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Comparative Phytochemistry of Polyacetylenes of the Genus *Artemisia* (Asteraceae): Compounds with High Biological Activities and Chemotaxonomic Significance

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Review

Comparative Phytochemistry of Polyacetylenes of the Genus *Artemisia* (Asteraceae): Compounds with High Biological Activities and Chemotaxonomic Significance

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Abstract: In spite of the many chemical reports on polyacetylenes of the genus *Artemisia* combining conclusions regarding their distribution and biological functions are widely missing. The aim of the present review was to arrange the diversity of polyacetylenes in the genus following biogenetic aspects and group them together into characteristic structural types. The co-occurrence of the dehydrofalcariol-type with the aromatic capillen-isocoumarin-type represents a characteristic biogenetic trend, clearly segregating species of the subgenus *Dracunculus* from those of the subgenera *Artemisia* and *Absinthium*, distinguished by the spiroketal enol ether- and/or linear triyne-type. Various accumulation trends to specific structures additionally contribute to a more natural species grouping within the subgenera. Biological activities were reported for all four structural types, ranging from antifungal, insecticidal, nematocidal, and cytotoxic properties to allelopathic effects. Of particular interest were their remarkable cytotoxic potencies, from which the very high values of dehydrofalcariin-3,8-diol may be associated with the pronounced affinity of this type to form extremely stable bonds to proteins acting in signaling pathways. The aromatic acetylene capillin inhibited the viability of various tumor cells in a dose- and time-dependent manner. Its potent apoptosis-inducing activity was induced via the mitochondrial pathway. A group of spiroketal enol ethers was identified as inhibitors of PMA-induced superoxide generation. Among them the epoxide of the isovalerate ester exhibited the highest potency. The ecological impact of acetylene formation became apparent by the allelopathic effects of DME of the linear triyne-type, and the aromatic capillen by inhibiting seed germination and growth of widespread weeds.

Keywords: polyacetylenes; polyynes; spiroketal enol ethers; aromatic acetylenes; isocoumarins; structural relationships; chemotaxonomy; biological activities; antifungal; insecticidal; nematocidal; cytotoxic; inhibition of superoxide generation; allelopathy

1. Introduction

1.1. Biosynthetic Aspects

Naturally occurring polyacetylenes (= polyynes) are characterized by the formation of triple bonds that can be derived from different metabolic routes. As derivatives of the isoprenoid, polyketide, or fatty acid pathway they are widely distributed in different organisms, including bacteria, marine invertebrates, fungi, plants and animals. However, the majority of polyacetylenes was shown to be derived from fatty acids and was mostly isolated from the three related plant families Asteraceae, Apiaceae, and Araliaceae [1–6]. The highest number with more than 1100 compounds was reported for the Asteraceae, where the three tribes Anthemideae, Heliantheae and Cynareae are especially rich in structural variation. With a number of well-known medicinal plants, such as species of the genera *Artemisia*, *Achillea*, *Matricaria* and *Tanacetum*, the Anthemideae

represents the best investigated tribe showing the highest diversity of polyacetylenes. Here, of special interest is the ability to synthesize aromatic rings from linear acetylenic precursors and the formation of unique spiroketal enol ethers [7,8]. All these tribus-specific structures were found in the large genus *Artemisia* comprising around 500 species. Together with other chemical features, such as different lengths of carbon chains and the number of conjugated triple bonds, they provide important chemotaxonomic criteria for an infrageneric grouping [1,9]. Due to the typical UV-spectra of polyacetylenes broad-based UV-HPLC comparisons of lipophilic extracts of *Artemisia* species informed about the accumulation and distribution of characteristic derivatives [10–13].

Based on extensive feeding experiments with ^{14}C - and ^3H -labeled precursors the main line of biosynthetic sequence of the fatty acid-derived acetylenes has already been determined. Starting with C_{18} -crepenynic acid, as the first monoacetylenic precursor in the Asteraceae, increasing desaturation at the distal part (near the methyl end) of the molecule leads to a group of methyl-triynes typical for many *Artemisia* species. Structural diversification is further created by oxidative chain-shortening and cyclization processes at the proximal part (near the carboxy group) [1,4,14,15]. A significant diversion step in the main biosynthetic route is the formation of C_{17} -diynes of the dehydrofalconol-type (Figure 1). This biogenetic trend can be regarded as a conservative chemical feature also known from other genera of the Anthemideae and even other tribes of the family Asteraceae. Moreover, with structurally corresponding, but more saturated, falcarinol- (= panaxynol-) type derivatives [16], this group of C_{17} -acetylenes was shown to represent also a significant chemical character of the two families Araliaceae and Apiaceae [17–20].

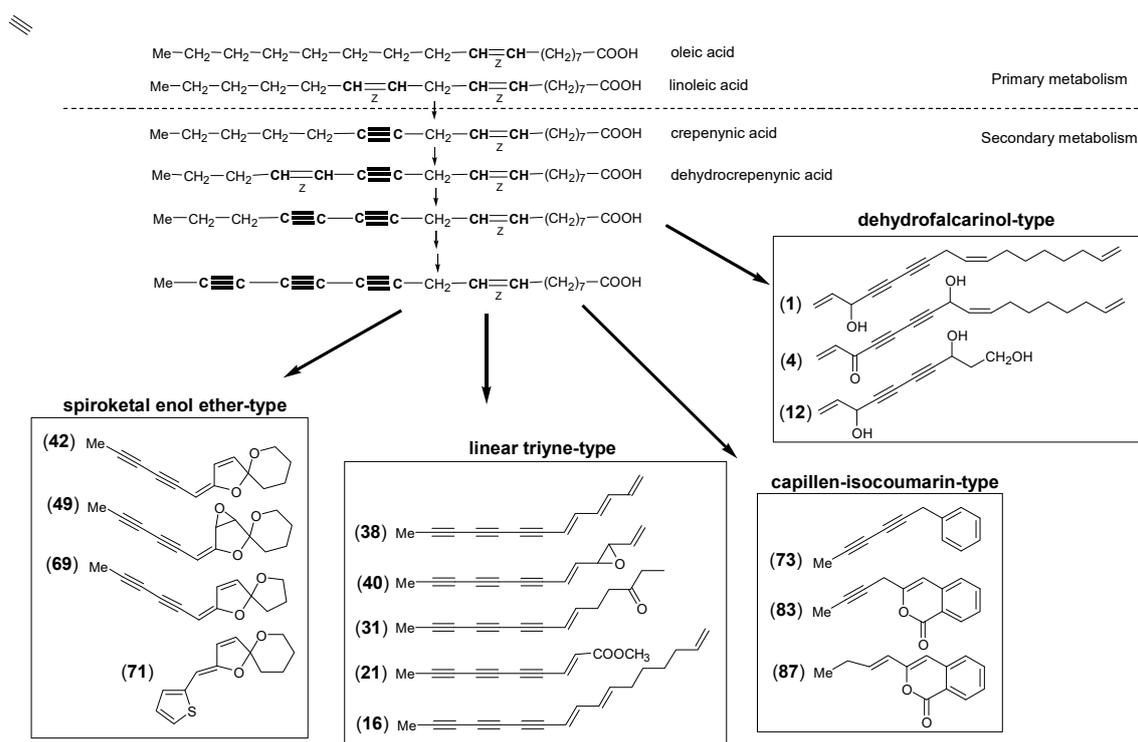


Figure 1. Desaturation of fatty acids and transformation to four structural types of polyacetylenes in the genus *Artemisia*.

1.2. Bioactive Properties

Starting with reports on the toxic acetylene cicutoxin, a C_{17} -compound from *Cicuta virosa* L. (Apiaceae) [21], and the antifungal activity of the aromatic acetylene capillin (77) from *Artemisia capillaris* Thunb. [22], followed by the discovery of the fish poison ichthyothereol (35), a C_{14} -acetylenic tetrahydropyran from *Ichthyothere terminalis* (Spreng.) Malme (Asteraceae) [23], different types of polyacetylenes were shown to possess a wide range of biological activities [24]. Apart from aromatic

derivatives [25–28] and spiroketal enol ethers [29–36], especially C_{17} -acetylenes of the falcarinol-type exhibited pronounced antifungal [37–46], insecticidal [42,43,45–48], nematocidal [46,49–51], antibacterial [52–54], and cytotoxic effects [20,52,55–63,73]. The ecological impact of acetylene formation became apparent by their function as phytoalexins [40,64,65], and by their photosensitizing [26,47,66–68] and allelopathic effects [69–71]. Improved analytical methods and the progress in evaluating bioassays greatly stimulated further investigations in this class of compounds summarized in a series of reviews [4,6,18,24,59,72–75].

1.3. Phytochemical Characters

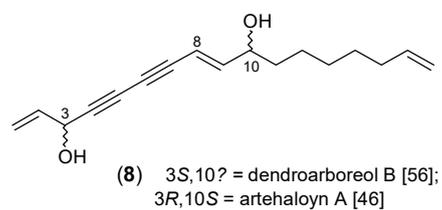
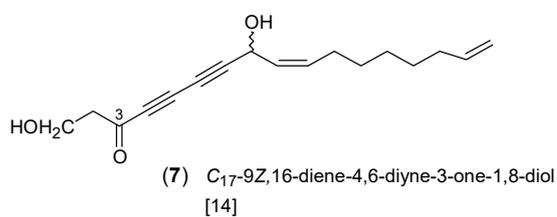
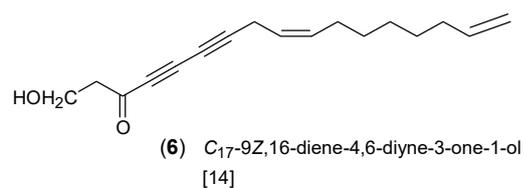
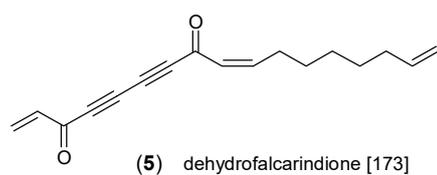
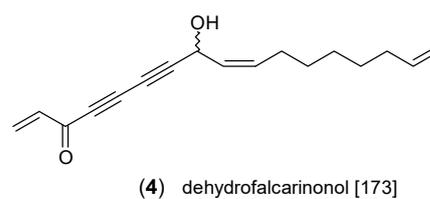
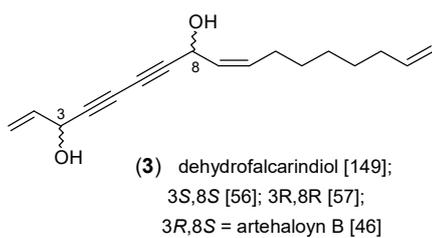
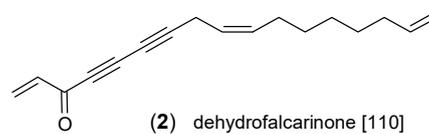
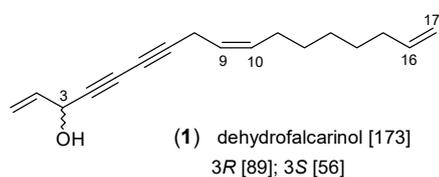
Species of the genus *Artemisia* are among the most widespread and widely used medicinal plants in the world. Consequently, they have been subject of many phytochemical studies focusing mainly on monoterpenes, sesquiterpene lactones, flavonoids, lignans, coumarins, and polyacetylenes [76–84,180]. The first naturally-occurring polyacetylene, a methyl *n*-decen-triionate or dehydromatricaria ester (DME) (**21**), was obtained by steam distillation from the roots of *Artemisia vulgaris* L. (“common mugwort”) almost 200 years ago [85]. Although different polyacetylenes were later also isolated by methods of essential oil production, careful lipophilic solvent extraction at room temperature was meanwhile preferred in view of the unstable derivatives [86]. Considering the biogenetic connections and different distribution within the genus, the polyacetylenes of *Artemisia* can be grouped into four structural types representing derivatives of: (a) dehydrofalcarinol, (b) capillen-isocoumarin, (c) spiroketal enol ether, and (d) linear triyne (Figure 1). The aim of the present review is to provide an updated overview about the structural diversity of polyacetylenes in the genus *Artemisia* and to summarize the many publications describing the various bioactivities. In addition, different distribution of the structural types within the genus should demonstrate to what extent polyacetylenes can serve as chemotaxonomic markers (Table 8).

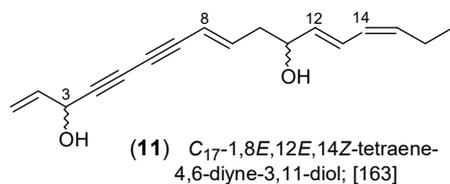
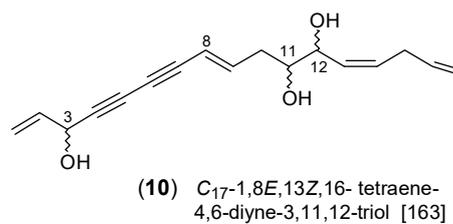
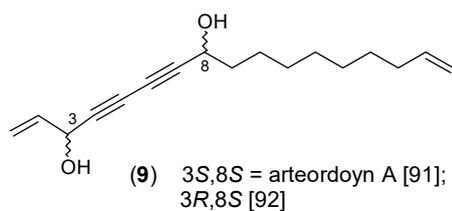
2. Structural Relationships

The conversion of the C-12 double bond of linoleic acid into the triple bond of crepenynic acid represents the first step in the formation of polyacetylenes in the Asteraceae. Further desaturation steps, performed by desaturase and acetylenase activities [4], lead to compounds with up to three conjugated triple bonds, widely distributed in *Artemisia*. An important biosynthetic trend diverges at the diyne-level leading to the dehydrofalcarinol-type, mainly occurring as C_{17} -derivatives. Chain-shortening of the C_{18} -triyne fatty acids, involving β - and α -oxidation, results in the formation of C_{14} - and C_{13} - intermediates, respectively, which are further modified either to the widespread linear triynes, or to the deviating structures of the spiroketal enol ether- and the capillen-isocoumarin-type (Figure 1). Beside this major desaturation pathway additional side reactions are proposed for the formation of the terminal vinyl end both in the linear triynes and in the dehydrofalcarinol group.

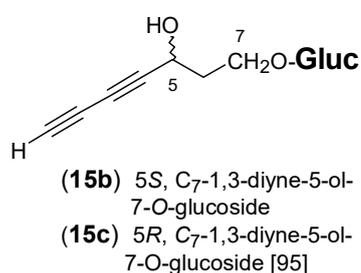
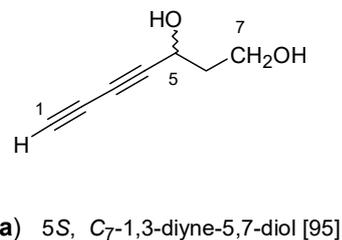
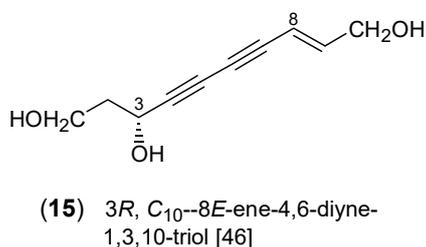
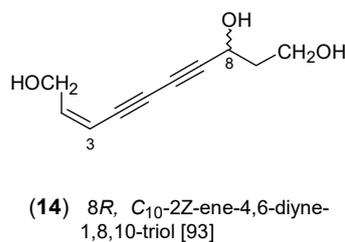
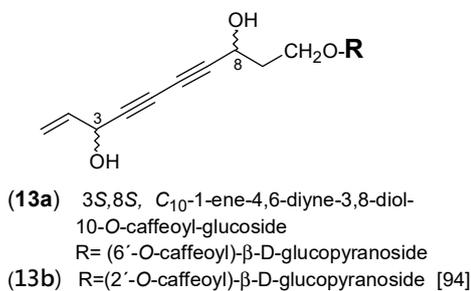
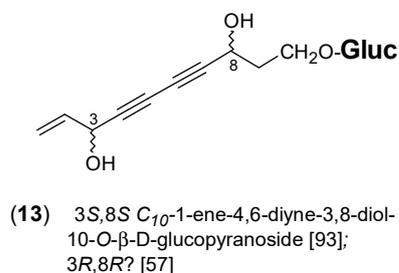
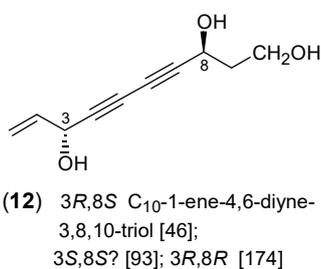
2.1. Dehydrofalcarinol-Type

The polyacetylenes of the dehydrofalcarinol-type (Table 1) are generally characterized by a C_{17} -1,9,16-triene-4,6-diyne basic structure linked with oxygen substituents at C-3 and C-8 position. As demonstrated in Figure 2, β -hydroxyoleic acid was proposed as biosynthetic precursor. After desaturation and expulsion of CO_2 , dehydration leads to the characteristic vinyl end group [87]. The formation of the second double bond at the other end of the carbon chain and the adjacent oxygen substitution can be explained by desaturation and hydroxylation [4]. As shown in Table 1, the central (*Z*)-configured double bond at C-9, derived from oleic acid, divides the molecule into a polar and an **apolar** region. The former is highly unsaturated and characterized by oxygen functionalities, while the latter consists of a saturated carbon chain terminated by a vinyl group. This double bond at C-16 of the dehydrofalcarinol derivatives is of particular chemotaxonomic significance representing a typical chemical feature of the family Asteraceae. By contrast, in the corresponding structures of falcarinol (= panaxynol) derivatives [16] of the related families Araliaceae, Apiaceae, and

Table 1. Dehydrofalcarinol-type acetylenes.**A** C₁₇- derivatives



B C₁₀- and C₇- derivatives



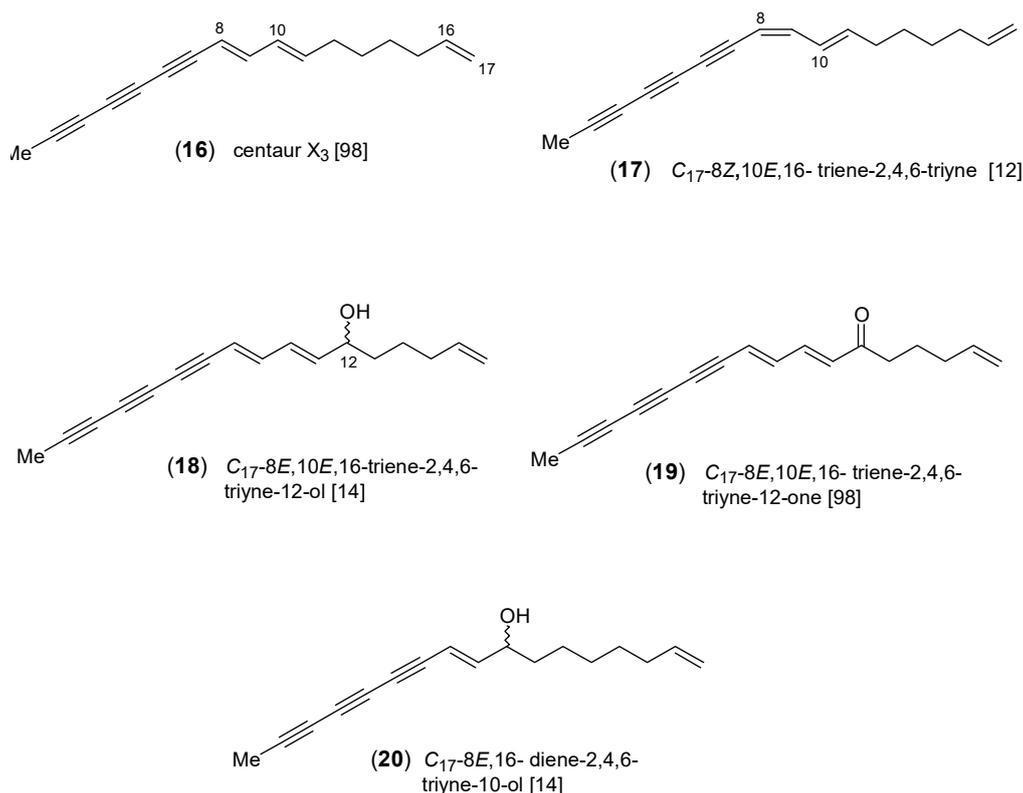
Further structural modifications, shown in compounds (8-11) (Table 1A), can be explained by intra-chain oxidation and conjugase activity [4]. Chain-shortening to the structurally related C₁₀-derivatives (12-15) (Table 1B) is supposed to be formed either *via* β-oxidation steps, or, regarding the co-existence of compounds (8) and (15) in *A. halodendron* [46], by a mid-chain cleavage [1]. Since only few glycosylated acetylenes are known so far, the formation of 10-*O*-glucoside (13) in the aerial parts of the three related species *A. monosperma* [57], *A. capillaris* [93], and *A. scoparia* [94] is of chemotaxonomic interest. In *A. scoparia* two isomeric caffeoylated glucosides (13a, b) additionally contribute to structural diversity of this type of acetylenes [94]. Moreover, from the aerial parts of *A. dracuncululus* three C₇-diynes (15a-15c) were isolated [95]. With respect to the already known trihydroxylated C₁₀-diyne (15), they may be regarded as a result of an additional C₃-cleavage.

2.2. Linear Triyne-Type

2.2.1. Centaur X₃

The widespread C₁₇-acetylene centaur X₃ (16) was first discovered in aerial parts of *Centaurea cyanus* L. ("cornflower") by Löfgren [96] and was later also found in essential oil of the roots of *A. vulgaris* [85]. The structure was elucidated by Bohlmann et al. [97] and is characterized by a methyl triyne-diene group combined with an isolated terminal double bond (Table 2). Its biosynthesis was proposed to involve β-hydroxyoleic acid as precursor [1]. The dominating (8*E*,10*E*)-isomer (16) was shown to co-occur with a second mono-(*Z*)-isomer which was initially presumed to be (8*E*,10*Z*)-configured. However, in a reinvestigation of *A. vulgaris* roots a close inspection of the ¹H-NMR spectra showed that the second isomer (17) is distinguished by (8*Z*,10*E*)-configuration. The double bond between C-8 and C-9 near the centre of the molecule and in conjugation to three conjugated triple bonds was assumed to (photo-) isomerize easily. Consequently, it is difficult to arrive at a decision concerning the original distribution of corresponding (*E*)- or (*Z*)-isomers in living plants [12]. The compounds (18) and (19) represent oxidation products of centaur X₃ (16), while the alcohol (20), isolated from *A. selengensis* Turcz. [98], can be regarded as biogenetic precursor (Table 2).

Table 2. Centaur X₃ and related C₁₇-derivatives.



2.2.2. Dehydromatricaria Ester (DME)

A frequently occurring polyacetylene of *Artemisia* is the methyl ester of C₁₀-triene-enoic acid, named dehydromatricaria ester (DME). The (*Z*)-isomer (**21**) was discovered as a readily crystallizing compound in the essential oil of the roots of *A. vulgaris* [85] and its structure was later determined by Bohlmann and Mannhardt [99] (Table 3). The formation of DME was proposed to be the result of a direct C₈-cleavage from a C₁₈-triynoic acid precursor (Figure 3). The (*E*)-isomer (**22**), initially obtained by synthesis, was originally isolated from the genus *Tripleurospermum* (published as *Matricaria*) [100] and was later found to be very common in the tribe Anthemideae [1]. Examining the seasonal variation of (*Z/E*)-isomerism it was shown that the (*Z*)-isomer (**21**) is the dominating compound in the roots of *A. vulgaris*, with increasing amounts from July to October [101]. However, a comparative analysis of 78 different samples of the *Artemisia* "Vulgares" group revealed a species-specific trend to accumulate either the (*Z*) (**21**)- or the (*E*)-isomer (**22**), suggesting a genetically fixed mechanism [13]. The isomers of a related butyrolactone were reported to be also common in the tribe Anthemideae [1]. However, in *Artemisia* only small amounts of the (*Z*)-isomer (**23**) [102] (Table 3) could be detected so far in the "Vulgares" group [13]. Further structural variation of DME is created by incorporation of sulfur, leading to the formation of thiophenes [103,104,179] (Figure 3). The dihydro-derivative DME-thiophene A (**24**) was isolated from the roots of two European samples of *A. absinthium* L. ("wormwood") [103]. It was later also detected in a sample originating from China together with DME-thiophene B (**25**). In this case, the two DME-derivatives were reported to coexist with a series of C₁₂-dithiophenes [104]. However, this type of thiophene is unknown from the genus *Artemisia* and has not been detected in the tribe Anthemideae. Moreover, regarding the occurrence of DME-derived thiophenes in *A. absinthium*, the biogenetically deviating structure of a new C₁₀-acetylenic thiophene in this species [105] should be reconsidered.

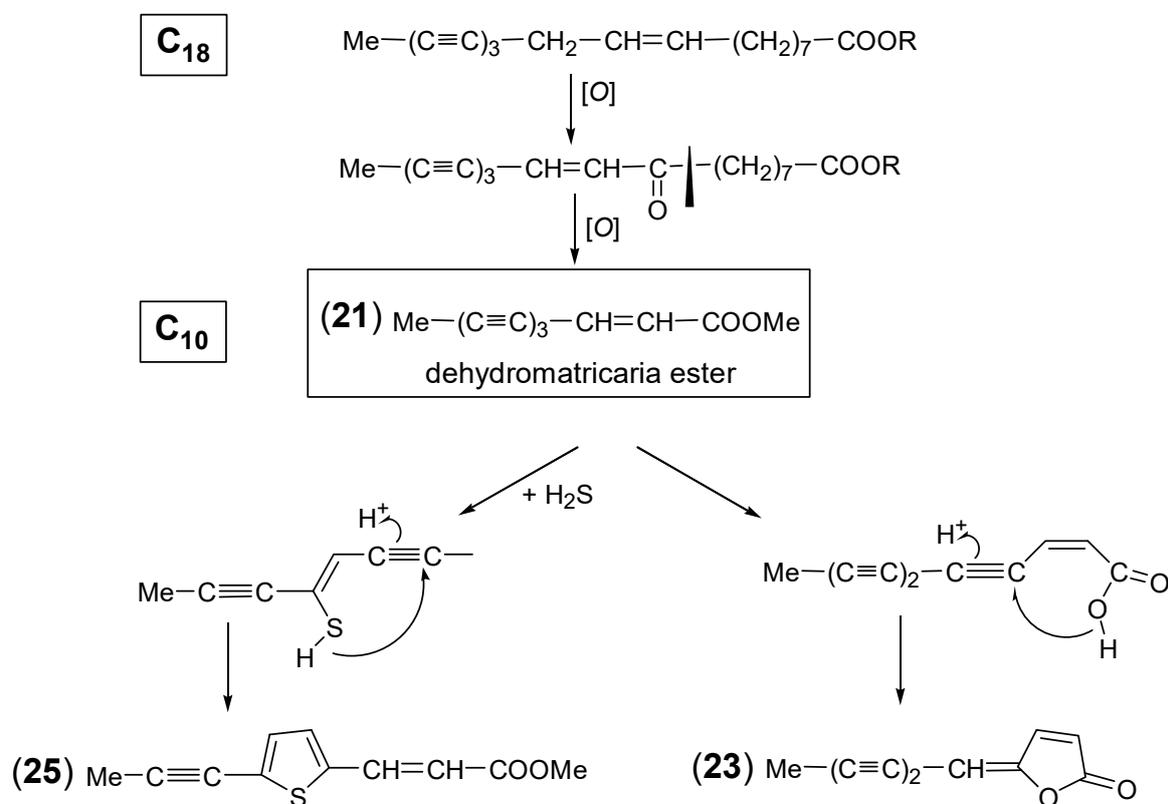
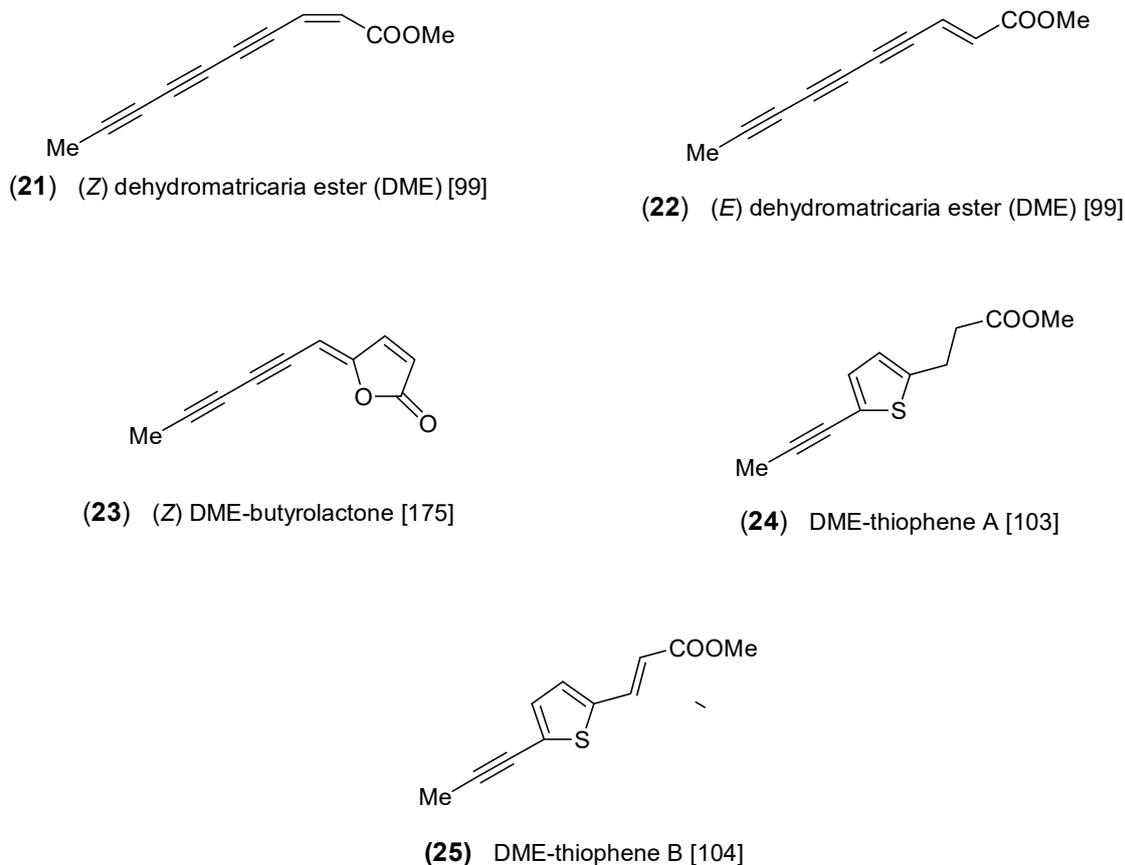


Figure 3. Biosynthesis of dehydromatricariaester (DME) (**21**).

Table 3. C₁₀-Acetylenes derived from dehydromatricaria ester (DME).

2.2.3. “Artemisia Ketone” (AK) and Related C₁₄-Derivatives

The C₁₄-triene-ene ketone (31) represents a typical polyacetylene of the tribe Anthemideae also widespread in the genus *Artemisia* [1,12,13]. Together with centaur X₃ (16) and DME (21) it was originally detected in the roots of *A. vulgaris* and its UV-spectrum suggested the presence of a triene-ene chromophore [85]. Due to the keto group at an unusual position the structure could be elucidated only after extensive experiments and was named “artemisia ketone” (AK) [106]. However, this trivial name was already used first for an irregular monoterpene. The biosynthetic sequence leading to an oxygen in a not allylic position was proposed by Bohlmann et al. [107, 1] (Figure 4). The corresponding alcohol (32) was first described for the roots of *Anacyclus pyrethrum* [102] and was also found to be common in the tribe Anthemideae. Its acetate (33) and the isovalerate ester of the structurally related keto-alcohol (34) were isolated from different species of the *Artemisia* “Vulgares” group [12,13]. Important key intermediates in this biosynthetic pathway are the C₁₄-triene-diene-alcohols (26) and (28) (Table 4). They lead to the formation of both the tetrahydropyranes ichthyothereol (35), its acetate (36) [23] and the thiophene rephienylol (37) from *A. reptans* C. Sm.[108] on the one hand, and to the chemotaxonomically important C₁₃-derivatives “triene-triene” (38) and pontica epoxide (40) on the other. The alcohol (26) and its acetate (27) are widely distributed in the tribe Anthemideae [7] and were frequently detected in the *Artemisia* “Vulgares” group [13]. The co-existence of the two acetates (27) and (30) in *A. afra* Jacq. together with (31, 36, 38), and (40) (Tables 4 and 5) [109] underlines the biogenetic connections demonstrated in Figure 4.

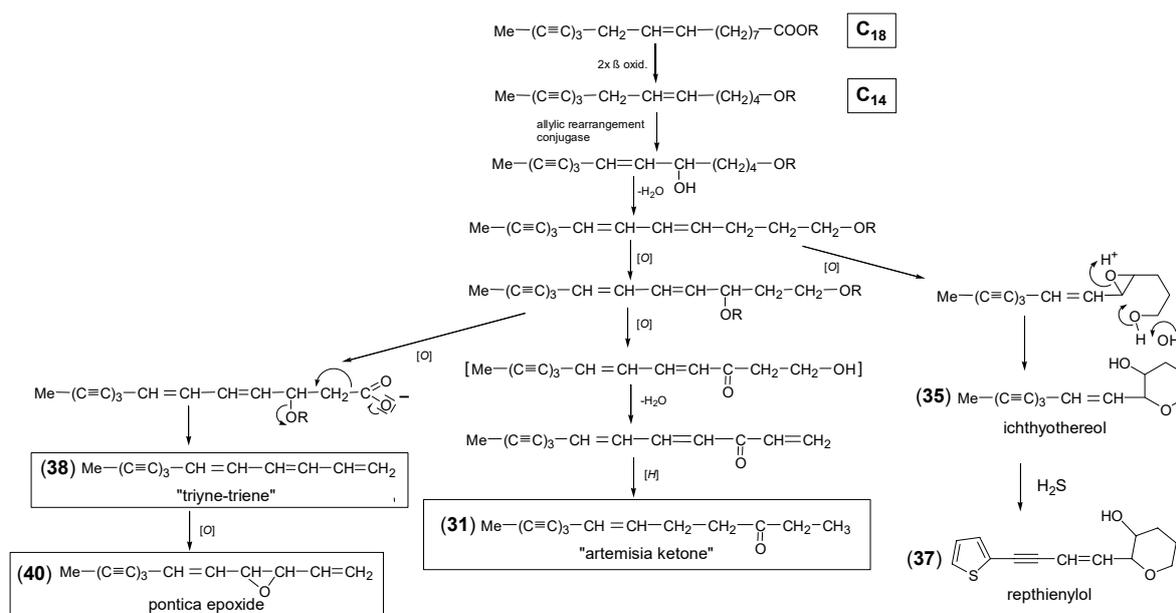


Figure 4. Proposed formation of "artemisia ketone" (AK) (31).

Table 4. "Artemisia ketone" (AK) and related C₁₄-derivatives.

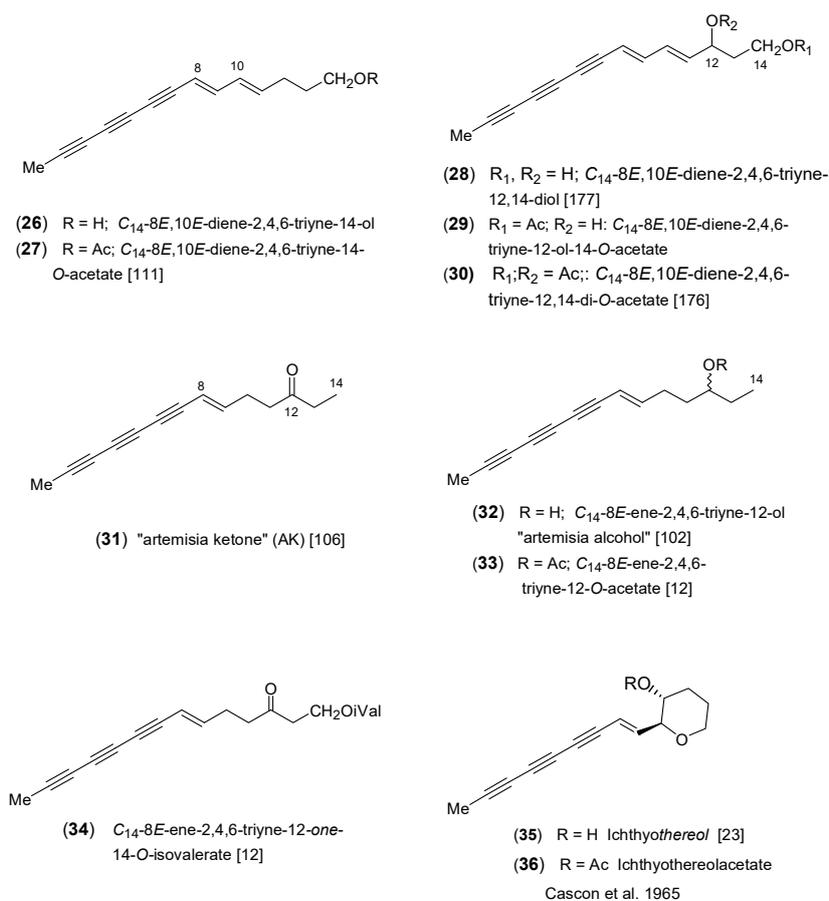
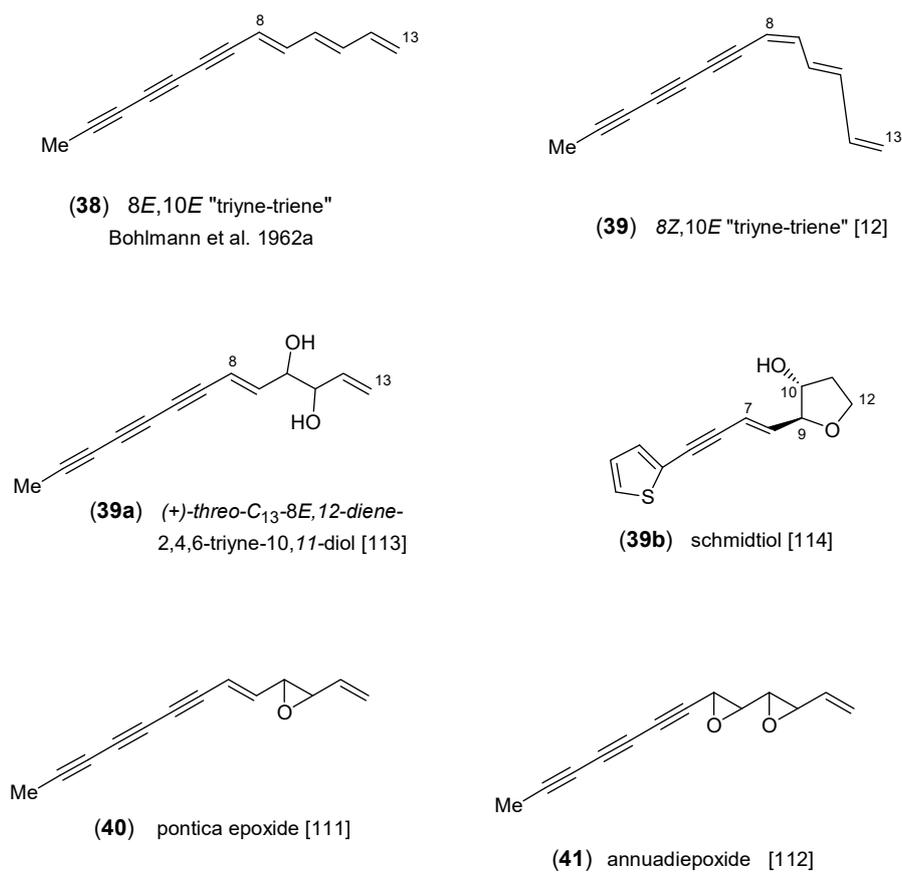


Table 5. "Triyne-triene", pontica epoxide, and related derivatives.

2.2.4. "Triyne-Triene" and Pontica Epoxide (PE)

The C₁₃-acetylene "triyne-triene" (38) is characterized by a fully conjugated system derived from a triyne-diene-diol intermediate (Figure 4). It was initially isolated from the roots of *Achillea ptarmica* L. and its characteristic UV-spectrum was detected in many species of the tribe Anthemideae [110]. In the genus *Artemisia* compound (38) was frequently reported for the "Vulgares" [13] and especially characterized species of the "Abrotana" group. As already pointed out for centaur X₃ (16), the central (*E*)-configured double bond, conjugated with three triple bonds, easily isomerizes to the (*Z*)-isomer (39) [12]. The widespread oxidation product (40) was detected in different genera of the Anthemideae and represents the first naturally occurring polyacetylene-epoxide. It was first isolated from the underground parts of *A. pontica* L. and named pontica epoxide (PE) [111]. From the aerial parts of *A. annua* L. pontica epoxide (40) was also isolated as major component along with a highly unstable diepoide, named annuadiepoide (41) [112]. In addition, the aerial parts were shown to contain the corresponding diol (39a) [113]. Inclusion of sulfur and demethylation lead to the C₁₂-thiophene schmidtliol (39b), isolated as minor component from the aerial parts of *A. schmidtiana* Maxim. Biogenetically, it is probably derived from a corresponding 12-hydroxy-9,10-epoxide precursor [114] (Table 5).

2.3. Spiroketal Enol Ether-Type

The formation of spiroketal enol ethers represents a typical chemical character of the tribe Anthemideae and plays a dominant role in acetylenic profiles of many *Artemisia* species [7,9,13]. Biogenetically, the bicyclic structure is derived from a linear triyne-ene-alcohol and is transformed via a ketoalcohol intermediate [115,116] (Figure 5). Due to their characteristic UV-spectra with only weakly defined broad maxima they can be clearly distinguished from other acetylenes (graphics in [1] and especially in [13]). They were isolated either as C₁₄-six- or C₁₃-five-membered ringenol ethers with stereochemically complex structures [117,118]. Both were reported to co-occur in *A. pedemontana*

Balb., where the 6-ringenol ethers dominated in the aerial parts and the 5-ringenols in the roots [119]. In the first report on structure elucidation Bohlmann et al. [120] described the isolation of the (*E*)-configured 6-ringenol ether (**42**) from *Tanacetum vulgare* L. and the corresponding 5-ringenol ether (**69**) from *Matricaria discoidea* DC. (syn.: *M. matricarioides*) together with the (*Z*)-isomers (**43**) and (**70**), respectively. Structural variation is created by ester groups mostly attached at position C-13 of the six-membered oxane ring (Table 6). The (*E*)-acetate (**44**) and the (*E*)-isovalerate (**46**) were isolated from *A. pedemontana* along with small amounts of the (*Z*)-isomers (**45**) and (**47**). All ester groups were shown to be uniformly attached at C-13 in axial orientation [119]. Further modification was reported for *A. caruthii* Wood with an acetoxy group attached at C-11 position (**48**) [12].

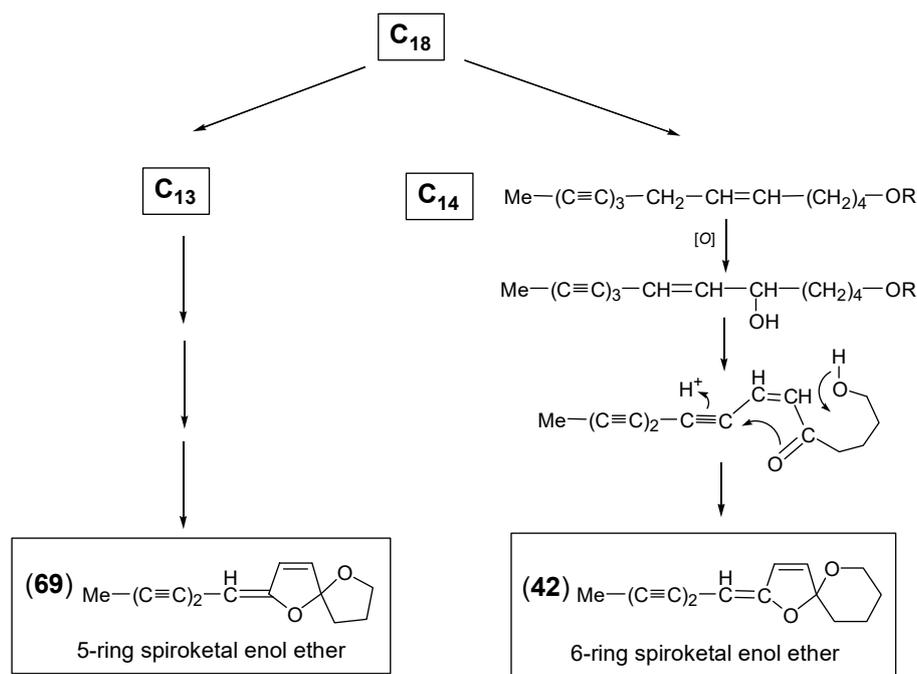
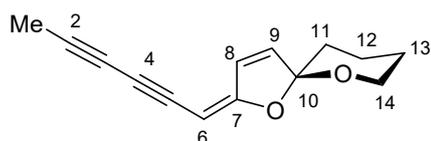


Figure 5. Biosynthesis of 5-ring (**69**) and 6-ring (**42**) spiroketal enol ether.

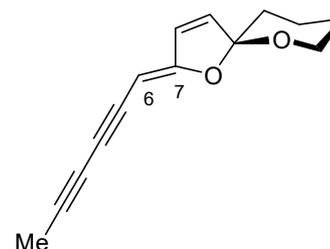
Additional oxidation leads to the formation of tricyclic epoxides of spiroketal enol ethers [121]. From *A. douglasiana* Bess. the epoxide of (*E*)-6-ringenol ether (**49**) was isolated along with the corresponding acetate (**50**) and isovalerate ester (**51**). However, the relative configuration of the epoxide-ring was not determined [122]. A series of related, but chromatographically deviating, epoxides was later detected in *A. selengensis* Turcz. Based on detailed stereochemical analysis it was shown that the 6-ringenol ether (**52**) represented a novel type of stereoisomers characterized by a “syn” arrangement of the epoxide-ring relative to the oxygen of the six-membered oxane ring [117]. This relative configuration could also be confirmed for the co-occurring acetate (**53**) and isovalerate ester (**54**), but is in contrast to the “anti” configured epoxides (**48-50**) found in *A. douglasiana* and other species investigated so far. The isovalerate group of (**54**) deviated by an equatorial orientation [12]. Ten years later a new epimer (**55**) was detected in the leaves of *A. lactiflora* Wall. ex DC. along with three known epoxides (**49-51**) and the new chlorohydrins (**56**) and (**57**) [29]. In a reinvestigation of *A. lactiflora* six closely related derivatives, named lactiflodiynes A-F (**58-63**), were isolated which showed different substitutions at C-8 and C-9 (Table 6). Their structures were elucidated by extensive spectroscopic methods, X-ray crystallography, chemical transformations, and CD. The absolute configuration of lactiflodiynes A (**58**) was determined to be 8R, 9S, 10S and 13R. It was shown that derivatives with an unsubstituted C-13 position contained a mixture of both, 10R and 10S analogues in the same plant, while in those with a substituted C-13 only 10S configuration was identified [118]. In addition, three further derivatives were isolated from *A. selengensis*, named artemiselenols A-C (**64-66**). The absolute configuration of artemiselenol A (**64**) was determined by X-ray crystallography to be 8R, 9S, 10S and 13S [123]. Inclusion of oxygen at C-6 leads to the two epimers (**67**) and (**68**) of a

keto-6-ringanol ether, isolated from the leaves of *A. feddei* H.Lév. & Vanot [124]. An important structural modification of spiroketal enol ethers is created by incorporation of sulfur, leading to the formation of thiophenes. The thienyl-substituted spiroketal (**71**) was isolated from the N-American *A. ludoviciana* Nutt. [125]. It was shown to represent the major constituent in several other *Artemisia* species accompanied by the dimeric derivative (**72**) [13,126]. From the aerial parts of *A. lactiflora* (10 kg) a novel C₁₄-diacetylenic compound was isolated, named artemisidiyne A (**72a**) [127]. Its unprecedented skeleton let expect biogenetic connections to the spiroketal-type pathway (Table 6).

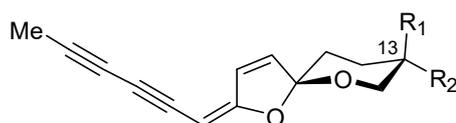
Table 6. Spiroketal enol ethers.



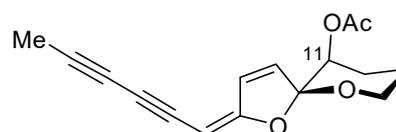
(**42**) (*E*) spiroketal enol ether
Bohlmann et al. 1961b



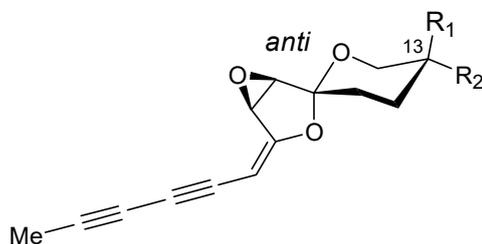
(**43**) (*Z*) spiroketal enol ether
Bohlmann et al. 1961b



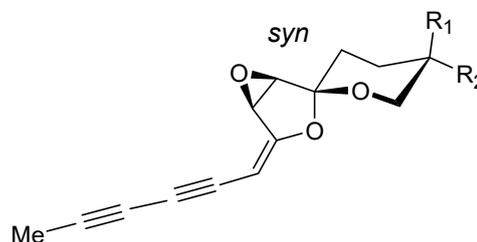
- 44** R₁ = OAc, R₂ = H; (*E*) spiroketal enol ether-13-O-acetate
45 (*Z*) isomer
46 R₁ = OiVal, R₂ = H; (*E*) spiroketal enol ether-13-O-isovalerate
47 (*Z*) isomer
 Bohlmann and Rode 1966



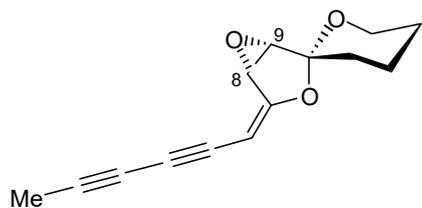
- 48** spiroketal enol ether-11-O-acetate
Wallnöfer et al. 1989



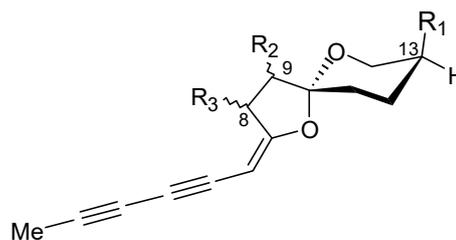
- 49** R₁, R₂ = H; (*anti*) epoxyspiroketal enol ether
50 R₁ = OAc, R₂ = H; (*anti*) epoxyspiroketal enol ether-13-O-acetate
51 R₁ = OiVal, R₂ = H; (*anti*) epoxyspiroketal enol ether-13-O-isovalerate
 Bohlmann et al. 1982
 Birnecker et al. 1988



- 52** R₁, R₂ = H; (*syn*) epoxyspiroketal enol ether
 Birnecker et al. 1988
53 R₁ = OAc, R₂ = H; (*syn*) epoxyspiroketal enol ether-13-O-acetate
54 R₁ = H, R₂ = OiVal; (*syn*) epoxyspiroketal enol ether-13-O-isovalerate
 Wallnöfer et al. 1989

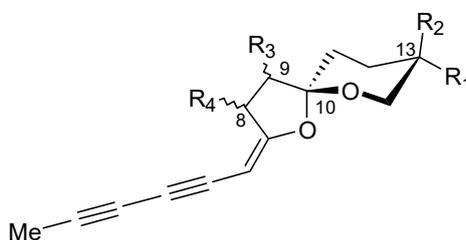


(55) (8,9-epi) epoxyspiroketal enol ether [29]



(56) $R_1 = H$, $R_2 = \alpha\text{-OH}$, $R_3 = \beta\text{-Cl}$; 8Cl, 9OH-spiroketal enol ether

(57) $R_1 = \text{OiVal}$, $R_2 = \beta\text{-OH}$, $R_3 = \alpha\text{-Cl}$; 8Cl, 9OH-spiroketal enol ether-13-O-risovalerate [29]



(58) $R_1 = H$, $R_2 = \text{OAc}$, $R_3 = \beta\text{-OH}$, $R_4 = \alpha\text{-Cl}$; lactiflodyne A [118]

(59) $R_1 = H$, $R_2 = \text{OH}$, $R_3 = \beta\text{-OH}$, $R_4 = \alpha\text{-Cl}$; lactiflodyne B [118]

(60) $R_1 = H$, $R_2 = \text{OiVal}$, $R_3 = \beta\text{-OH}$, $R_4 = \alpha\text{-Cl}$; lactiflodyne C [118]

(61) $R_1 = H$, $R_2 = \text{OAc}$, $R_3 = \beta\text{-OH}$, $R_4 = \alpha\text{-OH}$; lactiflodyne D [118]

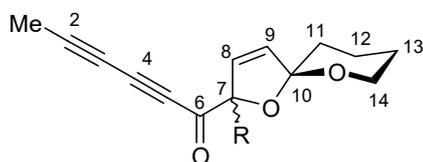
(62) $R_1 = H$, $R_2 = \text{OH}$, $R_3 = \beta\text{-OH}$, $R_4 = \alpha\text{-OH}$; lactiflodyne E [118]

(63) $R_1, R_2 = H$, $R_3 = \beta\text{-OH}$, $R_4 = \alpha\text{-Cl}$; lactiflodyne F [118]

(64) $R_1 = \text{OiVal}$, $R_2 = H$, $R_3 = \beta\text{-OH}$, $R_4 = \alpha\text{-Cl}$; artemiselenol A [123]

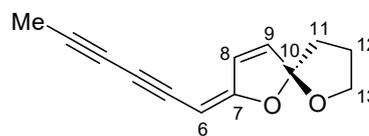
(65) $R_1 = \text{OiVal}$, $R_2 = H$, $R_3 = \beta\text{-OH}$, $R_4 = \alpha\text{-OH}$; artemiselenol B [123]

(66) $R_1 = \text{OH}$, $R_2 = H$, $R_3 = \beta\text{-OH}$, $R_4 = \alpha\text{-OH}$; artemiselenol C [123]

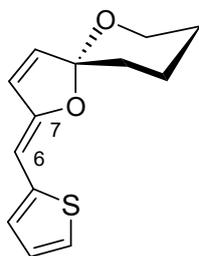


(67) $R = \alpha\text{-H}$, 6-oxo-(6-ring) spiroketal enol ether [124]

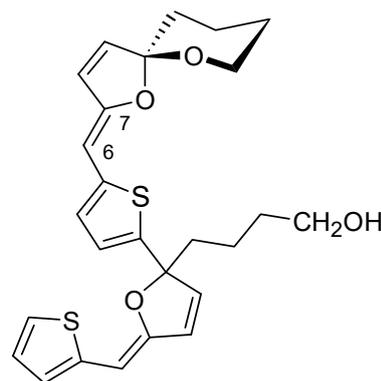
(68) $R = \beta\text{-H epimer}$ [124]



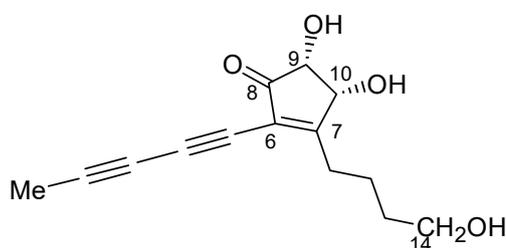
(69) (5-ring) (E) spiroketal enol ether
(70) (Z) isomer [120]



(71) (Z) thiophene spiroketal enol ether [125]



(72) dimeric thienyl-spiroketal enol ether [126]



(72a) artemisidiyne A [127]

2.4. Capillen-Isocoumarin-Type

Feeding experiments have shown that all aromatic acetylenes detected in *Artemisia* and in the tribe Anthemideae are derived from a linear C_{13} -triyne-enoic precursor. As demonstrated in Figure 6, the most important biosynthetic steps were proposed to be β -oxidation followed by a “Michael addition” leading to a cyclized ketoester, which is further converted to an aromatic intermediate. This aromatic ester represents the precursor of both the phenyl-diyne (Table 7A), and the isocoumarins (Table 7B) [1,14]. The first aromatic acetylenes were isolated from the essential oil of *A. capillaris* Thunb. and were identified as the phenyl-diyne capillen (73) [128] and capillin (77) [22]. In following GC/MS-analyses of *A. capillaris* the related derivatives capillon (79) [129], neocapillen (76), capillanol (80), and *o*-methoxycapillen (75) were also detected, from which (76) was supposed to be an artifact of (73) created by UV-irradiation [130–132]. Neocapillen (81), characterized by an acetylenic end group, was isolated from the lipophilic root extract of *A. dracuncululus* L. [133]. In addition, capillinol (78) was later obtained from *A. capillaris* collected in Korea [134]. From the aerial parts of *A. ordosica* Krasch. *o*-hydroxycapillen (74) was isolated together with arteordoyin B (82) [91]. Compound (74) was originally isolated from *Chamaemelum fuscatum* (Brot.) Vasc. (= *Anthemis fuscata* Brot.) and its structure elucidated by Bohlmann and Zdero [135]. The structure of arteordoyin B (82) (Table 7A) with an aromatic carboxy group and an enol functionality in the side chain can be regarded as biogenetic precursor of isocoumarins (Figure 6) [91].

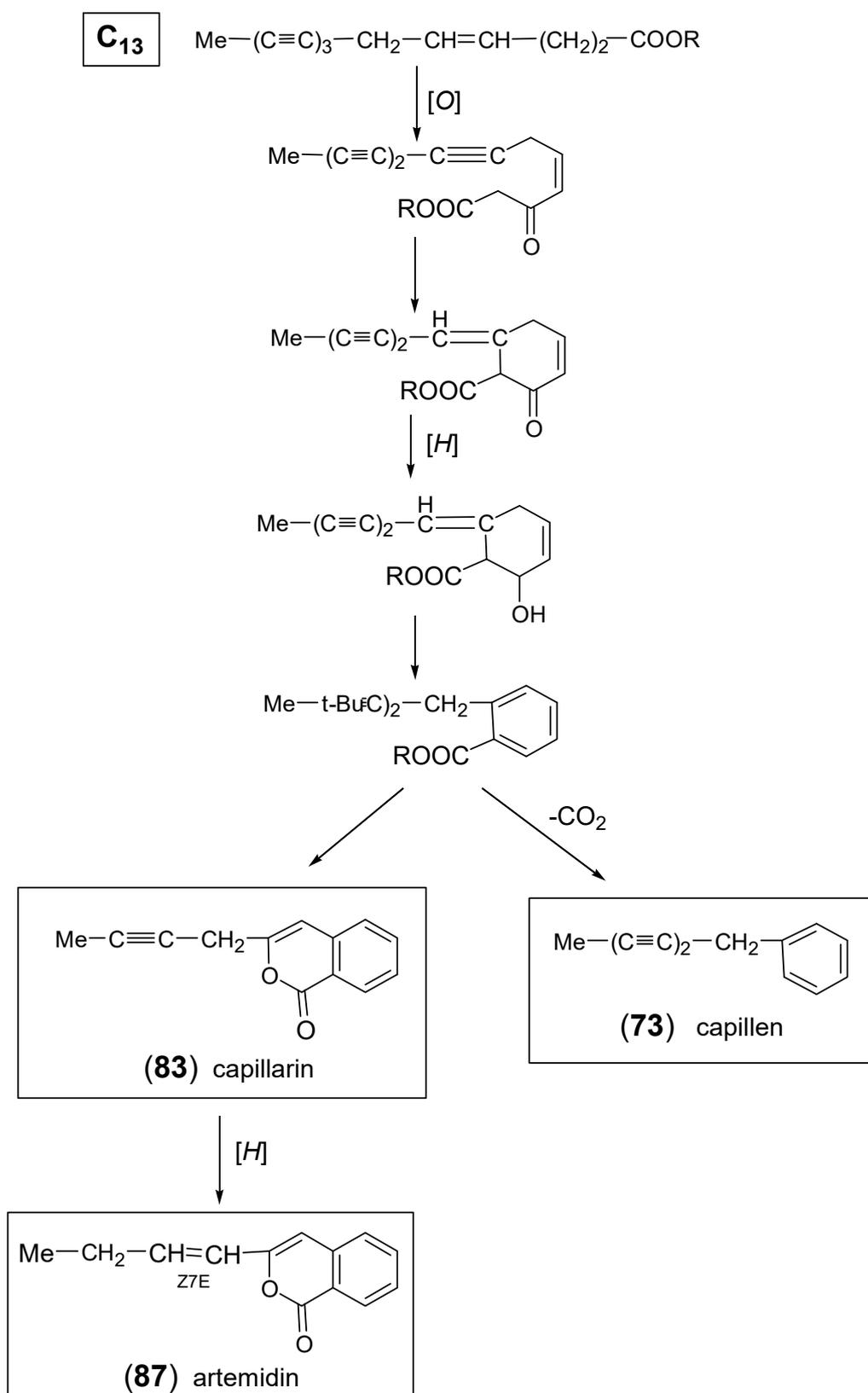


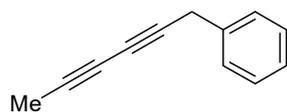
Figure 6. Biosynthesis of aromatic capillen (73) and isocoumarin (capillarin) (83).

The formation of isocoumarins (Table 7B) is an important biosynthetic step leading to major constituents in *Artemisia* species of the subgenus *Dracunculus* [7,11,27,95,136]. The acetylenic isocoumarin capillarin (83) was first isolated from *A. capillaris* [137] and was later also detected in *A. dracunculus* [133]. Structural variation is created by hydroxylation of the aromatic ring in 8-hydroxycapillarin (84) [138] and of the side chain, where it forms an ester with isovaleric acid (85) in

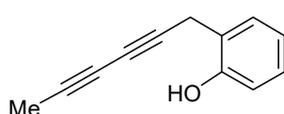
A. dracunculus [27] and with senecioic acid (86) in *A. arctica* Less., named capillarisen [139]. Another type of isocoumarin was also found in *A. dracunculus*, differing by an olefinic side chain. The corresponding derivatives were named artemidin (87), artemidinol (88), and artemidiol (92) [140–142]. Artemidin (87) was also reported independently for *Chamaemelum fuscatum* (Brot.) Vasc., where it was shown to coexist with the acetylenic capillarin (83), indicating close biogenetic connections [143]. In a reinvestigation of *A. dracunculus*, originating from Kyrgyzstan, the olefinic isocoumarins (*Z/E*)-artemidin (87), artemidinol (88), and the new 8-hydroxyartemidin (89) were isolated as major constituents [7]. As shown in a following chromatographic comparison of lipophilic root extracts of the taxonomically complex *A. dracuncus* group, different accumulation trends towards phenyl-diyne, acetylenic, or olefinic isocoumarins represent significant chemical characters [11]. Additional structural variation of the olefinic side chains of artemidins leads to the formation of epoxyartemidin (90), dracumerin (91), 2'-methoxydihydroartemidin (93), and 3'-hydroxyartemidin (94) [27].

Table 7. Aromatic acetylenes and isocoumarins.

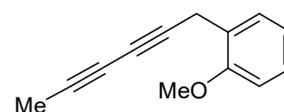
A Capillen derivatives (phenyl-diyne)



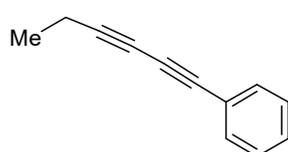
(73) capillen [129]



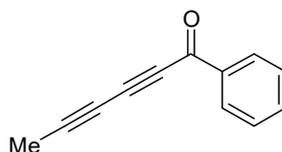
(74) o-hydroxycapillen [135]



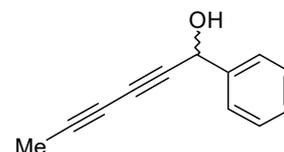
(75) o-methoxycapillen [130]



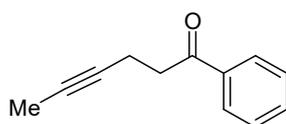
(76) neocapillen [132]



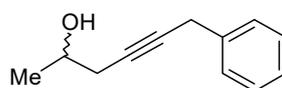
(77) capillin [22]



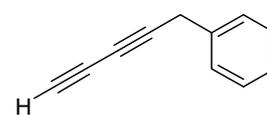
(78) capillinol [134]



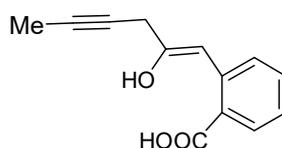
(79) capillon [128]



(80) capillanol [131]

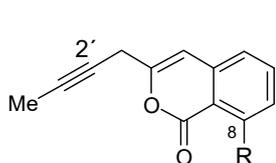


(81) norcapillen [133]



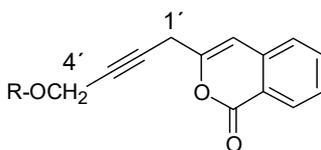
(82) arteordoy B [91]

B Isocoumarins (including biogenetically related olefinic derivatives)



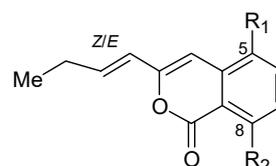
(83) R = H, capillarin [133,137]

(84) R = OH, 8-hydroxycapillarin [138]



(85) R = isovaleryl
capillarin isovalerate [27]

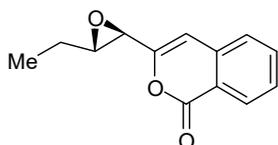
(86) R = senecioid
capillarisen [139]



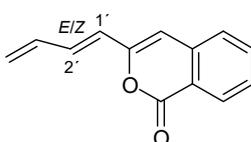
(87) R₁, R₂ = H, (Z/E) artemidin

(88) R₁ = OH, R₂ = H, artemidinol
[140,141,143]

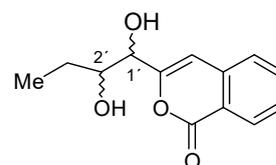
(89) R₁ = H, R₂ = OH, 8-hydroxy-
artemidin [178]



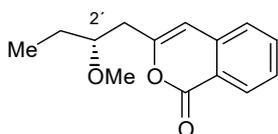
(90) epoxyartemidin [27]



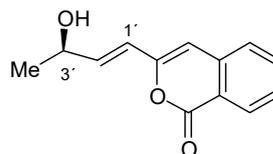
(91) dracumerin [27]



(92) artemidiol [142]



(93) 2'-methoxydihydroartemidin [27]



(94) 3'-hydroxyartemidin [27]

3. Biological Activities

3.1. Antifungal Activity

The discovery of the antifungal activity of safynol, a C₁₃-acetylene from safflower (*Carthamus tinctorius* L.; Asteraceae) [64], and falcarindiol, a C₁₇-acetylene from *Aegopodium podagraria* L. (Apiaceae) [37], awakened the biological interest in this class of compounds. This was further intensified by the exploration of the mode of action of falcarindiol against *Mycocentrospora acerina* (Hartig) Deighton, a storage pathogen of carrot (*Daucus carota* L.). Here, it was shown that 28 µg/ml burst bimolecular lipid membranes formed from lecithin or lecithin-cholesterol and caused haemolysis in erythrocytes [38,39]. The protective role of falcarinol and falcarindiol became apparent by their formation as phytoalexins in tomato leaves (*Lycopersicon esculentum* Mill.) [40]. This response to a fungal attack in a member of the Solanaceae, a family normally without polyacetylenes, impressively underlined the function of acetylene accumulation as defensive mechanism. Antifungal activity was later also reported for the structurally closely related dehydrofalcarinol (1) and dehydrofalcarindiol (3), isolated from *Artemisia borealis* Pallas [42,43]. Since their structures differ only by an additional isolated double bond, similar molecular mechanisms may be expected. A more recent study informed about antifungal properties of six derivatives (1, 3, 8, 9, 12, 15); Table 1). They were isolated from *A. halodendron* Turcz. ex Bess., and tested against five different fungi. The highest values for mycelial growth inhibition were reported for the 3R,10S-configured C₁₇-1,8,16-triene-4,6-diyne-3,10-diol, named arthaloyn A (8), and for 3R,8S-dehydrofalcarindiol (3) (= arthaloyn B) against the two fungi *Cladosporium curcumerinum* and *Magnaporthe oryzae*. The antifungal values were comparable with those of the commercial fungicide carbendazim [46].

A second group of antifungal acetylenes is represented by derivatives of the aromatic capillen-isocoumarin-type (Figure 1; Table 7). The first active compound was isolated from *A. capillaris* and named capillin (**77**) [22]. Two further antifungal derivatives, norcapillen (**81**) and capillarin (**83**), were obtained from the essential oil fraction of *A. dracuncululus* L. They were detected by bioautography on TLC-plates and tested against *Colletotrichum fragariae*, *C. gloeosporioides*, *C. acutatum*, and *Botrytis cinerea*. The isocoumarin capillarin (**83**) was shown to be more effective especially against *B. cinerea*, where 30 μmol caused 60% growth inhibition [144]. A more detailed analysis of 13 naturally occurring and 11 synthetic isocoumarins (including acetylenic and biosynthetically related olefinic derivatives) informed about structure-activity relationships in this group of compounds. It was shown that the structural variation of the butyl-side chain plays an important role for different activities [27]. The mechanism of action of the antifungal phenyl-heptatriyne was interpreted as disruption of membranes, enhanced in the presence of sunlight [26]. Regarding the similar molecular structures of capillen derivatives, it is tempting to assume similar mechanisms.

The antifungal activity reported for *A. absinthium* L. ("wormwood") [104] should be reconsidered, since the structures of the active C_{12} -dithiophenes apparently don't fit in with the chemical make-up neither of the genus *Artemisia* (Figure 1) nor the tribe Anthemideae. Antifungal activity was also reported for spiroketal enol ethers isolated from *Dendranthema zawadskii* (Maxim.) Kitam. (tribe Anthemideae), which were tested against the humanpathogenic fungus *Trichophyton mentagrophytes* [34]. However, in the genus *Artemisia* antifungal activities are solely established so far for derivatives of the dehydrofalcariinol- and aromatic capillen-isocoumarin-type (Figure 1).

3.2. Insecticidal Activity

On the basis of leaf-disk choice tests Yano [25] described the insect antifeeding properties of the essential oil of growing buds of *A. capillaris* against larvae of *Pieris rapae* ("cabbage white butterfly"). It was shown that the two aromatic acetylenes capillen (**73**) and norcapillen (**81**) were responsible for activity. In this connection a possible ecological role of aromatic acetylenes was proposed for their different accumulation in two chemotypes of *A. capillaris* in Japan, collected near the river bank and at the sea shore. While the roots of both were characterized by compounds (**73**) and (**76**), the aerial parts clearly differed by accumulating acetylenes only in plants from the river bank [145]. Follow-up studies indicated that both presence and different position of triple bonds in the side chain influenced activity and intensity [146,147]. Another aromatic acetylene with insecticidal property was reported for *A. monosperma* Del. [148]. However, the published structure was assumed to be incorrect [77,149]. Most likely, it represented again capillen (**73**). In the search for naturally occurring agrochemicals the essential oil of *A. ordosica* Krasch. was shown to possess repellent and fumigant activity against *Tribolium castaneum* ("flour beetle"). The active components were identified as the aromatic acetylenes (**73**, **76**, **77**), together with (*Z*)-DME (**21**) [150].

In addition to aromatic acetylenes, insecticidal properties were also reported for derivatives of the dehydrofalcariinol-type. While a preliminary screening already exhibited larvicidal activity of dehydrofalcariinol (**1**) and dehydrofalcariindiol (**3**) against *Aedes aegypti* ("yellow fever mosquito") [42,43], a more detailed test of six different derivatives (**1**, **3**, **8**, **9**, **12**, **15**) (Table 1) informed about structure-activity relationships. They were isolated from *A. halodendron* and tested against *Bradysia odoriphaga* ("chive gnat"; Diptera). While the C_{17} -derivatives (**1**, **3**, **8**, **9**) showed even higher values than the control azadirachtin, the C_{10} -derivatives (**12**, **15**) were clearly less toxic. Among the active compounds dehydrofalcariinol (**1**) was most effective, followed by arthaloin A (**8**) [46].

Insecticidal activity was also reported for acetylenes of the spiroketal enol ether-type [31,35,151]. In the genus *Artemisia* three derivatives (**42**, **43**, **69**), isolated from aerial parts and roots of *A. granatensis* Boiss., showed antifeeding effects against the three pest insects *Spodoptera littoralis*, *Rhopalosiphium padi*, and *Myzus persicae* [152]. Moreover, insecticidal activity is also known from pontica epoxide (PE) (**40**) [153] and (*Z*)-DME (**21**) [150], representing derivatives of the linear triyne-type (Figure 1).

3.3. Nematicidal Activity

Apart from the well-known nematicidal, acetylene-derived, thiophenes from *Tagetes* species ("marigold") [50,66] another type of nematicidal dithiophenes was reported for *A. absinthium* [104]. However, as already mentioned in section 2.3 (DME), the identity of the plant material should be reconsidered, since this structural type of acetylenes is unknown from the genus *Artemisia* as well as from the tribe Anthemideae. Polyacetylenes with nematicidal properties were first isolated from *Carthamus tinctorius* L.(Asteraceae) and identified as (E/Z)-isomers of C₁₃-ene-triyn-ene [154,155]. Significant nematicidal activity was later reported for the two C₁₇-acetylenes falcarinol and falcarindiol, isolated from *Hansenia weberbaueriana* (Fedde ex H. Wolff) Pimenov & Kijuykov (Apiaceae) [51]. From the lipophilic extract of *A. halodendron* six derivatives of the structurally related dehydrofalcarinol-type (**1**, **3**, **8**, **9**, **12**, **15**) (Table 1) were shown to exhibit remarkable effects against *Meloidogyne incognita* ("root-knot nematode"). Among the active compounds artemhaloyn A (**8**) showed the highest LC₅₀ value (0.21 ± 0.03 mg/l) which was much higher than that of the control abamectin [46].

3.4. Cytotoxic Effects

Cytotoxic acetylenes were first described for *Panax giinseng* C.A. Meyer (Araliaceae) and were identified as C₁₇-falcarinol (= panaxynol) derivatives [73]. Based on experiments with living membranes and artificial lipid bilayers, the cytotoxic effect was interpreted as result of membrane damage [156]. Tests with different cancer cells exhibited much higher growth inhibitory effect against malignant cells than against normal cells [52]. The high cytotoxicity of falcarinol-type acetylenes was speculated to be associated with their ability to form extremely stable carbocations, thereby acting as very reactive alkylating agents toward biomolecules [20,60]. The structurally corresponding dehydrofalcarindiol (**3**), isolated from *Dendropanax arboreus* (L.) Decne & Planch. (Araliaceae), was tested against four different tumor cell lines (Hep-G2, A-431, H-4IIE, L-1210) at 0.025 % (w/v) and showed 100% killing in all cell lines [55]. The comparison of cytotoxicities between three dehydrofalcarinols (**1**, **3**, **8**) and those of the corresponding falcarinols, coexisting in *D. arboreus*, showed that the inclusion of the characteristic vinyl end group led to a slight reduction of potencies [56]. In a follow-up study the 3R,8R-stereoisomer of dehydrofalcarindiol (**3**), isolated from *A. monosperma* Del., was tested against four colorectal (LS174T, SKOLO1, COLO320DM, WIDR) and two breast cancer cell lines (MDA231, MCF7) . The greatest efficacy was determined for dehydrofalcarindiol (**3**) with IC₅₀ values at 5.8 µg/ml against MCF7, and 9.6 µg/ml against COLO320DM. Interestingly, this was the opposite of how the latter cell line responded to the cytostatic doxorubicin, where it was highly resistant [57]. The pronounced antitumor activity of dehydrofalcarindiol (**3**) was also reported for the root extract of *Gymnaster koraiensis* (Nakai) Kitam. (Asteraceae) tested against L1210 mouse leukemia cells. Among eight different falcarinol-related C₁₇-derivatives, including gymnasterkoreaynes A-F, dehydrofalcarindiol (**3**) clearly showed the highest value with an ED₅₀ at 0.12 µg/ml [157]. Apart from these active C₁₇-compounds a new type of C₁₄-diacetylene, named artemisidiyne A (**72a**), was isolated from *A. lactiflora* and showed cytotoxic activity against HCT-8, BGC-823 and A 549 tumor cell lines with IC₅₀ values at 7.5, 1.1, and 4.6 µmol, respectively [127].

Whelan and Ryan [28] investigated the effects of the aromatic acetylene capillin (**77**) on four human tumor cell lines to examine both its anti-proliferative and pro-apoptotic property. Using HT 29 (colon), MIA PaCa-2 (pancreatic), HEP-2 (epidermoid of larynx), and A549 (lung) tumor cells capillin (**77**) inhibited their viability in a dose- and time-dependent manner. It was most efficacious against HEP-2 cells with IC₅₀ values at 2.8µmol (24h), 0.8µmol (48h), and 0.6µmol (72h). Around 25% of all tested cells displayed cell shrinkage and loss of cell-to-cell contact after treatment with 1-8µmol capillin (**77**). Apart from observations with fluorescence microscopy apoptotic cell death was additionally confirmed by flow cytometry and agarose gel electrophoresis. Capillin also caused accumulation of cells in S+G₂/M-phase of the cell cycle, increased glutathione levels in tumor cells, and inhibited synthesis of macromolecules (DNA, RNA, proteins).The potent apoptosis-inducing

activity of capillin was later also confirmed by using human leukemia HL-60 cells. In this investigation it was shown that capillin (**77**) was more potent than capillen (**73**), and cell death was induced *via* the mitochondrial pathway [158].

3.5. Allelopathic Effects

The C₁₀-acetylenic ester DME (**21**) and the related lactone **23** of the linear triyne-type (Figure 3) were shown to strongly inhibit the growth of seedlings of the widespread weed *Echinochloa crus-galli* (L.) P.Beauv. ("barnyard millet"). DME (**21**), detected in many *Artemisia* species, was investigated in *Solidago altissima* L., where its allelopathic effect was regarded as one of the factors of the great propagating potency of this plant [69]. In a follow-up study the two isomers **21** and **22** were found in the soil at the border of *S. altissima* communities in concentrations that were inhibitory to the test plants [70]. Inhibition of seed germination of six different plants was described for the aromatic polyacetylene capillen (**73**) isolated from the roots of *A. capillaris*. In this test capillen (**73**) completely inhibited germination of the four plants *Setaria italica*, *Brassica oleracea*, *Viola tricolor*, and *Daucus carota*. It showed only weak inhibition against *Chrysanthemum coronarium*, but no effect against *Medicago sativa* [71].

3.6. Miscellaneous Properties

3.6.1. Antibacterial Activity

Apart from the C₁₀-4,6-diyonic acid and its methyl ester, isolated from *Bellis perennis* L. (Asteraceae) [159], antibacterial acetylenes are mainly known from the family Apiaceae. Here, they were represented by C₁₇-derivatives of the falcarinol-type [44,53,54]. In the genus *Artemisia* the C₁₃-acetylene pontica epoxide (PE) (**40**) from the linear triyne-type (Table 5) was shown to significantly contribute to the antibacterial activity of the lipophilic extract of the aerial parts of *A. annua* L. It was tested against the Gram-positive *Clostridium perfringens*, the causative agent of necrotic enteritis, which leads to severe losses in poultry industry [113].

3.6.2. Antiviral Activity

Only scattered information is available on polyacetylenes with antiviral properties. Based on bioassay-guided fractionation significant activity against *Herpes simplex virus* type 1 (HSV-1) and 2 (HSV-2) was detected for spiroketal enol ether (**42**), a major constituent of many *Artemisia* species. HSV-1 and HSV-2 are enveloped viruses, characterized by a large linear double-stranded DNA genome, and are major human pathogens. In the case of the spiroketal (**42**) It was shown that adsorption inhibition and viricidal activity appeared to be not relevant. Instead, the most significant effects were the inhibition of virus penetration and a novel mechanism consisting of the specific arrest of viral gene expression and, consequently, the decrease of viral protein accumulation within infected cells [36]. Antiviral activity was also reported for the C₁₀-dehydrofalcarinol-type acetylenes (**13a**) and (**13b**) against *Hepatitis B virus* (HBV). They were isolated from the aerial parts of *A. scoparia* Waldst. et Kit. and were shown to represent rare caffeoyl-substituted glucosides [94]. However, since antiviral activity was also detected in other coexisting caffeoylated compounds without acetylenic structures [93], it can be assumed that here caffeoyl substitution is mainly responsible for activity.

3.6.3. Inhibition of Superoxide Generation

The leaf extract of *A. lactiflora* Wall. ex DC. (Table 8), an edible species from southeast Asia, was shown to inhibit PMA (phorbol myristate acetate)-induced superoxide (O₂⁻) generation. A group of spiroketal enol ethers were identified as active constituents, from which especially the epoxide of the isovalerate ester (**51**) was a potent inhibitor with an IC₅₀-value at 7.6 μmol. In contrast, the activities of the closely related derivatives (**49**) and (**55**) (Table 6) with IC₅₀ = 47 μmol and 43 μmol, respectively, were much weaker. The results informed about structure-activity relationships and suggested that

an acyloxy group at C-13 position enhanced inhibition, whereas the absolute configurations are not important [29]. In a follow-up study the authors confirmed the inhibition effects of spiroketal (**51**) on a variety of tumor promoter-induced biological responses, such as oxidative stress as well as tumor promotion in ICR mouse skin [30].

3.6.4. Anti-Inflammatory Activity

The anti-inflammatory activity of acetylenes was first reported for *Daucus carota* L., where it was investigated by determining attenuation of response to LPS (lipopolysaccharide)-induction. The isolated C₁₇-falcarinol derivatives reduced nitric oxide (NO) production in macrophage cells by as much as 65% without cytotoxicity [160]. In *A. halodendron* the activity was attributed to the two dehydrofalcarinol derivatives (**3**) and (**9**) (Table 1). They inhibited the levels of NO, TNF- α (tumor necrosis factor), and IL-6 (interleukin) in LPS-induced RAW 264.7 cells in a dose-dependent manner [92].

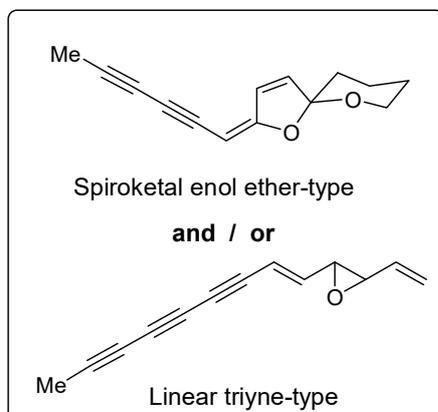
3.6.5. Inhibition of TGF- β 1- Induced Liver Cell Apoptosis

Experiments with transforming growth factor (TGF)- β 1-induced apoptosis in hepatocytes exhibited a strong inhibitory effect of the aromatic acetylenes capillin (**77**) and capillinol (**73**). They were isolated from *A. capillaris* as part of the Japanese herbal medicine "inchin-ko-to". Inhibition of undesired apoptosis induced by TGF- β 1 was expected to be beneficial for the treatment of various inflammatory liver diseases [161].

3.6.6. Anti-Diabetic Potential

The anti-diabetic potential of the two aromatic acetylenes capillin (**77**) and capillinol (**78**), isolated from *A. capillaris*, was investigated by testing the ability to inhibit the enzymes α -glucosidase, protein tyrosine phosphatase 1B (PTP1B), and rat lens aldose reductase (RLAR). In particular, capillin (**77**) showed potent inhibitory activity with an IC₅₀-value at 332.96 ± 1.44 μ mol against α -glucosidase, similar to the positive control acarbose with IC₅₀ = 320.33 ± 4.61 μ mol. In contrast, the efficacy of capillinol (**78**) against α -glucosidase and PTP1B was clearly weaker and showed even no activity against RLAR, suggesting that the keto group of capillin is the major determinant of its anti-diabetic potential [134].

Table 8. Infrageneric grouping of *Artemisia* based on the formation of characteristic structural types of polyacetylenes.



subg. *Artemisia*

"Vulgares"

<i>A. anomala</i>	<i>A. ludoviciana</i>
<i>caruthii</i>	<i>michauxiana</i>
<i>douglasiana</i>	<i>monophylla</i>
<i>dubia</i>	<i>montana</i>
<i>feddei</i>	<i>princeps</i>
<i>incisa</i>	<i>selengensis</i>
<i>integrifolia</i>	<i>stelleriana</i>
<i>koidzumii</i>	<i>tilerii</i>
<i>lactiflora</i>	<i>vulgaris</i>

"Abrotana"

<i>A. abrotanum</i>	<i>A. persica</i>
<i>afra</i>	<i>pontica</i>
<i>annua</i>	<i>vestita</i>
<i>gmelinii</i>	

subg. *Absinthium*

"Absinthia s.l."

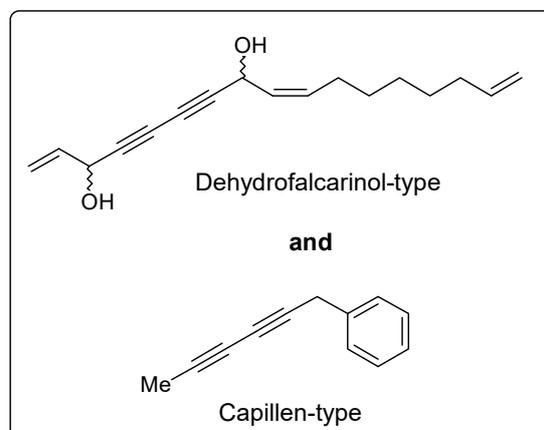
<i>A. pedemontana</i>	<i>A. frigida</i>
<i>assoana</i>	<i>granatensis</i>
<i>austriaca</i>	<i>mutellina</i>

"Absinthia s.str."

<i>A. absinthium</i>	<i>A. siversiana</i>
<i>arborescens</i>	<i>macrocephala</i>
<i>canariensis</i>	<i>jacutica</i>
<i>gorgonum</i>	

subg. *Seriphidium*

subg. *Tridentatae*



subg. *Dracunculus*

<i>A. borealis</i>	<i>A. halodendron</i>
<i>campestris</i>	<i>japonica</i>
<i>cappilaris</i>	<i>lamprocaulos</i>
<i>caudata</i>	<i>littoricola</i>
<i>commutata</i>	<i>monosperma</i>
<i>crithmifolia</i>	<i>ordosica</i>
<i>dracunculus</i>	<i>pycnocephala</i>
<i>eriopoda</i>	<i>scoparia</i>

"Heterophyllae"

<i>A. armeniaca</i>	<i>A. oelandica</i>
<i>atrata</i>	<i>panicii</i>
<i>laciata</i>	<i>punctata</i>
<i>latifolia</i>	
<i>A. arctica</i>	<i>A. norvegica</i>

4. Chemotaxonomy

The infrageneric classification of *Artemisia* is mainly based on floral characters and DNA-sequence data. According to that the species are traditionally separated into the five subgenera *Artemisia*, *Absinthium*, *Seriphidium*, *Dracunculus*, and *Tridentatae*. However, as pointed out in a

comprehensive treatise of the biology of the genus, many problems remained to be solved regarding a more natural taxonomic arrangement both at the subgeneric as well as the species level [162]. Apart from palynological and cytogenetic results promising contributions were also expected from phytochemical data. Stimulated by pharmaceutical interests most studies focused on the distribution and activity of sesquiterpene lactones and monoterpenes, while other typical classes of compounds, such as flavonoids, coumarins, lignans, and polyacetylenes, were less intensely investigated [77]. Due to the typical UV-spectra of polyacetylenes broad-based UV-HPLC comparisons of lipophilic crude extracts of a representative set of *Artemisia* species informed about the distribution of characteristic derivatives. Together with leaf and floral characters they were shown to represent chemical markers that corresponded remarkably well with the classical infrageneric classification (7, 9-11, 13]. Considering the biogenetic origin, their structures were grouped into the (a) dehydrofalcariol-, (b) capillen-isocoumarin-, (c) spiroketal enol ether-, and (d) linear triyne-type (Figure 1). One of the most striking chemical differences within the genus was the vicarious occurrence between types (a) and (b) in the subgenus *Dracunculus*, and types (c) and (d) in the other subgenera (Table 8).

Within the subgenus *Dracunculus* various aromatic acetylenes were shown to characterize different samples of *A. dracunculus* itself. In addition to dehydrofalcariol derivatives, the diploid representatives, published as *A. dracunculiformis*, *A. glauca*, and *A. pamirica*, mainly accumulated capillen (73), while the polyploids of *A. dracunculus* s.str. differed by isocoumarins (Table 7). The formation of capillarin (83) distinguished the decaploid sample from hexa- and octoploids, originating from central Asia, which mainly contained olefinic isocoumarins (87-89) [11]. The co-occurrence of structural types (a) and (b) was also shown to be typical for the taxonomically complex *A. campestris* – *A. capillaris* group. More detailed investigations revealed structural diversification of dehydrofalcariol derivatives by mid-chain oxidation and shortening to C₁₀-derivatives. They were isolated from the aerial parts of *A. eriopoda* Bunge [162] and *A. halodendron* [46]. The formation of structurally corresponding C₁₀-glucosides (Table 1) in *A. monosperma* [57], *A. capillaris* [93], and *A. scoparia* [94] underlined the common biogenetic trend. Considering this clear chemical segregation, the additional occurrence of dehydromatricaria ester (DME) (21) of the linear triyne-type in *A. ordosica* Krasch. is noteworthy [91,150].

Of particular chemotaxonomic interest is the predominance of dehydrofalcariols in the “Heterophyllae” and “Norvegicae”, two species groups placed in the subgenus *Artemisia* on the basis of morphological characters. The close phylogenetic relationship between the “Heterophyllae” and *A. norvegica* Fries. and *A. arctica* Less. was suggested by floral and cytological data [164]. The formation of dehydrofalcariolone (2) in *A. norvegica* (collected in Dovrefjell, Norway; Greger unpubl.) and the co-existence of dehydrofalcariol (1) with the aromatic acetylenes capillen (73), capillarin (83), and capillarisin (86) in *A. arctica* strengthened this proposal [139]. The detection of dehydrofalcariolone (2) in the taxonomically rather isolated E-Asiatic *A. keiskeana* Miq. suggested a relationship to the subgenus *Dracunculus* [9].

The formation of spiroketal enol ethers is a prominent chemical feature of the subgenera *Artemisia* and *Absinthium* (Table 8). In spite of infraspecific variation, leading to a lack of spiroketals in European samples of *A. vulgaris* L. [179] or within *A. princeps* Pamp., originating from Mt. Aso in Japan (Greger unpubl.), they represent a basic biogenetic trend of the “Vulgares” group within the subgenus *Artemisia* [13]. Structural variation was created by different ester groups, epoxidations, stereochemistries, and incorporation of sulfur. However, only C₁₄-derivatives of six-membered ringenol ethers were reported so far. By contrast, in the subgenus *Absinthium* the co-existence of C₁₃-five-membered ringenols (Figure 5) was detected in *A. pedemontana* Balb. [120] and in the alpine *A. mutelina* Vill. group [1,165]. This biogenetic trend was later also confirmed for *A. austriaca* Jacq. and *A. frigida* Willd. [10,166], as well as for *A. assoana* Willk. [167] and *A. granatensis* Boiss. [152]. In view of these results it appears of taxonomic relevance that in *A. absinthium* L. itself, and in the probably closely related shrubby members *A. arborescens* L. and *A. canariensis* Less. only the (Z)-isomers of 6-ringenol ethers (published as “trans”-configured) were detected [10]. The relationship of this species group, including *A. gorgonum* Webb., *A. siversiana* Ehrh. ex Willd., *A. macrocephala* Jacqem. ex

Bess., and *A. jacutica* Drob. was additionally confirmed by an accumulation of sesamin-type lignans [9,166,168–170]. With the accumulation of the lignan syringaresinol together with the 6-ringenol ether and its thiophene derivative the NW-African *A. reptans* C. Sm. [108] suggested also relations to this species group.

Apart from spiroketal enol ethers the two subgenera *Artemisia* and *Absinthium* are additionally characterized by acetylenes of the linear triyne-type (Figure 1; Table 8). Within the subgenus *Artemisia* a group of species deviates by a predominance of the “triyne-triene” (38) and particularly ponica epoxide (PE) (40), linked with a lack of spiroketals. This group, informally named “Abrotana”, includes *A. abrotanum* L., *A. afra* Jacq. [109], *A. persica* Boiss., *A. pontica* L. [111], and *A. annua* L. [112]. With the exception of *A. persica* they were previously placed in the section *Abrotanum*. The relationship of the “Abrotana” was also suggested by the formation of characteristic sesquiterpene-coumarin ethers [9,171].

Only scattered information is available on polyacetylenes of the subgenera *Seriphidium* and *Tridentatae*. As already pointed out previously, all Eurasiatic members of *Seriphidium* were characterized by a general reduction of acetylenes, comprising linear triynes combined with a lack of spiroketals, while in the N-American *Tridentatae* only small amounts of spiroketals were observed. They were detected in preliminary analyses due to their characteristic UV-spectra [9]. The biogenetic trend of subg. *Seriphidium* was later confirmed with the isolation and identification of the linear triynes centaur X₃ (16), “triyne-triene” (38) and PE (40) from the roots of *A. santonicum* L. ssp. *patens* (Neilr.) Person, collected in E-Austria (Bohlmann and Greger, unpubl.). These derivatives resembled that found in the subgenus *Artemisia*. In this connection it should be pointed out that the report on spiroketal enol ethers and sesamin-type lignans in *A. fragrans* Willd., a member of the subgenus *Seriphidium* [172], has obviously been based on misidentified plant material. Most likely, it was confused with *A. absinthium* [169].

As demonstrated in Table 8, acetylenes of the dehydrofalcariol-type play an important role for the infrageneric classification of *Artemisia*. They support not only the taxonomic segregation of the subgenus *Dracunculus*, but represent also a significant chemical character of the “Heterophyllae” group, previously placed in subgenus *Artemisia* [164]. With respect to the formation of dehydrofalcariols in the isolated, south-hemispheric Anthemideae genera *Eriocephalus* and *Coutla*, as well as their close structural relationship to falcariols, dominating in the families Pittosporaceae, Araliaceae and Apiaceae, this biogenetic trend is of special phylogenetic interest. In *Artemisia* this type of acetylenes was shown to be specifically linked to the formation of aromatic acetylenes of the capillen-isocoumarin-type (Figure 1). This differs from other findings in the tribe Anthemideae, where in the *Chrysanthemum* group aromatic acetylenes coexist with spiroketal enol ethers [1], and in the genus *Chamaemelum* (published as *Anthemis*) with DME of the linear triyne-type [143].

5. Declaration

The author declares no conflict of interest.

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