Tetrahedron Vol. 37, pp. 2199 to 2248, 1981
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0040–4020/81/122199–50$05.00/0
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TETRAHEDRON REPORT NUMBER 110

TERPENOID METABOLITES OF MUSHROOMS AND RELATED BASIDIOMYCETES

WILLIAM A. AYER* and LOIS M. BROWNE*
Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

(*Received in the USA* 18 *December* 1980)

"Under a toadstool
Crept a wee Elf
Out of the rain
To shelter himself
Under the toadstool
Sound asleep
Sat a big Dormouse
All in a heap"

OLIVER HERFORD

Since childhood many of us have been enchanted with that colorful and diverse form of plant life referred to as "mushrooms and toadstools". Their many shapes and forms, often appearing seemingly overnight in meadows and forests, afford both gastronomical delights and deadly poisons, and provide the backdrop for fantasies of fairies and elves. The ancient practice of *Soma* and the present day pursuit of the "magic mushroom", rotting tree roots which glow in the dark, "fairy rings" on our lawns, all may be attributed to similar forms of plant life. These are the reproductive and vegetative phases of a particular group of rather highly specialized and advanced fungi known as Basidiomycetes.

The basic vegetative body of a fungus (thallus)[1] is a multinucleate protoplast enclosed within a rigid wall. Its function is to absorb food materials and assimilate these into the protoplast, to grow, and to reproduce (either sexually or asexually; i.e. by becoming the reproductive structure or by serving as a foundation from which the reproductive structure develops). The thallus consists of a mass of fine, branched filaments called hyphae and known collectively as mycelium. The mycelia of the various species of mushrooms grow in the soil, on decaying wood or other organic litter, or in the tissues of living plant hosts. Under suitable environmental conditions they produce fruit-bodies (spore-producing organisms). The fruiting bodies produce large numbers of minute single cells (spores) which are dispersed by various means.

The morphological features of a particular fungus are affected by environment. A fungus that grows on several different host plants may possess a totally different form and structure on each host, different enough to warrant classification by existing keys into several families and genera. Fungi grown in the laboratory under controlled conditions often bear little resemblance to the natural form. This inherent variability of fungi has resulted in the formulation of systematic taxonomic arrangements in such bewildering arrays and with so much continual reshuffling that even professional mycologists have been known to regard fungal systematics as chaotic.[2] The currently favored taxonomical system is based on the organization of kingdoms as proposed by Whittaker.[3] He formalized a large body of reported data that indicated that living organisms of the world are not just "plant" or "animal" but are better separated into five kingdoms based on the mode of nutrition. Animalia (ingestive), Plantae (photosynthetic), Fungi (osmotrophic), Monera (including bacteria and blue-green algae), and Protista (unicellular eukaryotes). Whittaker's kindgom of Fungi (Table 1)[1] consists of two divisions: The division Eumycota is comprised of five subdivisions, one of which is the Basidiomycotina (Table 2).[4] The chemistry of the terpeniod metabolites of the Basidiomycotina comprises the topic of this review. The older taxonomical system, based upon two kingdoms of living organisms, listed four classes of Eumycophyta (true fungi;

Table 1.[1]

Kingdom Fungi

Division : Pantonemomycota	Division : Eumycota
Class : Oomycetes Hypochytridiomycetes	Subdivision : Mastigomycotina Class : Chrytridiomycetes Subdivision : Zygomycotina Ascomycotina Deuteromycotina Basidiomycotina

Table 2.[1,4]

BASIDIOMYCOTINA

Basidium (club-shaped cell in which meiosis occurs)

Teliomycetes	Hymenomycetes	Gasteromycetes
Mycelium form basidia Highly virulent, parasitic fungi Order: Uredinales (rust) Plant Parasites Pleomorphic Life Cycle Alternate Hosts or Single Host Ustilaginales (smut fungi) Plant Parasites Simple Life Cycle	Mycelium forms basidiocarp which form exposed basidiospores Two subclasses based on shape of basidium: Phragmo basidiomycetidae (jelly fungi) Basidia : Divided by a Partition Order: Tremellales Auricuriales Septobasidiales Holobasidiomycetidae (mushrooms, bracket fungi, polypores) Varied basidia Order: Exobasidiales Brachybasidiales Dacrymycetales Tulasnelales Aphyllophorales (bracket fungi) Agaricales (commercial mushroom)	Mycelium forms basidiocarp which form enclosed basidiospores Order: Podoxales Phallales (stinkhorns) Lycoperdales (puffballs) Gautierales Hymenogastrales Nidulariales (bird's nest fungi) Melanogastrales Sclerodermatales Tulostomatales

Table 3.[5]

Eumycophyta (True Fungi)

Class : Basidiomycetes (Club Fungi)

Order : Tremellales	Order : Agaricales	Order : Lycoperdales
Family : Auriculariaceae Tremellaceae Dacryomycetaceae	Family : Hypochnaceae Thelephoraceae Clavariaceae Hydnaceae Polyporaceae Agaricaceae	Family : Phallaceae Lycoperdaceae Hymenogastraceae Nidulariaceae

subdivision of Thallophytes) based on the method of reproduction. The club fungi (class Basidiomycetes) (Table 3)[5] was one of these, and its systematic classification roughly parallels that of Basidiomycotina. Both phylogenetic systems appear in the current literature although terminology from the older system is most frequently encountered. Both terminologies will be used in this review.

According to Ainsworth,[4] there are three classes of Basidiomycotina: the Teliomycetes, Hymenomycetes and Gasteromycetes (Table 2). The one unifying feature is the basidium (the cell in which meiosis occurs) which is usually a swollen club-shaped cell produced terminally. Another significant feature of the basidiomycetes is that a large part of the vegetative phase is a well-developed dikaryon (mycelium in which the cells contain two haploid nuclei). The basic life cycle of the Basidiomycotina is relatively simple: basidiospores germinate to form mycelia; the mycelium grows vegatatively forming the thallus which differentiates into a basidiocarp or a basidium-bearing mycelium, depending on the taxonomic group. The basidia then produce basidiospores completing the cycle.

The class Teliomycetes are composed of two orders of highly virulent parasitic fungi. Order Ustilaginales, the smut-fungi, so called because most of them produce powdery masses of black spores, are a group of highly specialized parasites which have a very simple life cycle. Some smuts form their spores in grasses, some induce gall formation (excessive localized growth of host tissue to form large balls that become filled with fungal hyphae), and a few (known as white smuts) produce light brown or colorless spores inside the host leaf. The most important economically are the grain smuts of cereals. Order Uredinales, the rust fungi, are specialized obligate parasites of flowering plants, conifers and ferns. There are some 4000 species, many of which are important economically because they infect cultivated plants. Rusts are pleomorphic, i.e. their life cycle may include the obligate requirement of growth on two different types of host plant and as many as five different morphological spore types.

The Hymenomycetes is the largest class of the Basidiomycotina. It includes all fungi that produce basidiospores exposed on a basidiocarp. The basidia of the Hymenomycetes are always formed on a hymenium (spore-bearing layer) and not from single dispersed cells. The Hymenomycetes is divided into two subclasses. Members of one subclass are characterized by a basidiocarp which is waxy and gelatinous. Because of this these fungi are often called jelly fungi. There are three orders in the subclass. Most species of the order Tremellales are parasitic on trees or grow saprophytically on their dead branches. The order Auriculariales are parasitic on mosses, leaves, stems of plants and occasionally on other fungi, while the order Septobasidiales are symbiotic and/or parasitic on scale insects that feed on living plants. The other subclass contains mushrooms, bracket fungi and polypores. With the exception of a few Gasteromycetes, all the terpeniod metabolites reported have been found in this subclass especially in the orders Aphyllophorales and the Agaricales (Table 4). The order Aphyllophorales is a large order containing species with diverse types of fruit-bodies including the bracket fungi, coral fungi and tooth fungi. One family of this order, the Polyporaceae, comprises the majority of the economically important wood-destroying fungi. The order Agaricales contain the well-known commercial mushroom and all similar forms. Agarics are universally distributed and grow in a variety of habitats including soil, wood and dung. The order includes the widely cultivated edible mushroom, *Agaricus bisporus*, together with such poisonous species as the "destroying angel" *Amanita virosa*. Some species contain intoxicating substances, e.g. *Psilocybe* is used by South American Indians to produce hallucinations. The mycelium of others is luminous, e.g. *Clitocybe illudens*. A number produce antibiotics, which are often of a terpenoid nature.

The third and last class, the Gasteromycetes, is characterized by the production of basidiospores inside basidiocarps which are completely enclosed in early development becoming exposed only when the fungus is fully mature. There are nine orders in the class, the most notorious being the order Phallales, or stinkhorns. Not only do they have a foul, pungent odor, but they are singularly unattractive. The order Lycoperdales include the classic puffballs. Thus far, terpenoid metabolites have been reported only for species in the order Nidulariales. The Nidulariales, bird's nest fungi, are so named because the mature fruit-body consists of a cup-like peridium containing small egg-like peridioles that resembles a bird's nest with eggs. Several species of *Cyathus* and *Mycocalia* produce antibiotic and antifungal compounds of a terpenoid nature which will be discussed later.

The *Basidiomycotina* provide a rich and varied source of terpenoids, especially sesquiterpenoids. Section I of the review covers the chemical literature to the end of 1979 (including *Chem. Abstr.*, Vol. 91), Section II discusses current reports to September 1980 (*Chem. Abstr.*, Vol. 93 (13)), and an Appendix† displays in tabular form the physical and spectral properties of all terpenes isolated to date. Several comprehensive reviews on specific aspects of terpene chemistry have appeared, the most

†An appendix containing structures and physical constants for all the metabolites isolated to date is available from the authors upon request.

Table 4. Distribution of terpenoid metabolities isolated from Basidiomycotina

Class Hymenomycetes
Subclass Holobasidiomycetidae

Order	Family	Genera
Agaricales	Boletaceae	Boletus
	Coprinaceae	Coprinus
	Russulaceae	Lactarius
		Russula
	Tricholomataceae	Clitocybe
		Collybia
		Coprinus
		Lentinus
		Marasmius
Aphyllophorales	Polyporaceae	Coriolus
		Fomes
		Fomitopsis
		Heterobasidion
		Lenzites
		Merulius
		Poria
		Trametes
	Stereaceae	Stereum

Class Gasteromycetes

Order	Family	Genera
Nidulariales	Nidulariaceae	Cyathus
		Mycocalia

notable being the yearly publication of The Chemical Society, A Specialist Periodical Report, *Terpenoids and Steroids*, Vols. 1–9. This review will discuss the chemistry of the sesqui- and diterpenoid metabolites which have been isolated from various species in the subdivision Basidiomycotina. Very little has been reported on monoterpenoids, and the triterpenoids, which are mainly lanosterol and ergosterol derivatives, have been well summarized.[6]

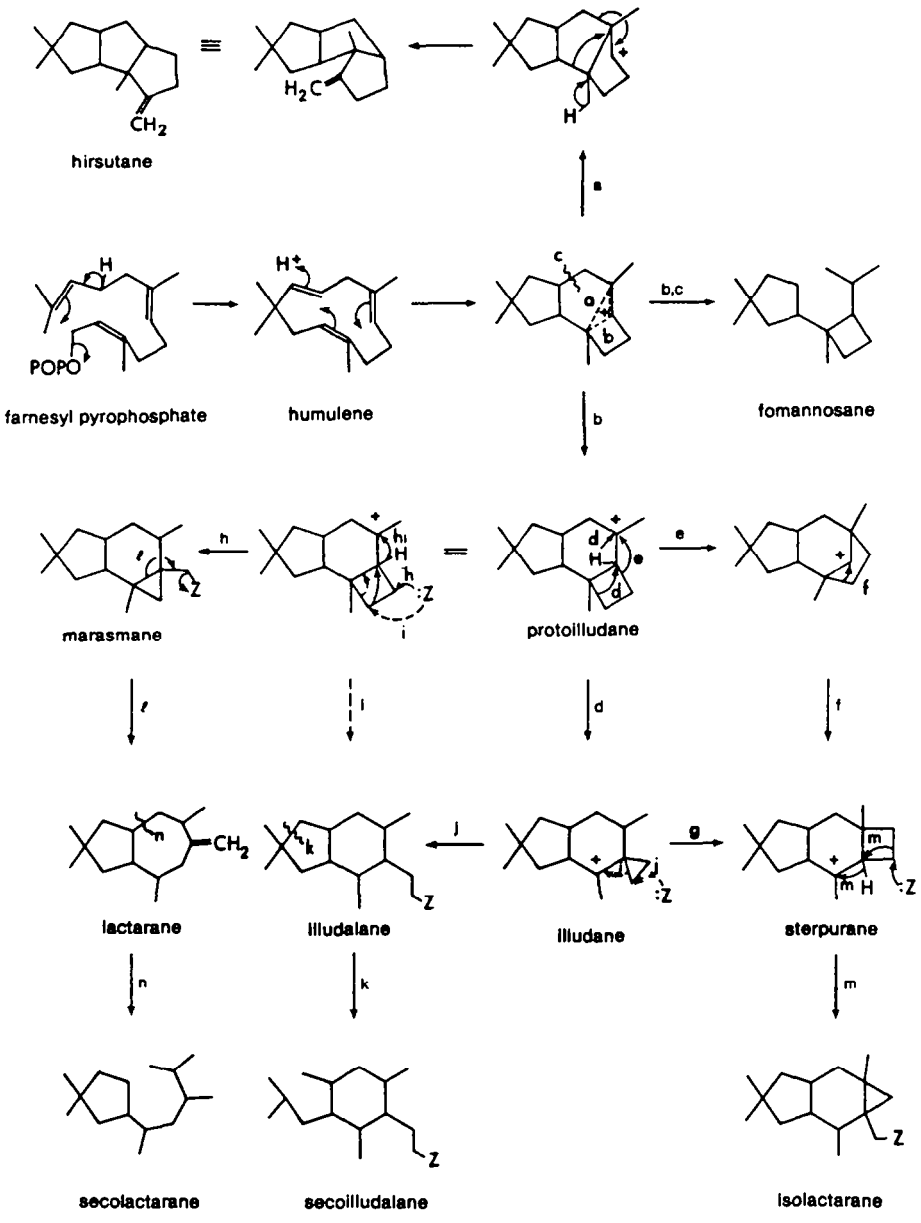
SECTION I

Sesquiterpenoids comprise the majority of the isoprenoid metabolities isolated from the Basidiomycetes. For convenience of discussion, the various types of sesquiterpenes found have been divided into groups based on their biogenetic origin. The largest group of metabolites are those which formally may be derived from humulene. The other group are sesquiterpenes of miscellaneous skeletal types including bicyclofarnesane and cuparane classes.

The biogenesis of the humulene-derived sesquiterpenoids comprising 11 different skeleton types are depicted in Scheme 1. Humulene, which arises by cyclization of farnesyl pyrophosphate, can be further cyclized to the hirsutane skeleton (path a) or to the protoilludane skeleton (path b). Rearrangement of a protoilludane cation may give rise to the illudane skeleton (path d), the sterpurane skeleton (path e,f or d,g) or the marasmane skeleton (path h). Bond cleavage of a suitable protoilludane intermediate leads to the fomannosane skeleton (path b,c) or to the illudalane skeleton (path i or d,j), whereas further bond cleavage of an illudalane gives the secoilludalane skeleton (path k). Rearrangement of a marasmane leads to the lactarane skeleton (path l) while rearrangement of a sterpurane gives rise to an isolactarane skeleton (path m). Bond cleavage of a lactarane (path n) gives the secolactaranes. The results of several biosynthetic investigations, discussed later, are consistent with this general scheme.

Hirsutanes

In 1947, Heatley *et al.*[7] reported that a fungus first encountered as a chance contaminant on an agar plate and tentatively identified as *Stereum hirsutum* produced a number of acidic metabolites, some of which had antibiotic properties. Some 18 years later Scott *et al.*[8a–c] utilizing material provided by the original investigators, re-examined the major metabolite and through a careful combination of chem-

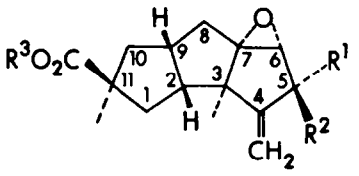


Scheme 1.

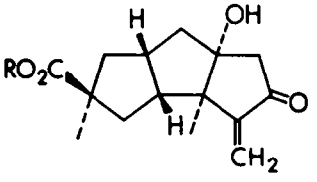
ical[8a,c] and X-ray[8a,b] studies were able to establish the structure of hirsutic acid. The IR and ^{1}H NMR spectra of hirsutic acid ($C_{15}H_{20}O_4$) showed the presence of the following groups: $\rangle$CHOH, $\rangle$C=CH$_2$, –COOH, 2 CH$_3$. The secondary alcohol was shown to be allylic by facile manganese dioxide oxidation of methyl hirsutate to the corresponding unsaturated ketone, which proved to be an exomethylene cyclopentanone. The fourth oxygen was shown to be present as an epoxide by lithium aluminum hydride reduction of hirsutic acid to give a triol which formed a diacetate upon acetylation. ^{1}H NMR studies of the triol diacetate and its oxidation product established the position of the epoxide relative to the allylic alcohol.

The complete structure of hirsutic acid (**1**) was established by X-ray diffraction studies of its *p*-bromophenacyl ester **2**. Irradiation with X-rays initiates an unusual molecular rearrangement without disruption of the crystal structure and with only minor changes in lattice parameters and intensities of the reflections. Structure analysis of two complete sets of intensity data by standard methods indicated that the irradiated crystals contained two different molecules randomly distributed, and established the structure and absolute configuration of the *p*-bromophenacyl ester of hirsutic acid as **2** and of the

rearrangement product as **3**. Complicatic acid (**4**) has been isolated from *Stereum complicatum* (Fr.)[9a,b] along with hirsutic acid. It seems quite likely that the fungus investigated by Heatley *et al.*[7] was *S. complicatum*, rather than *S. hirsutum*, since all subsequent attempts to obtain hirsutic acid from the latter have been unsuccessful.[8c,9a]

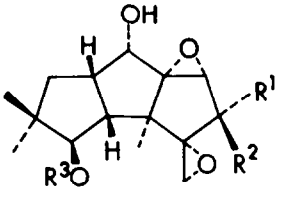


1 R^1=OH, R^2=R^3=H Hirsutic acid
2 R^1=OH, R^2=H, R^3=p$BrC_6H_4COCH_2$–
4 R^1=R^2=O, R^3=H

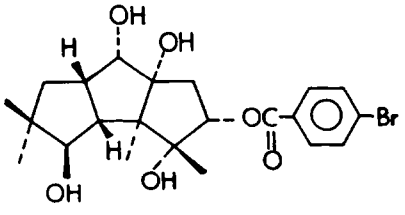


3 R=p$BrC_6H_4COCH_2$–

Other hirsutane-type sesquiterpenes with antibiotic and antitumor activity have been isolated from Basidiomycetes. The Japanese mushroom *Coriolus consors*[10a] produces coriolin (**5**)[10b,c] coriolin B (**6**)[10b] and coriolin C (**7**).[10b] These compounds were assigned the structures shown on the basis of spectroscopic analysis, biogenetic consideration and chemical transformation. The structure of coriolin (**5**) has been confirmed and the absolute configuration of **5** determined by X-ray analysis of its hexahydro-*p*-bromobenzoate derivative **8**.

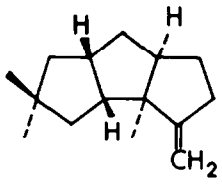


5 R^1=R^2=O, R^3=H Coriolin
6 R^1=OH, R^2=H, R^3=COC_7H_{15} Coriolin B
7 R^1=R^2=O, R^3=$COCHOHC_6H_{13}$ Coriolin C

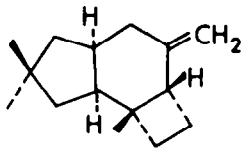


8

In 1976 Nozoe *et al.*[11] isolated and identified hirsutene (**9**), a compound which had been implicated in the literature as a possible biogenetic precursor of coriolin (**5**),[12a] from an extract of the mycelium of *Coriolus consors*. The co-occurence of hirsutene (**9**) with humulene and caryophyllene in the hydrocarbon fraction obtained from the extract of this fungus lent further support to the hypothesis that the hirsutane-type sesquiterpenes arise via a farnesyl precursor.[12a,b]

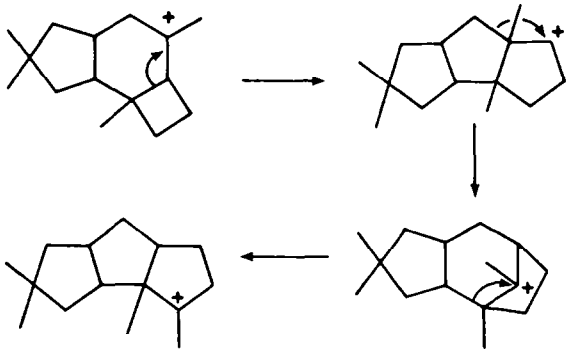


9 Hirsutene



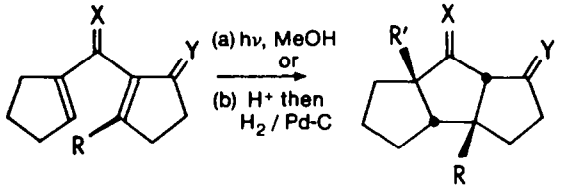
10

Recently Matsumoto *et al.*[13] have described the transformation of a derivative of $\Delta^{7(13)}$-protoilludene (**10**) into compounds possessing the hirsutene (**9**) skeleton. The key step involves a triple rearrangement of the type illustrated in Scheme 2.



Scheme 2.

Hirsutic acid and related metabolites possess a tricyclo[6.3.0.0^{2,6}]-undecane carbon skeleton with a *cis–anti–cis* stereochemistry at the ring fusions. To date, four syntheses of this tricycloundecane system[14] have been reported. Two of these syntheses,[14a,b] in each of which the key step involves creation of the central ring, in one case photochemically (a),[14a] and in the other by acid-catalyzed cyclization (b),[14b] lead to the undesired *cis–syn–cis* ring system (Scheme 3).



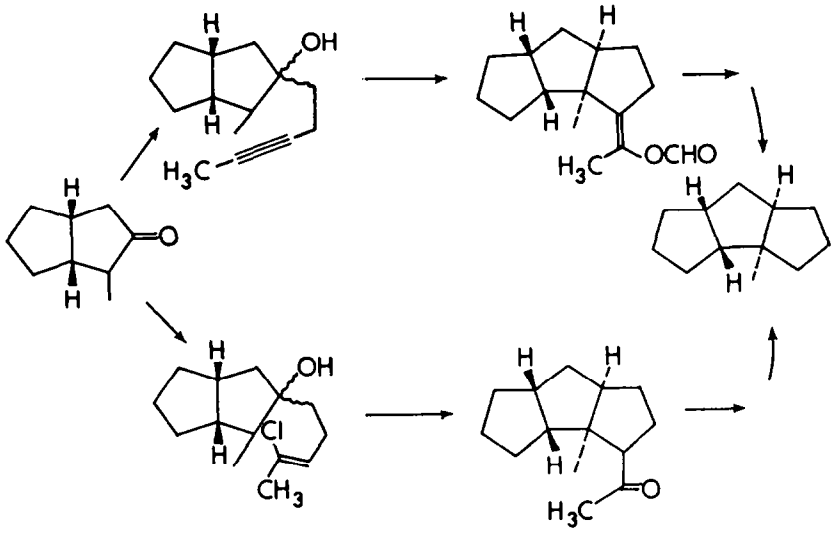
(a) X=H, H; Y=O; R=CH_3 (a) X=H, H; Y=O; R=CH_3; R'=OCH_3
or (b) X=O; Y=H, H; R=H (b) X=O; Y=H, H; R=R'=H

Scheme 3.

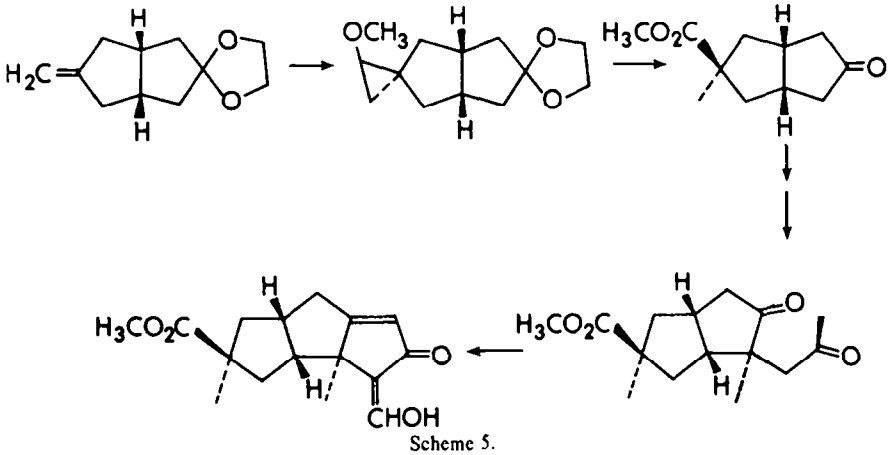
Lansbury[14c] has reported a stereoselective synthesis of trisnorhirsutane with the *cis–anti–cis* configuration by means of chloro-olefin annulation of a bicyclo[3.3.0]octanone derivative (Scheme 4).

Matsumoto *et al.*[14d] reported a stereochemically controlled synthesis of the hirsutane skeleton suitably functionalized for the total synthesis of hirsutic acid (**1**). In their synthesis (Scheme 5), the methylene derivative of the monoketal of *cis*-bicyclo[3.3.0]octane-3,7-dione was transformed stereoselectively to the methylated acid derivative by addition of methoxycarbene, acid cleavage of the resultant cyclopropane to an aldehyde, oxidation and esterification. The ketone was methylated then alkylated with methallyl chloride and ozonolyzed to the diketone. Aldolization was followed by introduction of the hydroxymethylene group to give the derivative shown in Scheme 5.

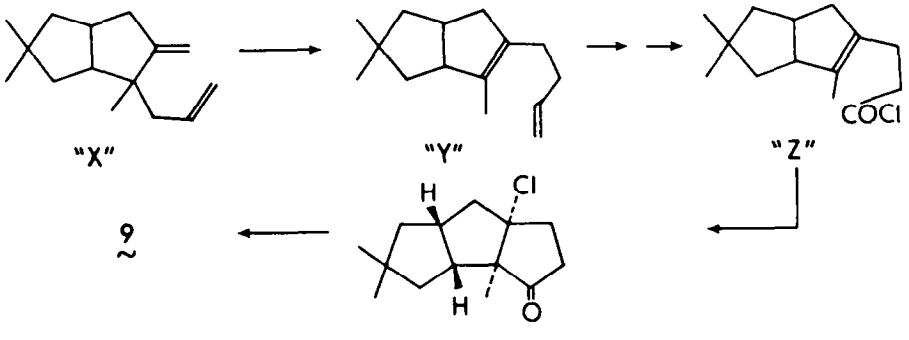
Three syntheses of hirsutene have been reported.[11,13,15] One of these involves the "biogenetic-type" conversion of protoilludene to hirsutene referred to above.[13] Another (Scheme 6) involves the Cope rearrangement of the bicyclooctane derivative "X" to "Y" followed by selective cleavage of the terminal olefin and intramolecular Friedel–Crafts cyclization of the derived acid chloride "Z" to give a chloroketone. Reductive removal of chlorine and Wittig methylenation provided hirsutene (**9**).[11]



Scheme 4.



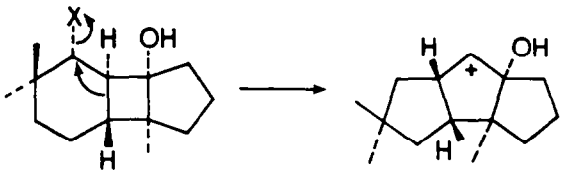
Scheme 5.



Scheme 6.

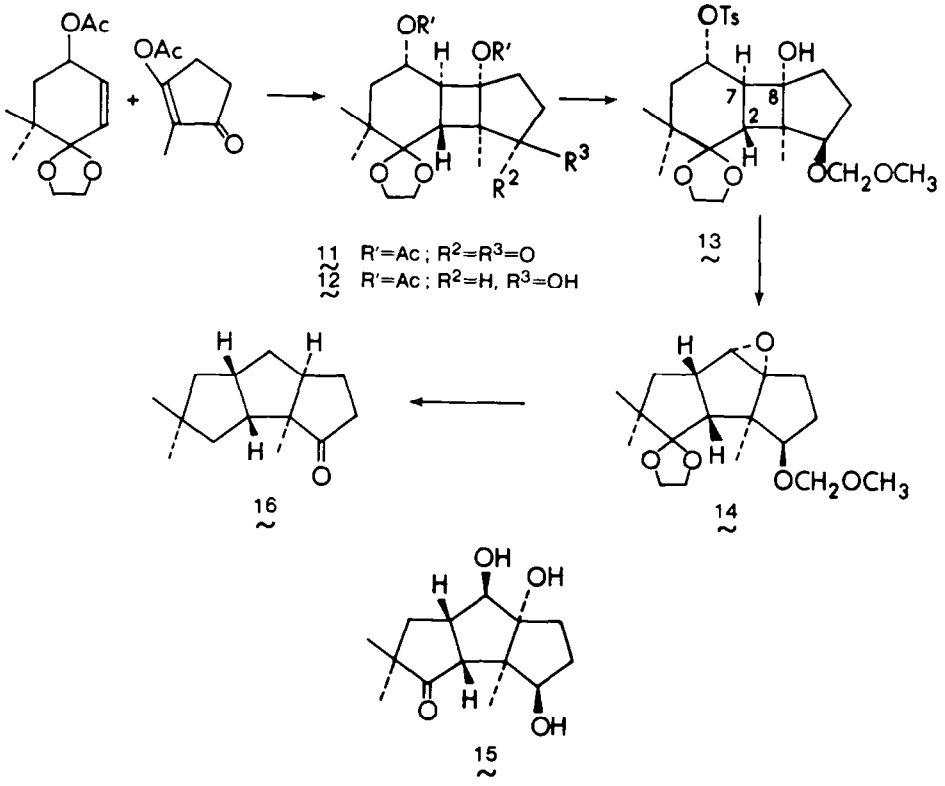
Recently, an elegant stereocontrolled synthesis of hirsutene (**9**) and potential precursors of coriolin (**5**) has been reported.[15] The key step in this approach is a unique skeletal rearrangement of a tricyclic 6–4–5 fused ring system to a *cis–anti–cis* tricyclic 5–5–5 fused ring system (Scheme 7).

The starting tricyclic compound was formed by photochemical cycloaddition of the ethylene ketal of 4-acetoxy-6,6-dimethyl-2-cyclohexenone with 2-methylcyclopentane-1,3-dione enol acetate (Scheme 8). Compound **11** (formed in 35% yield) was shown to be a head-to-head adduct of *cis–anti–trans* stereochemistry by X-ray crystallographic analysis of the *p*-bromobenzoate of the corresponding alcohol **12**. The functionality of compound **11** was modified to that of compound **13**. Skeletal rearrangement was



Scheme 7.

effected in high yield by heating **13** with potassium carbonate in aqueous acetone to give compound **14**. Compound **13** adopts a conformation in which the migrating C–2, C–7 bond is *trans* coplanar to the C–6 tosyloxy bond (C–7, C–8 cannot be coplanar). The sequential skeletal rearrangement of **13** is facilitated by breaking of parallel bonds to give the desired *cis–anti–cis* tricyclic compound **14**. The stereochemistry was confirmed by direct X-ray analysis of the corresponding ketotriol **15**. The synthesis of hirsutene was completed by functional group modification of **14** to form norketone **16**. Since the norketone had previously been transformed to hirsutene,[11] the synthesis of **16** completed the synthesis of hirsutene.

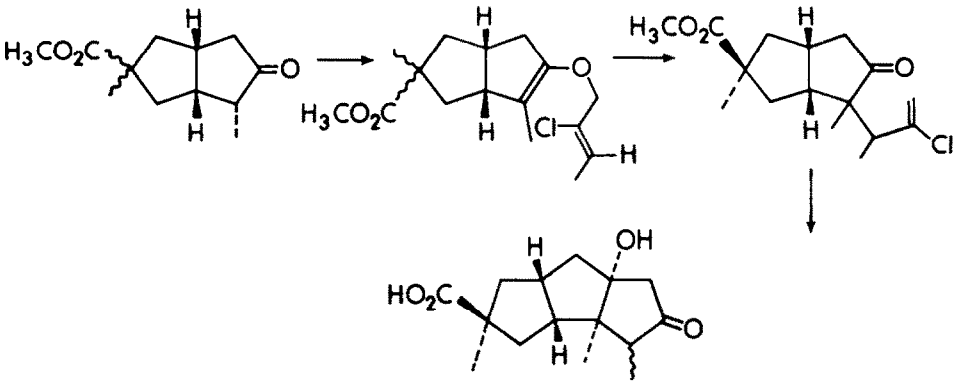


Scheme 8.

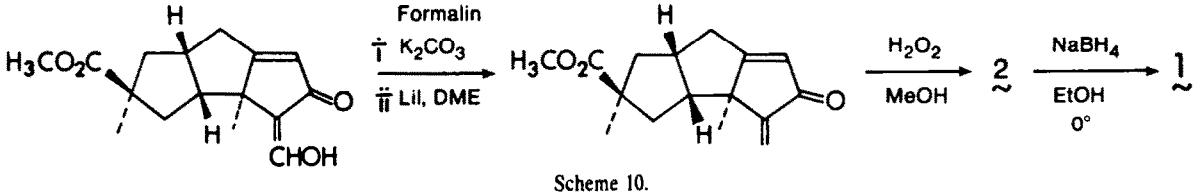
Lansbury *et al.*[16a,b] have reported two synthetic approaches to hirsutic acid (**1**). Each synthesis leads to a known degradation product of hirsutic acid. These are obtained by Claisen alkylation of a suitably functionalized bicyclic octanone, Claisen rearrangement, hydrolysis and aldol cyclization (e.g. Scheme 9).

Matsumoto *et al.*[16c] reported the completion of the synthesis of *dl*-hirsutic acid (**1**) in 1974. This stereospecific conversion of the tricyclic ketone prepared earlier by these same workers (see Scheme 5) was completed in four stages as outlined in Scheme 10.

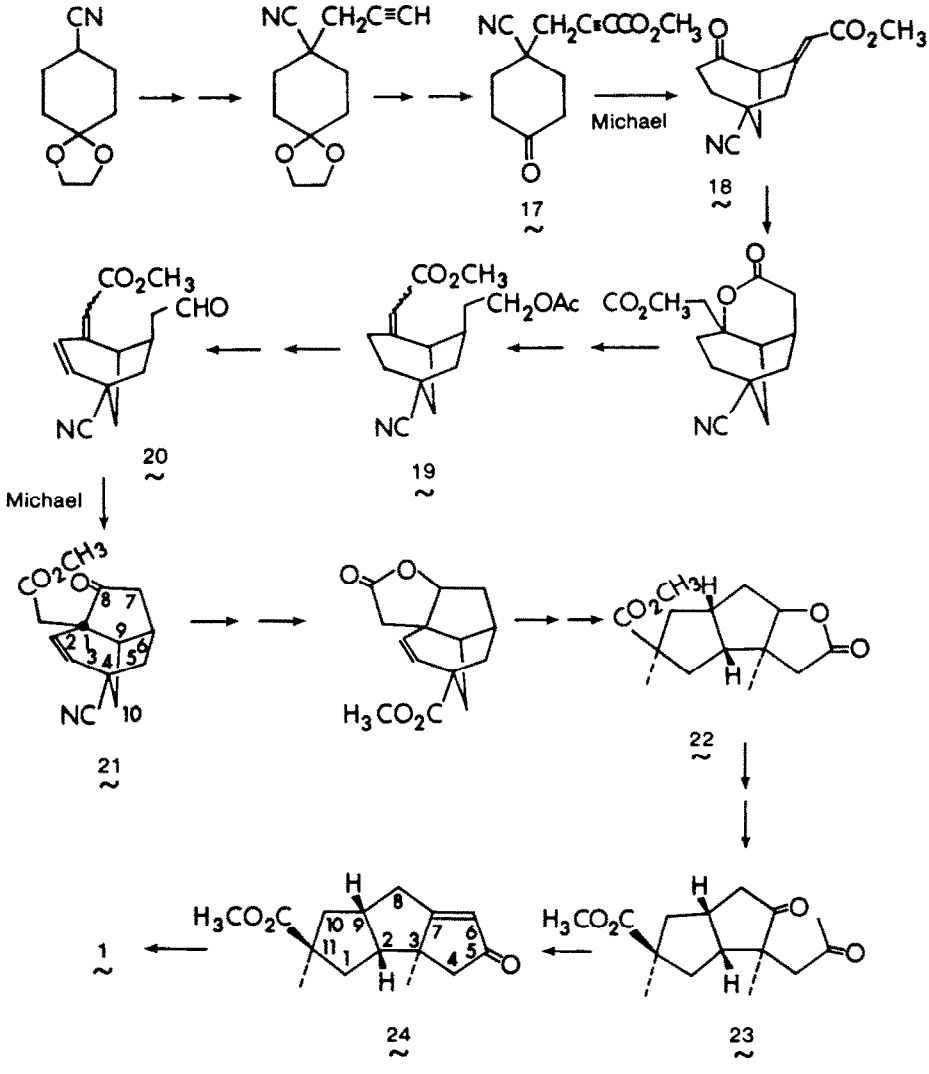
The work in the field of the hirsutanes has culminated recently with the report by Trost *et al.*[16d] of an elegant stereocontrolled synthesis of hirsutic acid (**1**). In this synthesis, 4 of the 7 asymmetric centers are fixed in the correct relative stereochemistry in a bridged-bicyclic compound which in turn is formed by two intramolecular Michael addition reactions. Unravelling of the polycyclic precursor leads to an



Scheme 9.



Scheme 10.



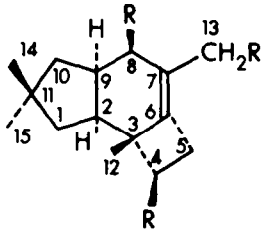
Scheme 11.

intermediate with the skeleton of hirsutic acid. The synthesis (Scheme 11) begins with the alkylation of 4-cyanocyclohexanone ethylene acetal with 1-trimethylsilylpropargyl bromide to give, after desilylation, a crystalline cyano acetal which is transformed by low temperature carboxylation, subsequent esterification, and hydrolysis of the acetal, to compound **17**. Compound **17** undergoes internal Michael addition to the keto enoate **18**. Hydrogenation, followed by a Reformatsky reaction gives the cyano lactone shown. Methanolysis of the lactone followed by reduction of the acid and acetylation affords **19**. Compound **19** is subjected to bromination, dehydrobromination and hydrolysis followed by oxidation of the alcohol to give aldehyde **20**. This in turn undergoes intramolecular Michael addition to form **21** in which the four chiral centers have the correct relative stereochemistry for conversion to hirsutic acid (C–9, C–1, C–6, C–4 in **21** correspond to C–2, C–3, C–9, C–11 in **1**). Compound **21** was reduced, hydrolyzed, and lactonized. Hydrolysis of the nitrile, ozonolysis and conversion of the former olefinic carbons to methyl groups was effected without isolation of intermediates, giving lactone **22**. The tricyclic lactone **22** was hydrolyzed and converted by standard methods to the known methyl ketone **23**.[14d] Aldolization of **23** gave **24**, a compound which earlier had been transformed to hirsutic acid (**1**).[16c]

Protoilludanes

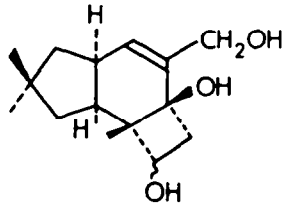
Illudol (**25**) is a biologically inactive metabolite produced by the Basidiomycetes *Clitocybe illudens*.[17a] The structure[17b-d] of illudol is of interest because it was the first isolated member of a group of compounds with a protoilludane skeleton. Previously this skeletal type had been proposed by several groups as a biosynthetic precursor of many families of the fungal sesquiterpenes (see Scheme 1) including the illudalanes, illudanes, and marasmanes.

The structure of illudol was established as **25** by McMorris *et al.* who recognized that the structural features deduced for the compound fitted nicely into the skeleton proposed earlier for a biogenetic precursor of illudin S. ^{1}H NMR spectra of illudol and its acetylated derivative revealed the presence of 3 quaternary methyls, a primary and two secondary hydroxyls. A UV maximum at 207 nm indicated a tetrasubstituted double bond. Catalytic hydrogenation of illudol gave three hydrogenolysis products, establishing the presence of an allylic primary and an allylic secondary alcohol. The remaining alcohol is a cyclobutanol since Jones oxidation of each of the hydrogenation products gave compounds whose IR spectrum showed absorption bands characteristic of a cyclobutanone (1785 cm^{-1}). The nature of the ring system was revealed by palladium–charcoal dehydrogenation: the major product was a pentamethylindane, which possesses two more methyl groups than illudol, the extra methyl groups resulting from opening of a cyclobutane ring. This evidence suggested a 4–6–5 tricyclic compound containing two allylic alcohols and a tetrasubstituted double bond as in structure **25**. The stereochemistry of the substituents was established later by synthesis.[18]

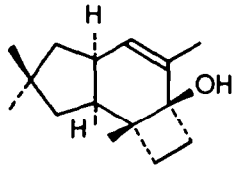


25 R=OH Illudol

25a R=H Δ^6-Protoilludene



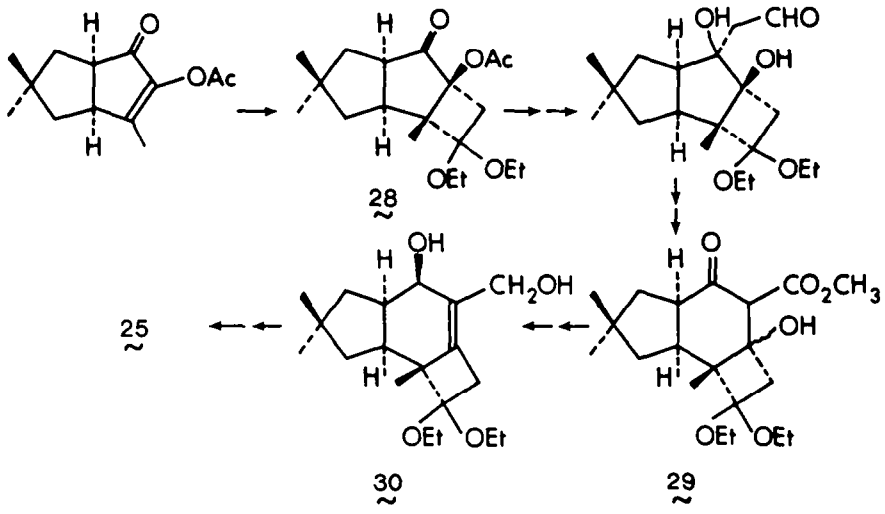
26 Neoilludol



27 Δ^7-Protoilluden-6-ol

Three other compounds with the protoilludane skeleton are known. Neolludol **26** has been isolated from *Clitocybe illudens*,[19] while a possible precursor hydrocarbon, Δ^6-protoilludene (**25a**) as well as Δ^7-protoilluden-6-ol (**27**) have been isolated from *Fomitopsis insularis*.[20] The structures of **25a**, **26** and **27** were determined from spectroscopic data and by comparison with intermediates available from synthetic studies.[21]

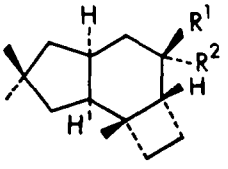
At the outset of the synthetic studies the complete stereochemistry of illudol (**25**) was not established. The structural relationship with other illudoids suggested a *cis–anti–cis* stereochemistry for **25** although the configurations of the secondary hydroxyl groups remained unknown. This point was clarified by the successful synthesis of racemic illudol by Matsumoto *et al.*[18] as outlined in Scheme 12.



Scheme 12.

The synthesis begins by photocycloaddition of 1,1-diethoxyethene to a bicyclooctenone. The *cis–anti–cis* stereochemistry[18a] of **28** was assigned on the basis that approach of the diethoxyethene would be from the less hindered convex face. Cycloadduct **28** was reacted with allylmagnesium bromide and the product was ozonized to give the aldehyde. Sequential oxidation, methylation and oxidative cleavage with concomitant aldol condensation gave the 5–6–4 tricyclic compound **29**. Compound **29** was dehydrated and reduced to give diol **30**. The *cis*-relationship between the angular methyl and the newly formed hydroxyl was assigned on the assumption that the bulky reducing agent would add from the less hindered side of the dehydration product. Treatment of **30** with acetone and tosic acid gave the unstable acetonide which was reduced from the less-hindered side to give, after hydrolysis, racemic **25**.

Matsumoto *et al.*[21] reported the synthesis of $\Delta^{7(13)}$-protoilludene (**31**) and the epimeric 7α- and 7β-protoilludanols (**32a,b**) by a route similar to that which they had developed for illudol. The results of several solvolysis studies of **31** and **32a,b** have been described.[22] These compounds have not been isolated from natural sources but are of interest since they are possible biogenetic intermediates of the illudoid sesquiterpenes.



31 $R^1 = R^2 = CH_2$
32a $R^1 = CH_3$, $R^2 = OH$
32b $R^1 = OH$, $R^2 = CH_3$

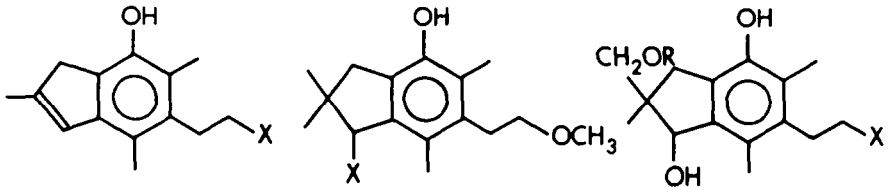
Illudanes

The Jack-o'-lantern mushroom (*Clitocybe illudens*), so-called because of its bioluminescent property, is commonly found in large clusters in the late summer in the eastern United States. *C. illudens*, when grown in liquid culture, produces toxic compounds which possess antibacterial and antitumor activity.[17a,23a,c] One of these toxic metabolites, illudin S (also called lampterol (lunamycin)) has been isolated from the Japanese bioluminescent moon-night mushroom, *Lampteromyces japonicus*.[24,25] The Japanese studies showed that illudin-S (lampterol) possesses very high antitumor activity.

The structures of the toxic metabolites, illudin S and illudin M, were first reported by McMorris and Anchel.[23b,c] Shortly after two different Japanese groups independently verified the structural assignment of illudin S (lampterol)[24,25] and established its stereochemistry[25c,d] and absolute configuration.[24c,25e] Illudin S ($C_{15}H_{20}O_4$) and illudin M ($C_{15}H_{20}O_3$) are closely related compounds. Both show a cross-

conjugated dienone chromophore in the ultraviolet. Upon acetylation, illudin S forms a diacetate which still shows hydroxyl absorption in the IR. Illudin M forms a monoacetate whose IR spectrum also shows hydroxyl absorption. Thus illudin S differs from illudin M by the presence of an extra hydroxyl group.

Catalytic hydrogenation of illudin S gives a phenol A which on treatment with acid gives two compounds assigned structures **33** and **34** on the basis of well-defined spectroscopic properties. On the other hand, catalytic hydrogenation of illudin M gives a single crystalline diol **35** which can be hydrogenolyzed to **36** on further treatment with hydrogen and a catalyst. Thus it follows that phenol **A** must be triol **37a**; compounds **33** and **34** arising from a "reverse Prins reaction", i.e. cleavage of the 1,3-diol in **37a** to give an indenol (**33** or **34**) and formaldehyde. The ^{1}H NMR of illudin S, illudin S diacetate, illudin M and illudin M monoacetate all show a high-field multiplet characteristic of a spirocyclopropane moiety.

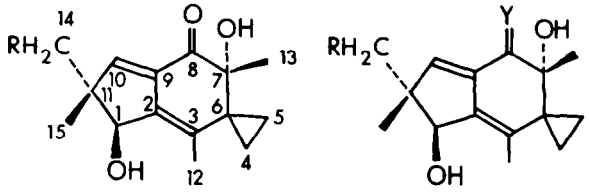


33 X = H
34 X = OCH_3

35 X = OH
36 X = H

37a R = X = H
37b R = COC_4H_9 X = OCH_3

Sodium borohydride reduction of illudin M gave a crystalline triol whose UV spectrum showed an absorption maxima characteristic of a conjugated diene, establishing the nature of the dienone chromophore. Treatment of the illudins with sodium metaperiodate afforded crystalline ketoacids which indicated the presence of an α-ketol. The structures on illudin S and illudin M thus are **38** and **39**, respectively. Other studies have established the stereochemistry and relative configuration of illudin S (38) to be that shown.[25c,d] The absolute configuration of the C-3 hydroxyl of illudin S was determined by Nakanishi and Harada[25e] by application of their then recently-formulated dibenzoate chirality rule to a suitable derivative of phenol **37b** and was verified by Matsumoto[24c] by the Bijvoet X-ray method. Nakanishi *et al.*[26] also report that illudin S and ergostatetra - 4,6,8(14),22 - en - 3 - one, both of which of which are present in the fruiting bodies and mycelia of *L. japonicus*, are fluorescent compounds which may be related to its bioluminescence.

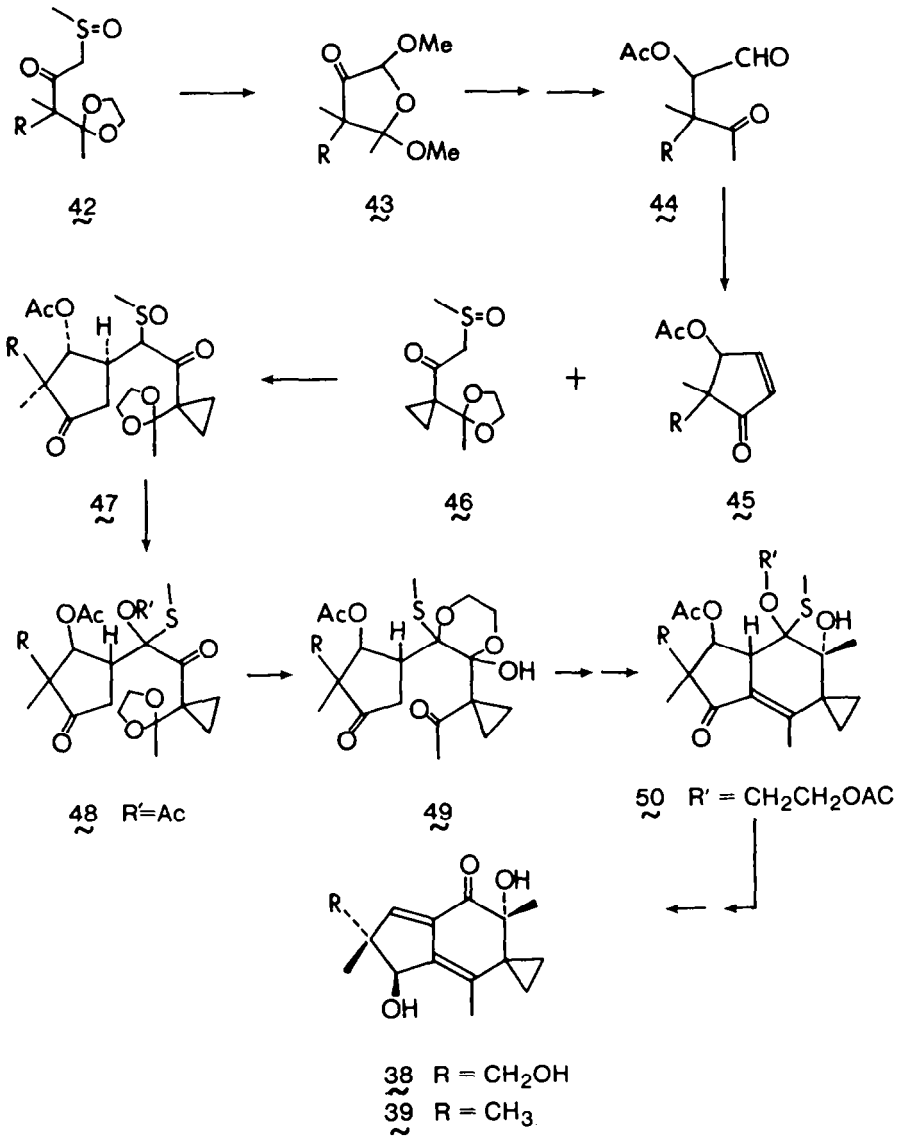


38 R = OH Illudin S
39 R = H Illudin M

40 R=OH, Y=αOH, βH Dihydroilludin S
41 R=H, Y=H, OH Dihydroilludin M

Two other compounds of this structure type have been reported. Dihydroilludin S (**40**) has been isolated from *L. japonicus*[27] while dihydroilludin M (**41**) has been isolated from *C. illudens*.[28] Interestingly it has been reported[29] that the chemical characteristics and many of the morphological characteristics of *Clitocybe illudens* suggest that it does not belong to the genus *Clitocybe*. Many *Clitocybe* species (except *C. illudens*) produce polyacetylenes but no humulene-related sesquiterpenes. *C. illudens* has been renamed *Omphalotous olearus*.[47]

The total synthesis of both *dl*-illudin S[30] and *dl*-illudin M[31] (Scheme 13) has been accomplished by Matsumoto *et al.* In earlier studies,[32] these workers reported the successful synthesis of the illudane skeleton by this method. Each of these syntheses is based upon Michael addition of a β-ketosulfoxide to a substituted cyclopentenone and modification of functionality suitable to effect aldol cyclization. The syntheses of illudin S or illudin M begins by conversion of the suitably substituted β-ketosulfoxide **42**[33a] with iodine in methanol to the tetrahydrofuranone **43**. Reduction of the carbonyl followed by acetylation and hydrolysis gave the ketoaldehyde **44** which underwent aldol cyclization to give a cyclopentenone **45**. Stereoselective Michael addition of the



Scheme 13.

cyclopropyl β-ketosulfoxide **46**[33b] provided a single product **47** which was converted to ketone **48** by Pummerer rearrangement. Treatment with ethanol effected intramolecular *trans*-ketalization followed by intramolecular migration[33c] of the ethylenedioxy group to form **49**. Treatment of **49** with base give a *cisoid* enone which was acetylated and then alkylated stereoselectively to form compound **50**. Compound **50** was reduced to a diol and the hemithioacetal removed by hydrolysis to provide *dl*-illudin S (R = CH_2OH) (**38**) or *dl*-illudin M (R = CH_3) (**39**). A more efficient route to illudin M based on the same synthetic scheme has been proposed by these authors.[31b]

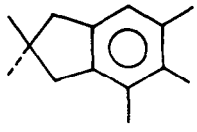
Marasmanes

Marasmic acid, first isolated in 1949 from the Basidiomycetes *Marasmius conigenus*,[34] is a toxic metabolite which shows antibacterial activity, especially against *Staphylococcus aureus*. Marasmic acid[35] has the molecular formula $C_{15}H_{18}O_4$. Examination of its IR and ^1H NMR spectrum indicate the presence of an α,β-unsaturated aldehyde with a β-vinylic proton, two quaternary methyl groups and a γ-lactol. The presence of a γ-lactol moiety is verified by conversion of marasmic acid into a methyl carboxylate dialdehyde upon treatment with diazomethane.

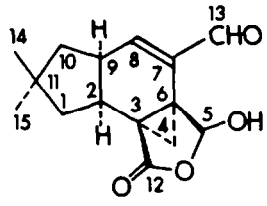
Information on the nature of the tricyclic carbon skeleton was obtained by reduction of marasmic acid with sodium borohydride followed by dehydrogenation with palladized charcoal. The product

consisted of two aromatic hydrocarbons, the more substituted being identified as the pentamethylindane **51**. This suggested the presence of the third ring as a cyclopropane ring and this was verified by spectroscopic data.

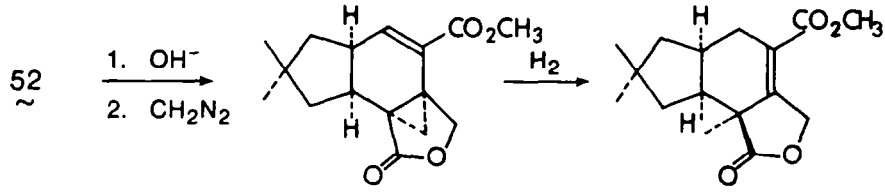
Consideration of the functionality including that the lactol hydrogen was a singlet in the ^{1}H NMR led to the postulation of several structural representations for marasmic acid. A distinction between these possibilities was made as follows. Treatment of marasmic acid with aqueous base, then methylation induced an internal Cannizzaro reaction, the product containing an α,β-unsaturated ester with a β-vinyl proton and a γ-lactone. Hydrogenation of the Cannizzaro product gave by 1,4-addition of hydrogen to the vinylcyclopropane system, a substance with a new quaternary methyl, a γ-lactone, and an unsaturated ester now lacking a vinyl proton. This result showed marasmic acid to be compound **52** (see Scheme 14).



51



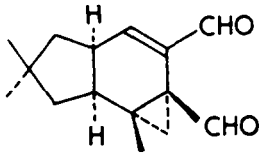
52 Marasmic Acid



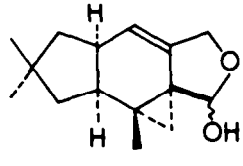
Scheme 14.

The partial X-ray crystal structure[17d] of marasmic acid shows it to have a *cis*-fused hydridane skeleton and although the results are not completely conclusive, favors the absolute configuration shown in **52**.

Other marasmane-type sesquiterpenes, isovelleral (**53**), isolated from *Lactarius vellereus* and *L. pergamenus*,[36] and compound **54** isolated from *F. insularis*[20] have been reported.

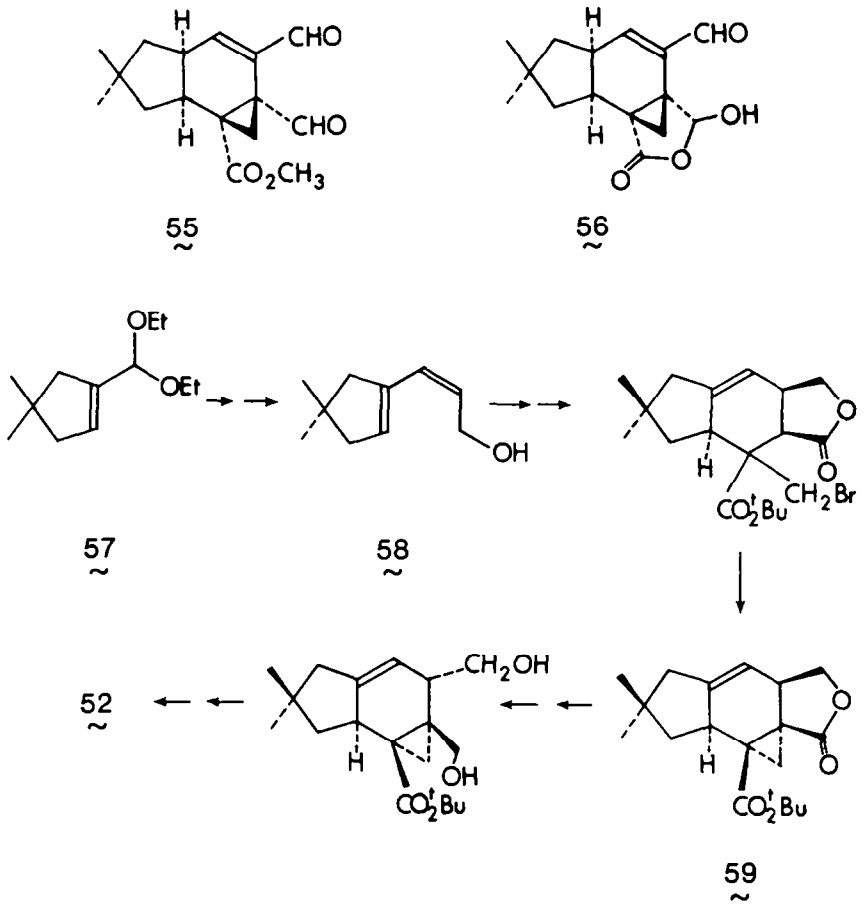


53



54

The synthesis of methyl isomarasmate (**55**) utilizing several photochemical transformations, has been reported by de Mayo *et al.*[37] In addition, Wilson and Turner[38] have reported the synthesis of the marasmic acid skeleton employing a Diels–Alder addition to form the hydrindan ring system and generation of the three-membered ring by photolysis of an intermediate pyrazoline. Later workers have shown the stereochemical assignment in this synthesis to be questionable, probably the isomarasmic acid skeleton is formed.[39] The total synthesis of (±)-marasmic acid (**52**) and (±)-isomarasmic acid (**56**) has been completed by Greenlee and Woodward.[39] Their method also employs a Diels–Alder approach to marasmic acid as is outlined in Scheme 15. Diethyl acetal **57** was allowed to react with ethyl vinyl ether and the resulting ethoxy acetal was hydrolyzed, then reduced to give the known diene alcohol **58**.[38,39] Diels–Alder reaction of **58** with bromomethylmaleic anhydride gave a mixture of lactone acids which were esterified with isobutylene. Treatment of this mixture of esters with strong base gave a single



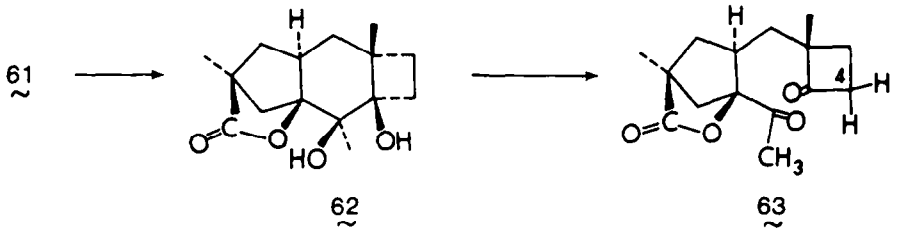
Scheme 15.

cyclopropane **59**. Compound **59** was reduced to a diol which was transformed to (±)-marasmic acid by oxidation to a dialdehyde and deesterification.

Sterpuranes

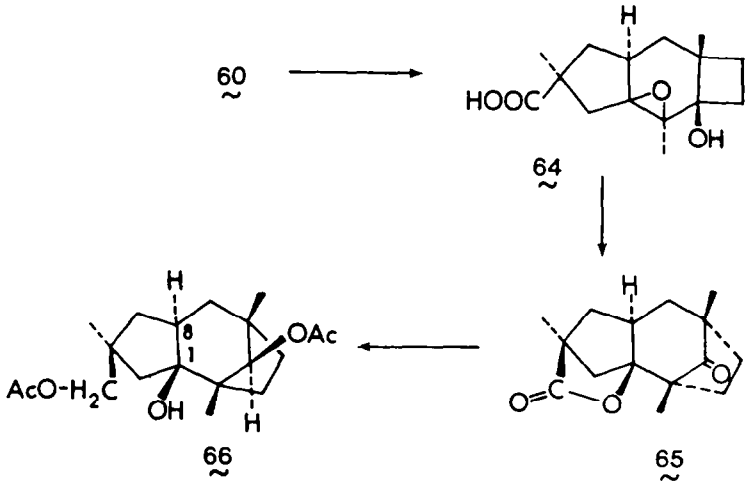
The fungus *Stereum purpureum* often found infecting fruit trees, mountain ash, cotoneaster and aspen causes "silver leaf disease", so-called because infected trees develop foliage with a dull leaden or metallic lustre. When *S. purpureum* is grown in liquid culture it produces sesquiterpenoid metabolites, a crude extract of which causes "silvering" in mountain ash seedlings. Several metabolites produced by this fungus have been isolated and three of the acidic metabolites have been shown to possess a sterpurane skeleton.[40]

Sterpuric acid, $C_{15}H_{22}O_3$, readily forms a methyl ester when treated with diazomethane. It contains a hindered tertiary hydroxyl group which is reflected by the fact that the formation of methyl O-acetylsterpurate requires prolonged treatment with acetic anhydride–pyridine. The remaining functionality of sterpuric acid (2 quaternary methyls, vinylic methyl, fully substituted double bond), and thus its tricyclic nature was apparent from examination of ^1H and ^{13}C NMR spectra. The mass spectrum of both sterpuric acid and dihydrosterpuric acid shows a prominent peak due to the loss of ethylene for which one explanation is cleavage of a cyclobutanol. This, together with a detailed analysis of the ^1H NMR of sterpuric acid and the assumption that it is derived without rearrangement from farnesyl pyrophosphate allows the derivation of structure **60** for sterpuric acid. Support for this structure was obtained from the reaction of methyl sterpurate (**61**) with osmium tetroxide (Scheme 16) which gave directly the γ-lactone diol **62**, presumably by spontaneous lactonization of an intermediate triol. Periodate cleavage of the diol gave compound **63** which contains a cyclobutanone, a methyl ketone and a γ-lactone as indicated by its IR and ^1H NMR spectra. These experiments provide direct evidence for the presence of a four-membered ring in sterpuric acid and serve to locate the carboxyl group at C–10 rather than C–6.



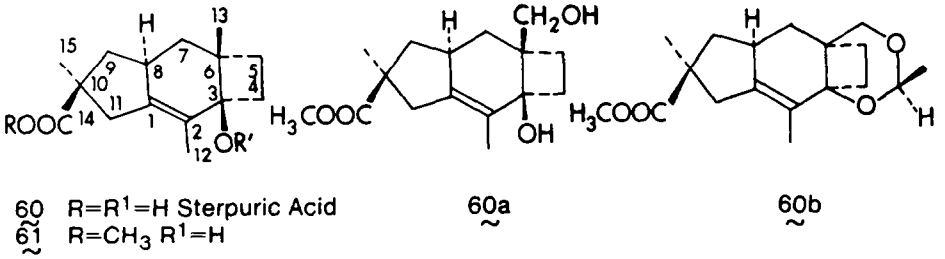
Scheme 16.

The assignment of stereochemistry in sterpuric acid was based upon the following experiment. *cis*-Epoxidation of sterpuric acid was effected with *m*-chloroperbenzoic acid to give an epoxide **64** (Scheme 17) which smoothly rearranged upon treatment with acid to a bicyclo[3.2.1]octanone **65** with



Scheme 17.

concurrent γ-lactone formation. The facile lactone formation indicates that the epoxide and thus the hydroxyl in **60** is *syn* to the carbomethoxyl group. The *cis*-relationship of the C-3 hydroxyl to the C-6 methyl was suggested by the large pyridine shift observed for this methyl group in the ^{1}H NMR of methyl sterpurate **61** whereas the configuration of C-8 was assigned on the basis of a pyridine shift study of the hydroxyacetate **66**. The results of an X-ray crystallographic study of sterpuric acid (**60**) place these chemical deductions on a firm basis.



60 R=R^1=H Sterpuric Acid
61 R=CH$_3$ R^1=H

60a **60b**

Two other metabolites of *S. purpureum*, hydroxysterpuric acid (**60a**) and hydroxysterpuric acid ethylidene acetal (**60b**) isolated as their methyl esters, have also been reported.

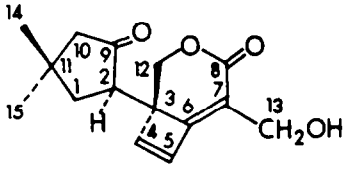
Interestingly the biogenesis of sterpuric acid may either arise by direct cyclization of humulene or by formation of a protoilludane intermediate followed by several skeletal rearrangements (d, g or e, f, Scheme 1). Preliminary experiments in these laboratories using ^{13}C labelled acetate indicate the latter pathway is followed.

Fomannosanes

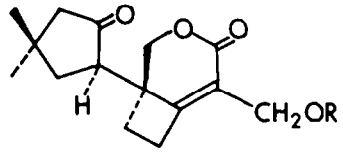
Fomes annosus, which is the cause of serious root rot in confers in North America and one of relatively few wood-destroying Basidiomycetes that cause death of host cells as well as decay of wood,

produces a biologically active sesquiterpenoid metabolite named fomannosin. Fomannosin shows biological activity against *Pinus taeda* seedlings and although it could not be detected in samples of naturally infected sapwood it was suggested that this phytotoxin might play a role in the pathogenic activity of *F. annosus*. Fomannosin has also been isolated from *Fomitopsis insularis*.[20,41]

Fomannosin ($C_{15}H_{18}O_4$) is non-crystalline and unstable. Spectroscopic data from fomannosin (**67**), its hydrogenation product dihydrofomannosin (**68a**), and dihydrofomannosin acetate (**68b**) show the presence of a primary allylic alcohol, a cyclopentanone carbonyl and a diene δ-lactone. The structure of **67** was determined by an X-ray crystallographic analysis of the *p*-bromobenzoyl urethane derivative (**68c**) of dihydrofomannosin. This established that compound **68c** possesses the constitution and relative stereochemistry shown and it follows that dihydrofomannosin has sturcture **68a**. The spectroscopic and chemical results define the location of the additional double bond in fomannosin and the toxin is assigned structure **67**. An attempt to establish the absolute configuration of **68c** using Bijvoet's anomalous dispersion method was unsuccessful.[42a,b] However, others have established the absolute configuration of fomannosin[43] as shown in **67** using dihydrofomannosin camphanate (**68d**), an ester derived from dihydrofomannosin and (−)-camphanic acid of known absolute configuration. A crystallographic analysis of this ester showed the absolute configuration of fomannosin to be 3*S*,2*R*.

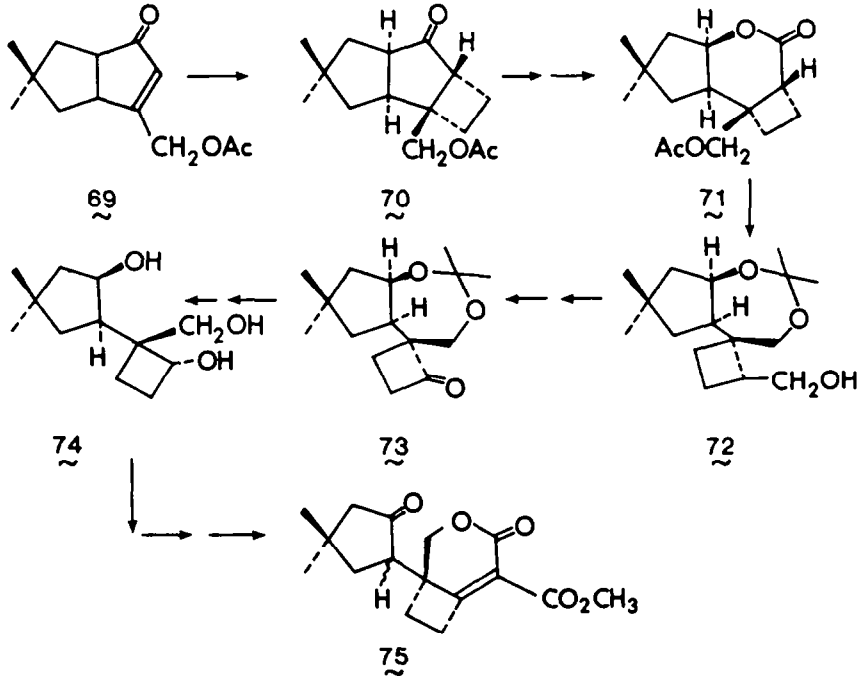


67 Fomannosin



68a R=H
68b R=Ac
68c R=p Br-C_6H_4 CONHCO-
68d R=Camphanyl-

A synthesis of the fomannosane skeleton has been described[44] (Scheme 18). Photochemical cycloadition of ethylene and acetoxyenone **69** gave a *cis-anti-cis* cycloadduct **70** along with the *cis-syn-cis* isomer. The former was converted to the lactone **71** with peracetic acid. Reduction of **71** to the triol, followed by acetonide formation gave **72**. The unprotected hydroxyl group was oxidized to an aldehyde



69 70 71 74 73 72 75

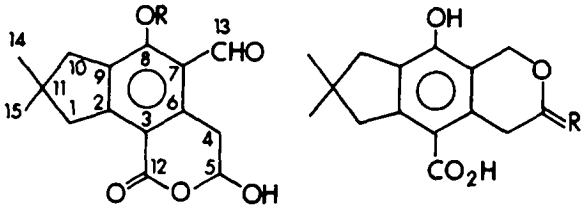
Scheme 18.

and the morpholine enamine was prepared. Subsequent photochemical oxidative cleavage afforded ketone **73**. The keto group of **73** was reduced and the acetonide removed to yield a triol **74**. Selective esterification of the primary hydroxyl of **74** with methyl malonlyl chloride, followed by oxidation to a diketone and intramolecular aldol condensation gave the final product **75**. The transformation of **75** into dihydrofomannosin (**68a**) has not yet been reported.

Illudalanes

Illudalic acid,[23a,45] illudoic acid,[45] illudacetalic acid,[46,47] and illudinine[45] are a group of structurally-related metabolites which have been isolated from the culture liquids of the Basidiomycete[5] *Clitocybe illudens* (syn. *Omphalotus olearus*).

Illudalic acid (**76a**) ($C_{15}H_{16}O_5$) shows UV absorption which shifts to longer wavelength in the presence of base. This, coupled with the presence of two low-field signals in the ^1H NMR and a strong carbonyl absorption band in the IR suggest the presence of an *o*-hydroxybenzaldehyde. In addition, the ^1H NMR spectrum of **76a** displays signals which indicate the following structural fragments: a cyclopentane possessing a *gem*-dimethyl group fused to a benzene ring and a $-CH_2-CHOH$ moiety. Comparison of the IR and ^1H NMR spectrum of illudalic acid (**76a**) with its acetylated derivative **76b** together with the fact that **76a** dissolves in sodium bicarbonate solution with the evolution of carbon dioxide suggest the presence of a δ-lactol. Treatment of illudalic acid with base gives a Cannizzaro-type reaction involving the aromatic aldehyde and the aldehyde derived from opening the lactol ring to yield a δ-lactone **77**. Since the aromatic aldehyde has been shown to be *ortho* to the phenolic hydroxyl, this reaction allows the complete assignment of the orientation of substituents on the aromatic ring of illudalic acid (**76a**) to be that shown.

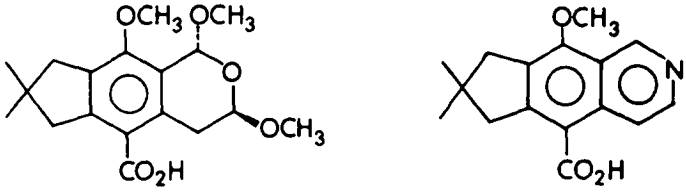


76a R=H Illudalic Acid
76b R=AC

77 R=O
78a R=H, OH Illudoic Acid
78b R=H, H

Illudoic acid[45] ($C_{15}H_{18}O_5$) has been tentatively assigned structure **78a** on the basis of its spectral properties and the similarity of these spectra to those of **78b**, a compound formed by catalytic hydrogenation of illudalic acid.

Illudacetalic acid,[46,47] first reported in 1972, has recently been correctly identified as the crystalline bis-acetal **79**. This structure revision was confirmed by synthesis.

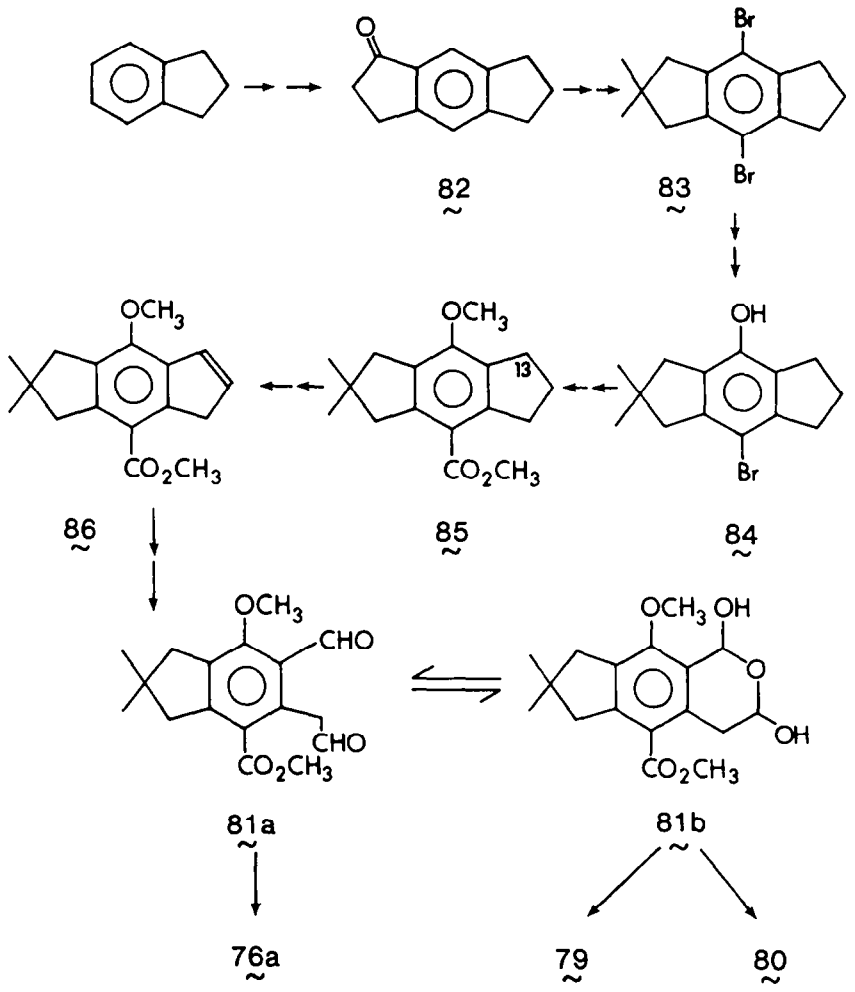


79 Illudacetalic Acid

80 Illudinine

Finally, illudinine (**80**),[45] $C_{16}H_{17}O_3N$, is an alkaloid also isolated from some strains of *C. illudens*. Illudacetalic acid (**79**) is readily converted to illudinine (**80**) by treatment with ammonia and it is probable that compound **79** is a biogenetic precursor of **80**.

Recently the total synthesis of illudalic acid (**76a**), illudacetalic acid (**79**) and illudinine (**80**) has been achieved.[47] In the synthetic scheme, each of the compounds **76a**, **79**, **80** was derived from a common



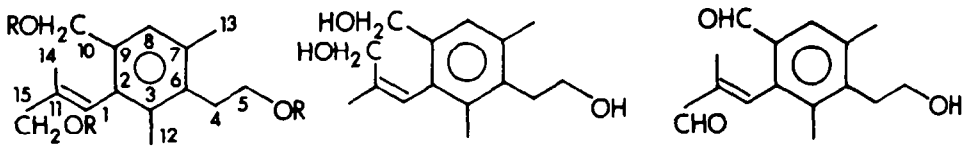
Scheme 19.

precursor, the dialdehyde **81** (Scheme 19). Friedel Crafts acylation of indan with β-chloropropionyl chloride followed by acid catalyzed cyclization gave both the linear and non-linear hydrindacenone. The desired linear hydrindacenone **82** was alkylated, then subjected to Clemmensen reduction. Bromination of the resultant hydrocarbon gave the dibromide **83**. Treatment of compound **83** with *n*-butyllithium gave an aryl carbanion which was transformed to phenol **84**. The phenolic hydroxyl group was protected, the Grignard reagent was formed and reacted with methyl chloroformate to give the methoxyl ester **85**. Selective functionalization at the desired benzylic position (C-13) was effected by chromic acid oxidation. Reduction of the resultant carbonyl to an alcohol followed by acid-catalyzed elimination gave the olefin **86** which was transformed to dialdehyde **81**, using osmium tetroxide-sodium metaperiodate. Illudalic acid was prepared from **81a** by saponification and demethylation. Illudacetalic acid **79** was prepared from the bis-hemiacetal methyl ester **81b** by treatment with excess trimethyl orthoformate and saponification whereas illudinine **80** was prepared from **81b** by treatment with ammonium acetate, then saponification.

Secoilludalanes

A new class, the secoilludalanes (cybrodins), which arise by cleavage k in Scheme 1 has recently been reported.[48] The cybrodins are produced by fermentation of a strain of *Cyathus bulleri*. The structures of the metabolites cybrodol (**87a**), isocybrodol (**88**), cybrodal (**89**), cybrodic acid (**90**), and trisnorcybrodolide (**91**) have been determined by spectroscopic analysis, chemical interconversion and synthesis of compound **91**.

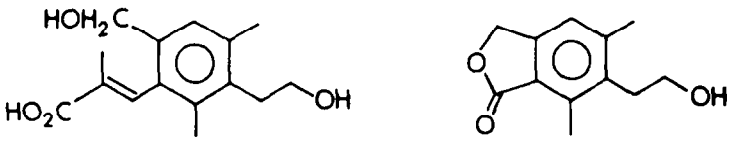
Cybrodol (**87a**) ($C_{15}H_{22}O_3$) obtained as an oil, shows hydroxyl and aromatic absorptions in its IR. The ^{1}H NMR and ^{13}C NMR of **87a** and its triacetyl derivative **87b** show that cybrodol is a pentasubstituted



87a R=H Cybrodol
87b R=Ac

88 Isocybrodol

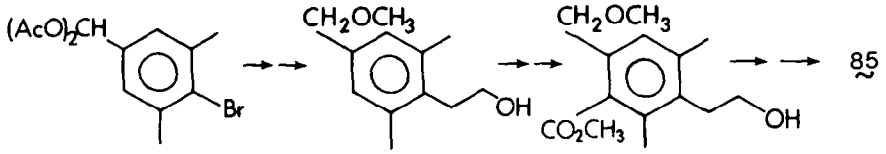
89 Cybrodal



90 Cybrodic acid

91 Trisnorcybrodolide

aromatic compound containing three methyl groups and three primary alcohols, one of which is allylic, another benzylic. This data is suggestive of a secoilludalane carbon skeleton. Ozonolysis of cybrodol (**87a**) followed by lactonization with camphor–sulfonic acid gave the phthalide **91** which is also naturally occurring. Synthesis of **91** (Scheme 20) unambiguously establishes its structure and also that of cybrodol



92 93 94

Scheme 20.

except for the stereochemistry about the double bond. The stereochemistry of cybrodol (**87a**) and its isomer isocybrodol (**88**) was established on the basis of comparison of the chemical shift of the vinylic methyl in the ^{1}H NMR of **87a** and **88** (shielded by aromatic ring in **87a**, deshielded in **88**).

The structures of two other metabolites cybrodal and cybrodic acid were established to be **89** and **90** respectively, on the basis of spectroscopic data and their conversion to cybrodol (**87a**) with lithium aluminum hydride.

Trisnorcybrodolide[49] was shown to be compound **91** by its unambiguous synthesis from 2-bromomesitylene (Scheme 20). Oxidation of 2-bromomesitylene with chromyl acetate gave acetal **92**. The acetal group was transformed to an ether by lithium aluminum hydride reduction followed by alkylation with iodomethane. Alkylation of the aryllithium with oxirane afforded the phenethyl alcohol derivative **93**, which was brominated and the alcohol group protected as the tetrahydropyranyl ether. Subsequent carbomethoxylation of the derived aryllithium with methyl chloroformate gave ester **94**, which could be converted directly but in low yield to phthalide **91** with trimethylsilyl chloride-sodium iodide. A better approach involved exchange of the tetrahydropyranyl protecting group with an acetyl group, cyclization with chlorotrimethylsilane-sodium iodide and hydrolysis. This sequence led to a high yield of compound **91** identical in all respects with naturally occurring trisnorcybrodolide.

Lactaranes†

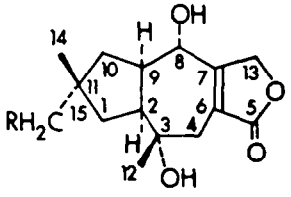
Lactarius rufus, a common European mushroom with a sharp, bitter taste, contains a milky cellular juice which exhibits antibiotic properties.[50a] Separation of an ethanolic extract of the fruiting bodies of

†The literature describing this class of compounds uses the names lacterane or vellerane interchangeably for the same carbon skeleton. At the *VI Conference on Isoprenoids*, held in Torún (1975) the Polish, Scandinavian and Italian workers agreed to name the skeleton lactarane and to number the carbon atoms according to the proposed biogenesis[56] as shown in **95**.

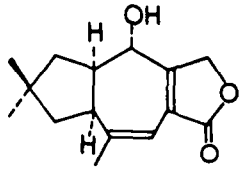
L. rufus has led to the isolation of several sesquiterpenes for which the name lactarorufins was proposed. One of these, lactarorufin A[50a-e] ($C_{15}H_{22}O_4$; also isolated from *L. blennius*,[50c] *L. trivialis*,[113] *L. torminosus*,[113] and *Russula sardonia*[115]) contains hydroxyl and an α,β-unsaturated γ-lactone as shown by its IR spectrum. No further functionality is evident and thus lactarorufin A is tricyclic. The ^1H NMR spectra of lactarorufin A and its monoacetyl derivative indicate the presence of a secondary hydroxyl, a tertiary hydroxyl, a *gem*-dimethyl group, and a methyl on a carbon bearing oxygen.

Dehydration of lactarorufin A monoacetate with thionyl chloride at low temperature gives anhydrolactarorufin A acetate, the spectral data of which indicate the presence of an $\alpha,\beta,\gamma,\delta$-unsaturated γ-lactone with both a vinyl methyl and a vinyl proton.

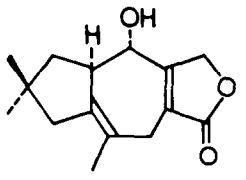
This information suggests structure **95** for lactarorufin A and **96** for anhydrolactarorufin A.[51] (Deconjugated anhydrolactarorufin A (**97**) has been isolated from *L. necator*[51a] and *L. torminosus*[113]). The position of the lactone carbonyl of the lactarorufins was originally assigned erroneously but this was corrected when an X-ray crystallographic analysis[52] of the *p*-bromophenacyl ester of lactarorufin B-3,8-ether (**98**) established the position of the carbonyl at C-5 rather than at C-13. Lactarorufin B (**99**) (isolated from *L. rufus*[51a]) previously has been correlated with lactarorufin A (**95**) by chemical conversion to a common derivative (Scheme 21).[51d] The relative stereochemistry of the substituents of **95**, **96**, **97**, **99** has been derived by analogy to **98**, and the observation of strong intramolecular hydrogen bonding in the IR spectrum of **95** and **99**. Examination of molecular models reveals this is only possible when the two hydroxyl groups are *syn*. Interestingly, this indicates that the formation of **98** proceeds by facile elimination of the tertiary hydroxyl at C-3 followed by intramolecular ether formation.



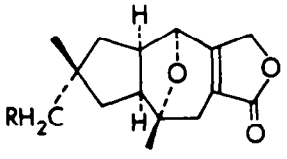
95 R=H Lactarorufin A
99 R=OH Lactarorufin B



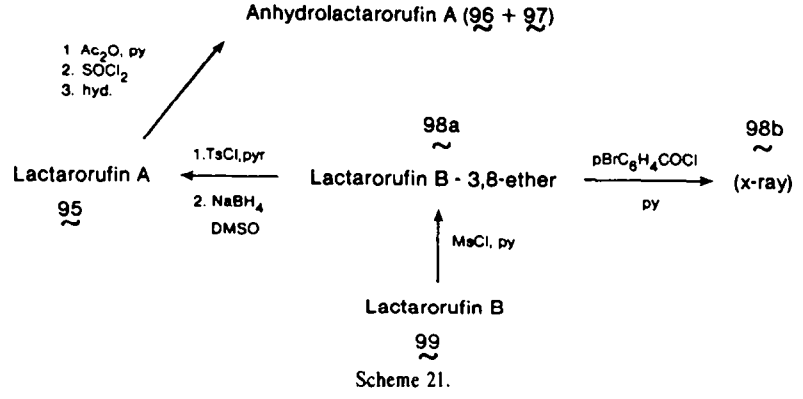
96



97

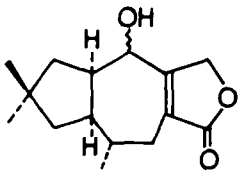


98 R=pBr-C_6H_4COO–

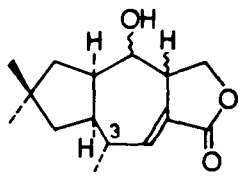


Scheme 21.

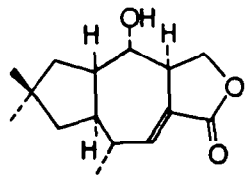
For compounds **95–99** and several other lactarane lactones, there exists some confusion in the literature as to the correct position of the lactone carbonyl. The structures presented for the following compounds: 3-deoxylactarorufin A (**100**),[51a,53] lactarorufin N (**101**)[51a] (from *L. necator*), blennin A (**102**) (isomeric with lactarorufin N, from *L. blennius*,[50f] *L. torminosus*,[113] *Russula sardonia*[115]), vellerolactone (**103**)[54] and pyrovellerolactone (**104**)[54] (from *L. pergamenus*, *L. vellereus*, *R. sardonia*[115]) may differ from



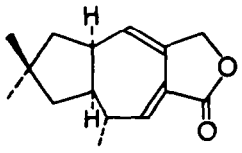
100



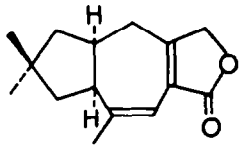
101 Lactarorufin N



102 Blennin A

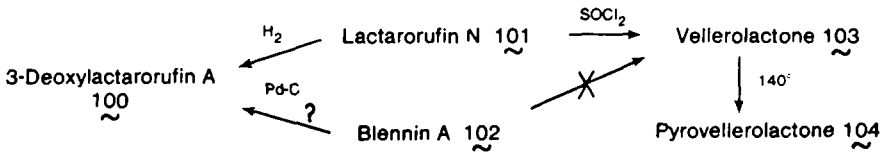


103 Vellerolactone



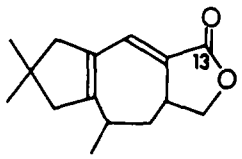
104 Pyrovellerolactone

those reported in earlier papers. They are believed to be correct as presented either by chemical correlation to **103** (Scheme 22), the structure of which was unambiguously established by X-ray crystallographic analysis of a synthetic intermediate[55b] or by definitive spectral data. It is important to note that the crystal structure of a synthetic intermediate established the relative configuration of the C–3 methyl to be *syn* to the ring junction hydrogens at C–2, C–9 as well as verifying the position of the carbonyl.

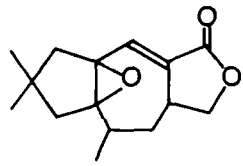


Scheme 22.

Two other lactarane lactones with the lactone carbonyl at C–13 have been reported. A diene lactone (**105**)[56] and an epoxylactone (**106**)[57] have been isolated from *L. scrobiculatus*.

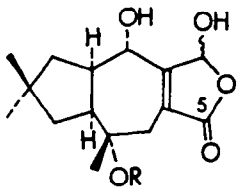


105

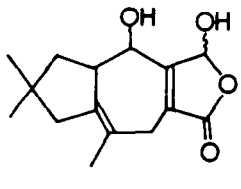


106

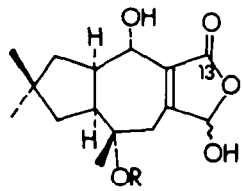
Five lactols, lactarolide A (**107**)[58] (*L. blennius, L. pallidus, L. scrobiculatus*), 3-0-ethyllactarolide A (**108**)[58] and blennin B (**109**)[50f] (*L. blennius*) with the lactol carbonyl at C–5 and lactarolide B (**110**)[58] (*L. blennius, L. pallidus, L. scrobiculatus*) and 3-0-ethyllactarolide B (**111**)[58] (*L. blennius, L. pallidus*) with the lactol carbonyl at C–13 have been reported. Vita-Finzi *et al.* have suggested that these γ-hydroxybutenolides are precursors of the two types of lactones found in the *Lactarius* species.



107 R=H Lactarolide A
108 R=Et



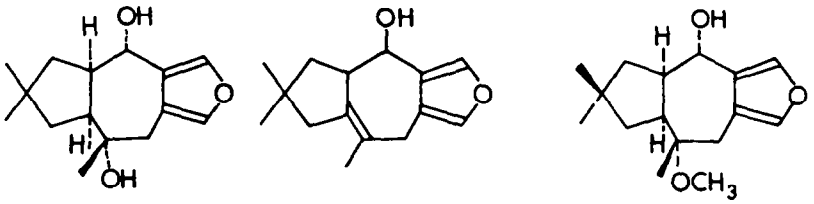
109



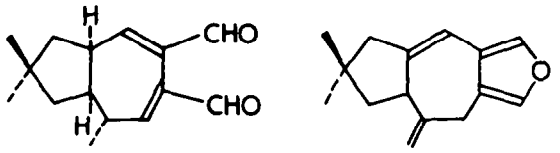
110 R=H Lactarolide B
111 R=Et

This was demonstrated by exposing an alcoholic solution of furan **112** to light and air. After several days the tlc of the solution suggested the presence of lactarorufin A (**95**), lactarolide A (**107**) and compound **108**. It is thought that **107** and **110** are natural compounds but that compounds **108** and **111** are artefacts arising from the isolation procedure.

Other lactarane metabolities include three furans, compound **112** (*L. blennius*,[50f] *L. scrobiculatus*,[56,116] *F. insularis*,[59] *L. trivialis*, *L. torminosus*,[113] *R. sardonia*[115]), compound **113** (*F. insularis*,[59] *L. Vellereus*, *L. pergamenus*, *L. helvus*,[60] *R. sardonia*[115]), compound **114** (*L. vellereus*, *L. pergamenus* and *L. helvus*[60]) and a dialdehyde, velleral (**115**)[61] (*L. vellereus* and *L. pergamenus*).

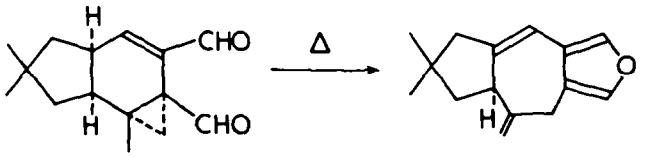


112 **113** **114**



115 Velleral **116**

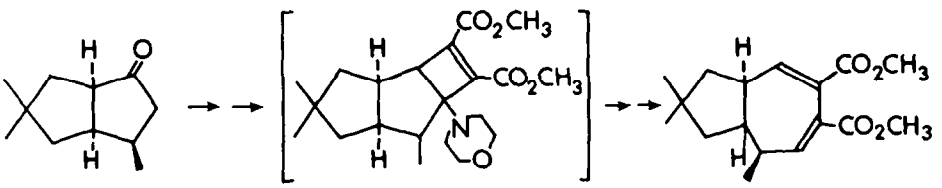
It is interesting that the biogenesis of the lactaranes, proposed to proceed through a marasmane precursor, has been supported by the recently reported biomimetic transformation of isovelleral (**53**) to a synthetic lactarane furan, pyrovellerofuran (**116**)[62] (Scheme 23).



53 **116**

Scheme 23.

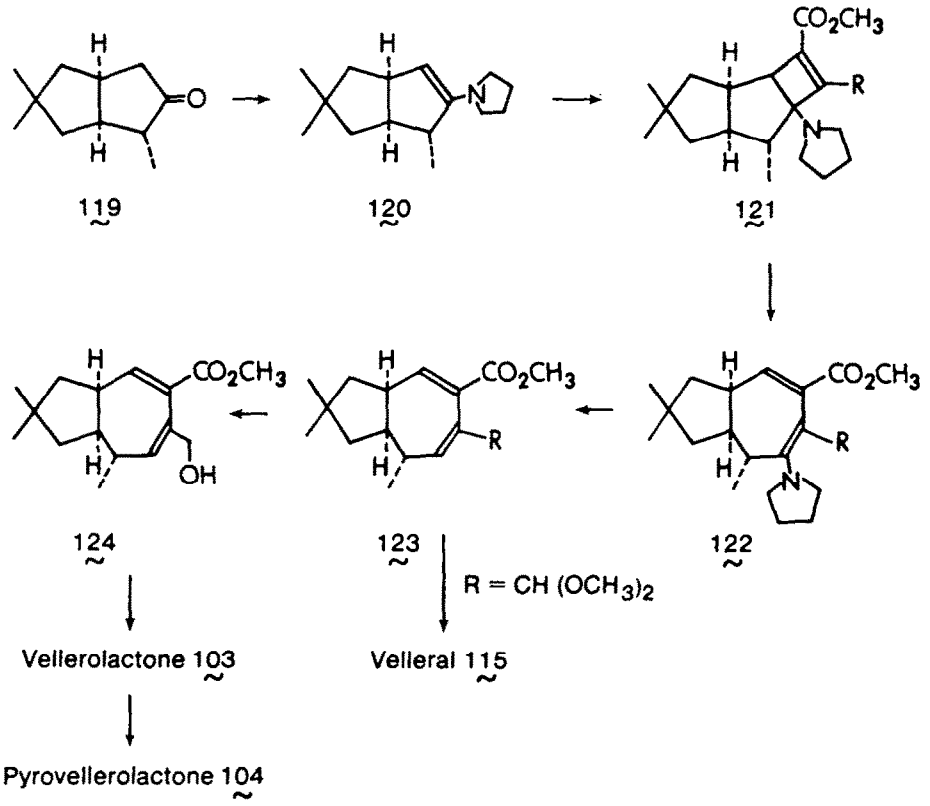
Two syntheses of the lactarane skeleton have been reported.[55,63] One synthetic route[63] to the skeleton of velleral (**115**) (Scheme 24) employs cyclobutene formation by addition of dimethyl acetylenedicarboxylate to the enamine of a bicyclo[3.3.0]octanone. This fused 4-membered ring compound undergoes thermal electrocyclic ring opening to give a cyclohepta-1,3-diene with the ester functions in the 2 and 3 position of the diene. Removal of the enamine function was accomplished with diborane to give



118

Scheme 24.

compound **118**. Subsequent studies (see below) show this compound is isomeric with **115** at the C–3 methyl.



Scheme 25.

These same authors successfully prepare racemic velleral (**115**), vellerolactone (**103**) and pyrovellerolactone (**104**) by another route.[55a] X-Ray crystallographic analyses of key synthetic intermediates in this (Scheme 25) and the previous (Scheme 24) syntheses together with spectroscopic data on synthetic stereoisomers of the natural compounds necessitate a revision of the earlier suggested structures for these compounds to one in which there is an epimeric methyl group at C–3 as shown in **115**, **103** and **104** and a carbonyl group at C–5 (**103** and **104**). This synthesis begins with bicyclic ketone **119** in which the C–3 methyl group is *syn* to the ring junction hydrogens. Enamine **120** (prepared from **119**) undergoes cycloaddition with an acetylene to a tetrolic ester **121** which undergoes fission of the four-membered ring to **122**. Subsequent hydrogenolytic deamination with diborane gave **123**. Functional group manipulation of **123** gave racemic velleral (**115**). Compound **123** was hydrolyzed to hydroxy acid **124** which was subjected to X-ray crystallographic analyses, thus establishing the relative stereochemistry of the synthetic intermediates. Lactonization of **124** gave vellerolactone (**103**) which was transformed to pyrovellerolactone (**104**) upon heating.

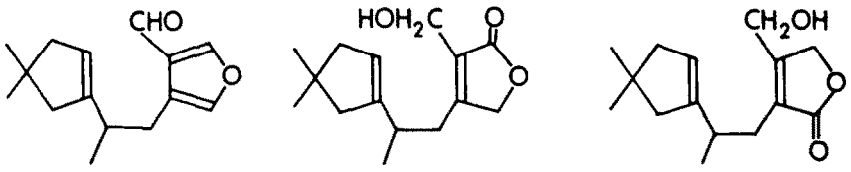
Secolactaranes

The metabolites isolated from *Lactarius* are mainly sesquiterpeniods of the lactarane-type skeleton, although a few secolactarane sesquiterpenoids have also been found. The first isolated secolactarane sesquiterpene was lactaral (*Lactarius vellereus, L. pergamenus*,[64] *L. scrobiculatus*[116]). The IR and UV spectrum of lactaral ($C_{15}H_{20}O_2$) showed the presence of a β-formylfuran. ^1H NMR and ^{13}C NMR studies indicated the presence of a *gem*-dimethyl group, a secondary methyl and a vinyl proton.

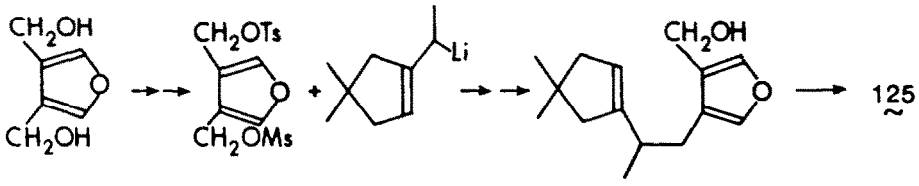
The co-occurrence of the lactarane sesquiterpenes velleral (**115**), vellerolactone (**103**) and pyrovellerolactone (**104**) from the same species supported the assignment of structure **125** to lactaral.

Two cyclopentene lactones of the secolactarane type have also been reported: lactaronecatorin A (**126**) (*L. necator*[51b]) and blennin C (**127**) (*L. blennius, L. scrobiculatus*,[50f] *L. trivialis, L. torminosus*[113]).

The structure of lactaral (**125**) has been confirmed by an unambigous synthesis[65] outlined in Scheme 26.



125 Lactaral 126 Lactaronecatorin A 127 Blennin C

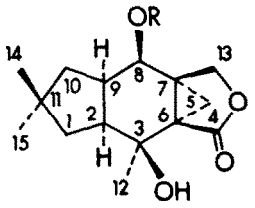


Scheme 26.

Isolactaranes

Isolactarorufin (Lactarorufin C) is a tetracyclic sesquiterpene lactone which was isolated from *Lactarius rufus*[50a] along with several other sesquiterpenes of the lactarane-type skeleton. The structure of isolactarorufin was established on the basis of chemical transformations and full spectral analysis and verified by X-ray.[66a,b] The IR spectrum of compound **128** shows it to be a dihydroxy γ-lactone. There is no further unsaturation (^{1}H NMR, ^{13}C NMR), thus it is a tetracyclic compound.

The ^{1}H NMR spectrum of **128a** and its monoacetate **128b** indicate the presence of *geminal* dimethyl, tertiary methyl and tertiary hydroxyl groups while the ^{13}C NMR spectrum shows the presence of 4 methylene carbons, one of which is the methylene group of a cyclopropane. This data led to the assignment of structure **128a** to isolactarorufin. The stereochemical assignment (which shows an epimeric C-3 methyl for **128a** with respect to lactarorufin A (**95**) is based upon an X-ray analysis[66b] of the *p*-bromobenzoate derivative of isolactarorufin (**128c**).



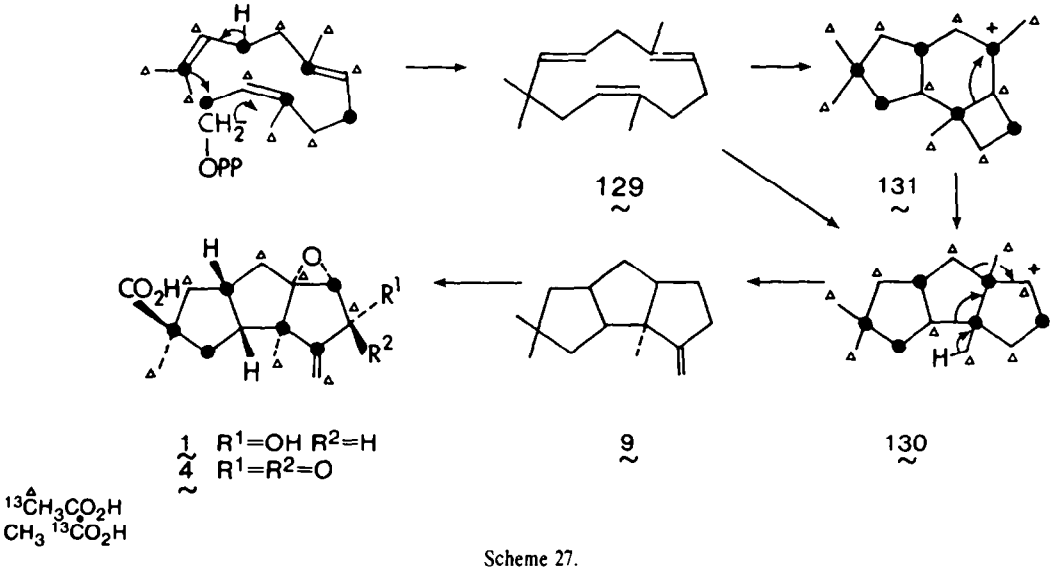
128a R=H Isolactarorufin
128b R=Ac
128c R=pBrC$_6$H$_4$CO–

The co-occurrence of isolactarorufin with lactarorufins poses an interesting problem from a biogenetic point of view. A protoilludane intermediate (Scheme 1) common to most polycyclic sesquiterpenes with a *gem*-dimethyl cyclopentane ring has been proposed. The lactarorufins (lactaranes) possibly arise by further rearrangement of a protoilludane through a marasmane to a lactarane whereas isolactarorufin (isolactarane) may be formed by rearrangement of a protoilludane through a sterpurane to an isolactarane. The recent isolation of sterpuric acid (sterpuranes) lends some support to this proposal.

Biosynthesis

The majority of the sesquiterpenes produced by the *Basidiomycetes* are unique to this class of fungus. The hirsutanes, protoilludanes, illudanes, secoilludalanes, marasmanes, hirsutanes, fomannosanes, lactaranes, isolactaranes, secolactaranes and sterpuranes have to date been isolated only from *Basidiomycetes*. The illudalanes represent a curious exception since they (in the form of the so-called pterosides) are also produced by plants. A generalized scheme which accounts for the formation of all the above skeletal types has already been presented in Scheme 1.

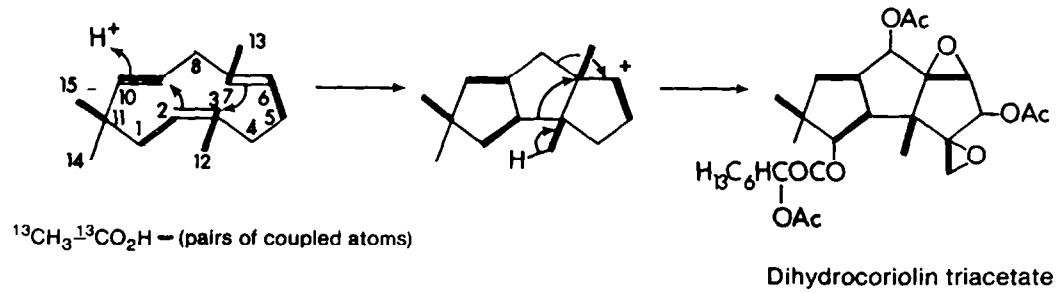
The biogenesis of hirsutic acid (**1**) as proposed by Scott *et al.*[67] involves a complex rearrangement of a farnesyl precursor via humulene and the hydrocarbon hirsutene (**9**). Early work on the biosynthesis of the hirsutane sesquiterpenes was hindered by the difficulty of growing the original culture, but the isolation of other hirsutanes from *S. complicatum*[9b] and *C. consors*[10b] removed this obstacle. Incorporation of [2-^{14}C]-mevalonic acid into [^{14}C]-hirsutic acid (which can be transformed to [^{14}C]-complicatic acid) established the terpenoid nature of these metabolites.[9b] Several theories have been advanced for the enzymic construction of the hirsutane skeleton from farnesyl pyrophosphate. Experimental evidence to support the theories has been obtained from the ^{13}C labelling patterns in hirsutic acid (**1**) and complicatic acid (**4**). In one study the compounds were isolated from cultures of *S. complicatum* supplemented with singly-labelled [1-^{13}C]acetate and [2-^{13}C]acetate, and the labelling pattern was established by ^{13}C NMR as summarized in Scheme 27.[68] The results are consistent with a mechanism



Scheme 27.

involving prior formation of a humulene-type precursor **129** and proceeding through a carbonium ion intermediate such as **130**. There are several routes to **130**, one of which invokes the intermediacy of the protoilludane precursor **131**.

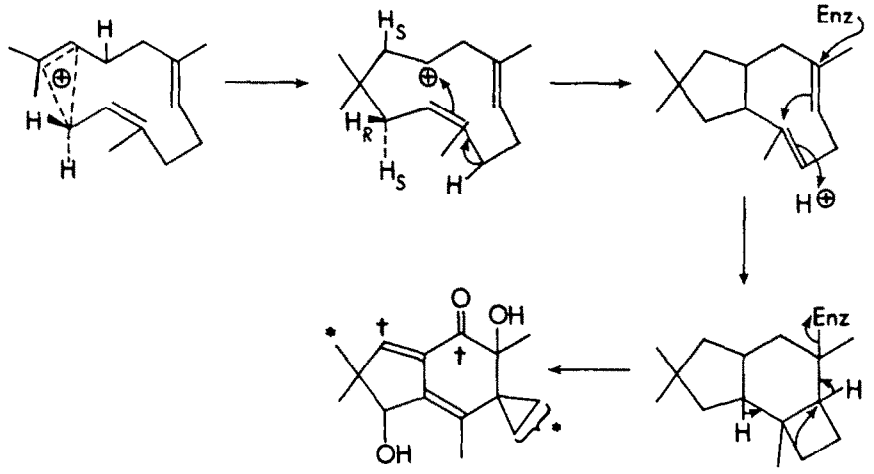
The recent isolation of the hydrocarbon hirsutene (**9**) along with humulene from *C. concors*[11] supports this biogenetic hypothesis. In another study, the pathway to the hirsutane skeleton was established from the ^{13}C NMR spectrum of the coriolins isolated after feeding doubly-labelled [1,2-^{13}C]acetate to *C. consors*. There are six intact acetate units in the tricyclic moiety and this observation is nicely accommodated by the route shown in Scheme 28.[69]



Scheme 28.

During the initial studies on the structure of illudin S (**38**) and illudin M (**39**), a hypothetical scheme for their biogenesis from farnesyl pyrophosphate through humulene and a protoilludane cationic intermediate was proposed.[23c] Subsequently it was shown that three molecules of [2-^{14}C]-mevalonate are incorporated into **38** and **39**, the labelling pattern being consistent with and supporting their biosynthesis via humulene.[70] The isolation of illudol (**25**)[17c] from *C. illudens* supported the intermediacy of a

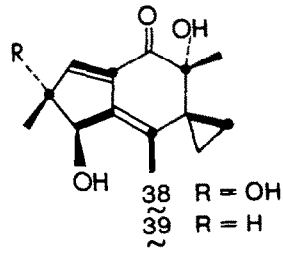
protoilludane cationic intermediate. In addition, the co-occurrence of Δ^6-protoilludene (**27**) with fomannosin, illudalanes, marasmanes and velleranes suggests that Δ^6-protoilludene may be the common precursor of these metabolites.[20] Hanson *et al.*[71a,b] have studied the biosynthesis of illudin M (**39**) in *C. illudens* using doubly labelled mevalonates. Incorporation of three [2,2-$^3H_2$-]-mevalonates was observed whereas one [4(*R*)-4-^{3}H]-mevalonate was incorporated. The retention of the [4(*R*)-4-^{3}H]-mevalonoid hydrogen atom is in accord with the suggested mode of cyclization of farnesyl pyrophosphate. The loss of a [2-$^3H_2$]-mevalonoid label in the cyclopropane ring suggests that humulene cyclizes to the illudane skeleton in a non-concerted manner (Scheme 29).[71a,b] In another study,[72] the observed coupling pattern in illudin M (**39**) and illudin S (**38**) derived from [1,2-$^{13}D_2$]acetate, and the induced coupling from [1-^{13}C]acetate, support the biosynthesis by the route proposed.



† [4(R)-4-^{3}H] - Mevalonate
* [2, 2 - $^3H_2$] - Mevalonate

39

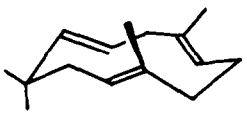
Scheme 29.



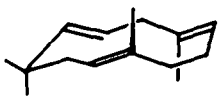
38 R = OH
39 R = H

$CH_3\,{}^{13}CO_2H$
$^{13}CH_3\,{}^{13}CO_2H$—(pairs of coupled atoms)

Matsumoto has suggested that the conformational behavior of humulene may dictate the course of the reaction.[73a,b] He has used molecular mechanics calculations to assess the relative stabilities of its conformers in solution. Four stable conformations CT, CC, TT and TC can be envisaged (C and T denote crossed and parallel arrangement of two double bonds, respectively). Noting the chirality of three bonds, eight possible stable conformers are *RSR*-CT, *RRR*-CC, *RRS*-TC, *RSS*-TT and the four enantiomers. (A prefix *RSR* represents the chiralities of the three double bonds $\Delta^{2,3}$, $\Delta^{6,7}$, $\Delta^{9,10}$ in turn). The chair–chair (CC) **132** and the chair–twist (CT) **133** conformations are singificantly more stable than the others. Interestingly Hg^{2+}-induced transannular cyclizations of humulene give only products derived from CC and CT conformations.[74] As well, the $AgNO_3$-humulene complex has been shown to adopt the CT conformation.[75] Matsumoto proposes that if the two conformations of humulene are kept almost unchanged during the reaction sequence, the existence of two biosynthetic pathways (CT → protoilludane and CC → hirsutane) is implied rather than the single route (CT → protoilludane → hirsutane).



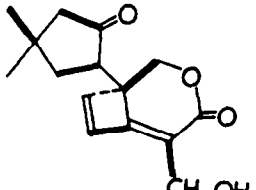
132 CC



133 CT

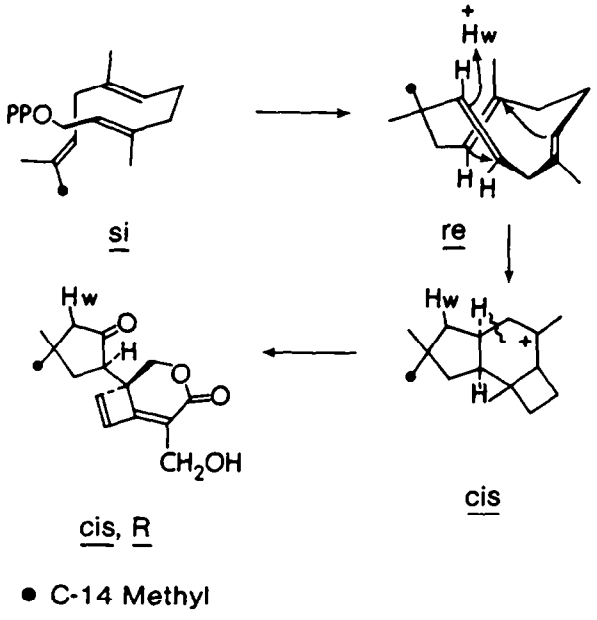
Arigoni has recently cited the need for a "simple and unifying stereochemical concept of sesquiterpene biosynthesis.[76] As a step in this direction, Cane *et al.*[77,78] have presented a detailed stereochemical analysis of the course of fomannosin biosynthesis based on ^{13}C incorporation studies. As well, these authors use the stereochemical concepts put forward to show how a similar analysis may be applied to a group of biogenetically related fungal metabolites (hirsutanes, marasmanes, illudanes).

Fomannosin (**67**) of known structure[42a,b] and absolute configuration,[43] was isolated from cultures of *Fomes annosus* grown on sodium [1,2-$^{13}C_2$] acetate enriched medium. The ^{13}C NMR spectrum of enriched **67** exhibited six pairs of C–C spin-coupled doublets as well as three enhanced singlets. The



67

observed labelling pattern supports a pathway in which mevalonate is converted to fomannosin through intramolecular cyclization of *trans,trans*-farnesyl pyrophosphate via humulene, a protoilludyl cation and oxidative cleavage of the appropriate bond (Scheme 30). Further ^1H NMR and ^{13}C NMR studies have shown that the enhanced singlet at 29.7 ppm in the ^{13}C NMR spectrum of enriched fomannosin corresponds to the *cis*-methyl (C-14) and that this methyl is biosynthetically derived from C-2 of mevalonate.



Scheme 30.

When *trans,trans*-farnesyl pyrophosphate cyclizes, electrophilic attack by the C–1 carbinyl carbon at C–11 may occur on the *re* or *si* face of the distal double bond. If attack occurs on the *re* face, the methyl group derived from C–2 of mevalonate becomes the *pro-S* methyl of humulene; if attack on the *si* face,

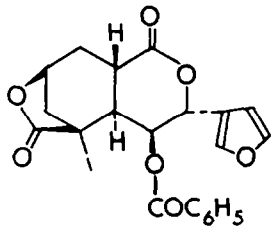
the same methyl becomes *pro-R*. The 9,10-double bond of humulene is now protonated at C–10 from either the *si* or *re* face and the concomitant intramolecular cyclization can generate either a *cis*- or a *trans*-fused cyclopentane ring in the resultant protoilludyl cation. For a sequence of cyclization to the *si* face of the FPP double bond, *re* protonation of the humulene and generation of a *cis*-fused cyclopentane, the fomannosin which is generated would have the following measurable characteristics: a *cis*-relationship between the cyclobutyl substituent and the methyl derived from C–2 of mevalonate and an *R* configuration at C–2. The entire sequence may be abbreviated *si, re, cis*: *cis, R*. Altogether there are eight different sequence possibilities.

The experimental data for fomannosin show that the *cis* methyl is in fact derived from C–2 of mevalonate and that the configuration of C–2 in **67** is indeed *R*.[43] This infers *si* attack on the distal double bond by the developing ion at C–1 in the cyclization of FPP. Assuming (by analogy to related metabolites) that the cyclopentane intermediate has a *cis* ring fusion, then protonation of humulene would occur from the *re* face. This predicts that the 10β-*trans* H of fomannosin is derived from the medium and that the H-10α originates from the 4-*pro*-R position of mevalonate. These predictions are being tested.

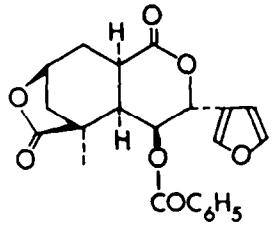
These stereochemical concepts have been used to analyze the data available on the biosynthesis of related fungal metabolites. The stereochemical description of the biosynthesis of illudol, illudin S and illudin M is the same as that for fomannosin: *si, re, cis*:*cis*: *R*, whereas the coriolins and hirsutic acid (antipodal to fomannosin) would be *re, si, cis*:*cis, S*. These results have interesting implications for the nature of enzyme reactions involved in cyclizing farnesyl pyrophosphate. Either free humulene is produced with *re* or *si* specificity or the absolute stereochemistry of the ultimate product dictates the folding of farnesyl pyrophosphate at the active site of the enzyme. Matsumoto[73b] comments that the conformation designated *RSR*-CT humulene is the precursor of illudiods and the *SSS*-CC humulene is that of the hirsutanoids in their biosynthetic transannular cyclization reactions.

Miscellaneous sesquiterpenes

Isolated examples of sesquiterpenes belonging to several different skeleton types have been reported. Two sesquiterpenes of the monocyclofarnesane type, collybolide (**134**) and isocollybolide (**135**) (which are artefacts resulting from as yet not isolated carboxylic acid precursors) have been isolated from the mushroom *Collybia maculata*. The structure of isocollybolide (**135**)[79a,b] was established by X-ray crystallographic analysis. The structure of collybolide (**134**), an isomer of **135** was established by chemical correlation: **135** isomerizes to **134** in the presence of trifluoroacetic acid.



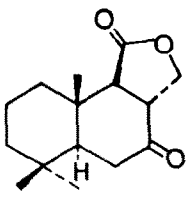
134 Collybolide



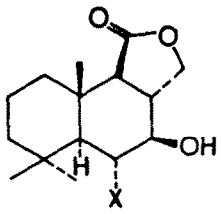
135 Isocollybolide

Three sesquiterpenes of the bicyclofarnesane type have been isolated from the bird's nest fungus *Mycocalia reticulata*.[80] 7-Ketodihydrodrimenin (**136**) and 7β-hydroxydihydrodrimenin (**137a**) had not been obtained previously from natural sources although both **136** and **137a** are known transformation products of natural products. 6α,7β-Dihydroxydihydrodrimenin (**137b**) is a new compound and its structure was established by physical methods. Another fungus, *Clitocybe illudens* produces a sesquiterpene having a cadinane skeleton[81] in addition to a number of sesquiterpenoids which are formally derivable from a protoilludane skeleton. Several strains of *C. illudens* when grown on an agar plate, produce crystals directly on the mycelial mat. These crystals have been identified as (+)-torreyol (**138**) by comparison with an authentic sample.

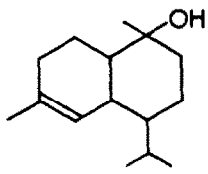
The liquid culture of the Basidiomycetes *Marasmius alliaceus* has yielded a sesquiterpene lactone, alliacolide (**139**) with a new carbon skeleton.[82] The structure of **139** was established by single crystal X-ray diffraction analysis. It is of interest that the skeleton of alliacolide is very similar to that of the pyrophosphate of artemesia alcohol (**140**). While the biogenesis of **139** has yet to be established, the



136

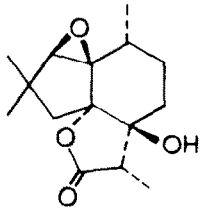


137a X=H
137b X=OH Dihydroxydihydrodrimenin

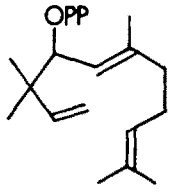


138

question arises whether precursors such as **140** should be considered in addition to farnesyl pyrophosphate in the biosynthesis of fungal sesquiterpenes.[82]

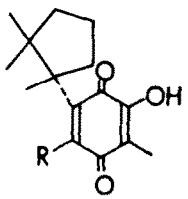


139 Alliacolide

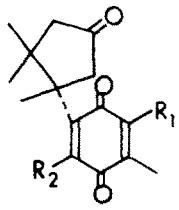


140

Helicobasidin (**141a**), a major pigment of *Helicobasidium mompa* (a fungus which causes violet root rot in many plants) was the first reported fungal quinone of an isoprenoid nature.[83a,b] Compound **141a** is an orange–red solid which is soluble in sodium carbonate and its violet, alkaline solution is decolorized with sodium dithionite. Helicobasidin absorbs 1 mole of hydrogen in the presence of a catalyst and the resulting colorless solution regains its original color on exposure to air with the regeneration of **141a**. These properties together with IR (hydroxyl, conjugated carbonyl) and UV absorption data indicate that **141a** is a benzoquinone derivative. Alkaline hydrogen peroxide oxidation of **141a** gave a monocarboxylic acid which was shown to be camphonanic acid by comparison with an authentic sample. This information, together with ^{1}H NMR data suggest structure (**141a**) for helicobasidin. Four other fungal quinones have been reported.[84a,b] Lagopodin A (**142a**) and lagopodin B (**142b**) have been isolated from *Coprinus lagopus* and *C. cinereus*, hydroxylagopodin B (**142c**) has been isolated from *C. macrorhizus* var *microsporus* and *C. cinereus*, whereas deoxyhelicobasidin (**141b**) has been isolated from *H. mompa*.[83c]



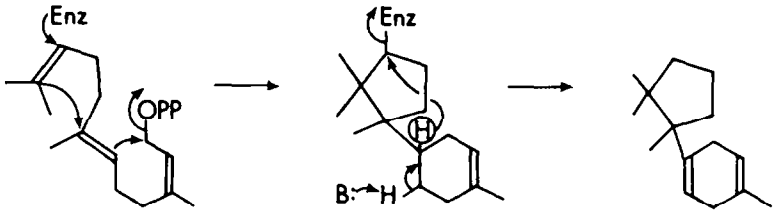
141a Helicobasidin R=OH
141b Deoxyhelicobasidin R=H



142a R_1=R_2=H Lagopodin A
142b R_1=H R_2=OH Lagopodin B
142c R_1=R_2=OH Hydroxylagopodin B

Several biosynthetic studies of helicobasidin have appeared. These reports, involving 1-^{14}C acetate and 2-^{14}C-mevalonate labelling studies show that **141** is of isoprenoid origin.[85a] In addition two independent studies[85b,c,d] using combinations of ^{3}H- and ^{14}C-labelled mevalonate lactone have shown that γ-bisabolene may be precluded in the biosynthesis of **141** and that a sequence from farnesyl pyrophosphate involving cyclization to a cuparenyl cation (Scheme 31) best fits the observed data. ^{13}C-labelling studies of helicobasidin are consistent with Scheme 31.[85e] Recently the use of ^{13}C NMR in the biosynthetic study of helicobasidin and the trichothecanes have provided further details regarding this group of structurally-related sesquiterpenes. Several members of the Deuteromycetes including *Fusarium*, *Trichothecium*, *Botrytis* and *Stochybotrytis* as well as members of the liverwort family

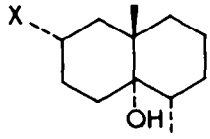
produce metabolites of the trichothecane skeleton. It is interesting that only two genera of Basidiomycetes have been reported to produce trichothecane sesquiterpenes. In view of the stated problems in mycological taxonomy and the great similarity of structure observed for the vast majority of Basidiomycetes sesquiterpenes, there may be some justification in aiding taxonomical classification by chemical categorization of metabolites.



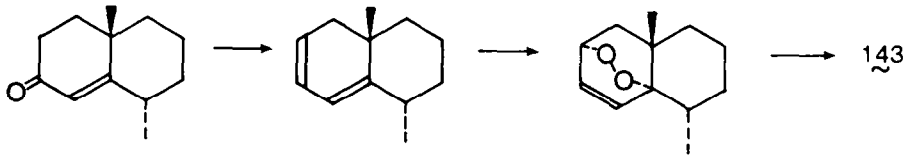
Scheme 31.

Merulidial, $C_{15}H_{20}O_3$, is a metabolite recently isolated from the Basidiomycetes *Merulius tremellosus* which shows antibiotic properties.[86] The structure of merulidial has not yet been determined.

Finally, a degraded eudesmane-type sesquiterpenoid, cybullol, has been isolated from the bird's nest fungus, *Cyathus bulleri*.[87a] Cybullol has been shown to possess structure **143** by a combination of chemical and physical methods and by chemical transformation into geosmin (**144**).[87a] Geosmin is a known fungal metabolite responsible for the "earthy" aroma of freshly plowed soil.[87b] The constitution of geosmin was first suggested by Gerber[88] and the structure and relative stereochemistry proven by Marshall's[89] stereoselective synthesis of the racemic form. A stereoselective synthesis of racemic cybullol (Scheme 32) which utilizes a sensitized photooxygenation of a suitably substituted hexalin intermediate **145** has been reported. Compound **145** is readily available from the known 6,10 - dimethyl - 4 - octal - 3 - one. In addition these workers report another stereoselective synthesis of racemic geosmin from a dimethyloctalone.



143 X=OH Cybullol
144 X=H



145

Scheme 32.

Diterpenes

Relatively few types of diterpenoids have been isolated from the Basidiomycetes. The largest group of metabolites are those derived from the bird's nest fungi (order Nidulariales, class Gasteromycetes) and only two other types of diterpenoids have been reported to date.

Cyathanes

In 1965 H. J. Brodie discovered a new bird's nest fungus of the genus *Cyathus* growing in the Canadian Rocky Mountains which he named *Cyathus helenae*.[90] Brodie succeeded in growing the fungus in liquid culture and showed that an ethyl acetate extract of the culture broth displayed pronounced antimicrobial activity.[91] Shortly thereafter we undertook a detailed study of the chemical

characterization of the active components and found that these metabolites belong to a new class of diterpenoids which have been named the cyathins (for a description of the trivial nomenclature of the cyathins see Refs. 91*a*, 92*b*).

The major component of the cyathin complex, isolated from *C. helenae*, was shown to consist of two compounds, cyathin A_3 ($C_{20}H_{30}O_3$) and allocyathin B_3 ($C_{20}H_{28}O_3$), which were separated by chromatography on silver nitrate impregnated silica gel. An exhaustive study of the spectra of allocyathin B_3 (the minor compound) and two of its derivatives (0,0-diacetyllallocyathin B_3 and allocyathin B_3 methyl acetal) allowed an unambiguous solution to the structural problem as is outlined below.[92]

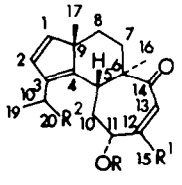
The solution infrared spectrum of allocyathin B_3 displays hydroxyl absorption and a broad band of medium intensity at 1650 cm^{-1} attributed to an α,β-unsaturated carbonyl group. This absorption band appears at the same position in the solid-phase spectrum in which it is much stronger and sharper. The decreased intensity in solution indicates that the carbonyl group is partially in a hemiketal form.

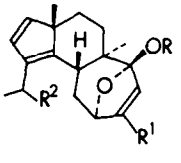
The UV spectrum of allocyathin B_3 methyl acetal shows only a diene chromophore whereas the UV spectrum of diacetylallocyathin B_3 shows a diene chromophore superimposed on an α,β-unsaturated carbonyl chromophore. A detailed analysis of the ^1H NMR spectrum of diacetylallocyathin B_3 indicates the presence of two quaternary methyl groups, an isopropyl group, two olefinic protons as an AB quartet, and two allylic acetates; one primary and one secondary. The double bond with two olefinic protons is not conjugated to the α,β-unsaturated carbonyl system, thus in order to complete the diene system allocyathin B_3 must contain a fully substituted double bond. Moreover, the UV spectrum is in good agreement with that of a 5,5-dialkylcyclopentadiene. The mass spectrum of allocyathin B_3 methyl acetal is dominated by an intense peak at *m/e* 141 corresponding to the ion $C_7H_9O_3$ which contains all three oxygen atoms of the ketal. This shows that the three oxygens in allocyathin B_3 are located on six contiguous carbon atoms which include the two allylic hydroxyls and the α,β-unsaturated ketone. Further, it is the secondary hydroxyl which is involved in ketal formation. It seemed unlikely that the unsaturated carbonyl system was part of a 6-membered ring and thus structures **146a⇄146b** for allocyathin B_3, **147** for diacetylallocyathin B_3 and **146c** for allocyathin B_3 methyl acetal were proposed.

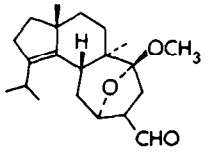
Cyathin A_3, which exists in solution in equilibrium between tautomeric forms **148a⇄148b**, and allocyathin B_3 (**146**) were correlated in the following manner. When a methanol solution of cyathin A_3 methyl acetal (**148c**) is stirred in a hydrogen atmosphere in the presence of palladized charcoal, it is isomerized to the aldehyde **149**. Treatment of allocyathin B_3 methyl acetal (**146c**) under these conditions causes the same isomerization to occur, concurrent with hydrogenation of the disubstituted double bond leading to aldehyde **149**, identical with that obtained from cyathin A_3. The constitution of cyathin A_3 has been independently confirmed by an X-ray crystallographic study which shows that crystalline cyathin A_3 exists in the hemiketal form **148b**.

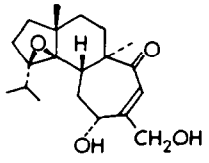
More recent work has clarified the structures of other metabolites of *C. helanae*, including cyathin B_3 (**150**), cyathin C_3 (**151**),[93] cyathin A_4 (**152**), neoallocyathin A_4 (**153**), and cyathin C_5 (**154**).[94] The structures of compounds **150**, **151**, **153** have been verified by chemical correlations (Scheme 33).

The antimicrobial activity of the total crude metabolites of *C. helenae* has been reported. Further testing has revealed that the components which are mainly responsible for this activity are the

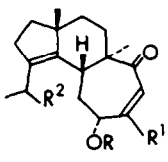


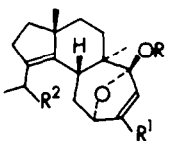




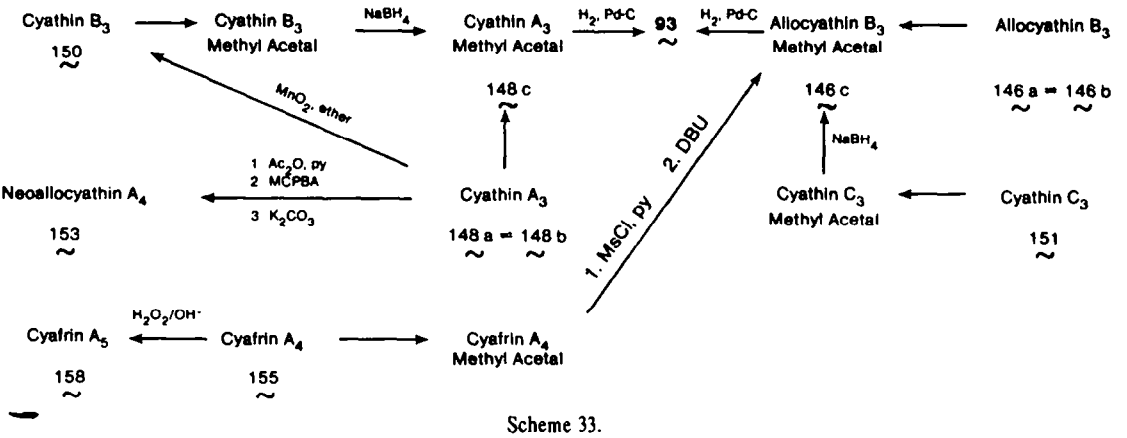


146a R=H R^1=CH_2OH R^2=CH_3 Allocyathin B_3 **146b** R=H R^1=CH_2OH R^2=CH_3 **149** **153** Neoallocyathin A_4
147 R=Ac R^1=CH_2OAc R^2=CH_3 **146c** R=CH_3 R^1=CH_2OH R^2=CH_3
151 R=H R^1=CHO R^2=CH_3 Cyathin C_3





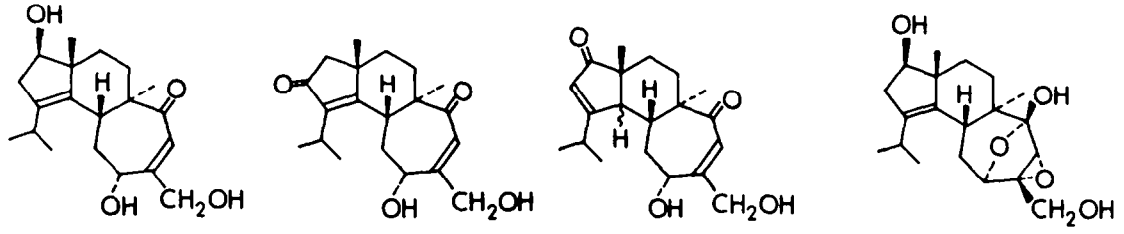
148a R=H R^1=CH_2OH R^2=CH_3 Cyathin A_3 **148b** R=H R^1=CH_2OH R^2=CH_3
150 R=H R^1=CHO R^2=CH_3 Cyathin B_3 **148c** R=R^2=CH_3 R^1=CH_2OH
152 R=H R^1=R^2=CH_2OH Cyathin A_4 **154** R=H R^1=CHO R^2=CO_2H Cyathin C_5



Scheme 33.

α,β-unsaturated aldehydes cyathin B_3 (**150**) and cyathin C_3 (**151**). Details of the *in vitro* antimicrobial activity are available, however recent results show that the activity of these compounds is not retained *in vivo*.[94]

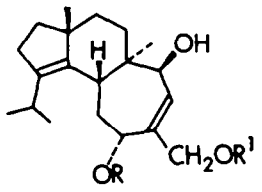
Other species of this genus have been examined. *Cyathus africanus*, a species of bird's nest fungus found growing on dead twigs at high altitude on Mount Kilamanjaro, produces cyathin A_3 (**148**) and allocyathin B_3 (**146**) along with four other diterpenoids.[95] These cyathin diterpenoids all contain oxygen functionality in ring A. Cyafrin A_4 (**155**) possesses a β-hydroxyl group at C-1 and has been correlated with allocyathin B_3 methyl acetal (**146c**) through mesylation–dehydromesylation (Scheme 33).



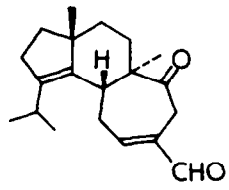
155 Cyafrin A_4 156 Cyafrin B_4 157 Allocyafrin B_4 158 Cyafrin A_5

Cyafrin B_4 is the ring A unsaturated ketone **156** while allocyafrin B_4 proved to be an isomeric ring A α,β-unsaturated ketone, this one with the carbonyl group located at C-1 as depicted in structure **157** . The most interesting metabolite of *C. africanus*, cyafrin A_5 (**158**) is assigned structure **158** on the basis of the following observations. The IR spectrum, both in solid state and in solution, does not show carbonyl absorption, indicating that cyafrin A_5 exists mainly in the hemiacetal form **158** with little contribution from the hydroxyketone tautomer. The ^{13}C NMR spectrum does not show carbonyl absorption and reveals the presence of only two olefinic carbons (C-3, C-4). The presence of the epoxide at C-12, C-13 was suggested by the observation that in the ^{13}C NMR spectrum the olefinic signals usually associated with these two carbons are replaced by two new signals in the region δ 55–65. This structural assignment was confirmed by transforming cyafrin A_4 (**155**) to cyafrin A_5 (**158**) by treatment with alkaline hydrogen peroxide in methanol (Scheme 33). The assignment of the stereochemistry of the epoxide ring is based upon the following considerations. In the hemiacetal form of the β-epoxide there is a serious non-bonded interaction between the oxirane oxygen and the β-hydrogen at C-5 whereas in the α-epoxide there appear to be no serious non-bonded interactions in the hemiacetal form. In addition, it is known that peracid oxidation of allylic alcohols results in an epoxide in which the epoxide oxygen is *cis* to the allylic hydroxyl. If the assumption is made that the hydroxyl group at C-11 directs the peracid epoxidation of the C-12, C-13 double bond, then the α-12,13-epoxide will be formed. Treatment of cyathin A_5 with *m*-chloroperbenzoic acid gave a diepoxide identical with that obtained from cyathin A_4. Recently it was discovered[96] that the mycelium of *Cyathus earlei* also contains diterpenoids of the cyathane type. The structures of six of these metabolites, cyathatriol (**159**), 11-0-acetylcyathatriol (**160**), 15-0-acetylcyathatriol (**161**), 11,15-0-diacetylcyathatriol (**162**), cyathin B_2 (**163**) and allocyathin B_2 (**164**) have been clarified. All six compounds show moderate antibiotic activity against *Staphylococcus aureus*.

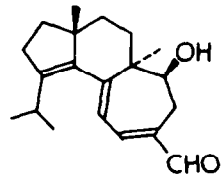
Another interesting structural type, the striatins, have recently been isolated from the mycelium of a European strain of *C. striatus*.[97] Striatin A was assigned structure **165**, a cyathin skeleton triply linked to



159 R=R¹=H Cyathatriol
160 R=AcR¹=H
161 R=H R¹=Ac
162 R=R¹=Ac

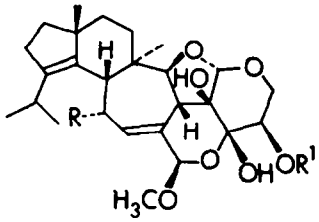


163 Cyathin B_2

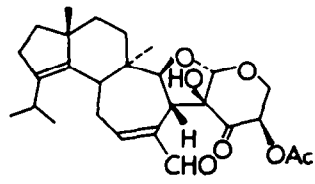


164 Allocyathin B_2

a pentose unit, on the basis of an X-ray crystallographic analysis. The structures of the closely related striatin B (**166**) and striatin C (**167**) were assigned by ^1H NMR spectroscopy. All striatins are very sensitive to water in the presence of traces of acid and undergo hydrolysis with the formation of keto aldehydes, e.g. striatin A **165** hydrolyzes to ketoaldehyde **168**.



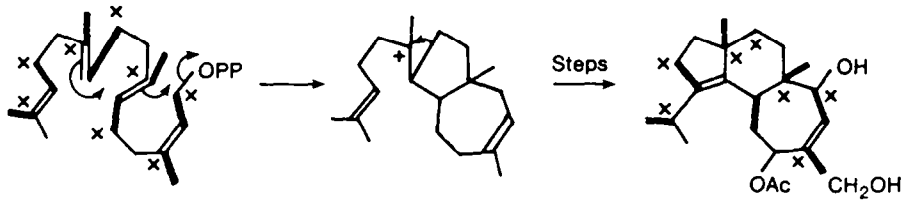
165 R=H R¹=Ac Striatin A
166 R=OH R¹=Ac Striatin B
167 R=OH R¹=H Striatin C



168

Biosynthesis

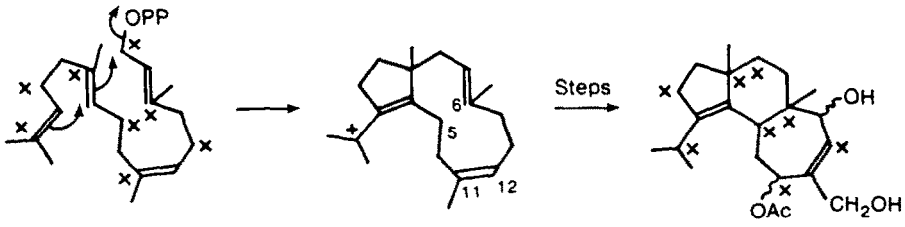
The biogenesis of the cyathanes has been investigated.[98] A study of the incorporation of ^{13}C-labelled acetate by *C. earlei* into cyathatriol (**159**) and its derivatives utilized ^{13}C NMR to trace the biosynthetic pathway. The ^{13}C NMR shifts assignments where based on an previous study of the cyathins.[99] Early on it was postulated that the carbon skeleton of the cyathins might arise by cyclization-rearrangement of geranylgeranyl pyrophosphate as in Scheme 34.[92b] However the recently isolated dolabellanes (**169**)



× [1 − ^{13}C] Acetate
− [1, 2 − ^{13}] Acetate

Scheme 34.

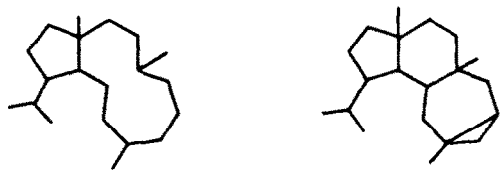
(which differ only in that they are bicyclic and that the C–12 methyl of cyathane appears at C–11 in dolabellane) as well as the newly discovered verrucosanes (**170**, the dolabellane skeleton in tetracyclic form) suggested that an alternate biogenesis through a dolabelladiene cation, subsequent C–5 to C–6 bond formation and C–11 to C–12 methyl migration could lead to the cyathanes (Scheme 35). These two possible biogenetic pathways may be distinguished by ^{13}C-acetate labelling. Incorporation of [1-^{13}C] acetate by *Cyathus earlei* gave 11-0-acetylcyathatriol (**160**), the ^{13}C NMR spectrum of which showed enrichment at C–2, 6, 8, 9, 10, 12, 14, 18, and the acetyl carbonyl in agreement with the biosynthetic pathway shown in Scheme 34. When [2-^{13}C] acetate was added to growing *C. earlei*, 11-0-acetyl-cyathatriol (**160**) enriched at the remaining carbons was obtained. These experiments serve to eliminate



× [1 − ^{13}C] acetate

Scheme 35.

from consideration the dolabellane route to the cyathins and are consistent with the pathway in Scheme 34.

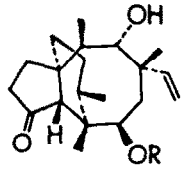


169 170

The pathway in Scheme 34 involves a molecular rearrangement which may be detected using doubly-labelled sodium acetate. The intact acetate units are shown as heavy lines (Scheme 34). The postulated rearrangement involves a scission of one of the acetate units (C–4, C–8) which will eliminate ^{13}C–^{13}C coupling between C–4 and C–8, and these two carbons, along with C–1, C–7, C–11 and C–19, should appear as singlets in the proton-decoupled spectrum of **160** derived from [1, 2–^{13}C] acetate if the C–4 to C–9 bond migration does occur. The results demonstrated that C–6 and C–8 are not coupled, again consistent with the molecular rearrangement shown in Scheme 34.

Miscellaneous diterpenes

Pleuromutilin, a compound with weak antibiotic activity against Gram positive bacteria, was isolated in the early 1950s from several species of Basidiomycetes (*Pleurotus mutilis*,[100a,b] *P. passeckerianus*,[100a,b] *Drosophila subatrata*[100c]). The chemistry of pleuromutilin was investigated independently by two different groups. Pleuromutilin (**171**) is the glycollic acid ester of mutilin (**172**). These structures, first reported by Arigoni (to date only in outline form without experimental detail[101]) are based on several interesting degradative reactions which are discussed below. Birch and co-workers have confirmed the structure of pleuromutilin to be **171** on the basis of a different set of degradative studies which have been detailed.[102]



171 R = $COCH_2OH$ Pleuromutilin
172 a R=H Mutilin
172 b R=Ac

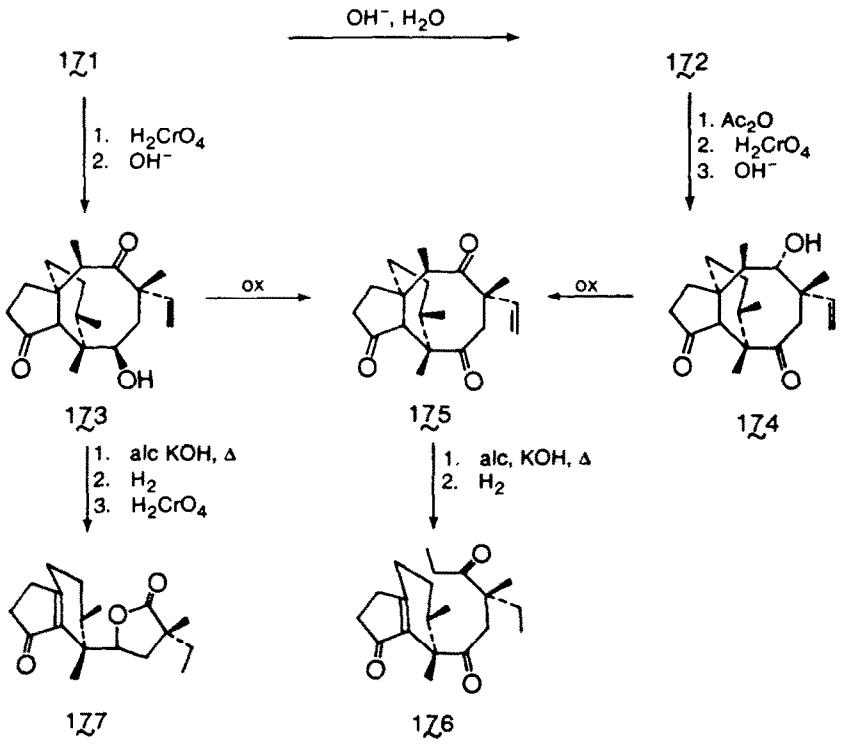
Anchel[100c] first established the molecular formula and showed that pleuromutilin possessed a ketonic carbonyl, two hydroxyl groups and an easily reduced double bond. Others established[101] the presence of a vinyl group and four methyl groups; two secondary methyls and two tertiary methyls as well as a cyclic 5-membered ketone. Bromination studies on dihydropleuromutilin diacetate indicated the presence of three hydrogens α to the carbonyl group.

The diterpenoid nature of **171** was shown by an at the time unusual application of tracer experi-

ments[101a,102a,b] to structure determination. Growth of *P. mutilis* in the presence of [1-^{14}C] acetic acid or [2-^{14}C] mevalonolactone gave 1.7% and 5.5% incorporation, respectively, into pleuromutilin.

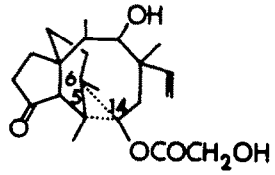
Selenium-induced dehydrogenation of the hydrolysis product mutilin (**172a**) gave 6,7-dimethyl-1-indanone in good yield. This experiment establishes the presence of a cyclohexane ring fused to a cyclopentanone and also shows the position of two of the four methyl groups in the natural product **171**.

The characterization of the environment of the other oxygen functionality in pleuromutilin (**171**) and its hydrolysis product mutilin (**172a**) was facilitated by the reactions shown in Scheme 36. Pleuromutilin

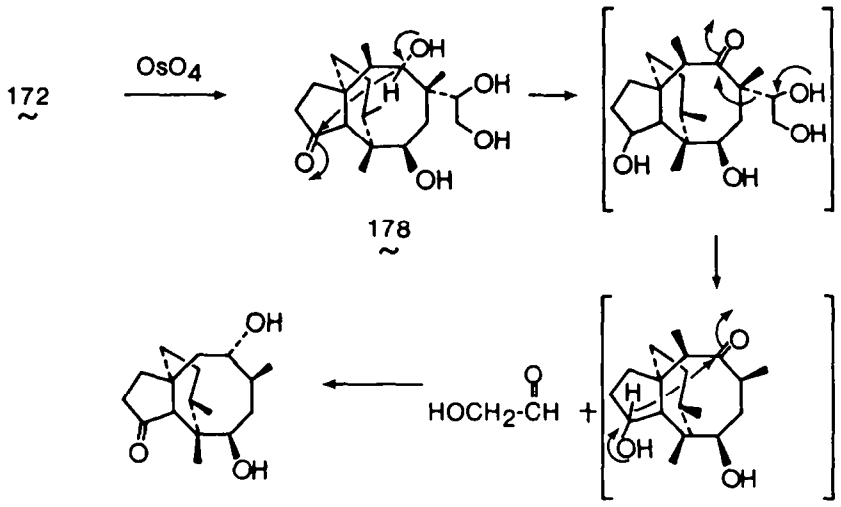


Scheme 36.

can be oxidized then hydrolyzed to a hydroxydiketone **173** which is different from hydroxydiketone **174** obtained by acetylation–oxidation–hydrolysis of mutilin. Both compound **173** and **174** give the same trione **175** on further oxidation. The characterization of these compounds showed that both hydroxyl substituents in pleuromutilin are secondary and that both are present in a ring with more than five members. Treatment of trione **175** with hot alcoholic potassium hydroxide effects a retro-Michael reaction to produce a cyclopentenone-dione **176**. This establishes that one hydroxyl is δ to the cyclopentanone carbonyl. The two hydroxyls were shown to be in a 1,4-relationship since the product obtained from treatment of hydroxydiketone **173** with hot alcoholic potassium hydroxide then hydrogenation and oxidation was a cyclopentenone-γ-lactone **177**. Further evidence for the structural framework of pleuromutilin was derived from the reaction sequence depicted in Scheme 37. Hydroxylation of mutilin (**172**) gives a keto tetraol **178** which undergoes a series of transannular Cannizzaro-type reactions with the liberation of glycollic aldehyde upon treatment with alcoholic potassium hydroxide. At this stage the characterization of pleuromutilin and its degradation products led to the partial structure **179** which contains all of the carbon atoms and oxygen functions of **171**. The position of the



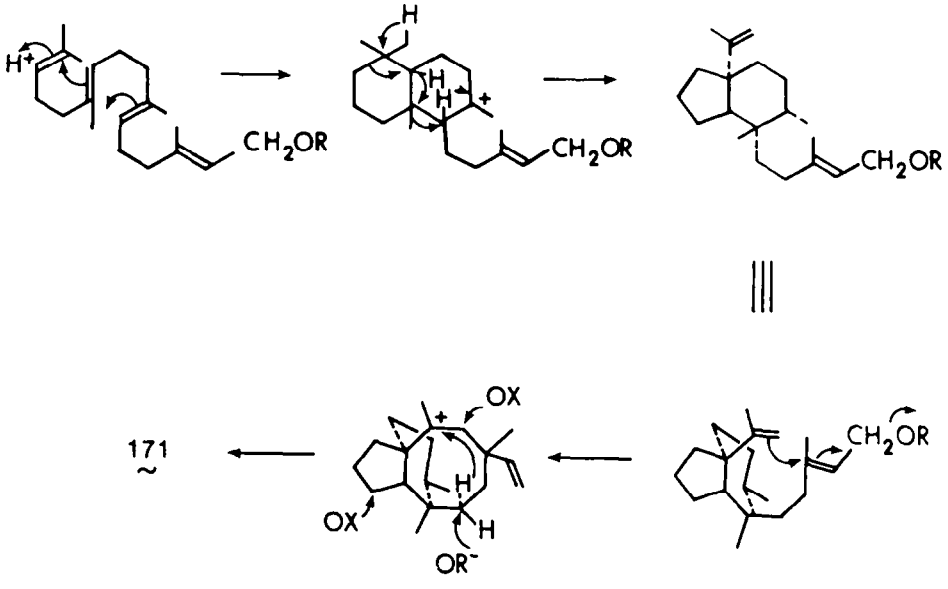
179



Scheme 37.

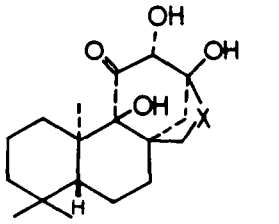
remaining carbon–carbon bond was established on the basis of the lowfield chemical shift of one of the tertiary methyl groups of pleuromutilin (**171**). The deshielding of the tertiary methyl could only be accounted for by a C-5, C-14 bond in **179**, not a C-6, C-14 bond. The stereochemistry of pleuromutilin was established chemically and then confirmed by an X-ray crystallographic analysis of the momobromoacetate of mutilin although the details of these investigations remain unpublished.[101b]

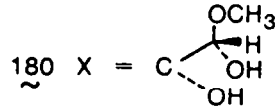
Early work on the biogenesis of pleuromutilin was reported by Birch *et al.*,[102] however Arigoni[101b] has established the detailed biosynthesis of compound **171** based on ^{14}C-labelling and degradative experiments. The biosynthetic route to pleuromutilin is outlined in Scheme 38.



Scheme 38.

The structures of two antibacterial diterpenoid metabolites isolated from the Basidiomycetes *Phlebia strigosozonata* have been reported.[103] The structures of phlebiakauranol (**180**) and phlebianorkauranol (**181**) were established by X-ray crystallographic analysis. Compounds **180** and **181** are highly oxygenated kauranes. Kauranes have not been isolated previously from Basidiomycetes, and are of interest since they are biogenetic precursors of the gibberellins.





180 X = C(OCH3)(H)(OH)(OH) Phlebiakauranol

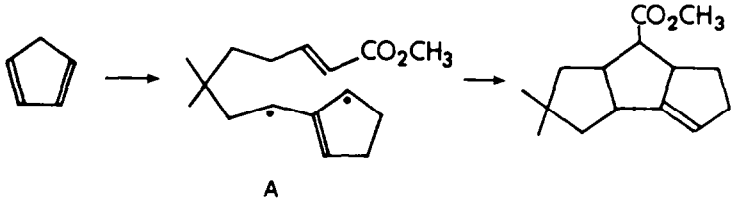
181 X = C=O Phlebianorkauranol

SECTION II

This past year has seen a flurry of activity in the terpenoid chemistry of the *Basidiomycetes*. Several new sesquiterpenes have been isolated, and novel syntheses, especially of the hirsutanes, have been described. This section will discuss the recent advances beginning with sesquiterpenoids and following the same order as in Section I.

Hirsutanes

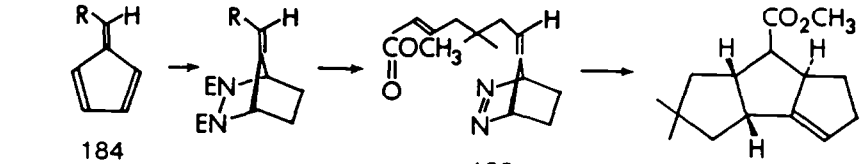
Several reports of new syntheses of hirsutanes have appeared. Little *et al.* have developed a regioselective and highly stereoselective synthesis of linearly fused tricyclopentanoids.[104a,b] Their method employs the first example of an intramolecular 1,3-diyl trapping reaction[104a] (Scheme 39) in



A

Scheme 39.

which two new carbon–carbon bonds are formed with creation of two 5-membered rings and the stereoselective generation of four asymmetric centers with the proper relative stereochemistry for further elaboration to hirsutene (9) or the coriolins (5), (6), (7). The synthesis of intermediate **182** (Scheme 40) begins with the synthesis of the bicyclic azo compound **183** (a convenient of source of diyl



184

R=CH2C(CH3)2CH2CH=CHCO2CH3

E=CO2CH2CCl3

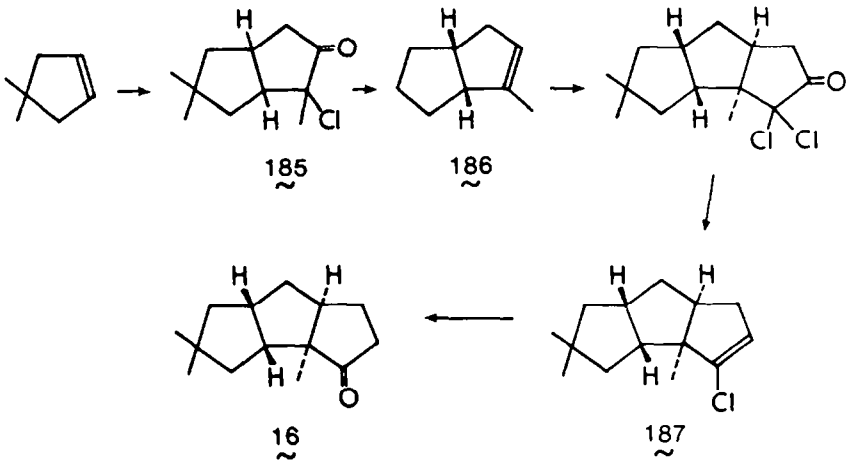
183

182

Scheme 40.

A) by a Diels–Alder addition of fulvene **184** and *bis*trichloroethylazodicarboxylate followed by selective hydrogenation to the bicyclic *bis*carbamate. This compound was transformed electrochemically to the bicyclic azo compound **183**. Thermolysis of **183** led to the stereoselective formation of **182**.

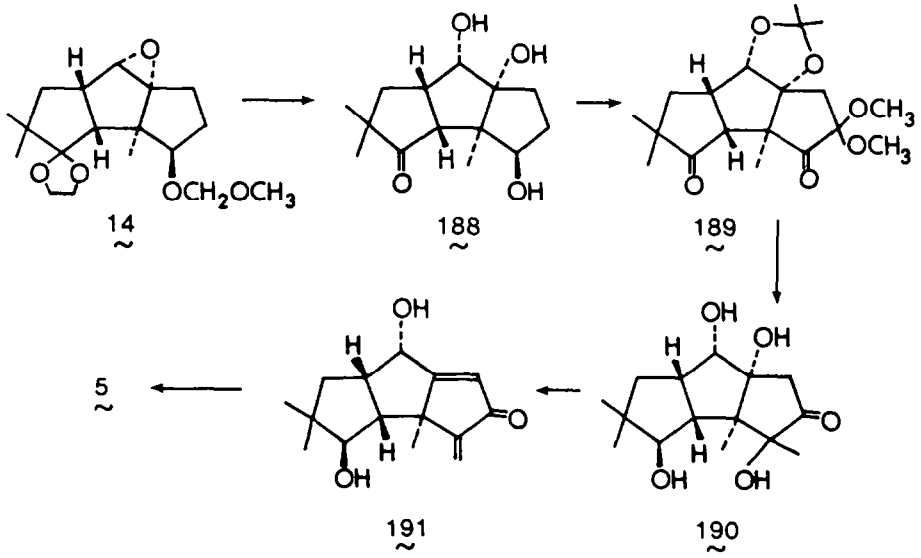
Greene[105] has recently described a three-carbon annulation procedure, which offers the possibility of iteration and thus affords a method for synthesis of the tricyclopentanoid carbon skeleton of the hirsutanes. He has employed this method in an elegant synthesis of hirsutene (Scheme 41).[106] Dimethylcyclopentene was converted to bicyclochloroketone **185** through cycloaddition with methylchloroketene



Scheme 41.

followed by ring expansion with diazomethane. Compound **185** was reduced to the chlorohydrin then transformed to an olefin **186** with chromous perchlorate. The third ring was stereo- and regioselectively joined to **186** using dichloroketene to produce a dichlorocyclobutanone. Sequential treatment with diazomethane, sodium borohydride and chromous perchlorate gave the vinyl chloride **187**. Acid hydrolysis gave known ketone **16**[11] which has previously been transformed to hirsutene.[11,13,15]

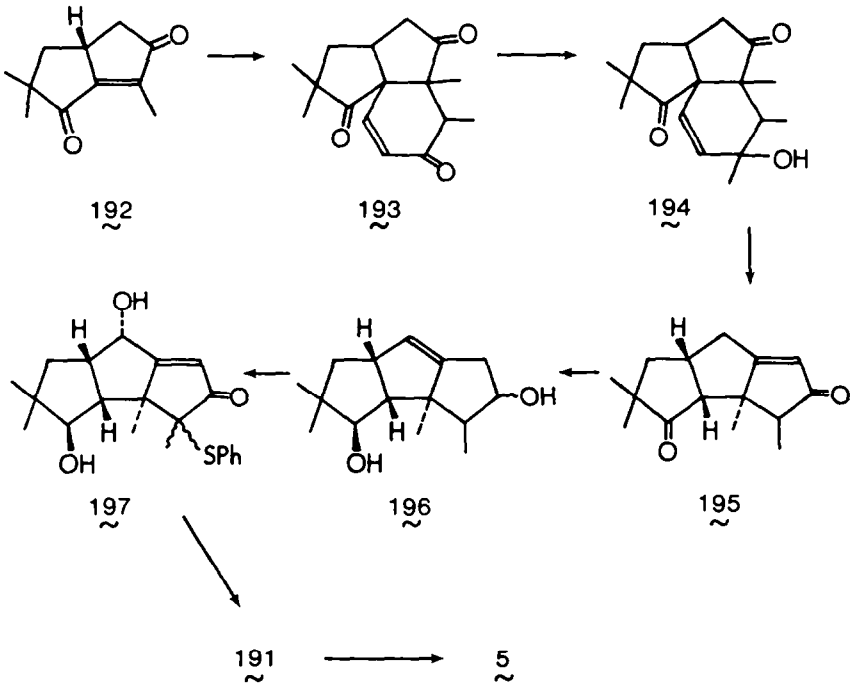
The total synthesis of racemic coriolin (**5**) has been achieved simultaneously by two different groups. Tatsuta *et al.*[107] have prepared coriolin (Scheme 42) by a stereocontrolled synthetic route similar to that



Scheme 42.

described in their synthesis of hirsutene.[15] Thus the epoxide **14**, the preparation of which is described in Scheme 8, was transformed to keto triol **188** by reductive elimination to an olefin, hydrolysis to a keto alcohol, and *cis*-dihydroxylation with osmium tetroxide-methylmorpholine-N-oxide. Protection of the *cis*-diol in **188** as an acetonide, oxidation to a diketone followed by bis-sulfenylation, then treatment with thallium trinitrate in methanol gave the keto dimethylacetal **189**. Treatment with methyllithium transformed the latter to a tertiary alcohol, which was reduced, then deprotected giving tetraol **190**. Selective acetylation of the secondary hydroxyls followed by elimination of the tertiary hydroxyls and deacetylation gave the unsaturated ketone **191**. Treatment of **191** with alkaline hydrogen peroxide gave (±)-coriolin (**5**).

In their synthesis of racemic coriolin (Scheme 43) Danishefsky *et al.*[108] constructed the tricyclopentane skeleton by adding an acetonyl fragment to enedione **192**. This was accomplished by means of a

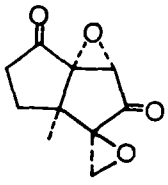


Scheme 43.

Diels-Alder addition of the silyl enol ether of ethyl vinyl ketone to **192** followed by conversion to the diketoenone **193**. Treatment of **193** with methyllithium gave **194** which was transformed to **195** by ozonolysis, Jones oxidation, decarboxylation, and aldolization–dehydration. The adjustment of functionality was achieved as follows. Deconjugation, then reduction gave a mixture of homoallylic alcohols. Further reduction of the C–1 carbonyl gave the diol **196**. Epoxidation from the α-face was readily achieved with *m*-chloroperbenzoic acid since the product of β-addition would be the energetically less favored *trans*-fused AB compound. The C–5 alcohol was selectively oxidized by the Corey–Suggs method. Further treatment with base followed by quenching with phenylthiophenylsulfonate effected transformation to compound **197**. This transformation proceeds through β-elimination of the epoxide followed by *in situ* enolization of the enone–dialkoxide in the α' sense. Oxidation of **197** with *m*-chloroperbenzoic acid then pyrolysis gave **191**. Compound **191** was converted to (dl)-coriolin by means of alkaline hydrogen peroxide.

Koyama *et al.*[109] have studied some structure-activity relationships for the coriolins. They have developed a hydrolysis method for removal of the C–1 octanoyl group of coriolin B (**6**) without opening its two epoxide groups which are essential for the biological activities.[109a] In addition they have developed a chemical conversion of coriolin B to coriolin.[109b]

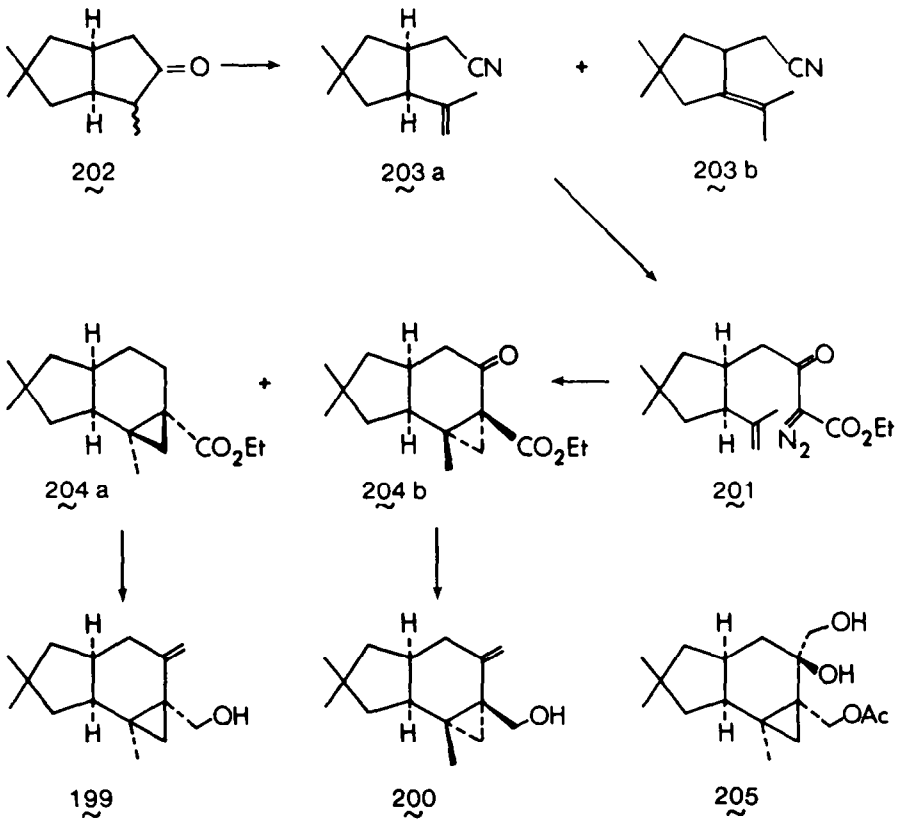
Matsumoto[110] has recently reported the synthesis of bicyclic coriolin models of type **198**.



198

Marasmanes

Nozoe *et al.*[111] have prepared cyclopropylcarbinyl alcohols **199** and **200** with marasmane and isomarasmane skeletons. Compounds **199** and **200** were synthesized from the azoketoester **201** (Scheme 44) by a route involving an intramolecular carbene insertion reaction. The synthesis begins with the bicyclic ketone **202** which was transformed to a 1 : 1 mixture of isomeric nitriles **203a** and **203b** after

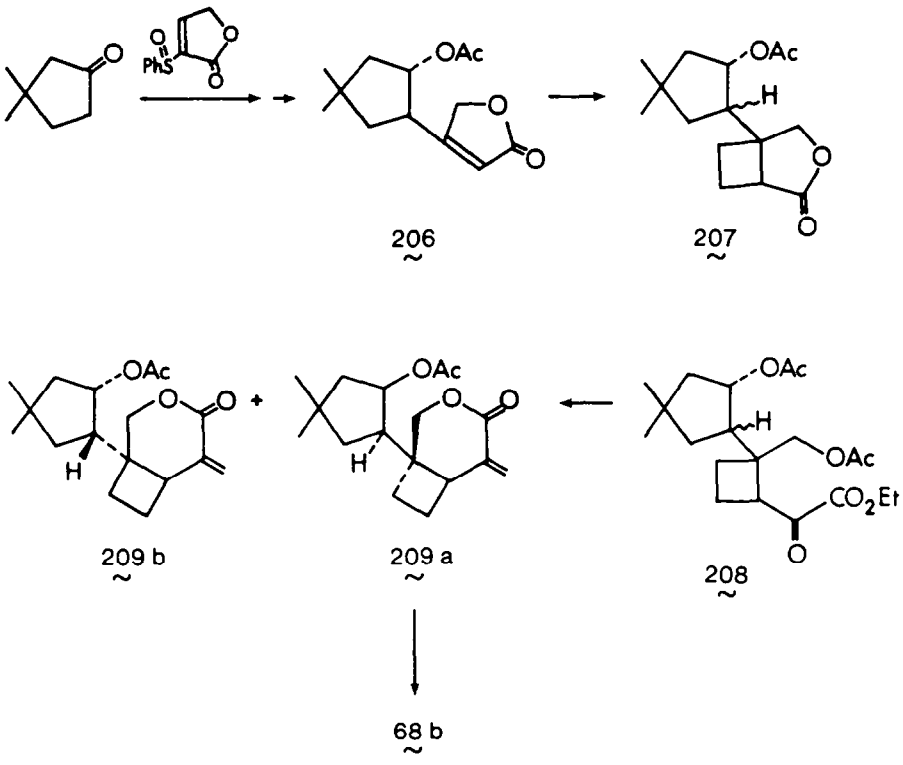


Scheme 44.

alkylation and abnormal Beckmann rearrangement. Compound **203a** was converted to the azoketoester **201** in a series of steps. The azoketoester when heated with trimethylphosphite-cuprous iodide gave two epimeric cyclopropyl ketones **204a** and **204b** and an unknown compound in the ratio of 5:1:1. After separation, both the major norketone **204a** and the minor norketone **204b** were subjected to Wittig methylenation, then reduction to give the corresponding cyclopropyl carbinyls **199** and **200**. The major compound **199** was found to have an isomarasmane-type skeleton by an X-ray crystallographic analysis of its derivative, compound **205**. Thus the norketone obtained as a major product in the carbene insertion reaction has the stereochemistry shown in **204a** and the minor norketone has the marasmane stereochemistry.

Fomannosanes

The synthesis of racemic dihydrofomannosin acetate (**68b**) has recently been completed.[112a] The synthetic strategy is based on earlier studies[112b] and involves the photoaddition fo a suitably substituted butenolide **206**, ring enlargement of the γ-lactonic photoadduct to a δ-lactone and functional group modification to form dihydrofomannosin acetate (Scheme 45). The starting butenolide **206** was prepared by Michael addition of the lithium enolate of dimethylcyclopentanone to α-phenylsulfinyl-$\Delta^{\alpha,\beta}$-butenolide then dehydrosulfenylation, reduction and acetylation. Photochemical addition of ethylene proceeded at low temperature to give a 1:1 mixture of photoadducts **207** which could not be separated. One carbon homologation with lithiated methylthiodithiane, acetylation and mercury(II)-catalyzed ethanolysis gave glyoxylate **208**. Compound **208** was transformed to an α-methylene ester by slow, inverse addition of Wittig reagent. The α-methylene esters were separated and cyclized to the α-methylene-δ-lactones **209a** and **209b**, respectively. Examination of Dreiding models and the ^{1}H NMR of **209a** and **209b** allowed the assignment of the fomannosin stereochemistry to **209a**. The assignment was confirmed by completion of the synthesis of dihydrofomannosin acetate **68b** from **209a** through a series of steps involving protection, hydroxylation, dehydration, hydrolysis and oxidation.

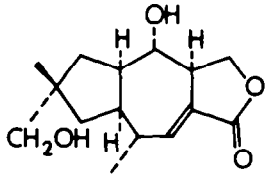


Scheme 45.

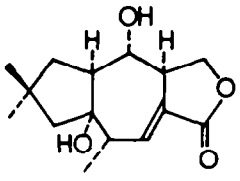
Lactaranes

The lactaranes are the most widely distributed sesquiterpenoids of the Basidiomycetes. The past year has seen the isolation and structure elucidation of eleven new members of this skeletal type.

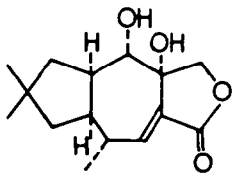
15-Hydroxyblennin A (**210**)[113] has been isolated along with known lactaranes from the edible mushroom *Lactarius torminosus*. The Finnish workers have applied gas chromatographic analysis to the lactone lactaranes[113b] and have used this technique to investigate the sesquiterpenoid fraction of *L. torminosus* and *L. trivialis*. A chemotaxonomic study by correlation of the known sesquiterpenoid composition of *Lactarius* species (summarized in tabular form in Ref. 113*c*) to generic subdivision of *Lactarius* is reported.[113c]



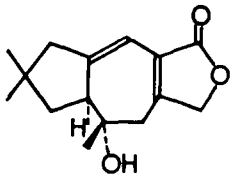
210 15-Hydroxyblennin A



211 Blennin D



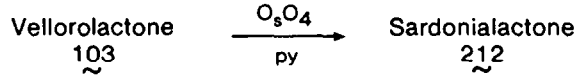
212 Sardonialactone



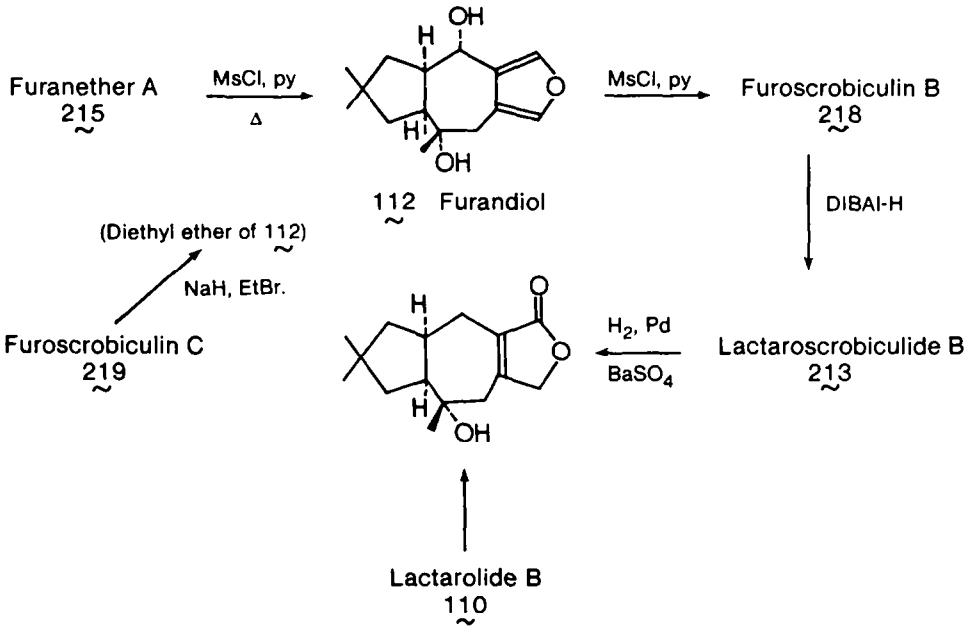
213 Lactaroscrobiculide B

Further spectral studies of blennin A (**102**)[114] have rigorously established the stereochemistry depicted. Different attempts to dehydrate blennin A to vellerolactone (**103**) have been unsuccessful. These results could be anticipated as in this case dehydration can only occur by means of a *cis*-elimination. Blennin A is isomeric with lactarorufin N (**101**) at C-7 and/or C-8. However lactarorufin N has been isomerized to 3-deoxylactarorufin A (**100**) (Scheme 22). It would be interesting to know if blennin A would also isomerize to **100** under similar conditions. Such a chemical correlation, potentially, would define the relative stereochemistry of 3-deoxylactarorufin A and thus lactarorufin N. As yet this correlation has not been reported.

Three other lactone lactaranes have been reported. The structures of blennin D (**211**) (*L. blennius*[114]) and sardonialactone (**212**) (*Russula sardonia*[115]) with the lactone carbonyl at C-5 were elucidated by spectral data and in the case of **212** by correlation with vellerolactone (Scheme 46) (osmylation of **103** yields **212**). Lactaroscrobiculide B was assigned structure **213** from spectral data and chemical correlation with furandiol **112** (Scheme 47).[116] It is interesting to note that the lactones with the carbonyl at



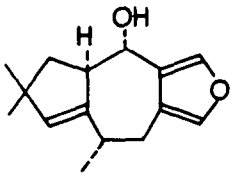
Scheme 46.



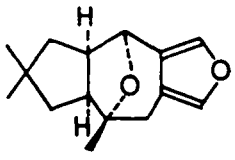
Scheme 47.

C-13 seem to be peculiar to *L. scrobiculatus*. Lactaroscrobiculide B (**213**) co-occurs with lactaroscrobiculide A (**105**) and epoxylactone **106**.

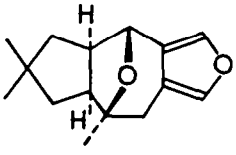
The structures and stereochemistry of seven new furan lactaranes have been elucidated by spectroscopic methods and by chemical correlations[115,116] Furosardonin A (**214**) and furanether A (**215**) have been isolated from *R. sardonia*[115] while **215**, furanether B (**216**), furoscrobiculin A (**217**), furoscrobiculin B (**218**), furoscrobiculin C (**219**), and furoscrobiculin D (**220**) have been isolated from *L. scrobiculatus*.[116] The chemical correlation of known furandiol **112** with **215**, **218** and **219** is outlined in Scheme 47. It is interesting to note that the lactaranes isolated from *L. scrobiculatus* and *R. sardonia* have different configurations at the C-3 methyl; C-12 is *syn* to the ring junction protons (H-2, H-9) when C-12 is *geminal* to hydrogen and *anti* when it is *geminal* to an hydroxyl group. An exception to this rule is furanether B (**216**).



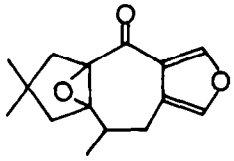
214 Furosardonin A



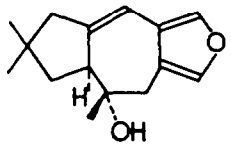
215 Furanether A



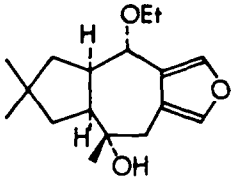
216 Furanether B



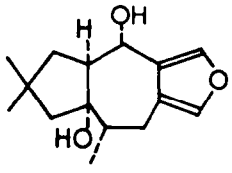
217 Furoscrobiclin A



218 Furoscrobiculide B



219 Furoscrobiculin C



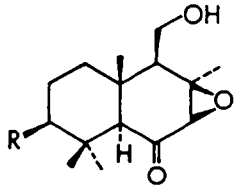
220 Furoscrobiculin D

Biosynthesis

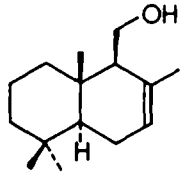
Previously[77] Cane has discussed the stereochemical aspects of the biogenesis of fomannosin (**67**) (Scheme 30). It was predicted that the H-10β of fomannosin is derived from the medium and that H-10α originates from the 4-*pro-R* position of mevalonate. This prediction has now been tested. [5,5-$^2H_2$]-mevalonate was administered to *F. annosus* and the fomannosin isolated was analyzed by ^2H NMR. The presence of deuterium at C-1 and C-5 was established and it was shown that no isotope was located at C-10.[117] This result is consistent with the deprotonation–reprotonation sequence proposed. The authors comment that the absence of deuterium at C-10 in fomannosin also casts doubt on the validity of the proposal[71a,b] of a series of hydride shifts in the biosynthesis of illudin M (**39**), a metabolite biogenetically closely related to fomannosin.

Miscellaneous sesquiterpenes

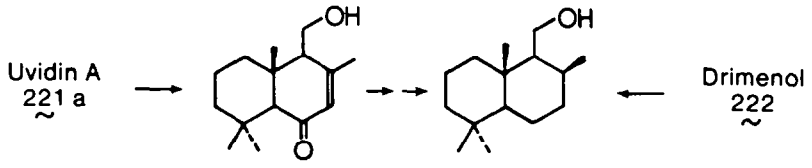
Three additional sesquiterpenes[118] with a bicyclofarnesane skeleton have been isolated from a Basidiomycetes, *Lactarius uvidus*. Uvidin A (**221a**), uvidin B (**221b**) and the previously known drimenol (**222**)[119] have been isolated from this mushroom. The structure and stereochemistry of the two uvidins have been determined by spectroscopic data and chemical reactions (Scheme 48).



221 a R=H Uvidin A
221 b R=OH Uvidin B

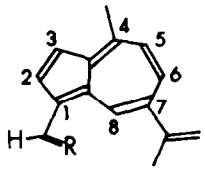


222 Drimenol

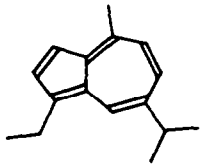


Scheme 48.

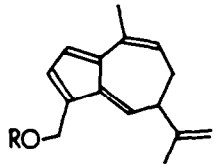
Azulenes have been obtained from a wide variety of plant sources. In almost all cases these pigments are not naturally occurring but are formed during isolation. Fresh sporophores of fungi from the genus *Lactarius* contain a latex which in a number of species is highly colored. One of these, lactaroviolin (**223**)[120] which is reddish-violet was first isolated in 1935 from *L. deliciosus*.[120a] Its structure was determined in the 1950s. Complete hydrogenation of **223** to perhydroguiazulene provided proof of the guaizulene carbon skeleton. The IR spectrum showed the presence of an aldehyde while the UV spectrum was characteristic of that of an azulene. Consideration of other spectral properties and chemical evidence allowed the assignment of structure **223** to lactaroviolin.[120b,c] This was proven by conversion into 1-ethyl-4-methyl-7-isopropylazulene (**224**) which was also prepared by total synthesis.[120d]



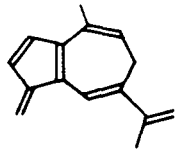
223 R=O Lactaroviolin
225 R=H_2 Lactarazulene
228 R=<H
OCO $(CH_2)_{16}$ CH_3



224



226 a R=H
226 b R=CO $(CH_2)_{16}$ CH_3



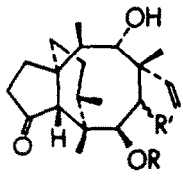
227 Lactarofulvene

Another azulene, the blue lactarozulene (**225**), was also isolated from *L. deliciousus*.[121] However, neither **223** or **225** occurs as such; the orange color of the fungus is due in European specimens to the extremely sensitive dihydroazulenes **226a** and **226b**[122] while fungi from California yield lactarofulvene **227**.[123] Recently the structure of a new naturally-occurring azulene, compound **228**, obtained from an acetone extract of the blue mushroom *L. indigo* has been determined by chemical and spectral methods.[124]

The pigment of *L. indigo* responsible for its natural blue color seems to be extraordinarily sensitive; being instantaneously converted to an intractable green substance upon addition of methanol to its solution in acetone, or on attempted chromatography. The structure of this and similar sensitive pigments of *Lactarius* are currently being investigated.

Diterpenes

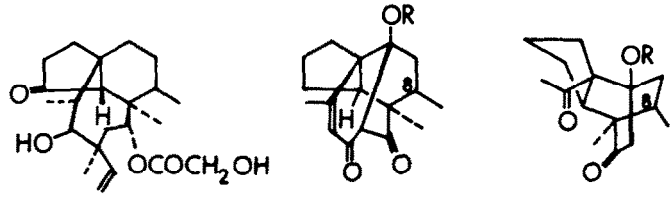
Two new pleuromutilin-related antibiotics, **229** and **230** have been isolatedd from *Cliptopilus pseudo-pinsitus* along with pleuromutilin (**171**) and 14-acetylmutilin (**172b**).[125] The structures of **229** and **230** were elucidated by chemical and spectroscopic methods. Compound **230** is the first compound of this class known to have an additional hydroxyl group in the tricyclic diterpene ring system.



229 R = $COCH_2O$-(glucose)-OH, R^1 = H

230 R = $COCH_2OH$, R^1 = OH

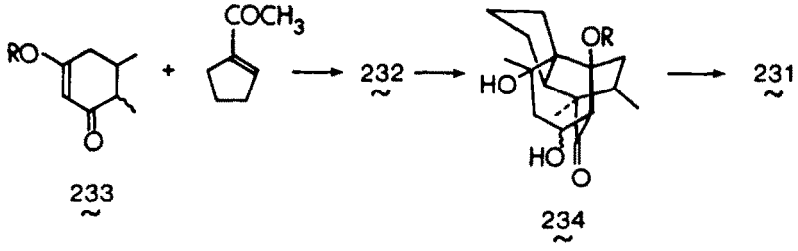
A versatile, one-step stereoselective synthesis of tricyclo[5.2.2.$0^{2,6}$]-undecane has been developed for use in a synthetic approach to pleuromutilin (**171**). The synthetic strategy to the tricyclic ring system with correct stereochemistry is based upon formation of the rigid tetracyclic compound **231**. Compound **231** can be derived from intermediate **232** (Scheme 49).[126]



171 Pleuromutilin 231 232

Scheme 49.

The synthesis begins with a remarkable one-step, stereoselective synthesis of **232** brought about by reaction of the kinetic enolate of **233** with 1-acetylcyclopentene at low temperature to give the *endo* adduct as the sole product. The stereochemistry of **232** was established by transformation to the bridged, tetracyclic compound **231** as outlined in Scheme 50. Treatment of **232** with allyllithium followed by ozonolysis with reductive workup gave the unstable aldehyde which cyclized under basic conditions to a mixture of diols **234**. Diols **234** were oxidized and smoothly dehydrated to the α,β-unsaturated diketone **231**. Transformation of **231** to pleuromutilin has not yet been reported.



233 234

Scheme 50.

In conclusion it may be pointed out that only a relatively small number of the hundreds of Basidiomycetes have been investigated. Many of the remaining species are involved in interesting biological phenomena[1,4,5] and thus hold the promise of providing new natural products, many of which will no doubt be terpenoid in nature. The fact that these fungi are often involved in biological processes indicates that the new metabolites will not only be interesting in a chemical sense, but that they may also be of biological interest and significance.

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