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POLYACETYLENES IN ARALIACEAE: THEIR CHEMISTRY, BIOSYNTHESIS AND BIOLOGICAL SIGNIFICANCE

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Key Word Index—Araliaceae; polyacetylenes; chemistry; distribution; biosynthesis; biological activities.

Abstract—Polyacetylenes are characteristic natural products of Araliaceae as they are of the closely related Umbelliferae. This review highlights recent findings on their distribution, chemistry, biosynthesis and biological activities.

INTRODUCTION

The distribution of polyacetylenes in the plant kingdom is of interest to chemotaxonomists since, when Basidiomycetes are excluded, they occur regularly in only seven families, namely Araliaceae, Campanulaceae, Compositae, Pittosporaceae, Oleaceae, Santalaceae and Umbelliferae [1]. Their biological properties also make them of interest to plant pathologists and pharmacologists. Although a number of excellent reviews have appeared [1–3], they are not very recent and only little is available about their occurrence in Araliaceae. This family comprises about 700 species in 55 genera [4, 5] and only 11 species from six genera have been investigated for polyacetylenes.

DISTRIBUTION AND CHEMISTRY

Table 1 gives the polyacetylenes isolated from the different species of Araliaceae. All isolated compounds (Fig. 1) are structurally closely related. The compounds are either C_{17}- or C_{18}-polyacetylenes, the C_{18}-compounds being either carboxy- or hydroxymethyl derivatives of falcarinol (**4**). It is characteristic that all compounds contain a terminal 3-hydroxy(or 3-oxo)hept-1-ene-4,6-diyne moiety and that the other terminal of all C_{17}-compounds consists of a saturated aliphatic C_7H_{15}-moiety. Several of the Araliaceae polyacetylenes are identical to acetylenes found widely distributed in the closely related family Umbelliferae.

Falcarinone (**1**) is common in Umbelliferae [1] and also

Table 1. Polyacetylenes in Araliaceae

Species	Compounds isolated (see Fig. 1)	Refs
Aralia elata Seem.	falcarinone (**1**)	[1, 6]
A. racemosa L.	falcarinone (**1**)	[1, 6]
	falcarinolone (**2**)	[1, 6]
A. mandschurica Seem.	falcarinone (**1**)	[1, 6]
	falcarinolone (**2**)	[1, 6]
A. nudicaulis L.	falcarinolone (**2**)	[6, 7]
A. californica S. Wats.	falcarinolone (**2**)	[1, 6]
	falcarindione (**3**)	[1]
Dendropanax trifidus Makino	octadeca-9(*Z*),17-dien-12,14-diyn-1,16(*R*)-diol (**9**)	[8]
	16(*R*)-hydroxyoctadeca-9(*Z*),17-dien-12,14-diynoic acid (**10**)	[8]
Hedera helix L.	falcarinone (**1**)	[7]
Panax ginseng C. A. Meyer	falcarinol (**4**)	[9]
	falcarintriol (**7**)	[10, 11]
	panaxydol (**8**)	[12, 13]
	heptadeca-1-en-4,6-diyn-3,9-diol (**6**)	[14]
Polyscias fructicosa Harms.	falcarinone (**1**)	[1, 6]
Schefflera arboricola	falcarinol (**4**)	[15]
S. digitata Forster	falcarindiol (**5**)	[16]

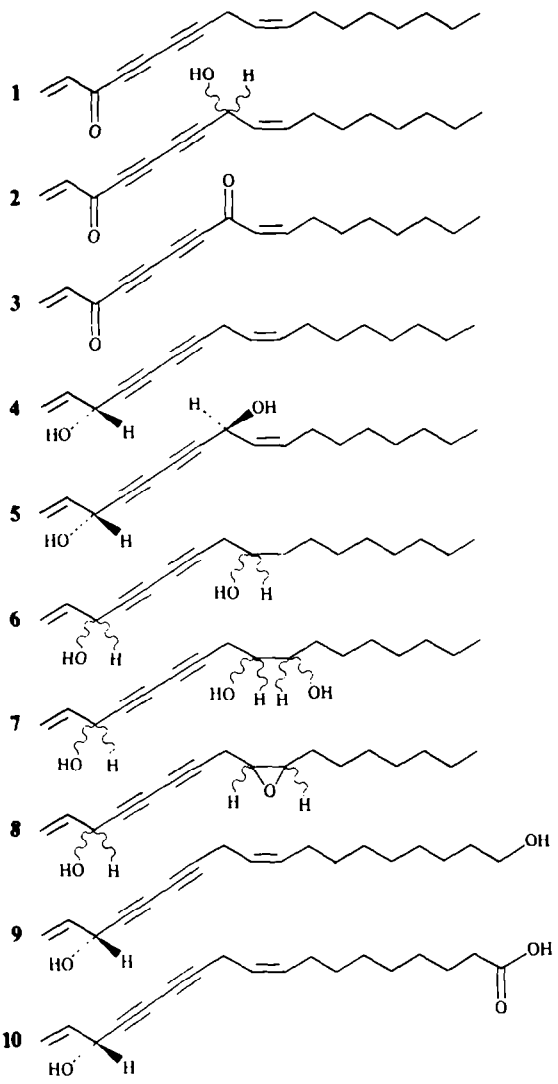
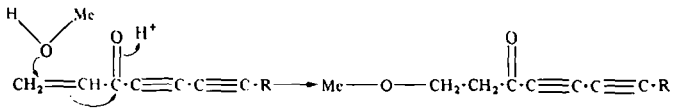


Fig. 1. Polyacetylenes isolated from different species of Araliaceae.



11 12

13 $Me\cdot\dot{C}H{=}CH\cdot\dot{C}{\equiv}C\cdot\dot{C}{\equiv}C\cdot\dot{C}H{=}CH\cdot\dot{C}O_2Me$

14 $Me\cdot C{\equiv}C\cdot C{\equiv}C\cdot C{\equiv}C\cdot CH{=}CH\cdot CH_2OH$

15 $Me\cdot(CH_2)_3\cdot CH\overset{Z}{=}CH\cdot(CH_2)_n\cdot CO_2Me \quad n = 2\text{-}7$

16 $Me\cdot C{\equiv}C\cdot C{\equiv}C\cdot C{\equiv}C\cdot CH_2\cdot CH\overset{Z}{=}CH\cdot(CH_2)_nCO_2Me \quad n = 2\text{-}7$

in Araliaceae, since five of 11 species examined from this family contain this compound. According to Bohlmann [1] falcarinone has also been isolated from *Panax ginseng* C. A. Meyer, but the references referred to [9, 17] describe isolation and structure determination of falcarinol and nothing is mentioned about falcarinone. A recent paper from 1983 reviewing polyacetylenes from *P. ginseng* C. A. Meyer does not mention falcarinone [10].

In Umbelliferae falcarinone is found, e.g. in *Oenanthe pimpinelloides* L. [7], *O. peucedonifolia* Poll [7], *Eryngium planum* L. [7], *Chaerophyllum temulum* L. [7] and *Pituranthus tortuosus* (Desf.) Benth. and Hook in which

falcarinone is found together with 11 other polyacetylenes [18]. In *Aegopodium podagraria* L. falcarinone occurs together with 12 other polyacetylenes. Falcarinone is also reported in a number of umbelliferous vegetables and spices such as parsnip, *Pastinaca sativa* L. [19], skirret, *Sium sisarum* L. [7], celery, *Apium graveolens* L. [1] and parsley, *Petroselinum crispum* (Miller) A. V. Hill [1].

Falcarinone (**1**) was isolated in 1961 from *Falcaria vulgaris* Bernh. (Umbelliferae) as the first polyacetylene of its kind with novel UV spectral characteristics typical of a 3-oxohept-1-en-4,6-diyne moiety (**11**) [7]. This structural element is also responsible for the reaction which falcarinone, and other related polyacetylenes (**11**), undergoes with methanol under acidic conditions giving rise to a Michael addition and the formation of the considerably more stable **12** [1]. The geometry of the C-9 double bond was established by synthesis of the (9*E*)-isomer. The structure was concluded to be heptadeca-1,9(*Z*)-dien-4,6-diyn-3-one (**1**) and this has been confirmed by synthesis [20].

Falcarinolone (**2**) was in 1961 described as a component of *Carum carvi* L. and is now known from a number of other umbellifers such as *Oenanthe pimpinelloides* L. [7], *Trachymene australis* L. [7], *Cryptotaenia canadensis* DC. [7], *Opopanax chironium* Kch. [21], *Sium sisarum* L. [7], *Aegopodium podagraria* L. [22] and *Daucus carota* L. [23], just as it is found in four *Aralia* species (Araliaceae) (cf. Table 1).

The constitution of falcarinolone was determined by Bohlmann [7] to be (+)-heptadeca-1,9(*Z*)-dien-4,6-diyn-8-ol-3-one (**2**) and the compound exhibits UV and IR characteristics similar to falcarinone (**1**) and reacts analogously with methanol under acidic conditions (**11** → **12**). The absolute configuration of falcarinolone has not been determined.

Falcarindione (**3**) occurs in *Aralia californica* S. Wats. [1], but was first reported together with falcarinolone from *Carum carvi* L. (Umbelliferae) [7]. The compound is additionally reported from the following umbellifers: *Cuminum cyminum* L. [1], *Sium sisarum* L. [7], *Oenanthe pimpinelloides* L. [7], *Silaus tenuifolius* DC. [1] and *Opopanax chironium* Kch. [21].

Falcarindione is extremely unstable and adds methanol under acidic conditions (cf. **11** → **12**), just as its UV and IR spectral characteristics are similar to those of **1** and **2**. The manganese dioxide oxidation of falcarinolone (**2**) to falcarindione (**3**) establishes the constitution of falcarindione as heptadeca-1,9(*Z*)-dien-4,6-diyn-3,8-dione (**3**).

Falcarinol (**4**) was first described by Takahashi *et al.* [9] in 1964 as a constituent of *Panax ginseng* C. A. Meyer and named panaxynol. The first constitutional formula proposal by Takahashi *et al.* [17] was proved wrong by the same group by synthesis [24]. In a subsequent publication Takahashi proposed panaxynol to be heptadeca-1,9(*Z*)-dien-4,6-diyn-3-ol (**4**) and confirmed its constitution by synthesis [12, 13, 25]. In 1966 Bohlmann [26] isolated falcarinol from *Falcaria vulgaris* Bernh. (Umbelliferae) and in 1967 Crosby and Aharonson [27] isolate a compound carotatoxin from *Daucus carota* L. (Umbelliferae), and proposed a constitutional formula for it. This formula was rejected in the same year by Bentley and Thaller, who showed that carotatoxin was identical to falcarinol [28]. The absolute configuration has been established by Larsen *et al.* [29] to be 3*R*.

Besides being present in *Panax ginseng* C. A. Meyer [9, 25] falcarinol is only found in one other Araliaceae: *Schefflera arboricola* [15], but falcarinol is known from Pittosporaceae [30] and occurs frequently in Umbelliferae [1], e.g. *Aegopodium podagraria* L. [22, 31], *Angelica acutiloba* var. *acutiloba kitagawa* [32], *Seseli gummiferum* Pall. [29] and *Pituranthus tortuosus* (Desf.) Benth. and Hook [18].

Falcarindiol (**5**) is only found in Araliaceae in *Schefflera digitata* [16], but is widely distributed in Umbelliferae [1, 18, 22, 31–36]. The first report on falcarindiol was by Bohlmann in 1966 from *Falcaria vulgaris* Bernh. (Umbelliferae) [26]. The constitution was determined to be heptadeca-1,9(*Z*)-dien-4,6-diyn-3,8-diol by Jones' group in 1969 [23] on falcarindiol isolated from *Daucus carota*. The absolute configuration was determined by Lemmich [36] to be 3*R*, 8*S*. Falcarindiol (**5**) is an unstable oil with a double 3-hydroxyhept-1-en-4,6-diyn moiety and is able to add two moles of methanol under acidic conditions (cf. **11** → **12**).

Heptadeca-1-en-4,6-diyn-3,9-diol (**6**) was isolated from a commercially available water-alcohol extract of *Panax ginseng* C. A. Meyer by Dabrowski *et al.* [14] and is not reported as occurring in other species. The constitution was deduced mainly from ^{1}H NMR and mass spectrometric data. The stereochemistry is unknown.

Falcarintriol (**7**) was isolated from the roots of *Panax ginseng* in 1982 by Sang Chul Shim *et al.* [10, 11]. The constitution was proposed as heptadeca-1-en-4,6-diyn-3,9,10-triol by comparison of its ^{1}H, ^{13}C NMR and IR spectroscopic data with those of falcarindiol. The stereochemistry is unknown.

Panaxydol (**8**) was reported in 1978 by Poplawski *et al.* [12, 13] as occurring in the roots of *Panax ginseng* C. A. Meyer. The proposed constitution as 9,10-epoxyheptadeca-1-en-4,6-diyn-3-ol was based on chemical reactions and the IR and ^{1}H NMR spectroscopic data. The constitution was confirmed by two dissimilar syntheses [13].

Octadeca-9(*Z*),17-dien-12,14-diyn-1,16(*R*)-diol (**9**). From the leaves of *Dendropanax trifidus* Makino, Kawazu *et al.* [8] isolated a C_{18}-diacetylene closely related to falcarinol (**4**). By chemical and spectroscopic methods the compound was shown to be octadeca-9(*Z*),17-dien-12,14-diyn-1,16-diol. The chirality of the C-3 centre was deduced using Brewster's rule [37].

16(*R*)-Hydroxy-octadeca-9(*Z*),17-dien-12,14-diynoic acid (**10**) is a second C_{18}-diacetylene isolated from *Dendropax trifidus* Makino [8]. Analysis of the spectroscopic data clearly showed that it was a carboxylic acid corresponding to the above mentioned **9**. Reduction of the methyl ester of **10** using lithium aluminum hydride afforded a compound in all respects identical to **9**. Thus the absolute configuration was established as *R*.

BIOSYNTHESIS

A comparison of the structures of polyacetylenes with those of oleic (**17**), linoleic (**18**), crepenynic (**19**) and dehydrocrepenynic (**20**) acids makes it reasonable to assume that the polyacetylenes are biosynthesized with the latter acids as precursors. Many precursor incorporation studies have confirmed this assumption [1, 38–41] and further that they are built up from acetate and malonate units [1, 3, 42–47].

Bu'Lock and co-workers [44] showed in 1961 that in *Polyporus antracophilus* the ester **13**, which is typical of

both plant and fungal C_{10}-acetylenes, incorporates ^{14}C from [1-^{14}C]acetate uniformly into alternate carbon atoms of the chain. Later they [45] showed that acetate is the starter group and that malonate extends the chain, since [2-^{14}C]malonate was incorporated specifically in the C-1–C-8 part of the chain and not in the terminal C_2-unit in dehydromatricarinol (**14**) isolated from *Tricoloma grammapodicum*. Further studies of Bu'Lock [38] in which *Tricoloma grammapodicum* was fed [10-^{14}C]oleic acid made it possible to isolate linoleic acid (**18**), crepenynic acid (**19**), dehydrocrepenynic acid (**20**) and dehydromatricarinol (**14**) with the C-10-labelling of oleic acid intact.

On incorporation of [1-^{14}C]acetate into *Santalum acuminatum*, which contains a number of C_{18}-polyacetylenes, Bu'Lock [43] showed that ^{14}C was incorporated specifically into the odd-numbered carbon atoms of palmitic acid, oleic acid and the C_{18}-polyacetylenic acids. The rate of incorporation indicated that palmitic and oleic acids are first formed and then transformed into the polyacetylenic acids.

In 1969 Bohlmann [40] demonstrated by synthesis of different carboxylic acid esters (**15**) and use of them in labelling experiments that only methyl oleate (**15**, $n = 7$) was a significant precursor in the biosynthesis of polyacetylenes of type **16** which are important precursors for many other polyacetylenes [1, 39, 48]. Other incorporation studies have further demonstrated that crepenynic (**19**) and dehydrocrepenynic (**20**) acids are precursors for polyacetylenes of type **16** [1].

With the above information together with known existence of the precursors (**17–21** and **10**) it is possible to deduce the sequence in Fig. 2 as the most likely pathway for the biosynthesis of falcarinol (**4**).

Biosynthesis of oleic acid (**17**)

The biosynthesis of the saturated fatty acids from acetate is well delineated [49–54] and the conversion of stearic acid into oleic acid with its inactivated 9(*Z*),10-double bond takes place in the presence of molecular oxygen, NADPH and a stereospecific enzyme system

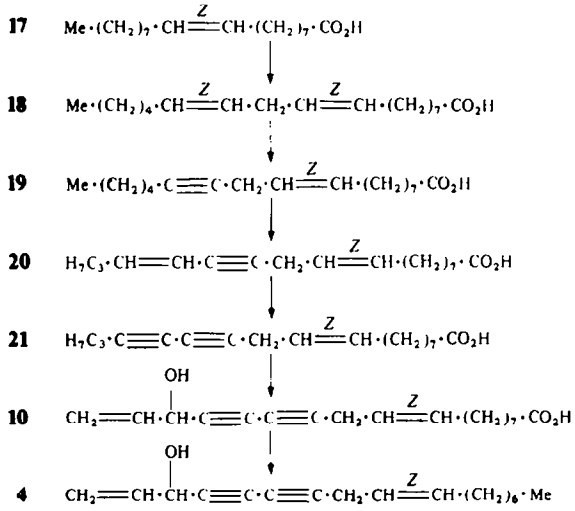


Fig. 2. Biosynthesis of falcarinol (**4**) in Araliaceae.

[49–51, 55, 56]. Bloch [55] has established by precursor incorporation studies that the dehydrogenation takes place by stereospecific removal first of the 9-*pro-R*-hydrogen and then of the 10-*pro-R*-hydrogen.

Polyacetylenes from oleic acid via crepenynic acid

There is at present not much known of the biological mechanism by which unsaturation is introduced in the series of acids given in Fig. 2. By analogy with the formation of the double bond in oleic acid (**17**) the reactions involved could be enzymatically catalysed oxidative dehydrogenations. Such a mode of synthesis would tally well with the range of structures found among the C_{18} acetylenic acids, and, furthermore, some of the same acids occur simultaneously in polyacetylene-producing plants and microorganisms [1].

Crepenynic acid (**19**) was isolated in 1963 from *Crepis foetida* L. (Compositae) [57] and has been used for many incorporation studies. Haigh *et al.* [58] has shown that crepenynic acid (**19**) is formed from oleyl-coenzyme A or oleic acid (**17**). If the CoA derivative is an intermediate, it seems likely that the first step is hydrolysis to the free acid, which is then oxidatively dehydrogenated to crepenynic acid. The participating enzyme system is not known, but contains probably Mg^{2+} and Cu^{2+}. The mechanism does not involve free linoleic acid, although this intermediate may be enzyme-bound [58]. As mentioned above, Bu'Lock has found that oleic and linoleic acids are precursors of crepenynic acid in *Tricholoma grammapodium* [38]. Incorporation studies have also shown that linoleic and crepenynic acids are both precursors of a considerable number of polyacetylenes [1, 38, 40, 59].

Dehydrocrepenyic acid (**20**) is known from polyacetylene producing fungi, e.g. *Tricholoma grammapodium* [1, 31], but not from higher plants [1]. Incorporation studies have shown that **20** functions as precursor of polyacetylenes in certain plants [1]. 9(*Z*)-Octadecen-12,14-diynoic acid (**21**) can arise by oxidative dehydrogenation of dehydrocrepenynic acid (**20**) and has further been shown by ^{13}C and ^{3}H incorporation studies to be incorporated into a number of polyacetylenes [1]. In Umbelliferae C_{17}-compounds with the same pattern of unsaturation are found. An example is **22** from *Heracleum sphondylium* L. [60].

16(*R*)-Hydroxyoctadeca-9(*Z*),17-dien-12,14-diynoic acid (**10**) may be formed by allylic oxidation and dehydrogenation of **21**. The order reaction is not known, but the co-occurrence of falcarinone (**1**) and 1,2-dihydrofalcarinone (**23**) in *Caucalis daucoides* L. [1] and *Conium maculatum* L. [60] could indicate that allylic oxidation is the first step.

Falcarinol (**4**) is proposed in Araliaceae to be formed by decarboxylation of the C_{18}-acid (**10**). This hypothesis is only based on the natural occurrence of **10** in this family. In Umbelliferae, in which C_{17}-compounds with the same pattern of unsaturation occur, decarboxylation seems to take place earlier with the C_{18}-acid (**21**) being decarboxylated to **23** which then, according to Fig. 3, could be transformed to falcarinone (**1**). On the other hand, from *Ainsworthia trachycarpa* Boiss. and *Pastinaca sativa* L. (Umbelliferae) containing falcarinone (**1**), falcarinol (**4**) and falcarindiol (**5**) [1], a C_{18}-aldehyde (**24**) closely related to falcarinone (**1**) has been isolated [19]. The conclusion must be that chain reduction here is the last step in the synthesis of falcarinone (**1**).

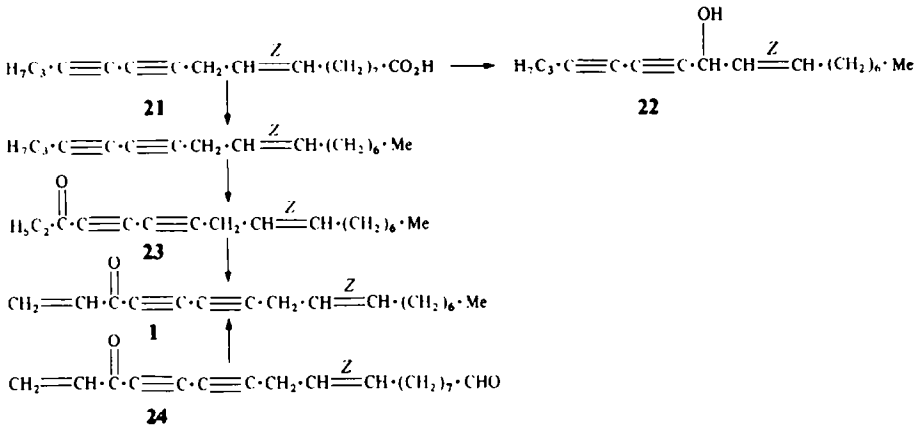


Fig. 3. Biosynthesis of falcarinone (1) in Umbelliferae.

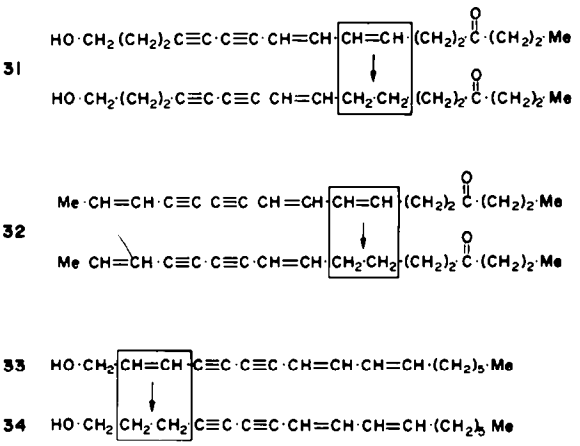
Figure 4 gives the biosynthetic relationship between the known polyacetylenes from Araliaceae. The C_{18}-diol (**9**) can only be related to the C_{18}-acid (**10**), but all other compounds must be synthesized from either falcarinol (**4**) or the C_{18}-acid (**10**).

Polyacetylenes from oleic acid via β-hydroxyoleic acid

Compositae contains 16,17-dehydro analogues to the C_{17}-polyacetylenes known from Araliaceae (Fig. 5). Dehydrofalcarinone (**25**) is common in *Artemisia* and *Helianthus* [1, 61], dehydrofalcarinol [26] is isolated from *Artemisia atrata* Lam. [26], dehydrofalcarinolone (**27**) from *A. crithmifolia* [26]. *Artemisia campestris* L. has given rise to dehydrofalcarindione (**28**) [26] and heptadeca-9(Z),16-dien-4,6-diyne (**29**) is found in *Chrysanthemum frutescens* [62]. The latter is a possible precursor for the former oxygen-containing compounds. Bohlmann [1, 26, 42] has therefore proposed that C_{17}-polyacetylenes such as falcarinol (**4**) of Umbelliferae and Araliaceae are formed through β-oxidation and decarboxylation of C_{18}-acids and, further, that 16,17-dehydro-polyacetylenes are intermediates in the biosynthesis (Fig. 6). Through incorporation studies Bohlmann has shown that oleic acid (**17**), as well as β-hydroxyoleic acid, are precursors for dehydrofalcarinone (**25**) in *Artemisia atrata* Lam. and that the shortening of the chain from C_{18} to C_{17} occurs through β-oxidation and then decarboxylation. The experiments do not indicate when decarboxylation occurs, but the biosynthetic scheme proposed by Bohlmann appears convincing [63] (cf. Fig. 6).

In another experiment with *Oenanthe pimpinelloides* L. Bohlmann [63] has shown that β-hydroxyoleic acid is the precursor for the C_{17}-polyacetylene (**30**), which possesses the saturated end group characteristic of the C_{17}-polyacetylenes of Umbelliferae and Araliaceae. If the corresponding 16,17-dehydro compound is an intermediate, the plant must have an enzyme system capable of converting the terminal vinyl group to a dihydro-compound.

The existence of the two sets of C_{17}-polyacetylenes (**31** and **32**) in *Oenanthe crocata* L. together with the established reduction in the same plant of isotopically labelled oenanthol (**33**) to the corresponding dihydro-compound (**34**) are indicative of the presence of such an



enzyme system, although it has yet to be isolated [1]. Additionally, the genus *Oenanthe* contains a large number of closely related polyacetylenes so that it is possible to set up other biosynthetic schemes.

Further incorporation studies are necessary before it is possible to conclude that polyacetylenes such as falcarinone and falcarinol from Umbelliferae and Araliaceae are biosynthesized either according to the pathway demonstrated for the 16,17-dehydroacetylenes of Compositae or by the pathway via crepenynic acid and the C_{18}-carboxylic acid corresponding to falcarinol.

BIOLOGICAL ASPECTS

Antifungal activity

Total inhibition against conidial germination of *Cochliobolus miyabeanus* has been observed at concentrations of 12.5 μg/ml of 9(Z),17(Z)-octadecadien-12,14-diyn-1,16(R)-diol and 50 μg/ml of 16(R)-hydroxy-9(Z),17(Z)-octadecadien-12,14-diynoic acid. Falcarinol (**4**) and falcarindiol (**5**) are reported active against several plant pathogens [31, 64–68].

Fungal attack on tomato plants, *Lycopersicon esculentum* L. (Solanaceae), is due to *Cladosporium fulvum* [64]. When healthy tomato plants are infected with this pathogen falcarinone (**1**), falcarindiol (**5**) and tetradeca-

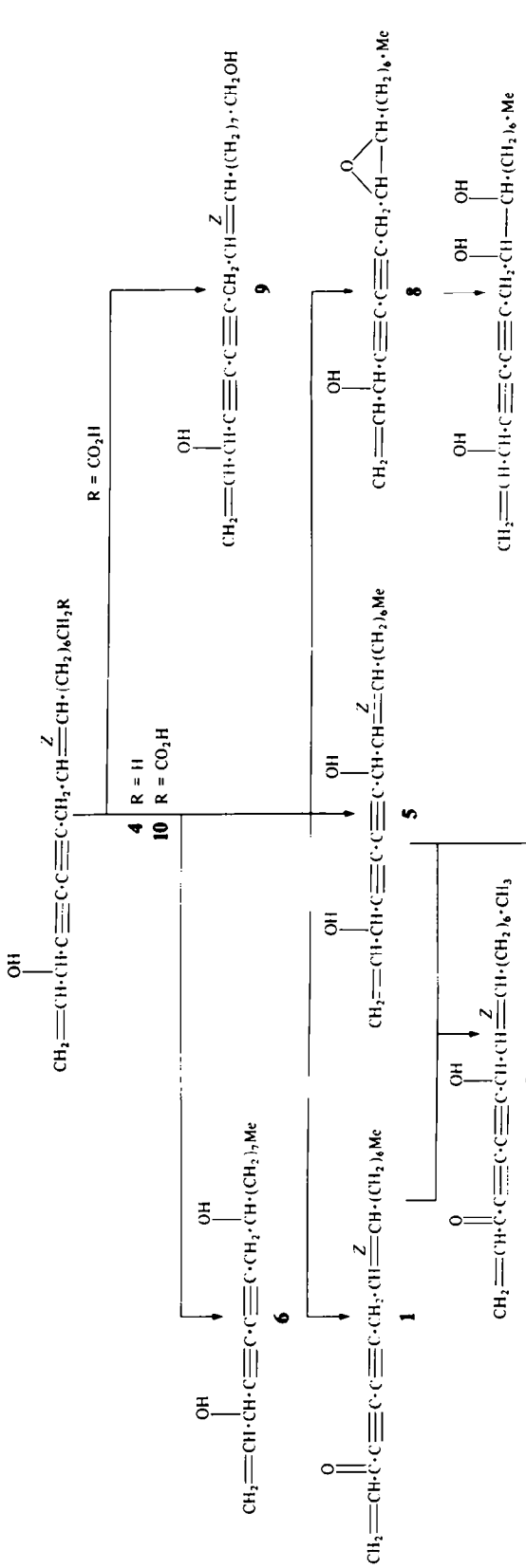


Fig. 4. The possible biogenetic correlation between polyacetylenes of Araliaceae.

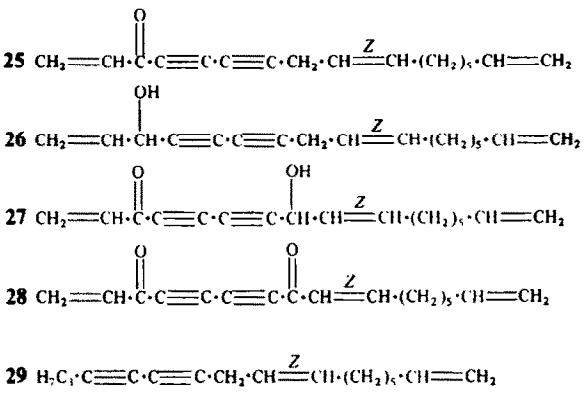


Fig. 5. Polyacetylenes from Compositae being 16-dehydro analogues to C_{17}-polyacetylenes characteristic of Araliaceae.

6(Z)-en-1,3-diyn-5,8-diol are formed [64]. These compounds can also be detected in tomato plants upon infection with *Verticillium albo-atrum* [69], but none of the three compounds has been isolated from uninfected plants [64]. Examination of the fungitoxicity of the same compounds against *Cladosporium fulvum* and *C. cacumerinum* shows falcarinol (**4**) to be the major inhibitor in the leaves. Due to purification problems, the concentration of falcarinol inhibiting growth of mycelium is not given, but the *in vitro* concentration for inhibition of growth of both fungi is 6 μg/ml of falcarinol, whereas the concentration of tetradeca-6(Z)-en-1,3-diyn-5,8-diol causing the same inhibition is about 3 times higher. The concentration of the fungicides in infected tissue is probably higher [64]. It is known in *Carthamus tinctorius* L. [1], *Vicia faba* L. [1], and *Daucus carota* L. [67] that an increase in the concentration of fungitoxic polyacetylenes occurs upon pathogen attack.

In some polyacetylene-producing plants the content of polyacetylenes depends on the season and in others, like *Aegopodium podagraria* L. (Umbelliferae), the content varies in the different parts of the plant. From *A. podagraria* L. falcarinol and falcarindiol have been isolated and their concentrations are especially high in young shoots (36 μg/g and 217 μg/g, respectively [31]). The antifungal properties were assessed and in Butt slides *Alternaria brassicola* and *Septoria nodorum* were totally inhibited by falcarindiol at a concentration of 20 μg/ml, whereas falcarinol at 200 μg/ml did not affect these fungi. The greater activity of the diol was confirmed in tests carried out using agar medium [31]. Harding and Heale [65] have shown that the inhibitory effect of falcarinol upon spore germination of *Botrytis cinerea* is considerably decreased when sucrose is present, and they suggest that the relatively weak inhibitory effect of falcarinol in the above experiments [31] could be caused by the experimental conditions.

In carrots, *Daucus carota* L. (Umbelliferae), falcarinol and falcarindiol seem to supplement each other in a defensive alliance against invading pathogens. With regard to concentration, falcarindiol dominates in the periderm, whereas falcarinol is the dominating polyacetylene in the phloem [65, 67]. Moreover, falcarinol and falcarindiol are specific in their toxicity against some of the pathogens attacking carrots. One pathogen, *Botrytis cinerea*, attacks carrots on storage, but not when they are fresh [65]. Falcarinol inhibits spore germination in *Botrytis cinerea* and its concentration is greatly increased when carrots are infected with this pathogen [67]. Infection with heat-killed conidia of *Botrytis cinerea* produces cell changes in the carrot tissue and this cell change could possibly trigger increased production of falcarinol [65, 70].

The other polyacetylenes present in *Daucus carota*, falcarindiol, falcarinolone and falcarindiol monoacetate, have no effect on *Botrytis cinerea* when infecting carrot slices [65]. The bacterium *Erwinia carotovora* also attacks *Daucus carota*, but is not affected by falcarindiol in concentrations up to 100 μg/ml [66]. It is conceivable that the bacterium is able to metabolize falcarindiol in carrots [66].

Falcarindiol, however, is antifungal against *Mycocentrospora acerina*, which attacks carrots on storage [66]. The cladymospora of *Mycocentrospora acerina* adsorb falcarindiol from test solutions, without metabolizing it [66]. Microscopy reveals that falcarindiol destroys the membrane and cytoplasma of cladylospora of *Mycocentrospora acerina* [66] and in young hyphae falcarindiol causes bursting of the tips resulting in cytoplasmic leaking [66, 68].

The effect of falcarindiol on human erythrocytes has

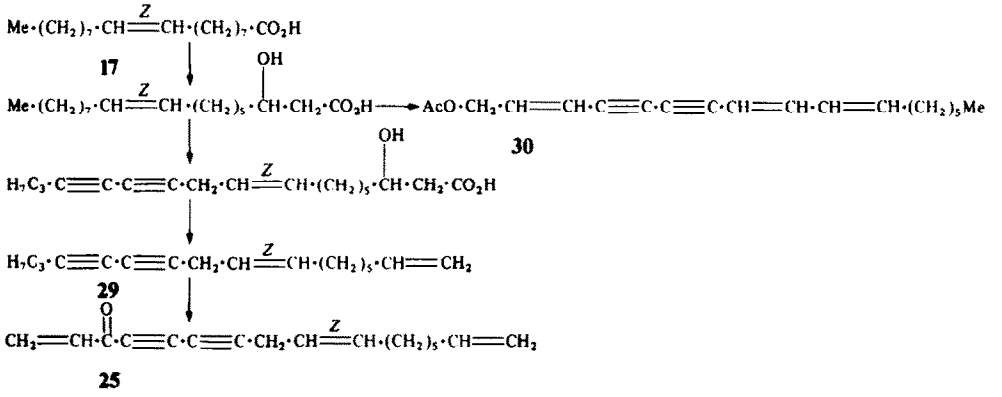


Fig. 6. Biosynthetic scheme proposed by Bohlmann [63] for the biosynthesis of dehydrofalcarinone (**25**) involving β-hydroxyoleic acid.

also been investigated [66, 71]. A concentration of 1.1 $\times 10^{-4}$ M of falcarindiol brings about 12% of haemolysis in 15 min at 22°. The haemolysis is light independent and is not related to acetylcholinesterase; it must be due to perturbation of the lipid bilayer [71]. The effect of falcarindiol on artificial lipid bilayer membranes depends upon the concentration. For lecithin-cholesterol membranes the critical concentration is between 10^{-4} and 10^{-5} M. For concentrations between 10^{-5} and 10^{-8} M falcarindiol does not affect the membrane, whereas falcarindiol in a concentration of 10^{-4} destroys the membrane in 5 min [66]. The destructive ability of falcarindiol is presumably due to its hydrophobic nature. The aliphatic terminal moiety of falcarindiol is adsorbed on the hydrophobic groups of the phospholipids in the biological membranes and at a critical concentration of *ca* 10^{-4} M the lipid bilayer is destroyed, forming mixed falcarindiol–phospholipid micelles [66].

Pharmacology

Falcarinol and falcarindiol have been examined for their toxicity upon injection into mice [27, 32]. Falcarinol was found to produce neurotoxic symptoms, whereas falcarindiol does not seem to have any acute effect. Falcarinol is also toxic to the indicator organism *Daphnia magna* Straus [27].

From ancient times Chinese folk medicine has made use of a crude extract of *Angelica acutiloba* var. *acutiloba kitagawa* due to its analgesic, sedative and antibacterial effects [32]. Chemical examination of this extract has revealed seven compounds all being local anaesthetics. Of these falcarinol, falcarindiol and falcarinolone are the most effective [32]. The local anaesthetic effect was tested in a 'writing test', which is not completely specific, since compounds such as amphetamine, chlorpromazine and mephenezine which are not local anaesthetics all react positively in this test. The bradykinin-test is more specific and falcarindiol reacts positively in this test, whereas falcarinol and falcarinolone have not been tested due to lack of material [32].

For many years *Panax ginseng* C. A. Meyer has been considered as one of the most valuable drugs in Korea, China and Japan. Recent investigations have shown that an extract of the roots inhibits growth of murine leukemia and Sarcoma cells and also inhibits DNA, RNA and protein synthesis in murine ascitic Sarcoma [10]. It is not proved that the polyacetylenes in the plant are responsible for the growth inhibition of the cancer cells.

In Thailand extracts of different unidentified *Schefflera* species are in use for treating asthma [72], and extracts of *S. octophylla* are used in the treatment of liver and rheumatic diseases and also as a tonic [73]. The active principles responsible for these effects are not known.

There is folk-lore evidence that the leaves of *Schefflera digitata* have been used by the Maoris in New Zealand to treat skin diseases such as ringworm [16]. Extracts of the leaves of this plant have been tested for activity against a variety of dermatophyte fungi of the species *Microsporum* and *Trichophyton* and were found to be remarkably specific by inhibiting spore germination and growth of the mycelium for these dermatophytes, but much less active against other common bacteria, fungi and yeasts [16]. The leaves were found to contain falcarindiol as the antifungal principle [6].

In dermatophytes falcarindiol destroys the plasma membrane. By microscopy it is possible to observe that falcarindiol causes the plasma membrane to shrink away from the cell membrane and has a further destructive effect on the internal cell structure, possibly through destruction of the lysosome membranes [16]. The effect of falcarindiol on the mycelium, which is of importance from a clinical point of view, has been examined in shaken flasks and shows that a concentration of 50 μg/ml can inhibit growth of mycelium of *Microsporum gypsum* for as long as two weeks [16].

Several members of Araliaceae have been reported to cause allergic contact dermatitis and skin irritation [5, 74, 75]. The relation between clinical effect and content of active principles has, only to a minor extent, been examined and only two species causing allergy and skin irritation have been examined for polyacetylenes. The sap of ivy, *Hedera helix*, contains falcarinone [7] and also causes skin irritation and allergic contact dermatitis [5, 74, 75], but nothing is known about a possible causal relation. *Schefflera arboricola* contains falcarinol and possibly other closely related polyacetylenes [15] and is known to cause allergic contact dermatitis [76]. Patch testing of fractions obtained upon chromatographic separation of leaves and stems showed positive response for the fractions containing falcarinol. Falcarinol has been isolated and has been shown to be the major allergen of this plant [15, 77].

REFERENCES

1. Bohlmann, F., Burkhardt, F. and Zdero, C. (1973) *Naturally Occurring Acetylenes*. Academic Press, London.
2. Sørensen, N. A. (1968) *Rec. Adv. Phytochem.* **1**, 187.
3. Jones, E. (1966) *Chem. in Britain* 6.
4. Hegnauer, R. (1964) *Chemotaxonomie der Pflanzen*, Vol. 3, p. 173. Birkhäuser, Basel.
5. Mitchell, J. and Rook, A. (1979) *Botanical Dermatology, Plants Injurious to the Skin*. Green Grass, Vancouver.
6. Muir, A. D. and Walker, J. R. L. (1979) *Chem. N. Z.* **43**, 94.
7. Bohlmann, F. (1961) *Chem. Ber.* **94**, 958.
8. Kawazu, K. and Noguchi, H. (1973) *Tetrahedron Letters* **33**, 3131.
9. Takahashi, M. and Isoi, K. (1964) *J. Pharm. Soc. Japan* **84**, 752.
10. Shim, S. C. and Koh, H. Y. (1983) *Bull. Korean Chem. Soc.* **4**, 183.
11. Shim, S. C. and Koh, H. Y. (1983) *Phytochemistry* **22**, 1817.
12. Poplawski, J., Wrobel, J. T. and Glinka, T. (1978) *11th International Symposium on Chemistry of Natural Products* **3**, 104.
13. Poplawski, J., Wrobel, J. T. and Glinka, T. (1980) *Phytochemistry* **19**, 1539.
14. Dabrowski, Z., Wrobel, J. T. and Wojtasiewicz, K. (1980) *Phytochemistry* **19**, 2464.
15. Hansen, L. and Boll, P. M., *Phytochemistry* (in press).
16. Muir, A. D., Cole, J. L. and Walker, J. R. L. (1982) *Planta Med.* **44**, 129.
17. Takahashi, M. and Yoshikura, M. (1964) *J. Pharm. Soc. Japan* **84**, 757.
18. Schulte, K. E. and Pötter, B. (1977) *Arch. Pharm.* **310**, 945.
19. Jones, E., Safe, S. and Thaller, V. (1966) *J. Chem. Soc. (C)* 1220.
20. Bohlmann, F. (1965) *Chem. Ber.* **98**, 3010.
21. Bohlmann, F. (1968) *Chem. Ber.* **101**, 525.
22. Schulte, K. E. and Wulfhorst, G. (1977) *Arch. Pharm.* **310**, 285.

23. Bentley, R. K., Bhattacharjee, D., Jones, E. and Thaller, V. (1969) *J. Chem. Soc.* (*C*) 685.
24. Takahashi, M. and Yoshikura, M. (1966) *J. Pharm. Soc. Japan* **86**, 1051.
25. Takahashi, M. and Yoshikura, M. (1966) *J. Pharm. Soc. Japan* **86**, 1053.
26. Bohlmann, F. (1966) *Chem. Ber.* **99**, 3552.
27. Crosby, D. G. and Aharonson, N. (1967) *Tetrahedron* **23**, 465.
28. Bentley, R. K. and Thaller, V. (1967) *Chem. Commun.* 439.
29. Larsen, P. K., Nielsen, B. E. and Lemmich, J. (1969) *Acta Chem. Scand.* **23**, 2252.
30. Bohlmann, F. (1968) *Chem. Ber.* **101**, 1889.
31. Kemp, M. S. (1978) *Phytochemistry* **17**, 1002.
32. Tanaka, S. and Ikeshiro, Y. (1977) *Arzneim. Forsch/Drug Res.* **27**, 2039.
33. Cichy, M., Wray, V. and Höfle, G. (1984) *Annalen* 397.
34. Lemmich, E. (1979) *Phytochemistry* **18**, 1195.
35. Kern, J. R. and Cardellina, J. H. (1982) *J. Nat. Prod.* **45**, 774.
36. Lemmich, E. (1981) *Phytochemistry* **20**, 1419.
37. Brewster, J. H. (1959) *J. Am. Chem. Soc.* **81**, 5475.
38. Bu'Lock, J. D. and Smith, G. N. (1967) *J. Chem. Soc.* (*C*) 332.
39. Jones, E., Thaller, V. and Turner, J. L. (1975) *J. Chem. Soc. Perkin Trans.* 1, 424.
40. Bohlmann, F. (1969) *Chem. Ber.* **102**, 3283.
41. Bohlmann, F. (1967) *Chem. Ber.* **100**, 3183.
42. Bohlmann, F. (1967) *Fortschritte Chem. Org. Naturst.* **XXV**, 1.
43. Bu'Lock, J. D. and Smith, G. N. (1962) *Biochem. J.* **85**, 35.
44. Bu'Lock, J. D., Allport, D. C. and Turner, W. B. (1961) *J. Chem. Soc.* 1654.
45. Bu'Lock, J. D. and Smalley, H. M. (1962) *J. Chem. Soc.* 4662.
46. Bu'Lock, J. D. and Smith, G. N. (1963) *Phytochemistry* **2**, 289.
47. Bu'Lock, J. D. (1964) *Prog. Org. Chem.* **6**, 86.
48. Jones, E., Piggin, C. M., Thaller, V. and Turner, J. L. (1977) *J. Chem. Res.* (*M*) 0744.
49. Tedder, J. M., Nechvatal, A., Murray, A. W. and Carnduff, J. (1972) *Basic Organic Chemistry, Part 4, Natural Products.* John Wiley, London.
50. Torssell, K. B. G. (1984) *Natural Product Chemistry.* John Wiley, New York.
51. Walsh, C. (1977) *Enzymatic Reaction Mechanisms.* W. H. Freeman, San Francisco.
52. Gibson, D. M. (1965) *J. Chem. Educ.* 236.
53. Popjak, G. and Tietz, A. (1955) *Biochem. J.* **60**, 147.
54. Sedgwick, B., Morris, C. and French, S. J. (1978) *J. Chem. Soc. Chem. Commun.* 193.
55. Schroepfer, G. J. and Bloch, K. (1965) *J. Biol. Chem.* **240**, 54.
56. Bloomfield, D. K. and Bloch, K. (1960) *J. Biol. Chem.* **235**, 337.
57. Mikolajzak, K. L. and Smith, C. R. (1964) *J. Org. Chem.* **29**, 318.
58. Haigh, W. G., Morris, L. J. and James, A. T. (1968) *Lipids* **3**, 307.
59. Bohlmann, F. (1968) *Tetrahedron Letters* **15**, 1801.
60. Bohlmann, F. (1971) *Chem. Ber.* **104**, 1322.
61. Bohlmann, F. (1962) *Chem. Ber.* **95**, 1320.
62. Bohlmann, F. (1968) *Chem. Ber.* **101**, 532.
63. Bohlmann, F. (1969) *Chem. Ber.* **102**, 1702.
64. De Wit, P. J. G. M. and Kodde, E. (1981) *Physiol. Plant Pathol.* **18**, 143.
65. Harding, V. K. (1980) *Physiol. Plant Pathol.* **17**, 277.
66. Garrod, B., Lea, E. J. A. and Lewis, B. G. (1979) *New Phytol.* **83**, 463.
67. Harding, V. K. and Heale, J. B. (1981) *Physiol. Plant Pathol.* **18**, 7.
68. Garrod, B. and Lewis, B. G. (1982) *Trans. Br. Mycol. Soc.* **78**, 533.
69. Elgersma, D. M., Weijman, A. C. M., Roeymans, H. J. and van Eijk, G. W. (1984) *Phytopathol. Z.* **109**, 237.
70. Heale, J. B., Dodd, K. and Gahan, P. B. (1978) *Ann. Appl. Biol.* **89**, 310.
71. Towers, G. N. H., Wat, C. K., MacRae, W. D., Yamamoto, E. and Lam, J. (1980) *Phytochem. Photobiol.* **32**, 167.
72. Tuntiwachwuttikul, P. (1982) *J. Sci. Soc. Thailand* **8**, 115.
73. Adam, G. and Lischewski, M. (1982) *Phytochemistry* **21**, 1385.
74. Roed-Petersen, J. (1975) *Contact Derm.* **1**, 57.
75. Boyle, J. and Harman, R. M. H. (1985) *Contact Derm.* **12**, 111.
76. Hammershøy, O. (1981) *Contact Derm.* **7**, 57.
77. Hansen, L., Hammershøy, O. and Boll, P. M., *Contact Derm.* (in press).