

The Diterpenoids of the Genus *Marrubium* (Lamiaceae)

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The occurrence and chemical structures of labdane diterpenoids from the genus *Marrubium* are reviewed and the published ¹³C NMR spectroscopic data for these compounds is presented. The pharmacological activities and biogenesis of these diterpenoids are also reported.

Keywords: *Marrubium*, Lamiaceae, labdanes, biological activities, biogenesis.

The genus *Marrubium* (Lamiaceae) includes about 40 species [1], which grow mainly in areas along the Mediterranean Sea and in the temperate zone of the Eurasian Continent; in Asia they are found in Iraq, Iran, Uzbekistan, Pakistan, and India. *M. vulgare* is naturalized in North America and Australia, and aqueous and hydroalcoholic extracts of flowering aerial parts have been used in folk medicine. The genus is known to produce many diterpenoids, whose structures are presented in the present review. A previous paper [2] reported the history, medicinal uses, pharmacology, and *in-vitro* culture of *M. vulgare*, and diterpene biosynthesis in the species.

The best known of these diterpenoids, and the first one to be isolated and characterized, is marrubiin. It was extracted from *M. vulgare* L. (white horehound) around 1850. The determination of its structure was a real challenge for more than a century, with the first paper on its structure appearing in 1855 [3]; other papers were published during the 19th century [4-8]. Gordin [9] suggested that marrubiin (present formula C₂₀H₂₈O₄) contained a γ -lactone ring, whose opening by alkaline hydrolysis gave marrubic acid C₂₀H₃₀O₅. More advanced methods since 1930 [10-14] and between 1948-1953 [15-17] brought partial solution. Only from 1952 until 1968 was the problem of the complete structure and stereochemistry solved through extensive studies [18-34]. Other papers [35-37] reported several reactions, which confirmed the structures **1** for marrubiin and **2** for marrubic

acid. The labdane skeleton shown by marrubiin is a typical marker of the genus *Marrubium*. In fact, all the diterpenoids isolated from species of this genus have a labdane backbone. The occurrence of the diterpenoids in each taxa is reported in Table 1.

The hypothesis [19] that marrubiin was not a true natural product was confirmed in 1969 [38]. Indeed **1** is an artifact, originating from the isomerization, under mild conditions, of premarrubiin, the authentic natural product, with opening of the 9-13 cyclic ether and aromatization of the furanic ring. Later, premarrubiin was found [39] to be a mixture of the two C-13 epimers, 13*R*-premarubiin (**3**) and 13*S*-premarubiin (**4**).

In the last fifty years, marrubiin (**1**) has also been detected in *M. incanum* Desr. [40], *M. alysson* Pomel [41], *M. sericeum* Boiss. [41], *M. supinum* L. [41], *M. anisodon* C. Koch [42], *M. globosum* Bentham ssp. *globosum* [43], and *M. trachyticum* Boiss. [44] (Table 1), and other similar diterpenoids were found in *M. vulgare* after 1968. In that year, two products were isolated [36]. The first one, marrubenol (**5**), was the already known [19] product obtained by lithium aluminium hydride reduction of marrubiin. The second product, indicated as marrubiin hemiacetals (**6**) (probably a mixture of stereoisomers), easily transformed into marrubiin and is probably a precursor of **1**. The correct structure is given now in this review (see under *M. globosum* ssp.

libanoticum). In the same year, two diterpenoids were isolated from the aerial parts of *M. vulgare* collected in Moldavia [45]. The first, named marrubiol, is in fact identical to marrubenol (**5**). The structure of the second, named vulgarol, was elucidated some years later [46] as **7**. Later, vulgarol was found also in *M. anisodon* [42].

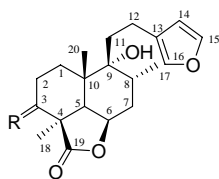
The search for more new diterpenoids was extended to other species of the genus *Marrubium* (Table 1). From *M. peregrinum* L., peregrinol was isolated [47] and its structure elucidated as **8** [48]. Later peregrinol was found in *M. praecox* Janka (syn. *M. pestalozzae* Boiss.), *M. leonuroides* Desr., *M. catariifolium* Desr. and *M. vulgare* [49]. In a preliminary paper [50] on the extractives from these species, the authors quoted also the isolation of peregrinol (**8**) from *M. propinquum* Benth.

From *M. peregrinum*, two new diterpenoids were isolated [47,51]: peregrinine (**9**) and tetrahydroperegrinine (**10**). Structurally, peregrinine

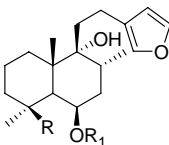
is 3-oxo-marrubiin, whereas in **10** the furanic ring is reduced to the tetrahydro derivative. No configuration at C-13 was given for **10**.

Simultaneously, peregrinine (**9**) was isolated [40] also from *M. incanum* Desr. Peregrinine occurred [52] also in *M. friwaldskianum* Boiss., together with its prefuranic derivative preperegrinine (**11**). Two species growing in the Iberian peninsula yielded new diterpenoids. From *M. sericeum*, apart from the known marrubiin (**1**) and marrubenol (**5**), the new 19-acetyl-marrubenol (**12**) and 6-acetyl-marrubenol (**13**) were isolated [41]. *M. supinum* contained marrubiin (**1**) and the new premarrubenol and 6-acetyl-premarrubenol, the stereochemistry of which at C-13 was not defined, and thus premarrubenol could have either structure **14a** or **14b**, and 6-acetyl-premarrubenol could be either **15a** or **15b** [41].

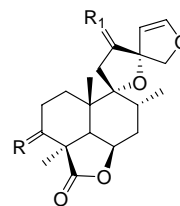
The investigation of *M. polyodon* Boiss. [53] yielded the new prefuranic derivative polyodonine (**16**),



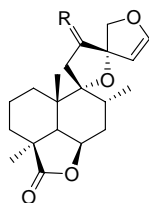
1 R = H₂
9 R = O



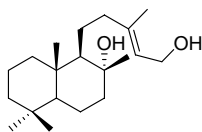
2 R = COOH R₁ = H
5 R = CH₂OH R₁ = H
12 R = CH₂OAc R₁ = H
13 R = CH₂OH R₁ = Ac



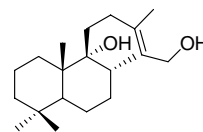
3 R = H₂ R₁ = H₂
11 R = O R₁ = H₂
16 R = H₂ R₁ = O



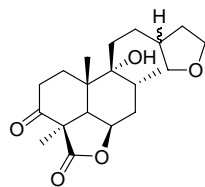
4 R = H₂
17 R = O



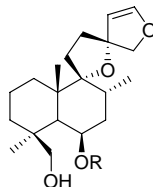
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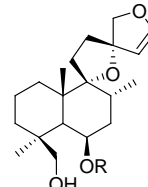
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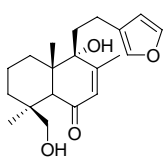
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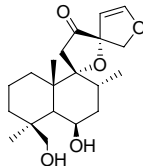
14a R = H
15a R = Ac



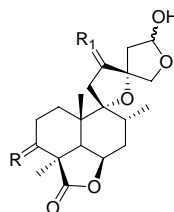
14b R = H
15b R = Ac



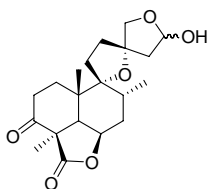
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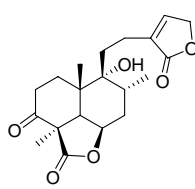
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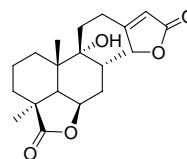
- 20 15 α -OH R = O R₁ = H₂
 21 15 β -OH R = O R₁ = H₂
 24 15 α -OH R = O R₁ = O
 25 15 β -OH R = O R₁ = O
 27 15 α -OH R = H₂ R₁ = H₂
 28 15 β -OH R = H₂ R₁ = H₂ } 6



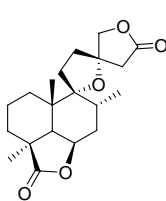
22 15 α -OH
 23 15 β -OH



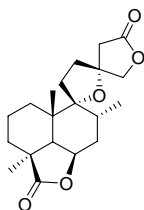
26



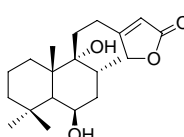
29



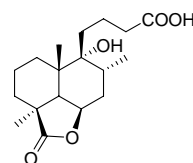
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33

showing the structure of 12-oxo-premarrubiin. At the same time, another paper [54] reported two prefuranic derivatives occurring in *M. astracanicum* Jacq: marrubinone A (17) and marrubinone B. The latter substance appears to be identical to polyodonin (16).

A novel furolabdane, anatolione (18), was isolated [55] from *M. parviflorum* Fischer et C. A. Meyer. It does not have the 6,19- γ -lactone ring, which is replaced by a 6-oxo-19-hydroxy system.

M. globosum Benth. ssp. *globosum* yielded marrubiin (1), marrubinone B {polyodonin} (16), and the new prefuranic derivative marrubiglobosin (19). Its configuration at C-13 was proved by NOE experiments [43].

A recent paper [56] reported the isolation of several labdane diterpenoids from *M. velutinum* Sm. and *M. cylleneum* Boiss. et Heldr. The first species contained four known diterpenoids: peregrinine (9),

marrubinone B {polyodonin} (16) and the inseparable epimeric mixture of 9 α ,13*R*-15,16-bis-epoxy-15 α -hydroxy-3-oxo-labdane-6 β ,19-olide (20) and 9 α ,13*R*-15,16-bisepoxy-15 β -hydroxy-3-oxo-labdane-6 β ,19-olide (21). The last two products had been previously isolated from *Leucas neufliaseana* [57], but not from a *Marrubium* species. Moreover, *M. velutinum* yielded five new diterpenoids: the inseparable epimeric mixtures of the hemiacetals velutine A (22) and 15-*epi*-velutine A (23), velutine B (24) and 15-*epi*-velutine B (25), and velutine C (26) [56]. From *M. cylleneum*, three products were isolated: marrubiin (1) and the inseparable mixture of the new cyllenine A (27) and 15-*epi*-cyllenine A (28). The configurations at C-13 and C-15 of compounds 20-28 were elucidated by NOE experiments.

Quite recently *M. globosum* ssp. *libanoticum* (Boiss.) P. H. Davis was investigated. From the acetone extract of the aerial parts, the diterpenoid 29 was isolated, which had not previously been described as

Table 1: Occurrence of diterpenoids in *Marrubium* taxa.

Taxa	Compounds
<i>M. alysson</i>	1 [41]
<i>M. anisodon</i>	1 [42], 7 [45,46]
<i>M. astracanicum</i>	16, 17[54]
<i>M. ayardii</i>	3, 4 [66]
<i>M. catariifolium</i>	8 [47,48]
<i>M. cylleneum</i>	1, 27, 28 [56]
<i>M. friwalskianum</i>	9, 11 [52]
<i>M. globosum</i> ssp. <i>libanoticum</i>	27, 28, 29, 30, 31, 32, 33 [58,59]
<i>M. globosum</i> ssp. <i>globosum</i>	1, 16, 19 [43]
<i>M. heterocladum</i>	1 [66]
<i>M. incanum</i>	1, 9 [40]
<i>M. leunuroides</i>	8 [49]
<i>M. parviflorum</i>	18 [60]
<i>M. peregrinum</i>	8 [47,50], 9, 10 [47,51]
<i>M. polyodon</i>	16 [53]
<i>M. praecox</i>	8 [49]
<i>M. propinquum</i>	8 [50]
<i>M. sericeum</i>	1, 5, 12, 13 [41]
<i>M. supinum</i>	1, 14, 15 [41]
<i>M. trachyticum</i>	1 [44]
<i>M. velutinum</i>	9, 16, 20, 21, 22, 23, 24, 25, 26 [56]
<i>M. vulgare</i>	1 [9-36], 3 [39], 4 [39], 5 [36], 7 [45,46], 8 [47], 27, 28 [36,39]

a natural product, although it had been reported a long time ago [39] as a semisynthetic derivative prepared by chemical transformation of marrubiin. The product, named marrulibanoside, is, therefore, a new natural product; more detailed spectroscopic data of the compound were also reported [58].

From the ethanolic extract of *M. globosum* ssp. *libanoticum*, several other diterpenoids were isolated and identified [59]. Two of them, cyllenine A (**27**) and 15-*epi*-cyllenine A (**28**), had been isolated previously from *M. cylleneum*. The lactones **30** and **31** had been described previously as synthetic derivatives of marrubiin [39]. However, **30**, with a 13*S* configuration, was isolated and characterized from *Leonotis ocymifolia* var. *raineriana* [60] and from *L. leonurus* [61-63]. The stereoisomer **31** with a 13*R* configuration was isolated from *M. globosum* ssp. *libanoticum* now for the first time [59]. The new natural product, 13,14- γ -lactone **32**, is remarkable for being devoid of the usual 19,6- γ -lactone, which is substituted by a pair of methyl groups on C-4; this new product, 6-deacetyl-vitexilactone, is the deacyl derivative of vitexilactone, a labdane occurring in *Vitex rotundifolia* [64,65]. Structurally remarkable is the bisnor-labdane marrulanic acid (**33**), which lost the two carbon atoms C-14 and C-15. When re-examining the NMR spectrum of the lactone

obtained [36] by oxidation of the mixture **6**, it was observed [59] that the signals for H-16 and H-14 are identical to those of the lactone **31**. Consequently, it can be asserted that product **6** was a mixture of cyllenine A (**27**) and 15-*epi*-cyllenine A (**28**).

In 1989-1990, two endemic species harvested in Morocco were investigated: *M. heterocladum* Hemberger et Maire yielded only marrubiin (**1**), whereas *M. ayardii* Maire contained the epimeric 13*R*-premmarrubiin (**3**) and 13*S*-premmarrubiin (**4**) [66].

Pharmacological activity of *Marrubium*

Aqueous extracts of *M. vulgare* have been used in folk medicine to cure a variety of diseases. They were used in ancient Egyptian times [67] as an expectorant cough remedy, and in ancient Greek medicine to treat bites from rabid dogs [68]. In Europe, in Indian Ayurvedic medicine, and in North American aboriginal medicine, the species was largely used to treat wheezing, tuberculosis, chronic bronchitis, whooping cough and colds. Use of *M. vulgare* as an expectorant, antitussive, choleric and antihypertensive is still common in folk medicine [69-73]. Recent studies on its use as an antihypertensive confirmed a vasorelaxant activity of marrubiin and marrubenol on smooth muscles and arteries by inhibition of the contraction evoked by KCl, by blocking the L-type calcium channels [74-77]. Other studies found a remarkable analgesic activity of marrubiin and some semisynthetic derivatives [78]. A potent antinociceptive activity was reported [79], and antispasmodic effects on isolated tissues were recorded for the hydroalcoholic extract of *M. vulgare* [80]. An antifeedant activity of marrubiin has been investigated [81]. Studies on the choleric activity of both marrubiin and marrubic acid have also been reported [82].

Also observed were cardiovascular [83], antidiabetic [84-85], an analgesic [86], an antipyretic [87], and abortive activities [88]. It was found that sodium and magnesium salts of marrubic acid retard the germination of wheat seeds [89], alcoholic fermentation by yeast [90], and the development of *Rhizopus nigricans* [91]. The activity against *Bacillus anthracis* was tested *in vivo* on hens [92]. Antioxidant activity was also observed [93].

The acetone extract of *M. globosum* ssp. *libanoticum* reduced rat paw oedema induced by carrageenin [58]; this activity, seems to be due to marrulibanoside, as a consequence of iNOs and COX-2 inhibition.

Table 2: ^{13}C NMR data (CDCl_3) of *Marrubium* diterpenoids.

C	1 [2]	5 [76]	9 [56]	16 [54]	17 [54]	19 [43]	20/21 [56]	22/23 [56]	24/25 [56]
1	28.7 t	33.8 t	28.6 t	28.3 t	28.7 t	33.7 t	29.1 t	29.1/29.0 t	28.8 t
2	18.2 t	18.5 t	34.0 t	17.8 t	17.9 t	18.4 t	34.1 t	34.1/34.0 t	33.8 t
3	28.4 t	40.7 t	207.0 s	28.2 t	28.2 t	40.6 t	206.2 s	206.2 s	206.0 s
4	43.8 s	38.9 s	53.0 s	44.0 s	43.6 s	39.0 s	53.6 s	54.2 s	54.0 s
5	44.9 d	49.3 d	46.4 d	44.4 d	44.4 d	49.0 d	47.4/48.0 d	47.4/47.3 d	46.7 d
6	76.2 d	65.9 d	74.8 d	75.7 d	75.7 d	65.5 d	74.6/75.0 d	74.9/74.5 d	74.2 d
7	31.6 t	38.9 t	30.9 t	31.2 t	31.1 t	38.3 t	31.4 t	31.6/31.5 t	31.2 t
8	32.4 d	31.1 d	31.4 d	32.0 d	31.3 d	31.4 d	31.6 d	31.1 d	31.5 d
9	75.8 s	77.0 s	75.0 s	84.6 s	85.1 s	86.8 s	90.5/90.2 s	90.7/90.3 s	86.1 s
10	39.8 s	43.4 s	39.8 s	38.6 s	39.3 s	42.1 s	39.4/39.1 s	39.3 s	39.9 s
11	35.2 t	34.9 t	34.5 t	40.1 t	39.4 t	40.6 t	29.3 t	29.4 t	39.2 t
12	21.0 t	21.5 t	20.8 t	212.5 s	213.6 s	213.8 s	34.4/37.7 t	34.7/37.0 t	217.0 s
13	125.0 s	125.4 s	124.6 s	92.7 s	93.1 s	92.8 s	90.9/90.4 s	89.9/89.3 s	89.8 s
14	110.7 d	110.8 d	110.5 d	102.8 d	102.6 d	102.9 d	45.9/48.0 t	46.0/47.2 t	46.3/46.7 t
15	143.1 d	142.8 d	143.0 d	151.3 d	151.9 d	150.8 d	99.4/99.2 d	98.8/98.5 d	98.9/99.5 d
16	138.6 d	138.5 d	138.5 d	77.9 t	79.1 t	78.0 t	77.1/77.7 t	76.9/77.4 t	75.0/75.8 t
17	16.6 q	16.2 q	15.8 q	15.7 q	16.3 q	15.7 q	17.1/16.9 q	17.2/17.0 q	15.7 q
18	23.0 q	27.8 q	20.3 q	22.6 q	22.6 q	27.1 q	20.5 q	20.5 q	20.8 q
19	183.8 s	69.1 t	174.8 s	183.3 s	183.3 s	68.9 t	174.2 s	174.4 s	174.5 s
20	22.3 q	19.6 q	17.9 q	23.7 q	23.6 q	20.1 q	19.1 q	19.2/19.1 q	18.2 q

Table 3: ^{13}C NMR data (CDCl_3) of *Marrubium* diterpenoids.

C	26 [56]	27 [59]	28 [59]	29 [58]	30 *	31 [59]	32 [59]	33 [59]
1	28.8 t	28.9 t	28.8 t	28.9 t	29.3 t	29.3 t	34.3 t	28.5 t
2	34.1 t	17.8 t	18.0 t	18.3 t	17.9 t	17.9 t	18.6 t	18.1 t
3	207.0 s	28.0 t	28.1 t	28.5 t	28.1 t	28.1 t	43.7 t	28.3 t
4	53.7 s	44.0 s	44.0 s	44.0 s	44.0 s	44.0 s	34.8 s	43.8 s
5	46.7 d	46.4 d	46.4 d	45.0 d	46.0 d	45.9 d	48.8 d	44.7 d
6	74.9 d	75.9 d	76.4 d	76.0 d	75.9 d	75.9 d	67.3 d	76.3 d
7	31.7 t	31.7 t	31.7 t	32.4 t	31.7 t	31.6 t	40.2 t	31.5 t
8	32.1 d	31.8 d	31.8 d	31.6 d	31.8 d	31.9 d	31.3 d	32.2 d
9	74.3 s	92.1 s	90.5 s	75.6 s	92.2 s	92.0 s	75.9 s	75.5 s
10	40.2 s	39.1 s	38.9 s	40.0 s	38.9 s	39.0 s	43.6 s	39.7 s
11	31.2 t	29.4 t	29.6 t	32.5 t	28.8 t	29.0 t	31.7 t	34.2 t
12	20.7 t	34.6 t	37.7 t	25.0 t	36.9 t	36.9 t	25.4 t	20.2 t
13	134.2 s	90.1 s	90.0 s	171.0 s	86.0 s	86.0 s	171.3 s	34.1 t
14	144.7 d	45.8 t	48.6 t	115.3 d	41.9 t	43.0 t	114.9 d	177.4 s
15	68.8 t	99.3 d	99.1 d	174.1 s	174.6 s	174.5 s	174.1 s	
16	174.9 s	77.2 t	77.6 t	73.3 t	78.6 t	78.3 t	73.2 t	
17	16.3 q	17.4 q	17.2 q	16.8 q	17.4 q	17.3 q	16.2 q	16.5 q
18	20.5 q	23.1 q	22.9 q	23.2 q	23.0 q	23.0 q	24.6 q	22.9 q
19	174.8 s	183.4 s	183.8 s	183.8 s	183.4 s	183.4 s	33.8 q	184.0 s
20	18.1 q	23.4 q	23.6 q	22.5 q	23.4 q	23.4 q	19.4 q	22.3 q

* NMR data obtained by us and not previously published.

Biogenesis of marrubiin

Recently it was proved [94] that the biosynthesis of marrubiin follows a non-mevalonate pathway, and is consistent with the alternative pathway via trioses. On the contrary, the biogenesis of the sterols occurring in *M. vulgare* is in accordance with the acetate-mevalonate pathway. These results question

the real biosynthetic pathway of all the other labdane diterpenoids occurring in nature.

^{13}C NMR data

Tables 2 and 3 report a complete list of all ^{13}C NMR spectroscopic data quoted in the literature for the diterpenoids isolated from *Marrubium* species.

References

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