 was removed by solid-state thiocarbonylimidazolation and subsequent radical cleavage.



Scheme 12. Synthesis of **231** and forskolin, **322** by Hagiwara *et al*.



Scheme 13. Synthesis of erigerol, **324** by Mergelsberg *et al*.



Scheme 14. Synthesis of hispanolone **183**/prehispanolone **188** by Wong *et al.*

At the present time, it appears more synthetic routes to the Ziegler intermediate, for the synthesis of forskolin **322**. These approaches constitute formal synthesis of the mentioned natural product [2].

Synthesis of erigerol, 324

The synthesis of erigerol **324** [163] Scheme **13**, utilized as starting material the known bicyclic ketone **XLI**, easily available through a Diels Alder reaction of ethyl 3-cyclopropylidene-propenyl ether and 2,6-dimethyl benzoquinone. The side chain carbons were incorporated successively by acetylide addition to the adequate octalone and ulterior addition of acetaldehyde. Finally by HWHE reaction, intramolecular Michael adition and adequation of the functional groups and the natural compound weresynthesized.

Synthesis of hispanolone 183/prehispanolone 188

For the synthesis of hispanolone **183** [164-168] the ketone of Wieland-Miescher **XLIV** was used as starting material. Prehispanolone **188** was synthesized from hispanolone **183**. Scheme **14**. Wieland-Miescher ketone **XLIV** was transformed into enone **XLV** using a new methodology. The carbón skeleton was completed by Sonoghasira reaction, with participation or the acetylenic intermediate **XLVI** and 3-bromofurane. Intermediate **XLVII** was obtained by oxidation of the hydroxyderivative **XLVI** with PCC, and the later intermediate was synthesized by reaction of **XLV** with the adequate acetylide. Finally by reduction and silylation of C-7 followed by epoxidation, reduction and oxidation led (±)-hispanolone **183**.

Protection of hispanolone **183** followed by silylation and furane oxidation gave the γ-butanolide **L**, that by cyclization in basic conditions gave the dioxoespiroderivative system, from which after reduction of the lactone and deprotection prehispanolone **188** was obtained.

CONCLUSIONS

A literature review of diterpenes with labdane structure and more than one oxygenated function in the B ring has been done. 334 compounds that have been classified in 14 groups, depending on the B ring oxidation level, have been isolated so far. These compounds constitute an interesting type of natural products because some of them, as forskolin, have shown important biological activities. However, the biological activity of many of them is unknown because they have not been tested yet. In this review, the synthesis of this kind of compounds carried out so far has also been described.

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