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THE DAUCANE (CAROTANE) CLASS OF SESQUITERPENES

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Key Word Index—*Ferula*; *Laserpitium*; *Sium*; Umbelliferae; daucane sesquiterpenes; isodaucanes.

Abstract—The daucane/carotane class of sesquiterpenes is reviewed. Aspects of their chemistry, stereochemistry, spectroscopy and biogenesis are discussed. All the known daucanes are listed, together with their sources, in the Appendix.

INTRODUCTION

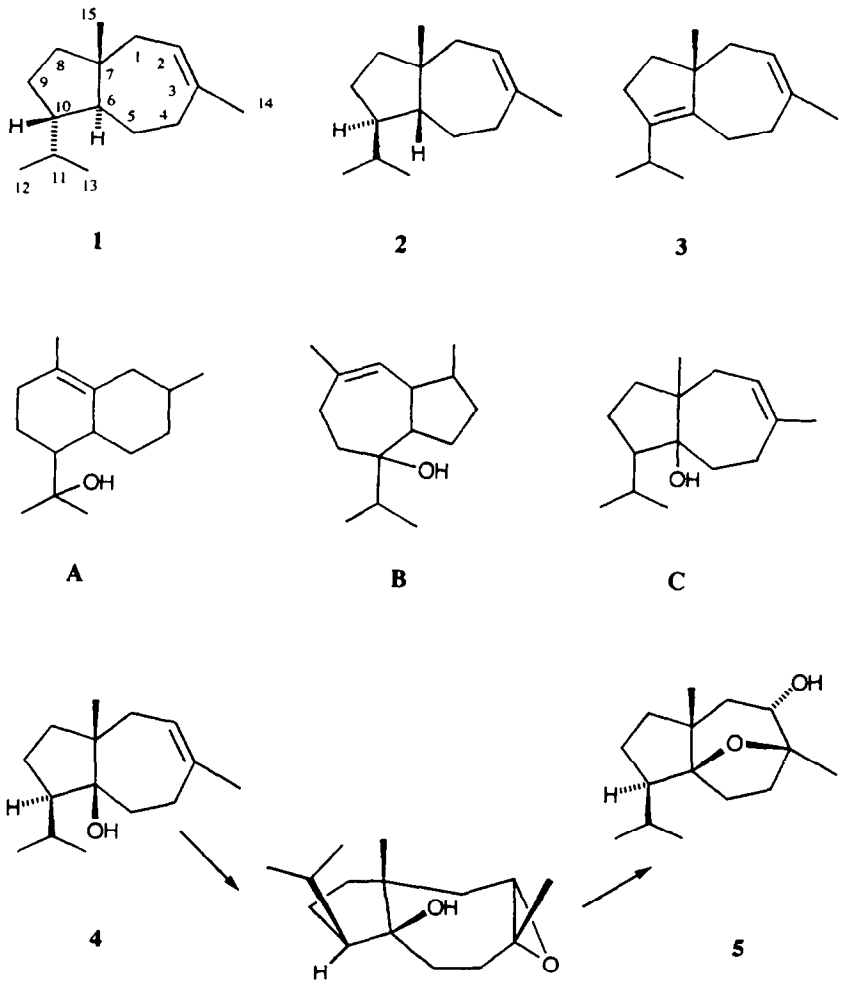
The daucane class of sesquiterpenes is a relatively small group of compounds which, for a long time, seemed to be restricted to members of the plant family Umbelliferae [1]. In recent years, daucane derivatives have also been found in the Compositae, Rosaceae, the Bryophyta, fungal and marine sources. Since the last readily accessible review on the daucanes [2], the number of examples has increased significantly. Despite the advances in information retrieval, it seems that erroneous claims of the isolation of new compounds plague the area of natural products research. The section under review is no exception. Added to this is the fact that in times of rapid expansion of a particular field, errors in structural assignment are sometimes left uncorrected, thus complicating the task of subsequent researchers. The primary aim of this review is to present, in graphical form, all the compounds so far classifiable as daucanes, together with their origin and literature references. In addition, aspects of their chemistry, spectroscopy and biogenesis are covered. It is hoped that this might provide a reasonably extensive background to this class of compounds and help to avoid duplication of effort.

In the literature, the names carotane and daucane are used interchangeably although, historically, daucane has precedence. Furthermore, the majority of the examples known to data are based on a skeleton (**1**) which is stereochemically distinct, albeit biogenetically related, to that of the hypothetical parent skeleton (**2**) of the daucane/carotane class. However, the diene (**3**) which is formally derivable from both skeletons has been named daucane [3]. Several different numbering systems have been used, none of them complying with systematic rules for numbering the azulene skeleton. In this review, daucane will be used as the preferred name for both skeletons, in preference to carotane which could be confused with carotene. The numbering system shown in (**1**) is recommended on the grounds that it reflects the numbering of the acyclic C_{15} biogenetic precursor.

HISTORICAL ASPECTS

The first daucane derivative to have been chemically investigated appears to be laserpetin, the bitter principle of *Laserpitium latifolium* (Umbelliferae), whose constitution was studied by Feldmann in 1865 [4]. The structure was fully defined in 1970 [5] but only after much chemical work on simpler members of the class had disclosed the basic skeleton of this group of sesquiterpenes. One of these simpler compounds was daucol (**4**) (Scheme 1), which was isolated in 1909 during an investigation of the ethereal oil of carrot seeds (*Daucus carota* L.) [6]. A different sesquiterpene alcohol, carotol (**5**), was isolated from the same source in 1925 by Asahina and Tsukamoto [7]. The structure of carotol, the compound contributing to the smell of fresh carrots, was investigated by Sorm and Urbanek [8–10] some 23 years later. Although the structure first suggested proved to be wrong [11–13], the simple relationship between daucol and carotol was established. Treatment of carotol with perphthalic acid gave a compound, with properties in agreement to those recorded for the oxide prepared from carotol by Asahina and Tsukamoto, which was shown to be identical to daucol [11–13].

By 1960, three skeletons **A** [8–10], **B** [14, 15] and **C** [11–13] had been proposed for carotol. Only **C** could be regarded as having a regular sesquiterpene skeleton. The extensive work of F. Sorm and his group [11–13] pointed to structure **C**, a conclusion supported by spectroscopic studies with the then emerging proton NMR technique [16]. The assignment of relative configuration was pursued by French workers [17, 18] and was confirmed by an



Scheme 1. Correlation of carotol (4) with daucol (5).

X-ray crystallographic study on the (±)-alaninate hydrobromide derivative of daucol [19]. The absolute configuration of carotol, daucol and daucene was determined by chiroptical (CD) studies on α-bromodaucone and daucone [17, 18]. Synthetic correlation with (−)-dihydrocarvone [20, 21] and *R*-(+)-limonene [22] further substantiated the assignment.

The next daucane sesquiterpene to have its structure completely defined was laserpetin (**6**). The source of this compound, *L. latifolium*, has long been known in folk medicine [23]. Since its isolation in 1865, several attempts had been made to establish its molecular formula [24–26] and much chemical work was carried out [27, 28] before the relative configuration was established by chemical [29, 30] and X-ray methods [31]. Two other daucanes have been isolated from this plant [32–35]. The absolute configuration of laserpitin was established some 16 years after its characterization [5]. The difficulty in securing the structure and stereochemistry of laserpetin stemmed from the fact that it presented essentially a new stereochemical class of the daucane skeleton.

ASPECTS OF THE CHEMISTRY OF THE DAUCANES

General

Most of what is known about the chemistry of the daucanes was discovered during the period 1950–1970 and can be found in the papers describing the structural elucidation of carotol, daucol and laserpitin mentioned above. It is not the intention to cover those aspects in this review. However, these papers contain an array of derivatives, some of which may turn out to be naturally occurring. Researchers in this area should check these papers to ensure that the claim of the novelty of the natural compound they have isolated stands up to scrutiny. In the following, some general chemistry of the daucanes is emphasized.

The conversion of carotol to daucol by treatment with peracids has been mentioned above. This reaction is now known to proceed via the intermediate 2,3-α-epoxide which undergoes ring opening with the participation of the tertiary hydroxyl group at C6 (Scheme 1). In contrast,

a similar reaction on carotol acetate leads to a mixture of the 2,3-α- and the 2,3-β-epoxides [18]. This can be rationalized as follows. Daucanes with the 6-hydroxyl-*cis*-hydroazulenic systems can adopt two main conformations. In one, the seven membered ring has the twist-chair conformation and the C6-hydroxyl group hydrogen-bonds with the double bond. Epoxidation of this conformer occurs from the underside and ring opening with participation of the 6-hydroxy group ensues. In carotol acetate, the absence of hydrogen bonding allows the other conformation, in which the 7-membered ring is in the twist-boat conformation, to become significant. For this case, β-epoxidation is also possible [36].

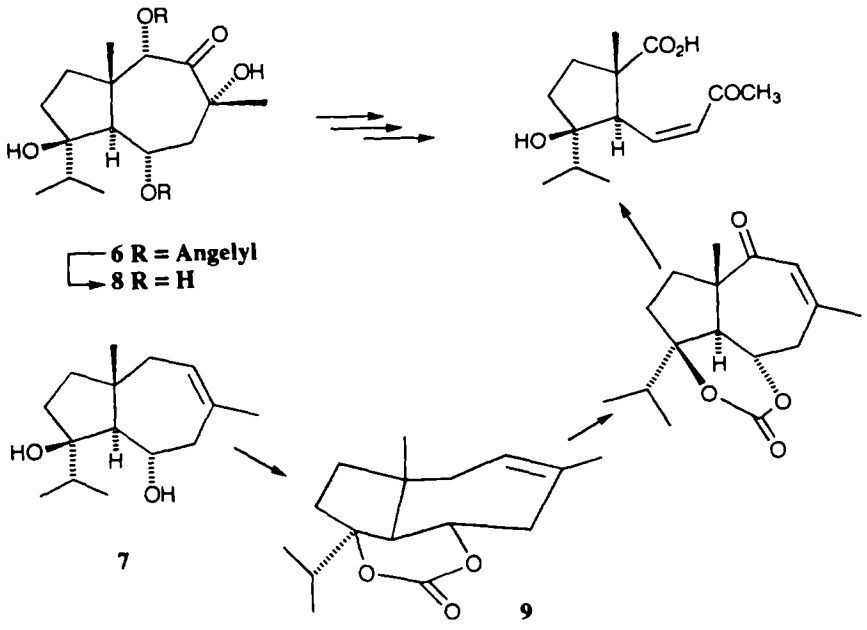
As can be predicted from Dreiding models, in the *cis*-fused arrangement the top face of the molecule is generally more exposed to approach by reagents [36, 37]. In the *trans*-fused system more of the α-face is exposed and, for example, epoxidation occurs from the underside even in the presence of 1α,5α-dioxygenation [38, 39].

A large number of daucane derivatives contain two or more oxygenation sites in which at least one hydroxyl group is esterified. A variety of simple aliphatic and aromatic acids are involved (see Appendix). Acylated derivatives of jaeschkeanadiol (**7**) form by far the largest group of this type. Jaeschkeanadiol has been chemically interrelated with laserpetin [40]. The gross structure was determined by standard reactions which included establishing the presence of a 1,3-diol by formation of an α,β-unsaturated ketone. All but the stereochemistry of the alcohol at C5 was confirmed by correlation with the degradation product of laserol (**8**) (Scheme 2). The assignment of the stereochemistry at C5 as α- was deduced from NMR studies of the cyclic carbonate (**9**) in which H5 appeared as a *ddd* at δ4.25 displaying two large ($J = 10.5$, 10.5 Hz) and one small ($J = 5.5$ Hz) coupling constants.

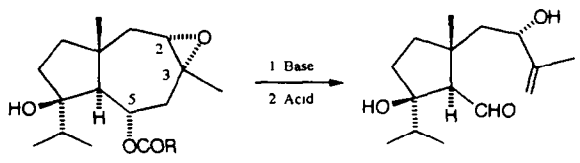
Many examples of acylated daucane derivatives have been found (Appendix). Although selective hydrolysis of the acyl groups have been noted, no general patterns have emerged [39, 41]. Notably, with systems containing 2,3-epoxy-5-acyloxy moieties, base hydrolysis followed by addition of excess acid leads to epoxide ring opening and C-C bond fragmentation (Scheme 3) [39].

Perhaps one of the more interesting recent developments in the field of daucane chemistry is the identification of a number of daucane peroxides on the leaves of *Rosa rugosa* (Rosaceae) [42–47]. These peroxides (e.g. **10** and **11**) all seem to arise from autooxidation of carota-1,4-dien-14-al (**12**). The processes involved have been duplicated *in vitro* and appear to arise from 1,5-endoperoxy-3-ene radical systems as intermediates (Scheme 4) [48, 49]. One of these end products is rugosal A (**10**) which is present in high concentration in leaf extracts and is produced in the trichomes of the leaf. Since it shows antifeedant activity against tobacco hookworm larvae and has antimicrobial activity, it is regarded as a defence substance. The absolute configuration of carota-1,4-dien-14-al (**12**) was established by its synthesis from (+)-carotol (**5**) [50].

A number of daucane derivatives have been isolated from members of the Compositae. From the perspective of biological activity, the most interesting is lasidiol angelate (**13**) isolated from *Lasiantheae fruticosa* (35 mg from 2.3 kg of leaves) [51]. This compound was isolated by bioassay-guided fractionation by monitoring for repellency against the leafcutter ant (*Atta cephalotes*, Hymenoptera, Formicidae, Attini). Lasidiol angelate was interrelated with carotol (**5**) as follows. Reduction with $LiAlH_4$ gave the 1,6-diol which on oxidation with PCC yielded the keto alcohol (**14**). Photooxidation of carotol (**5**) gave the tertiary alcohol (**15**), which was oxidized with



Scheme 2. Interrelationship of laserpitin (**6**) with jaeschkeanadiol (**7**).



Scheme 3. Acid-catalysed fragmentation.

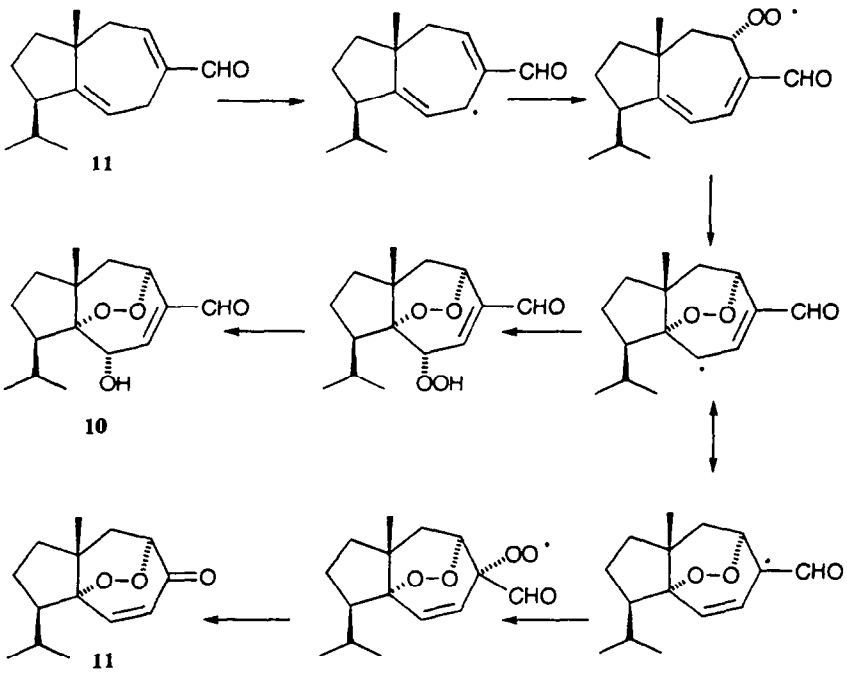
PCC to yield the same keto alcohol (**14**). Since reduction of **14** with 9-borabicyclo[3.3.1]nonane also gave predominantly the 1,6-diol, the hydroxyl at C1 was assigned the α-configuration. Both lasidiol angelate (**13**) and **14** are potent repellents towards the leafcutter ant.

The first daucane isolated from a fungal source was aspterric acid (**16**) which is produced by a strain of *Aspergillus terreus* IFO-6213 (Deuteromycotina) [52]. The structure was proposed on the basis of chemical degradation and NMR spectroscopic analysis. X-ray crystallographic studies on the derived *p*-bromobenzoate confirmed the structure and also showed that the absolute stereochemistry was the same as for the plant derived daucanes. A total synthesis of aspterric acid has been described [53]. Aspects of the biosynthesis of aspterric acid were also investigated. Feeding ^{13}MeCOONa and ^{14}MeCOONa simultaneously to the fungus resulted in a 1.32% incorporation into aspterric acid. The ^{13}C NMR spectrum of the labelled acid showed ^{13}C-enrichment at C2, 4, 6, 8, 10, 12, 13, and 14. ^{13}C–^{13}C coupling (J = 42.7 Hz) between C6 and C10 was observed, indicating that these linked carbons were derived from C2 of acetic acid.

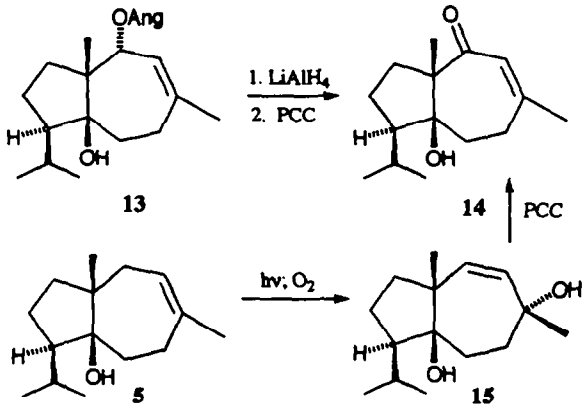
Another fungal daucane derivative (**17**), erroneously claimed to be the first, was isolated from *Gliocladium virens* IFO 9166 (Ascomycotina). The structure and relative configuration were established entirely from spectral data which included results from HETCOR, 2D-INADEQUATE and NOE difference techniques [54]. The metabolite from *G. virens* showed activity against *Candida albicans* strains. Fulvoferruginin (**18**) is the first daucane isolated from a Basidiomycete [55]. Its structure was determined by spectroscopic and X-ray crystallographic studies and the absolute configuration rests on chiroptical measurements. This metabolite is structurally related to hercynolactone (**19**), the only daucane so far isolated from liverworts [56].

A daucadiene hydrocarbon (**20**) was recently described as a metabolite of a relatively rare marine sponge, a *Higginsia* species [57]. The relative stereochemistry was assigned on the basis of spectroscopic analysis and by reference to model compounds. In this context, it is interesting to note that another sponge, *Epipolasis reiswigi*, produces the daucane isoprenologue (**21**) of known relative [58, 59] and absolute stereochemistry [59]. The metabolites from the sponges share the same relative stereochemistry as far as the perhydroazulene system is concerned. Daucane isoprenologues have also been obtained from terrestrial plants [60, 61].

The relationship between the daucanes and the acorane sesquiterpenes merits some comments (Scheme 6). This first emerged from the observation that the synthetic isoprenoid (**22**), prepared from racemic dehydrolinalool or R-(+)-limonene, on treatment with formic acid, was converted into daucene (**3**) and the acoradiene (**23**) [22, 62]. The synthetic carotol-ether (**24**) also could be conver-



Scheme 4. Formation of daucane peroxides.

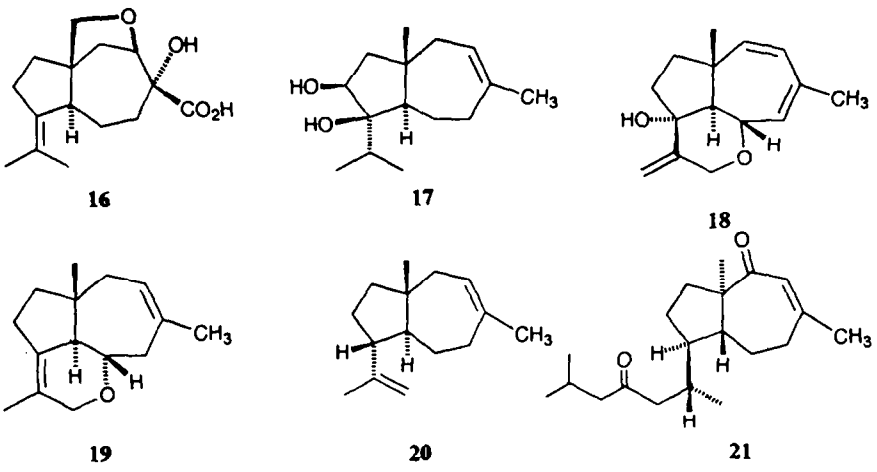


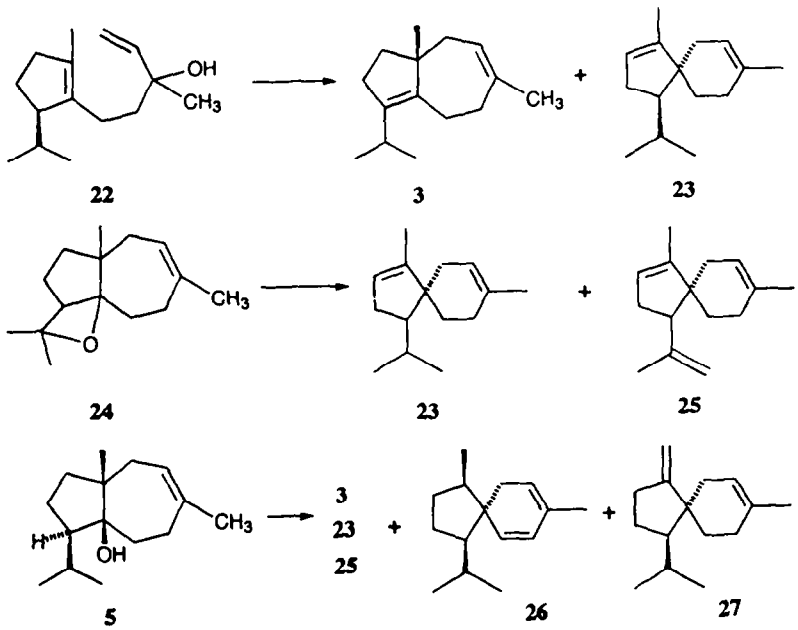
Scheme 5. Interrelation of lasidiol angelate (13) with carotol (5).

ted into 23 as well as the acoratriene (25) with dichloroaluminum hydride [63]. Elimination of the oxygen at C-6 in carotol (5) or carotol acetate provides daucane (3), acoradienes (23, 26 and 27) and the acoratriene (25) [50, 64, 65], the proportion formed of each depending on the conditions used. It is significant that the 2,3-double bond is necessary for the rearrangement to take place [64]. Furthermore, the acoradienes are themselves converted to daucenes under acidic conditions *in vitro*, albeit with racemization [65]. This observation may be considered of some significance and will be taken into account in the discussion on the biosynthesis of the daucanes.

Relative and absolute stereochemistry

The relative configuration of a number of daucane derivatives has been established or confirmed by X-ray





Scheme 6. Formation of daucanes and acoranes.

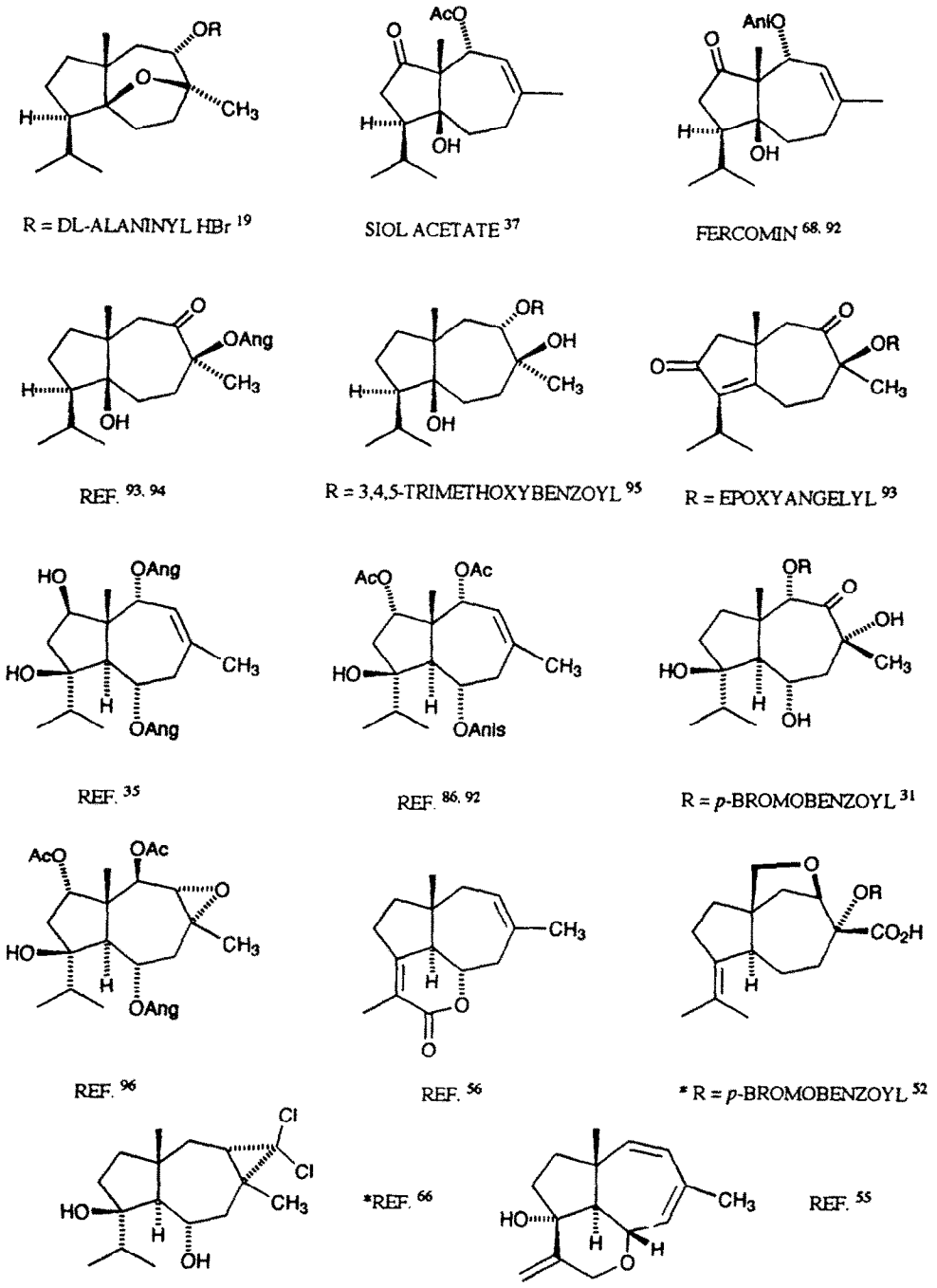


Fig. 1. Structures of daucanes studied by X-ray diffraction methods (relative configuration only, except for those marked *).

diffraction studies (Fig. 1). The determination of absolute configuration of the daucanes by this method appears to be restricted to only two examples; aspterric acid (**16**) [53] and the dichloro jaeschkeanadiol derivative (**28**) [66]. Although no comment is made in the original paper as to its origin, this last compound is most likely an artefact of the isolation procedure. Exposure of chloroform to a basic reagent (e.g. chromatographic support) could conceivably generate the dichloromethylene carbene which would insert into the double bond of jaeschkeanadiol (**7**), a known metabolite from the source reported to produce **28**.

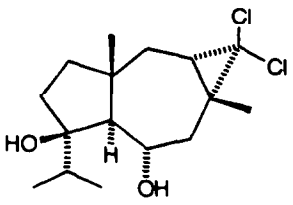
NMR spectroscopy

In recent times, a large number of daucane derivatives have been isolated and, for the most part, their structures have been assigned on the basis of detailed NMR (^{1}H-

and ^{13}C-) spectroscopic techniques. In Figs 2 and 3 the ^{13}C NMR, spectral details of the perhydroazulenic portion of representative daucanes are collected. A compilation of the spectroscopic data for the sesquiterpenes from *Ferula* species, mostly daucanes, up to 1987 is available [67]. NMR spectroscopy is a powerful technique and greatly facilitates the structural determination of daucane derivatives. However, overreliance on this technique or casual application is littered with pitfalls. A single illustrative example should suffice. The lactone fercolide, isolated from *F. communis* var *communis*, has been assigned structure (**29**) on spectroscopic grounds [68]. A short time later, a similar lactone, feruginin, was reported from *F. jaeschkeana* and assigned structure (**30**) also on the basis of NMR measurements including limited NOE results [69]. A comparison of the ^{1}H and ^{13}C NMR spectral parameters [68, 69] suggests that these two compounds have identical skeletons. In particular, the ^{13}C chemical shifts show a remarkable degree of correspondence for compounds that are stereochemically different at three asymmetric carbons. Unfortunately, the stereochemistry of feruginin had been assigned by comparing its ^{13}C NMR parameters with those of a daucane [70] for which the structure originally proposed had been corrected [36] a short time before the isolation of feruginin was reported.

The isodaucane class

In recent years, several members of a related class of sesquiterpenes have been isolated from natural sources. The skeleton represented in this class has been named



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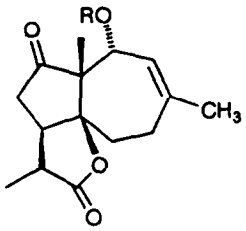

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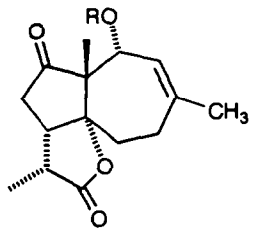

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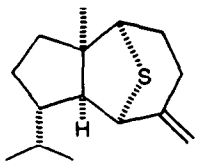

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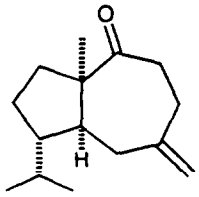

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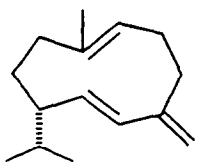

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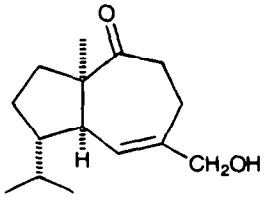

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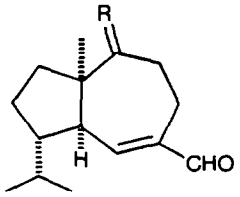
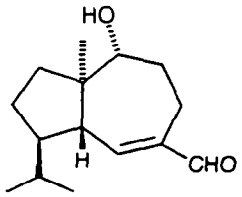


35 R = α-OH; β-H
36 R = O



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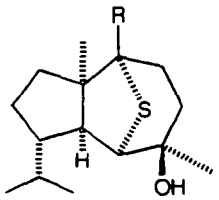
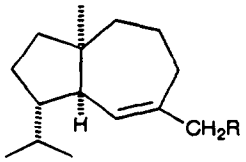


38 R = OH
39 R = H



40 R = NC
41 R = NCS

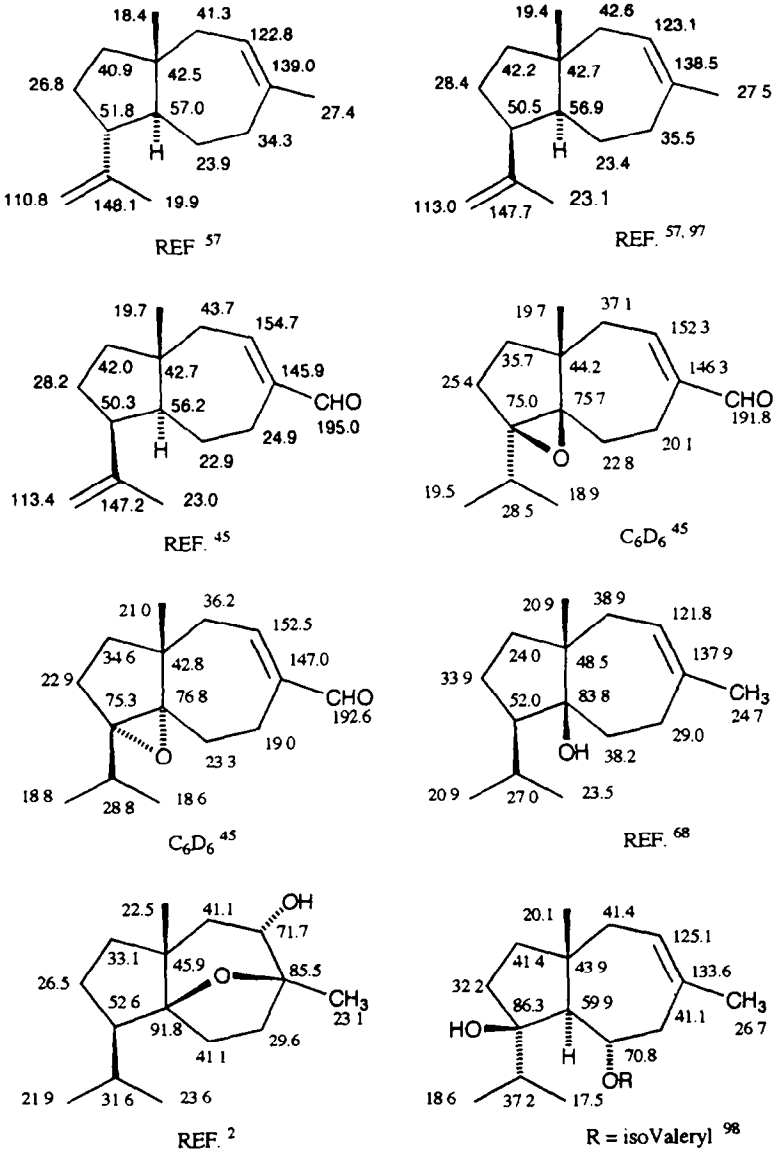


Fig. 2. ^{13}C NMR parameters for selected daucanes (in $CDCl_3$, unless otherwise noted).

isodaucane [71] and differs from the daucanes in the position of C14 which is now attached to C4. The first example of this type was (−)-mintsulfide (**31**), found as a constituent of peppermint [72] and clary sage oil [73]. The 1,5-epoxy analogue of mintsulfide and the eneone (**32**) are also present in clary sage oil [73]. The structure and absolute configuration of (−)-mintsulfide have been secured by X-ray diffraction methods and by synthesis from (−)-germacrene D (**33**) [72]. Aphanamol I and II (**34** and **35**) were isolated [74] as the minor toxic principles of the fruits of the timber tree *Aphanamixis grandifolia* and their absolute configuration established by synthesis [75]. Aphanamol II co-occurs [71] with the corresponding ketone (**36**) in the Paraguyan medicinal plant, *Chromolaena laevigata*, and **36** has also been isolated from a *Neomiranda* sp. [75]. *Critonia quadrangularis* produces aphanamol II and the 6,10 diepimer (**37**) [76], and compounds (**35–37**) have been reported as constituents of *Senecio crassiflorus* [77]. The epoxide (**38**) and the hemiacetal (**39**) have been isolated from the Vietnamese medicinal plant *Homalomena aromatica* [78]. Isodaucanes are not restricted to terrestrial sources since the isonitrile (**40**) and isothiocyanate (**41**) were isolated from the marine sponge *Acanthella acuta* [79]. It is noteworthy that all these examples, with the exception of **37**, contain the *cis*-fused ring junction with the isopropyl group in a *syn*-disposition. Synthetic [72] and biomimetic transformations [80] of germacrene-D yield products with the isodaucane skeleton. It is tempting to assume that the biosynthesis of these compounds arises from a similar macrocyclic intermediate. Interestingly, as mentioned below, the intermediacy of a germacrene in the biosyn-

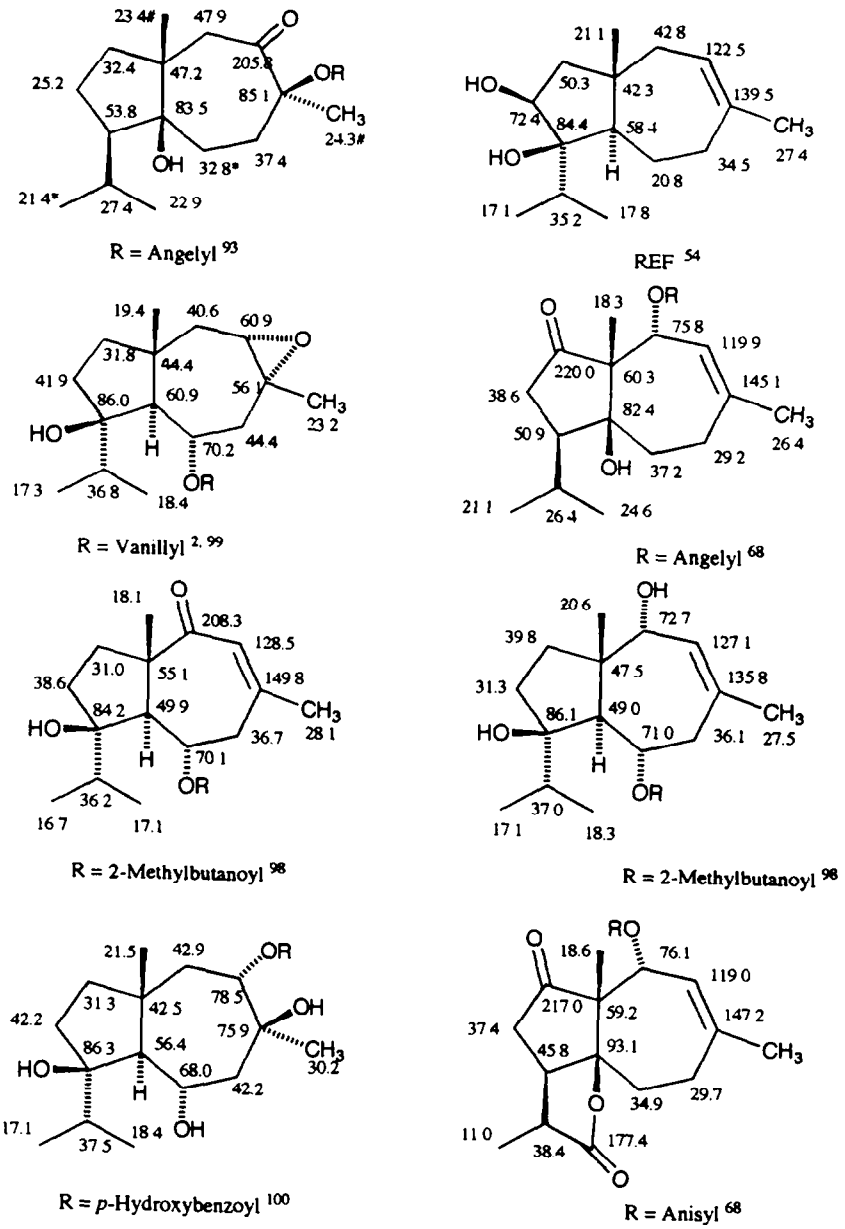


Fig. 3. ^{13}C NMR parameters for selected daucanes (in $CDCl_3$, unless otherwise noted).

thesis of the daucane skeleton was eliminated by radiotracer studies [81]. A possible biosynthetic origin from a bicyclic cadinol has been proposed [71]. The suggestion [73] that the skeleton contained in these compounds be named 'salvialane' has the merit of not implying a similar biosynthetic origin to that of the daucanes.

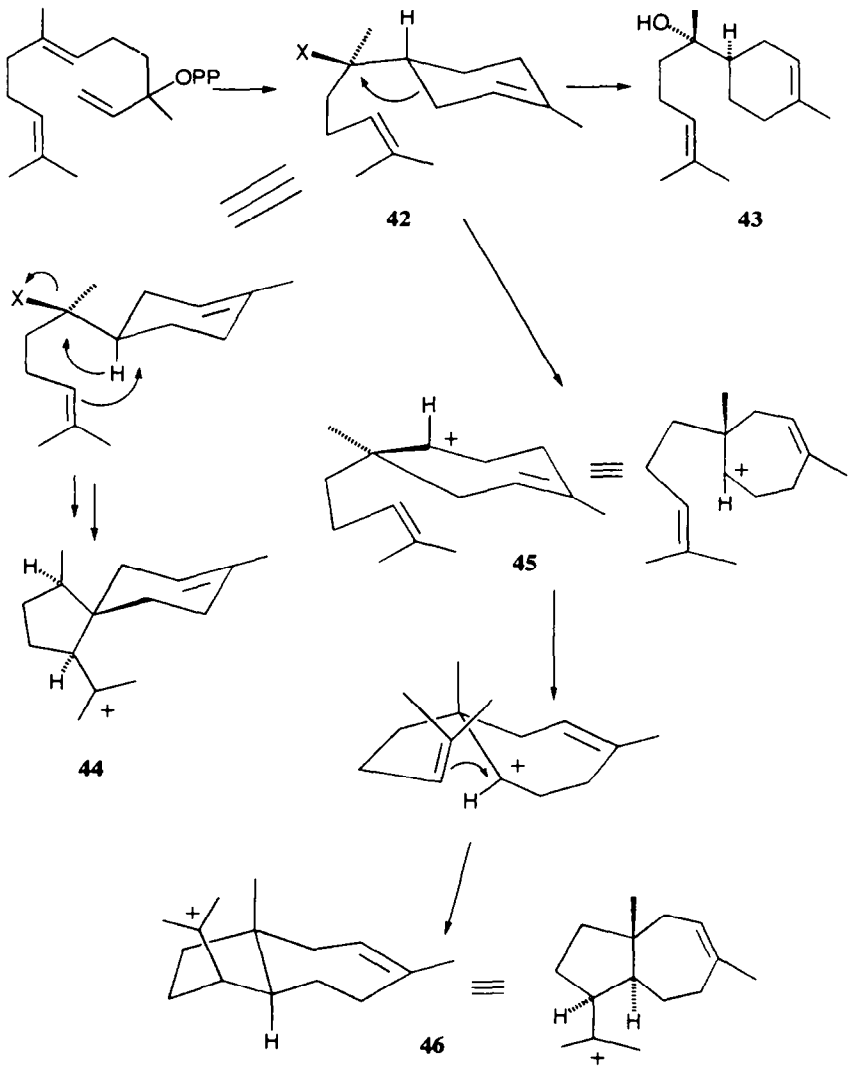
Biosynthesis

Despite the structural simplicity of the daucane skeleton, the biogenesis of this bicyclic system has been a matter of conjecture for some time. In the first study of the biosynthesis of the daucanes, sodium (1-^{14}C) acetate fed to growing carrot plants was incorporated into carotol [81]. The radioactive carotol was oxidatively degraded to yield acetic acid, the carbons of which originated from C-3 and C-14. This contained 16% of the total radioactivity, as expected for the cyclization of *cis, trans* farnesyl pyrophosphate without any methyl group transposition. This result eliminates a sequence which involves the formation of a macrocyclic germacrene. The only other study of this type involved incorporation of 2-^{14}C- and 2-^{13}C-labelled acetates into aspterric acid produced by *Aspergillus terreus*. ^{13}C-enrichment of C2, 4, 6, 8, 10, 12, 13 and 14 and ^{13}C–^{13}C coupling between C-6 and C-10 was observed. Although this result was taken to mean that

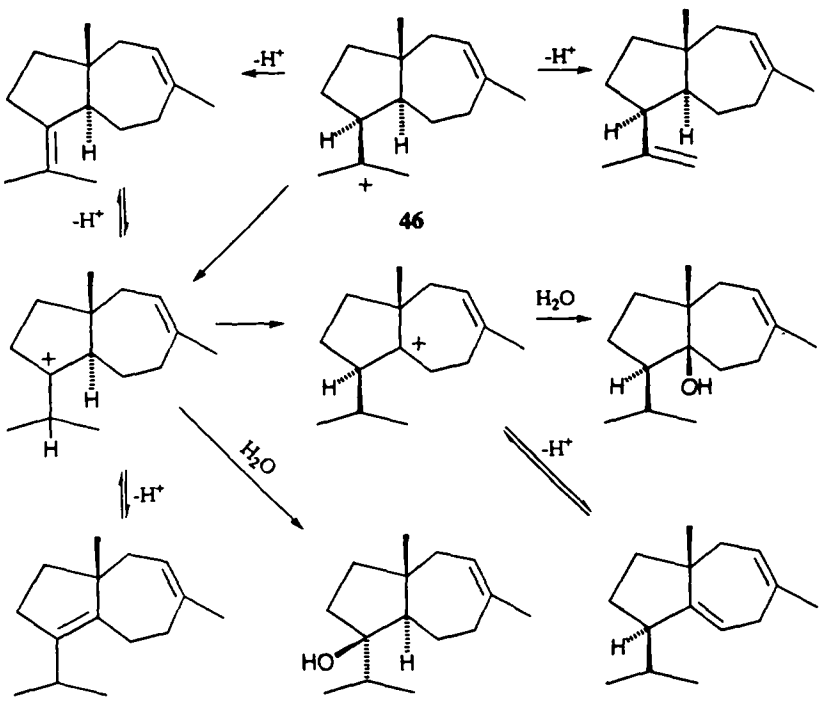
formation of the daucane skeleton occurred with concerted cyclization of *cis, trans* farnesyl pyrophosphate, this is not necessarily the case.

A biosynthetic sequence for the generation of the daucane skeleton is illustrated in Scheme 7. The underlying assumptions in devising this sequence are as follows. Although daucanes are often accompanied in nature by sesquiterpenes of other skeletal types, germacranes, guaianes, himalachanes, humulanes and selinanes [67], none of these are readily rationalized as arising from a common cyclic precursor which could generate the perhydroazulenic ring system of the daucanes. On the other hand, the co-occurence of bisabolanes and acoranes with daucanes in *R. rugosa* suggests a biosynthetic correlation between the three structural types [45, 46] particularly when the *in vitro* interconversion between the daucane and acorane skeletons is taken into account [64, 65]. In the scheme, the most economical route that allows generation of these three types is developed. Thus, in cyclization steps only *trans*-addition to the double bonds is considered. In hydride or C–C bond shifts, the migrating groups are considered to have a *trans*-antiperiplanar relationship.

As shown in the scheme, the stabilized species (**42**) arising from cyclization of the acyclic tertiary pyrophosphate can become the precursor to the bisabolene alcohol (**43**), the acorene ion (**44**) and the cycloheptenyl ion (**45**) which can be regarded as a precursor of the daucanes. Formation of the cyclopentane ring could generate the tertiary carbonium ion (**46**) with a *trans*-fused ring junction. This ion can partition between a number of isomeric ions arising from 1,2-hydride shifts and, for each ion, elimination of a proton or participation of water neutralizes the charge (Scheme 8). The generation of the marine daucane (**17**), in which the isopropylene group at C-10 is *trans* to the C-7 methyl group, can be accommodated by allowing the formation of the C-6–C-10 bond to occur by attack of the *si*-face of C-10 to C-6.



Scheme 7. Hypothetical scheme for the biosynthesis of the daucanes.



Scheme 8. Possible fate of the daucanyl ion (**46**).

Biological activity

The biological activity of some naturally occurring daucanes has already been mentioned. However, no systematic study of the range of bioactivity exhibited by these compounds has been carried out. Increasingly, daucanes are being individuated by bioassay-guided fractionations and isolations. In one of the early applications of this approach, lasidiol angelate (**13**) was found to be a potent repellent towards the leafcutter ant [51]. The daucane (**17**) is antagonistic towards several *Candida albicans* strains [54]. Fulvoferruginin (**18**) shows modest activity against Gram-positive bacteria, significant antifungal activity to *Paecilomyces varioti* and cytotoxic activity towards HeLa cells [55]. The modest antifertility and hormonal properties of some jaeschkeanadiol esters from *Ferula jaeschkeana* have been reported [82].

An aqueous extract of damaged leaves of *Rosa rugosa* was found to inhibit the growth of microorganisms [42]. The active principle, rugosal A (**10**), is an endoperoxy daucane which accumulates in the leaf trichomes, shows marked antifungal activity against *Cladosporium herbarum*, and has antifeedant properties against tobacco cutworm larvae [47]. Whereas the corresponding acid is non-fungitoxic [44] the methyl ester has activity comparable to that of **10**. This last seems to be produced as a result of damage to plant tissues. It appears likely that some of these compounds have a major defensive role in the plant.

THE UMBELLIFERAE; THE MAJOR SOURCE OF DAUCANES

Although daucanes have been isolated from various sources (Table 1), the majority so far have been found in members of the plant family Umbelliferae in general and the genus *Ferula* in particular. Daucanes have been isolated from the rhizomes, aerial parts, fruits and latex of many umbelliferous species. There seems little doubt that the stimulus to studying the phytochemistry of these species came from their widespread use as food and medicinal plants. The sequel summarizes aspects of the cultural and medicinal significance of species of the

Table 1. Natural sources of daucanes

Compositae	Marine sponge
Ageratum fastigiatum	*Higginsia* sp.
Blainvillea acmella	
Calea prunifolia	Rosaceae
Heliopsis helianthoide	*Rosa rugosa*
Inula crithmoides	
Iva xanthifolia	Umbelliferae
Lasiantheae fruticosa	*Daucus carota*
Vernonia galpini	*Ferula* species
Xanthium catharticum	*Laserpitium halleri* subs *halleri*
	Laserpitium latifolium
Cupressaceae	*Selinium vaginatum*
Fokiena hodginsii	*Sium latifolium*
	Sium latijugum
Fungi	
Aspergillus terreus	Valerianaceae
Gliocladium virens	*Nardostachys chinensis*
Marasmus fulvoferrugineus	
Hepaticae	
Barbilophozia lycopodioides	
Barbilophozia hatcheri	

Umbelliferae, some of which have been subsequently shown to produce daucanes.

The Umbelliferae was the first family of flowering plants to achieve general recognition. Because of their distinctive chemistry reflected in odour, flavour, esculence and toxicity, members of this family were familiar prehistorically to many peoples. References to the Umbelliferae can be found dating back to ancient Crete and the Chinese classic of materia medica, Pen Ts'ao Chin (300–200 B.C.). The Indians of Mexico had developed a crude botanical classification that included some Umbelliferae [82].

'Narthekodes' was the name given by Theophrastus of Eresus to the Umbelliferae, a plant family which he defined and recognized to include dill, coriander, anise, cumin and fennel. In Greek art, Dionysius was frequently depicted as holding a dried stalk of the plant. Subsequently, the name was translated into Latin as *Ferula*, meaning dried stalk or fennel. The Greek Herbal of Dioscoroides lists over 50 species of Umbelliferae under the general heading of herbs. Members of this family have been used for food, beverages and medicinals, some being highly poisonous [83].

The genus *Ferula* is found throughout Eurasia. Some 130 species are distributed in the Old World from the Mediterranean to Central Asia and also in Macronesia, and approximately 172 species are known world-wide [84]. Members of the *Ferula* genus are characterized by the production of coumarins and sesquiterpenes of the germacrane, himalachane, humulane, selinane, guaiane and daucane class. A number of them became well known for their production of gum-resins which were widely recognized for their medicinal value. Some of the better known are listed below.

(a) Ammoniacum; this gum-resin is derived from *Dorema ammoniacum* (Umbelliferae) but the name is also commonly used to describe similar resins from *Ferula* spp. In each case, on incision of the plant, the resin exudes as a latex which hardens to a solid resinous mass. In the case of *F. foetida* a foul odour is associated with the resin (asafetida) produced (referred to as devil's dung). It possesses a bitter, acrid and biting taste and a strong garlic odour arising from the presence of sulphur compounds. Small amounts were used in condiments and sauces and it, reputedly, has been used as an antispasmodic.

(b) Galbanum; a resin obtained from *F. galbaniflua*. It is related to asafetida and sagapenum and has a long history. It is believed to have been used by the Israelites as an ingredient in incense. The resin is referred to by

Table 2. Reputed uses of selected members of the Umbelliferae

Plant	Uses
F. alliacea Boiss.	Carminative, intestinal antiseptic; used for scorpion stings, hysteria, epilepsy [23].
F. assa-foetida L.	Source of asafetida, gum-resin, used in flavouring; expectorant, carminative, laxative, antispasmodic, emmenagogue, anthelmintic; used in veterinary medicine [23, 83, 87].
F. communis L.	Called 'narthex' by Romans; medicinal plants; latex
var and subsp	of some species toxic to stock; used as an antihysteric and for dysentery [68, 85, 86, 88, 89].
F. communis var *brevifolia*	Medicinal plant, toxic to animals and humans [90].
F. elaeochytris Korovin	Aerial parts added to diet of sheep and cattle to increase fertility [34].
F. foetida (Bunge) Regel	Medicinal, same uses as for *F. assa-foetida* [23].
F. galbaniflua Boiss. & Buhse	Galbanum (gum-resin), antispasmodic, expectorant, carminative, stimulant; used for hysteria, amenorrhea, tumours, boils, swellings. Church incense, used in perfumery [23, 87].
F. jaeschkeana Vatke	Similar gum-resin to asafetida; used for wounds and bruises [40].
F. marmarica Asch. & Taub	Source of gum ammoniac [23].
F. narthex Boiss.	Asafetida gum-resin, possibly a spice [23].
F. orientalis var *orientalis*	Source of ammoniacum, medicinal uses [85, 88].
F. persica Willd.	Source of sapagenum gum-resin, uses as for *F. assa-foetida* and *galbaniflua*.
F. rublicaulis Boiss.	Source of galbanum, uses as for *F. galbaniflua*.
F. schair Borszcs.	Source of galbanum, uses as for *F. galbaniflua*.
F. sumbul (Kauffmann)	Antispasmodic, stimulant, carminative, nervous
Hook f. Sumbul	system disorders, for cholera, *delirium tremens* and gleet; used as perfume, incense.
F. szoswitziana DC.	Source of gum-resin; used for rheumatism [23].
F. tingitana L.	Source of ammoniac gum-resin; used in medicine [23, 88].
Laserpitium latifolium L.	Used in beer; stomachic, veterinary medicine; root used as tonic, diuretic, emmenagogue, purgative.
L. prutenicum L.	Root used for skin disease.
(*L. selenoides* Crantz)	
L. siler L.	As a condiment and in liqueur; emmenagogue,
(*L. montanum* Lam.)	stomachic, diuretic, vulnerary, and for toothache.
Sium latifolium L.	Diuretic, antiscorbutic, aperitive. Root-stock said to be poisonous.
S. sisarum L. and	Roots of var *sisarum* cultivated, food, coffee
varieties	substitute, as tonic and digestive.
Sium spp.	Widely regarded as poisonous.

*Unless otherwise specified, data is from ref. 83.

Horace and Pliny and the Romans apparently used it in fumigation.

(c) Sagapenum; a gum-resin from *F. persica* with the unpleasant odour of asafetida.

F. orientalis L. var *orientalis*, a medicinal plant from the subgenus Peucedanoides (Boiss.) Korovin (Apiaceae), according to Discoroides is a source of "ammoniacum". Two other possible sources are *F. tingitana* L. and *F. communis* L. subsp. *communis*. The latter is a medicinal plant [85] which has been used as an anti-hysteric and for the treatment of dysentery. *F. communis* is also a latex-containing plant in the Mediterranean reputed to be toxic to livestock [86]. It causes an often lethal haemorrhagic disease, ferulosis, similar to those of poisoning from sweet-clover and it has been suggested that *Ferula communis* contains anti-thrombinic coumarins. In Sardinia, both toxic and non-toxic varieties occur.

A listing of species of the three genera *Ferula*, *Laserpitium* and *Sium*, some of which have been shown to be sources of daucanes, and their reputed uses is collected in Table 2.

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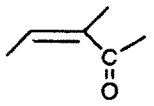
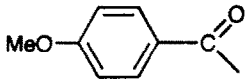
APPENDIX

This appendix contains the structures, origin and literature references for all the daucanes isolated so far. Corrections have been made where the original literature was ambiguous.
The structures have been listed, approximately, in order of increasing level of nuclear oxygenation. Derivatives based on the same skeleton, but carrying different acyl groups, have been combined. The key to the abbreviations used for acyl groups is as follows:

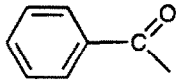
Ang = Angelyl



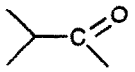
Anis = Anisyl



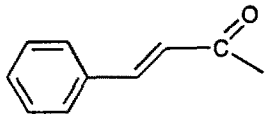
Benz = Benzoyl



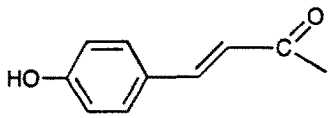
iBu = *iso*-Butanoyl



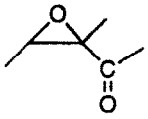
Cinn = Cinnamyl



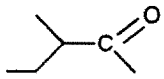
Coum = Coumaryl



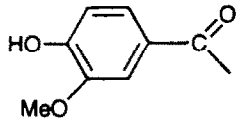
Epoxyang = Epoxyangelyl



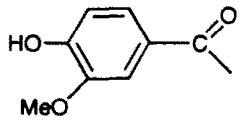
2MeBu = 2-Methylbutanyl



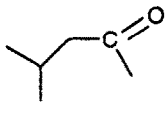
Van = Vanillyl

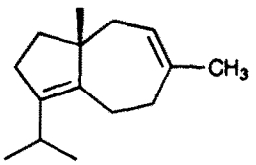


Ver = Veratryl

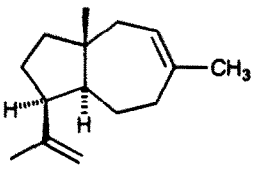


iVal = *iso*-valeryl

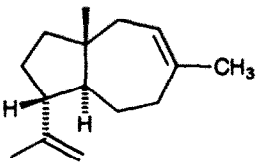




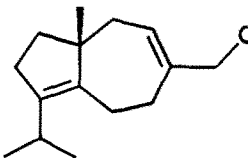
Daucus carota [3]



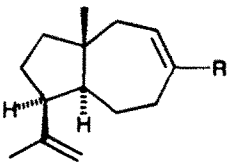
Vernonia galpinii [57, 97, 138]



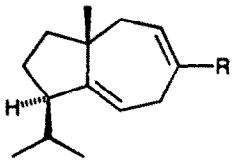
Higginsia sp.[57]



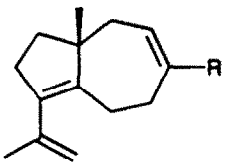
Ferula communis
subsp *communis* [68]
F. tingitana [101]



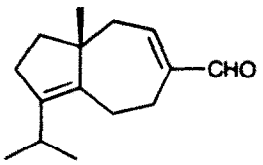
R = CH_2OH
Rosa rugosa [46]
R = CHO
R. rugosa [45]
R = CO_2H
R. rugosa [45]



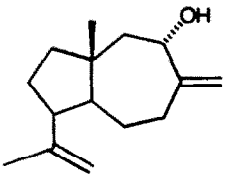
R = CH_3
Rosa rugosa [138]
R = CHO
R. rugosa [43, 47]
R = CO_2H
R. rugosa [43]



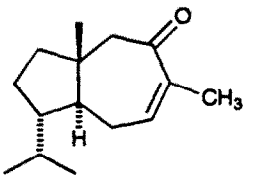
R = CHO
Rosa rugosa [45]
R = CO_2H
Rosa rugosa [45]



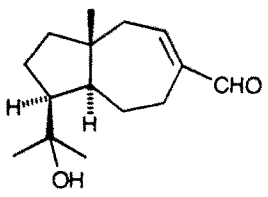
Rosa rugosa [45]



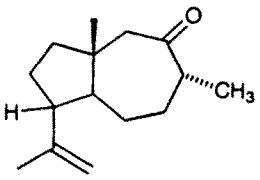
Fokienia hodginsii [102]



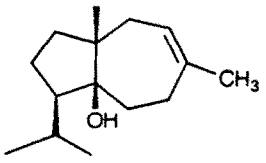
Calea prunifolia [103]



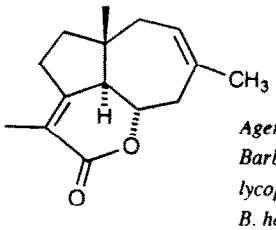
Rosa rugosa [45]



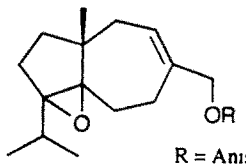
Fokienia hodginsii [102]



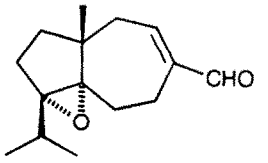
Daucus carota [7-10]



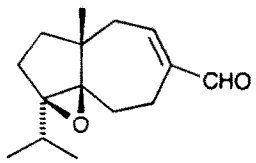
Ageratum fastigiatum [104]
Barbilophozia lycopodioides [56]
B. hatcheri [56]



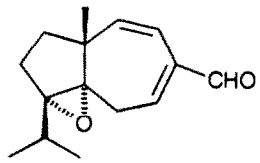
R = Anis
Ferula communis subsp *communis* [86]



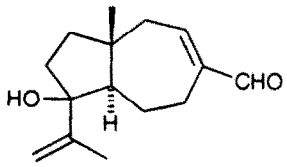
Rosa rugosa [45]



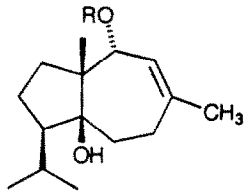
Rosa rugosa [45]



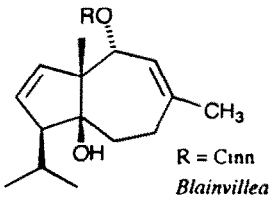
Rosa rugosa [45]



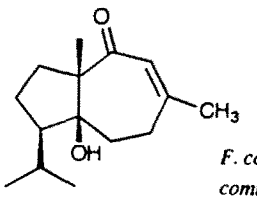
Rosa rugosa [45]



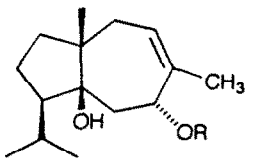
R = Ang
Lasiantheae fruticosa [51]
R = Cinn
Blainvillea acmella [105]
R = Anis
B. acmella [105]
Iva xanthifolia [106]
Xanthium catharticum [107]



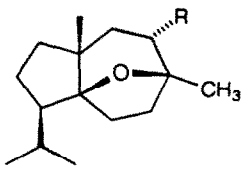
R = Cinn
Blainvillea acmella [105]



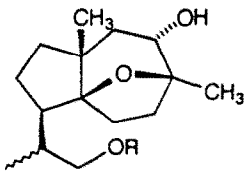
F. communis subsp *communis* [68]



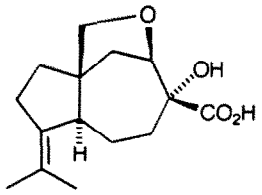
R=Ac
R=Ver
F. linkii [108]



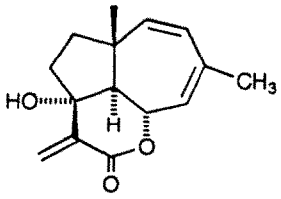
R = H
Daucus carota [109]
R = OH
D. carota [6]
F. linkii [108]



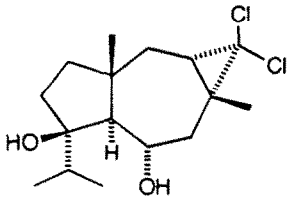
R = Van
F. rigidula [110]



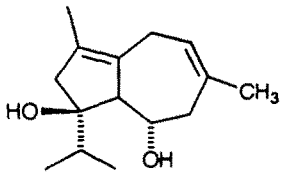
Aspergillus terreus [52]



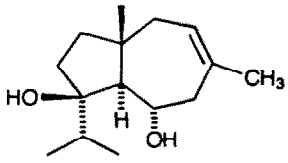
Marasmus fulvoferrugineus [55]



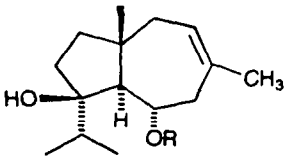
F. jaeschkeana [66]



F. jaeschkeana [111]



F. jaeschkeana [40, 69, 112]
F. sinaica [113]



R = Ang
F. communis [90]
F. elaeochrytris [34]
F. jaeschkeana [112]
F. linkii [98]
Heliopsis helianthoide [135]

R = iVal
F. linkii [98]

R = 2MeBu
F. linkii [98]

R = Cinn
F. rigidula [110]

R = Coum
F. rigidula [110]

R = Ben
F. elaeochytris [34]
F. jaeschkeana [112]
F. rigidula [110]
F. sinaica [113]

R = *p*-Hydroxybenzoyl
F. communis [87]
F. elaeochytris [34]
F. lancerottensis [115]
F. kuhistanica [114]
F. jaeschkeana [69, 112]
F. orientalis var *orientalis* [89]
F. rigidula [110]
F. sinaica [113]
F. tenuisecta [114]

R = Anis
F. communis subsp *communis* [86]
F. communis [87]
F. elaeochytris [34]
F. kuhistanica [116]
F. linkii [39, 98]
F. rigidula [110]
F. sinaica [113, 117]

R = 3,4-Dihydroxybenzoyl
F. akitschkensis [118]
F. jaeschkeana [112]

R = Van
F. jaeschkeana [69]
F. orientalis var *orientalis* [89]
F. elaeochytris [34]
F. rigidula [110]
F. tenuisecta [119]

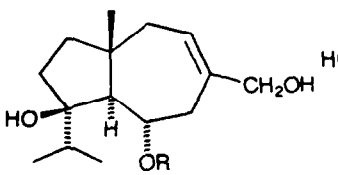
R = Ver
F. communis var *brevifolia* [91]
F. akitschkensis [120]
F. linkii [98]

R = 3-Hydroxy-4-methoxy benzoyl
F. tenuisecta [119]

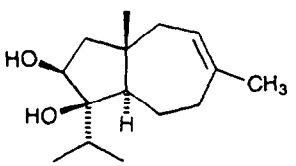
R = 3,4,5-Trimethoxybenzoyl
F. pallida [121]

R = 2-Hydroxybenzoyl
F. elaeochytris [34]
F. jaeschkeana [112]
F. rigidula [110]

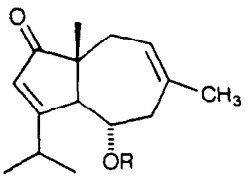
R = 3,4-Methylenedioxy benzoyl
F. jaeschkeana [112]



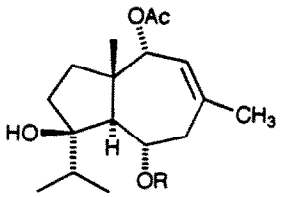
R = *p*-Hydroxybenzoyl
F. jaeschkeana [122]



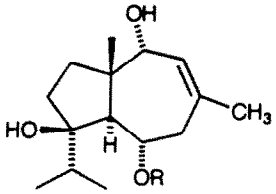
Gliocladium virens [54]



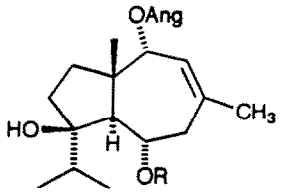
R = Anis
Ferula communis subsp *communis* [86]



R = Anis
F. communis subsp *communis* [86]
R = iVal
F. linkii [39]

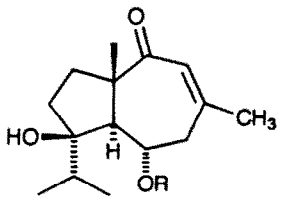


R = H
F. latipinna [38]
R = Anis
F. communis subsp *communis* [86]
R = 2MeBu
F. linkii [98]
R = Ang
F. communis var *brevifolia* [91]



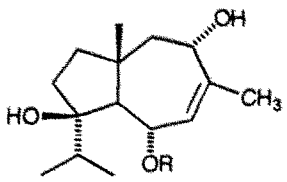
R = Ver
F. communis subsp *communis* [86]
R = Ang
F. pallida [123]
F. latipinna [38]
R = Benz
F. communis subsp *communis* [86]

R = *p*-Hydroxybenzoyl
F. communis var *brevifolia* [91]
F. latipinna [38]
F. sinaica [113]
F. tingitana [101]
R = Anis
F. communis subsp *communis* [86]
F. latipinna [38]

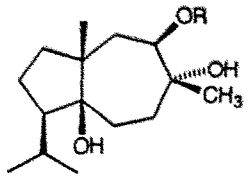


R = H
F. linkii [98]
F. sinaica [100]
R = Ang
F. communis [90]
F. lapidosa [124]
F. latipinna [38]
F. linkii [98]
R = 2MeBu
F. linkii [98]
R = iBu
F. linkii [98]
R = iVal
F. communis [90]

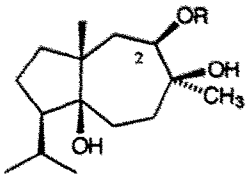
R = *p*-Hydroxybenzoyl
F. linkii [98]
F. sinaica [100]
R = Anis
F. communis [90]
F. linkii [98]
R = Van
F. latipinna [38]
R = 3,4,5-Trimethoxybenzoyl
F. pallida [125]
R = 3,4-Methylenedioxy-5-methoxybenzoyl
F. pallida [125]



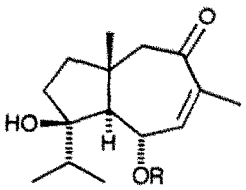
R = *p*-Hydroxybenzoyl
F. lancerottensis [115]
F. sinaica [126]
R = Van
F. rigidula [110]



R = H
F. linkii [98]
R = Anis
F. lancerottensis [115]
R = Ang
F. linkii [127]



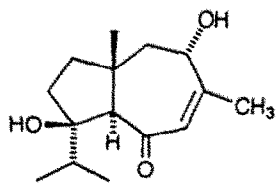
R = 3,4,5-Trimethoxybenzoyl
F. pallida [95]
2-oxo
F. tenuisecta [94]



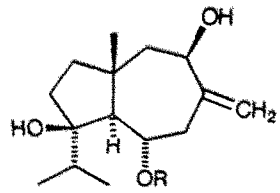
R = H
F. lancerottensis [115]
R = *p*-Hydroxybenzoyl
F. sinaica [100]
F. lancerottensis [115]
F. jaeschkeana [99]
F. linkii [93]
F. orientalis
var *orientalis* [89]
F. rigidula [110]

R = Anis
F. linkii [93]
F. lancerottensis [115]
R = Van
F. orientalis
var *orientalis* [89]
F. rigidula [110]
R = Ver
F. linkii [93]

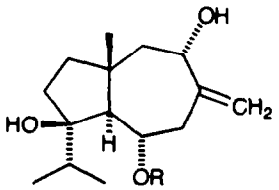
R = Cinn
F. rigidula [110]
R = Coum
F. rigidula [110]



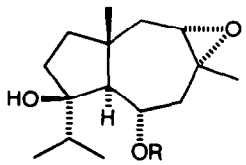
F. jaeschkeana [128]



R = *p*-Hydroxybenzoyl
F. sinaica [100]

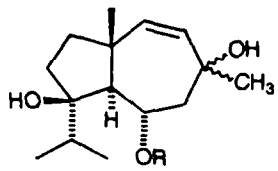


R = H
F. sinaica [113]
R = iVal
F. linkii [129]
R = *p*-Hydroxybenzoyl
F. jaeschkeana [122]
F. sinaica [100]
R = Van
F. rigidula [110]

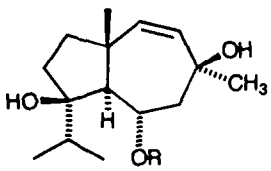


R = iVal
F. linkii [39]
R = *p*-Hydroxybenzoyl
F. lancerottensis [115]
F. jaeschkeana [112]
F. orientalis
var *orientalis* [89]
R = Anis
F. linkii [39]
F. rigidula [110]

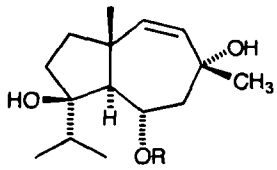
R = Van
F. orientalis
var *orientalis* [89]
F. jaeschkeana [99]
R = Ver
F. linkii [39]
R = Cinn
F. rigidula [10]



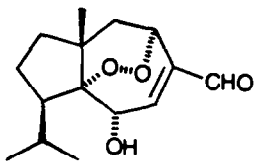
R = *p*-Hydroxybenzoyl
F. jaeschkeana [128]
R = iVal
F. linkii [93]



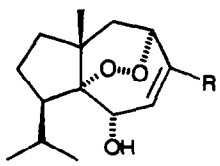
R = H
F. sinaica [113]
R = Van
F. rigidula [110]



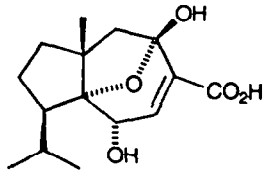
R = Van
F. rigidula [110]



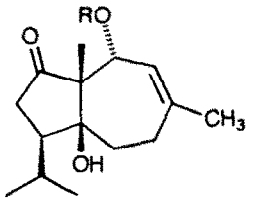
Nardostachys
chinensis [137]
Rosa rugosa [42, 47]



R = CO_2H
Rosa rugosa [42, 47]
R = CO_2Me
R. rugosa [44, 47]

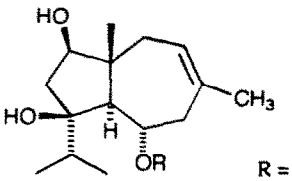


Rosa rugosa [44]

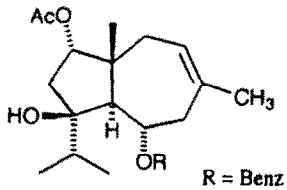


R = Ac
Sium latifolium [37]
S. latijugum [130]
R = Ang
Laserpitium halleri subsp *halleri* [36]
Selinum vaginatum [130]
Inula crithmoides [70]
(structure revised in ref 36)

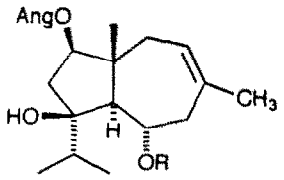
R = *p*-Hydroxybenzoyl
F. communis [87]
R = Anis
F. communis [90]
F. communis subsp *communis* [68]
F. tingitana [101]



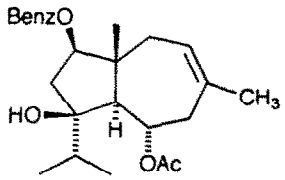
R = H
F. akitschkensis [131]
F. jaeschkeana [111]
R = *p*-Hydroxybenzoyl
F. jaeschkeana [111]
R = Anis
F. sinaica [100]
R = Van
F. jaeschkeana [132]



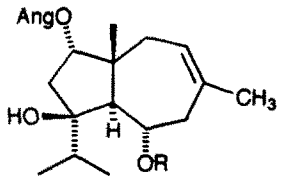
R = Benz
F. communis subsp *communis* [86]
R = *p*-Hydroxybenzoyl
F. communis var *brevifolia* [91]
R = Anis
F. communis subsp *communis* [86]



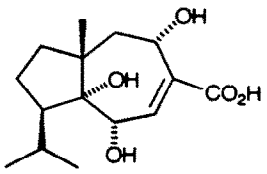
R = H
F. jaeschkeana [111]
R = *p*-Hydroxybenzoyl
F. akitschkensis [131]
R = 3,4-Dihydroxybenzoyl
F. akitschkensis [118]
F. jaeschkeana [112]



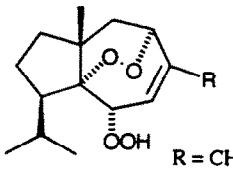
F. sinaica [133]



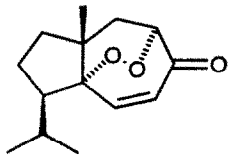
R = Ang
F. communis [90]



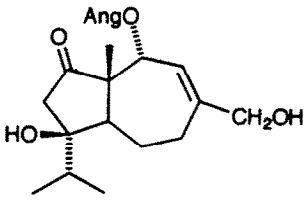
Rosa rugosa [44]



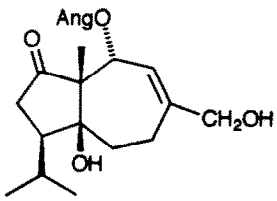
R = CHO
R = CO_2H
Rosa rugosa [47]



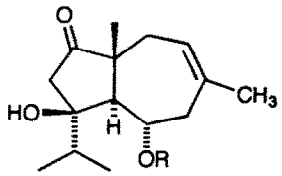
Rosa rugosa [44]



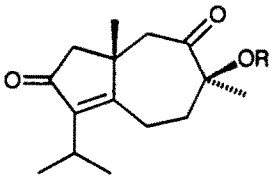
F. sinaica [133]



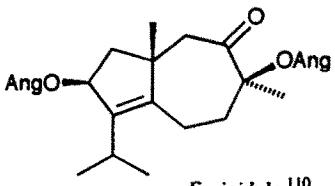
F. sinaica [113]



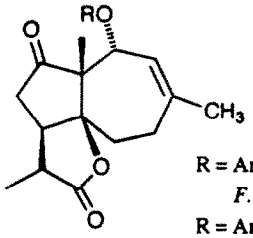
R = *p*-Hydroxybenzoyl
F. jaeschkeana [112]



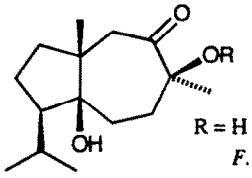
R = Ang
F. communis [90]
F. linkii [93, 98]
F. latipinna [38]
R = Epoxyang
F. linkii [93, 98]



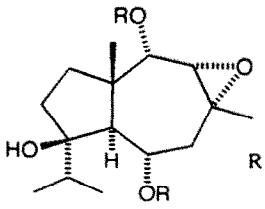
F. rigidula [110]



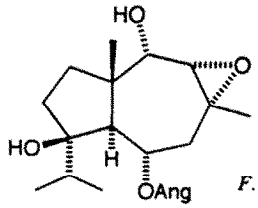
R = Ang
F. jaeschkeana [69]
R = Anis
F. communis
subsp *communis* [68]



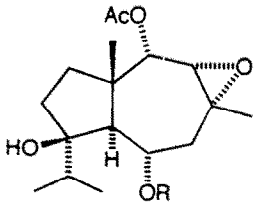
R = H
F. latipinna [38]
R = Ang
F. linkii [93]
F. latipinna [38]
F. tenuisecta [94]



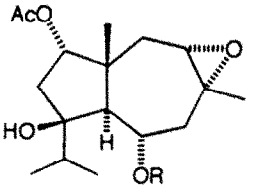
R = H
F. latipinna [38]



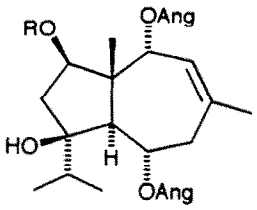
F. lapidosa [134]



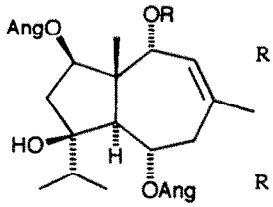
R = H
F. linkii [39]
R = Ang
F. latipinna [38]
F. linkii [39]
R = iVal
F. linkii [39]



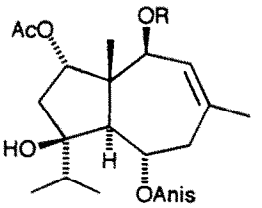
R = Ver
F. lapidosa [136]



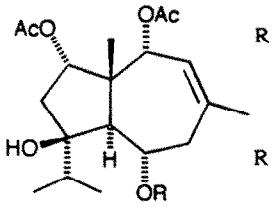
R = H
F. tingitana [35, 101]
R = Ac
F. tingitana [101]



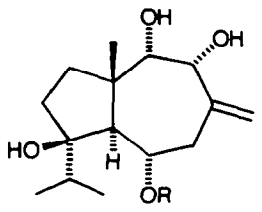
R = H
F. tingitana [101]
Laserpitium latifolium [35]
R = H 2,3α-epoxide
L. latifolium [27]
R = Ac
F. tingitana [101]



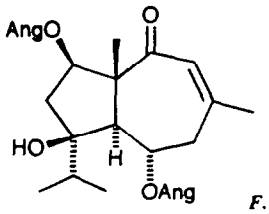
R = H
F. communis subsp *communis* [86]
R = Ac
F. communis subsp *communis* [86]
F. sinaica [117]



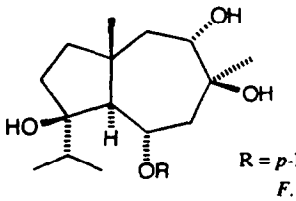
R = Anis
F. communis subsp *communis* [86]
R = Ver
F. communis subsp *communis* [86]



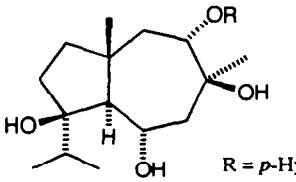
R = iVal
F. linkii [129]
R = Ang
F. linkii [129]



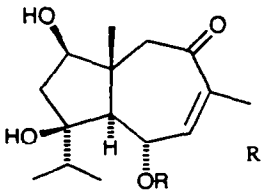
F. sinaica [100]



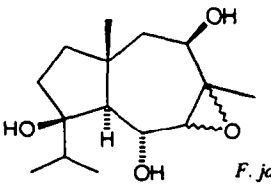
R = *p*-Hydroxybenzoyl
F. sinaica [113]



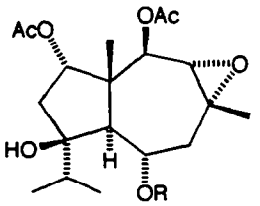
R = *p*-Hydroxybenzoyl
F. sinaica [100]



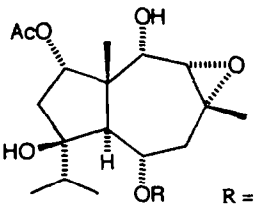
R = *p*-Hydroxybenzoyl
F. sinaica [100]



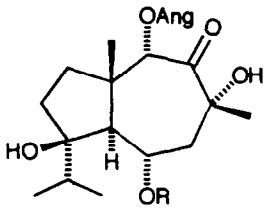
F. jaeschkeana [99]



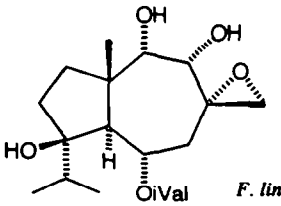
R = Ang
F. lapidosa [96]



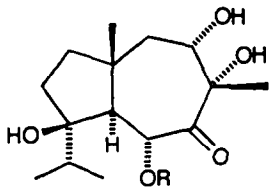
R = Ver
F. lapidosa [96]



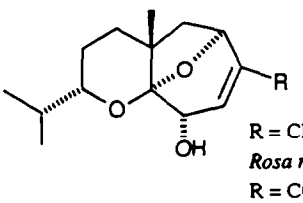
R = iBu
Laeserpitium latifoiium [41]
R = Ang
L. latifolium [4, 5, 41]



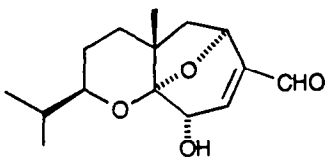
F. linkii [129]



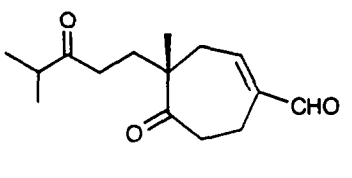
R = *p*-Hydroxybenzoyl
F. jaeschkeana [66]



R = CHO
Rosa rugosa [46]
R = CO_2H
R. rugosa [44]



Rosa rugosa [46]



Rosa rugosa [46]