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REVIEW ARTICLE

THE OCCURRENCE, STRUCTURE ELUCIDATION AND BIOSYNTHESIS OF THE SESTERTERPENES

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Key Word Index—Sesterterpenes; occurrence; structure elucidation; biosynthesis; review.

INTRODUCTION

COMPOUNDS derived from the five-carbon isoprene,[1] unit are amongst the most widely distributed in Nature, at least 4000 having been isolated. These terpenoid compounds fall mainly in the classes of the monoterpenes (C_{10}), the sesquiterpenes (C_{15}), the diterpenes (C_{20}), the steroids, the triterpenes (C_{30}) and the carotenoids (C_{40}). Until quite recently no compounds had been characterized which were formed from five isoprene units, namely the sesterterpenoids (C_{25}). Although this class still forms a rare group of natural products, rapid progress has been made since 1965, both in the area of structure elucidation and biosynthesis. A brief review appeared in Turner's excellent monograph,[2] but a more comprehensive account of the occurrence, chemistry and biosynthesis of these compounds is now appropriate. This review presents the published data to November 1973, and the known sesterterpenes are divided into five structural types shown in Table 1.

TABLE 1. SESTERTERPENE STRUCTURE TYPES

Linear	Ophiobolane	Cheilanthatriol	Retigeranic acid	Gascardic acid
3,7,11,15,19-Pentamethyl -2-*cis*-6-*trans*- eicosadien-1-ol **1**	Ophiobolin *A* **16**	Cheilanthatriol **31**	Retigeranic acid **34**	Gascardic acid **38**
Geranylnerolidol **2**	Ophiobolin *B* **19**	Scalarin **33**		
Geranylfarnesol **3**	Ophiobolin *C* **20**			
Ircinin-I **6**	Anhydroophiobolin *A* **21**			
Ircinin-II **7**	Ophiobolin *D* **22**			
Fasculatin **10**	Ophiobolin *F* **24**			
Furospongin-3 **11**	Ceroplastol I **26**			
Furospongin-4 **12**	Ceroplasteric acid **27**			
Variablin **15**	Ceroplastol II **28**			
	Albolic acid **29**			
	Cheilanosin **30**			

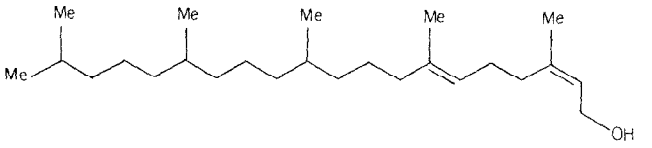
[1] RUZICKA, L., ESCHENMOSER, A. and HEUSSER, H. (1953) *Experientia* **9**, 357.
[2] TURNER, W. B. (1971) in *Fungal Metabolites*, p. 248. Academic Press, New York.

ISOLATION AND STRUCTURE ELUCIDATION OF THE SESTERTERPENES

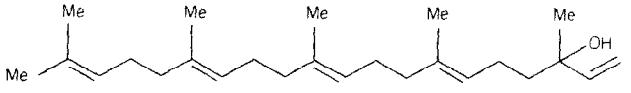
*Sesterterpenes of the linear type**

In 1969 Japanese workers[3] isolated, by silica gel chromatography of the unsaponifiable lipid extract of *Solanum tuberosum*, a pale yellow oil. The IR spectral properties of this oil indicated an allylic primary alcohol and an additional trisubstituted olefin. The MS of the acetate indicated an important fragment at *m/e* 350; in each case no parent ion was observed due to a facile loss of HOAc. The two olefinic bonds were therefore confirmed and the fragmentation pattern of the perhydroderivative indicated that the compound contained a linear combination of hydrogenated isoprene units. Comparison with the acetate of the parent compound indicated that the olefinic bonds were located in the terminal units.

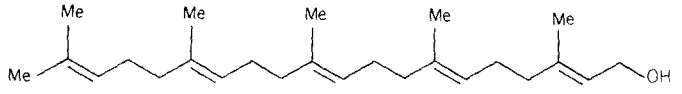
The NMR spectrum showed the presence of a *cis* terminal allylic alcohol unit with a methyl group at 1·71 ppm and olefinic and methylene protons at 5·38 and 4·03 ppm respectively. The remainder of the spectrum confirmed a *trans* olefinic bond at C-6.[4] The structure 3,7,11,15,19-pentamethyl-2-*cis*-6-*trans*-eicosadien-1-ol (**1**) was assigned to this compound.



(1) 3,7,11,15,19 – Pentamethyl – 2-*cis* –6– *trans* – eicosadien – 1–ol



(2) Geranylnerolidol



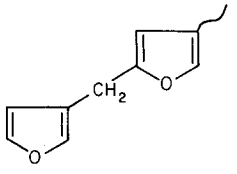
(3) Geranylfarnesol

The first acyclic sesterterpenoid isolated, however, was all-*trans*-geranylnerolidol (**2**) obtained from *Cochliobolus heterostrophus*,[5] the phytopathogenic fungus responsible for the leaf spot disease in maize. A molecular ion (M^+) at *m/e* 358 ($C_{25}H_{42}O$) was observed together with hydroxyl and vinyl absorptions in the IR spectrum. Characteristic signals were observed at 1·64 ppm for a methyl group *cis* and at 1·57 ppm for the methyl groups *trans* to the olefinic protons in the isoprene residues.

* In this context the term linear indicates the absence of formation of any additional carbon–carbon bonds compared with a linear combination of isoprene units.

[3] TOYODA, M., ASAHINA, M., FUKAWA, H. and SHIMIZU, T. (1969) *Tetrahedron Letters* 4879.
[4] BATES, R. B., GALE, D. M. and GRUNER, B. J. (1963) *J. Org. Chem.* **28**, 1086.
[5] NOZOE, S., MORISAKI, M., FUKUSHIMA, K. and OKUDA, S. (1968) *Tetrahedron Letters* 4457.

A closely related compound, geranylfarnesol (**3**) was isolated from the wax of the insect *Ceroplastes albolineatus*.[6] Spectral studies indicated the compound to be isomeric with geranylnerolidol (**2**), however the compound was easily oxidized to a conjugated aldehyde with chromium trioxide/pyridine so that a primary allylic alcohol was present rather than a vinyl group. The NMR spectrum proved definitive, indicating the presence of four *trans* olefinic bonds and the structure geranylfarnesol (**3**) was proposed.



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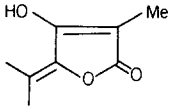
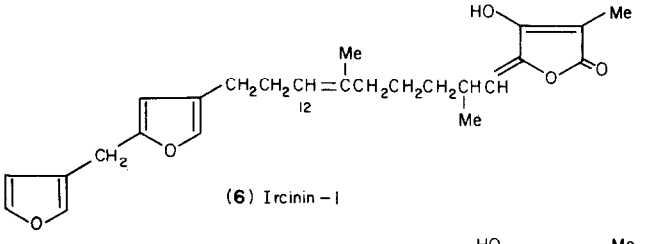
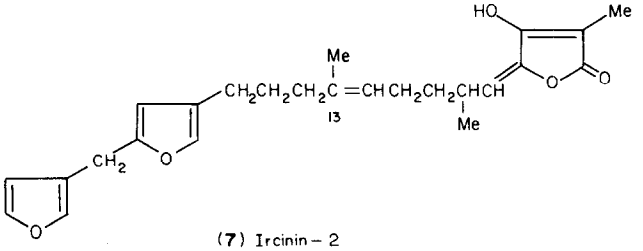


(5)

A number of more elaborate linear sesterterpenes have recently been isolated from marine sponges of the family Porifera. From the sponge *Ircinia oros*, Fattorusso *et al.* isolated[7] two compounds which they called ircinin-1 and ircinin-2 as an inseparable mixture. The MS indicated a molecular formula of $C_{25}H_{30}O_5$ and spectral evidence suggested the presence of an enol and an α, β-unsaturated α-lactone (1635 and 1735 cm^{-1}). The NMR spectrum indicated the presence of two furan rings linked by a single methylene group located at the β-position of a monosubstituted furan. This system must be at one end of the molecule and by the isoprene rule[1] it was suggested that group **4** was present. Double resonance experiments indicated the presence in the molecule of the group $-CH_2-CH(Me)-CH=C<$.



(6) Ircinin – 1

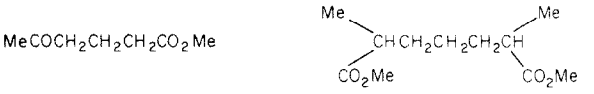


(7) Ircinin – 2

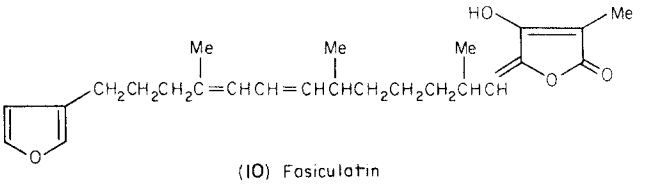
Evidence was also obtained that a tetronic acid group of the type **5** was present as the other terminal unit, for partial reduction gave a tetrahydroderivative which upon methylation gave *two* methyl enol ethers as expected for a 4-oxo-α-lactone. Further experiments, however, showed that a mixture of compounds was in fact present. Oxidative ozonolysis gave malonic, succinic, 2-methyl-6-oxoheptanoic, 5-oxohexanoic and 2-methyl glutaric

[6] Rios, T. and Perez, C. S. (1969) *Chem. Commun.* 214.
[7] Cimino, G., De Stefano, S., Minale, L. and Fattorusso, E. (1972) *Tetrahedron* **28**, 333.

acids, thereby defining the positions of the olefinic bonds in the parent molecules. In addition hydrogenation gave a single dodecahydroderivative containing a new methyl doublet in place of two signals at 1·55 and 1·66 ppm (total 3H). This, and extensive spectroscopic evidence of hydrogenated, acetylated and methylated derivatives, as well as biogenetic reasoning, indicated structures **6** and **7** for ircinin-1 and ircinin-2 respectively, no stereochemistry being assigned to the isolated double bonds in each compound.



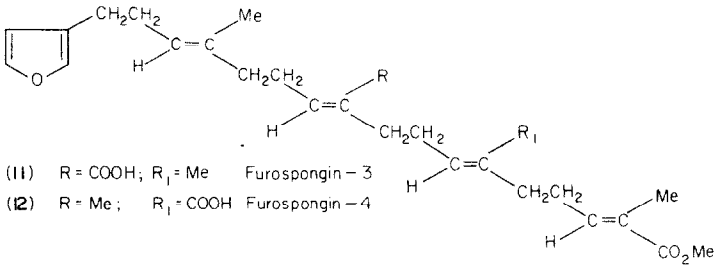
(8) (9)



(10) Fasiculatin

A compound isolated from *Ircinia fasciculata*,[8] fasciculatin ($C_{25}H_{34}O_4$), was found to be closely related to **6** and **7.** Again a tetronic acid group was suggested both by spectral evidence and chemical reaction but only a single mono-β-substituted furan ring was observed in the NMR and MS. Double resonance experiments again indicated a $-CH(Me)CH{=}C\lessdot$ moiety as part of a *trans* diene system. Ozonolysis of fasciculatin followed by oxidation and esterification gave methyl 5-oxohexanoate (**8**) and methyl 2,6-dimethyl pimelate (**9**). The structure of fasciculatin is therefore represented by **10.**

From the acetone extract of the marine sponge *Spongia officinalis*, the Italian group isolated a colourless oil, $C_{26}H_{36}O_5$. Although homogeneous by TLC, a mixture of isomers (furospongin-3 and -4) was present which, like ircinin-1 and -2, could not be separated.[9]



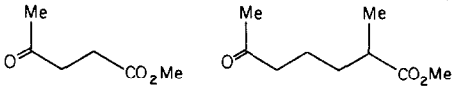
(11) R = COOH; R_1 = Me Furospongin – 3
(12) R = Me; R_1 = COOH Furospongin – 4

Again a β-substituted furan moiety was observed as well as an α,β-unsaturated carboxylic acid and a methyl ester. Examination of the NMR spectrum indicated that olefinic hydrogens were *trans* to the former and *cis* to the latter. The presence of two additional olefinic protons and appropriate methyl groups indicated that another linear sesterterpene was

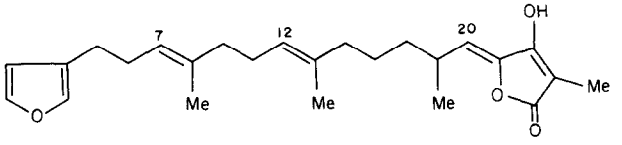
[8] CAFIERI, F., FATTORUSSO, E., SANTACROCE, C. and MINALE, L. (1972) *Tetrahedron* **28**, 1579.
[9] CIMINO, G., DE STEFANO, S. and MINALE, L. (1972) *Tetrahedron* **28**, 5983.

present. The positions of the olefinic bonds and the relationship of the carboxylic acid and methyl ester groups along the chain was determined from the MS. In both isomers there was an initial loss of $-CH_2-CH=C(Me)CO_2Me$, but in one case an isoprene unit was subsequently lost whereas in the other case a carboxy-isoprene unit was removed from the chain. Furospongin-3 and -4 were therefore shown to be **11** and **12** respectively.

A further compound in this interesting series, variabilin, was recently isolated in 0·2% yield from *Ircinia variabilis*.[10] Isomeric with fasciculatin (**10**), it differed only in that two vinyl methyl signals were observed in the NMR spectrum, together with a broad two-proton multiplet in the olefinic region. Once again placement of the double bonds was made possible after product analysis. In this case dimethylsuccinate, methyl levulinate (**13**) and methyl 2-methyl-6-oxoheptanoate (**14**) were obtained after esterification. The olefinic bonds are therefore located at positions 7 and 12, their stereochemistry being unknown but probably *trans*. Variabilin therefore probably has the structure **15.**



(13) (14)



(15) Variabilin

It should be noted that in ircinin-1 (**6**), ircinin-2 (**7**), fasciculatin (**10**) and variabilin (**15**) the stereochemistry at C-20 is not known. The linear furano sesterterpenoids isolated appear to be related to a series of C_{21}-furanoterpene derivatives isolated from other members of the Porifera, e.g. from *Spongia* spp.[9,11–13] and *Hippospongia communis*.[12,13] No precursor relationships have been established.

Sesterterpenes of the Ophiobolane type.[14]

This is the largest group of sesterterpene structure types known, there being some 11 examples, all based on the 5-8-5 ring system (e.g. **16**).

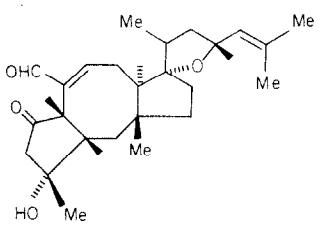
Ophiobolin (cochliobolin) was the first compound of this series,[15] to be isolated although the structure was not determined for some eight years.[16] It is a white crystalline substance m.p. 180–2°, soluble in organic solvents and was claimed to exhibit a UV max at 248 nm.[14] The compound was first obtained from the fungus responsible for the helmin-

[10] FAULKNER, D. J. (1973) *Tetrahedron Letters* 3821.
[11] FATTORUSSO, E., MINALE, L., SODANO, G. and TRIVELLONE, E. (1971) *Tetrahedron* **27**, 3909.
[12] CIMINO, G., DE STEFANO, S., MINALE, L. and FATTORUSSO, E. (1971) *Tetrahedron* **27**, 4673.
[13] CIMINO, G., DE STEFANO, S., MINALE, L. and FATTORUSSO, E. (1972) *Tetrahedron* **28**, 267.
[14] TSUDA, K., NOZOE, S., MORISAKI, M., HIRAI, K., ITAI, A., OKUDA, S., CANONICA, L., FIECCHI, A., GALLI KIENLE, M. and SCALA, A. (1967) *Tetrahedron Letters* 3369.
[15] ORSENIGO, M. (1957) *Phytopathol. Z.* **29**, 189.
[16] NOZOE, S., MORISAKI, M., TSUDA, K., IITAKA, Y., TAKAHASHI, N., TAMURA, S., ISHIBASHI, K. and SHIRASAKA, M. (1965) *J. Am. Chem. Soc.* **87**, 4968.

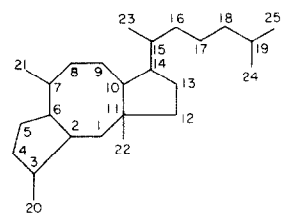
TABLE 2. NMR SPECTRUM OF OPHIOBOLIN *A*

Chemical shift (ppm)	Number of protons	Multiplicity, coupling constant (Hz)	Assignment
0·82	3	*s*	
1·08	3	*d*, *J* 6·5	
1·34	3	*s*	
1·70	6	*s*	
2·77	2	AB *q*, *J* 20	$-CH_2-CO-$
3·20	1	*d*, *J* 11	$-\overline{CH}-CO-$
4·43	1	*q*, *J* 8	$-\overline{CH}-C<\!\!-O-$
5·15	1	*d*, *J* 8	$-\overline{CH}=C<$
7·13	1	*t*, *J* 8	α,β-unsaturated
9·26	1	*s*	aldehyde system

thosporium leaf spot disease of rice, *Helminthosporium oryzae*.[15] The same compound was later obtained from the phytopathogenic fungi, *Cochliobolus miyabeanus*,[17,18] *Helminthosporium tuscicum*,[19] *C. heterostrophus*,[20] *H. leersi*,[20] *H. panici-miliacei*[20] and *H. zizaniae*.[20] The original molecular formula $C_{24}H_{32}O_4$[18] was later changed to $C_{25}H_{36}O_4$[17] when the mass spectrum was obtained, and the UV spectrum was later[17] amended to a maximum at 238 nm. The IR spectrum indicated the presence of hydroxyl, 5-membered ketone and α,β-unsaturated carbonyl moieties. Although the NMR spectrum (Table 2) defined many of the aspects of the molecule, a single structure could not be deduced.[16]



(16) Ophiobolin – *A* (ophiobolin, cochliobolin or cochliobolin *A*)



(17) Numbering of ophiobolanes

X-Ray crystallographic analysis[16] of the bromomethoxy derivative gave the structure **16** for ophiobolin (the numbering of this skeleton is shown in **17**). The NMR features[16] indicated in Table 2 are clearly discernible in this structure.

Ophiobolin *A*, as the compound is now called, was thus the first C_{25} isoprenoid derivative whose structure was determined, a notable achievement since it has led to the structure elucidation of a variety of closely related C_{25}-derivatives.

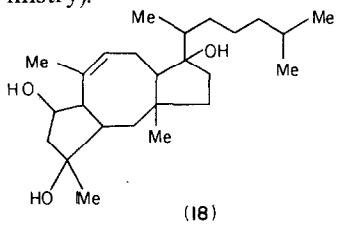
At about this time Canonica *et al.*[14] published their work on the structure of cochliobolin from *Helminthosporium oryzae*. A series of fascinating chemical transformations too extensive to describe here brought them to two alternative formulae from which, on mass

[17] NEELAMEGHAN, A. (1959) *Hindustan Antibiot.* **2**, 13.
[18] NAKAMURA, M. and ISHIBASHI, K. (1958) *J. Agr. Chem. Soc. Japan* **32**, 739.
[19] ISHIBASHI, K. (1961) *J. Agr. Chem. Soc. Japan* **35**, 323.
[20] ISHIBASHI, K. (1962) *J. Agr. Chem. Soc. Japan* **36**, 226.

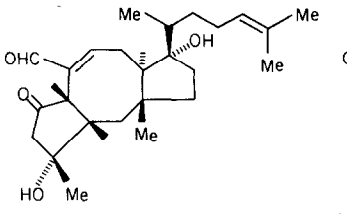
spectral evidence, one structure was deduced, identical with that for ophiobolin *A*.[21] Indeed, the physical constants of the two compounds were essentially identical.

In 1960 Ohkawa and Tamura isolated from *Cochliobolus miyabeanus* two compounds ophiobolosin *A* and ophiobolosin *B*.[22] Analytical and spectral data on these compounds[23] indicated that the former compound was identical with zizanin, a compound previously obtained by Ishibashi from *Helminthosporium zizaniae*.[24] Ophiobolosin *B* may not belong to the sesterterpenoid group since definitive data are lacking.

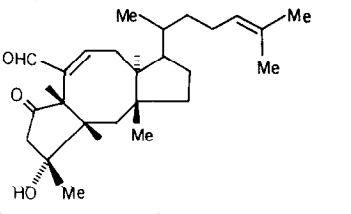
From young cultures of *Helminthosporium oryzae*, Canonica *et al.*[25] isolated a compound which they called cochliobolin *B*. The compound differed from cochliobolin *A* (ophiobolin *A*) (**16**) in that it contained a tertiary hydroxyl group at C-14 instead of the oxygen bridge between C-14 and C-17 (previously characterized by a peak at *m/e* 165 in the MS of these compounds). The UV spectrum was essentially identical with that of **16**, but the NMR spectrum exhibited the expected differences. In particular, there was a shift in the C-23 methyl group absorption from 1·12 ppm in **16** to 0·84 ppm in cochliobolin *B* and the absence of a multiplet at 4·45 ppm due to the C-17 proton in **16**. The C-16 vinylic proton in **16** was also less complex than in cochliobolin *B*. The two compounds, **16** and cocholiobolin *B*, were interrelated by successive $LiAlH_4$ and H_2/Pd–C reductions of each compound to afford **18**. Cochliobolin *B* therefore has the structure **19** (without stereochemistry).



(18)



(19) Ophiobolin *B* (or Cochliobolin *B* or Zizanin *B*)



(20) Ophiobolin *C* or Zizanin *A*

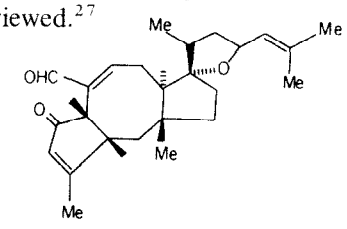
Independently, Nozoe *et al.*[26] at the same time published their results on two of the three additional compounds they had isolated from the cultured broths of *Helminthosporium zizaniae* and *Ophiobolus heterostrophus*.[16] The spectral data of zizanin *B*, m.p. 173°, ($C_{25}H_{38}O_4$) indicated a close similarity with ophiobolin *A* (**16**), but that an additional hydroxyl group was present in place of the tetrahydrofuran ring. Reduction ($LiAlH_4$) of ophiobolin *A* (**16**) gave a separable mixture of triols one of which upon treatment with Li–liq. NH_3 afforded a tetraol, CrO_3–pyridine oxidation of which gave zizanin *B*. The latter therefore has the structure **20**.

The gross structure of this compound is identical with that obtained by Canonica *et al.*[25] for cochliobolin *B* (**19**) and the close correspondance of the physical properties of these two compounds with ophiobolosin *A*[22,23] and zizanin[24] indicate that they are probably all identical. The name ophiobolin *B* has been proposed for this compound (**19**).[14]

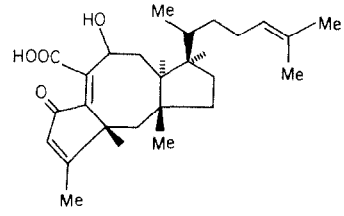
The second compound obtained by Nozoe *et al.*,[26] zizanin-*A*, also showed a similar UV spectrum to **16** and **20**. The NMR spectrum was almost identical to that of ophiobolin

[21] Canonica, L., Fiecchi, A., Galli Kienle, M. and Scala, A. (1966) *Tetrahedron Letters* 1211.
[22] Ohkawa, H. and Tamura, T. (1960) 25th Meeting of the Central Branch of Agricultural and Chemical Society of Japan, Nagoya, Japan.
[23] Ohkawa, H. and Tamura, T. (1966) *Agr. Biol. Chem. (Tokyo)* **30**, 285.
[24] Ishibashi, K. (1962) *J. Antibiot. (Tokyo)*, **A 15**, 88.
[25] Canonica, L., Fiecchi, A., Galli Kienle, M. and Scala, A. (1966) *Tetrahedron Letters* 1329.
[26] Nozoe, S., Hirai, K. and Tsuda, K. (1966) *Tetrahedron Letters* 2211.

B except for a slight shift to higher field for the secondary methyl group. The MS indicated that zizanin-*A* was missing an oxygen function compared to **20.** This evidence and a number of chemical transformations indicated that zizanin-*A* has the structure **20.** The preferred name is now ophiobolin *C*.[14] Some of the work on ophiobolins *A*, *B* and *C* has been reviewed.[27]



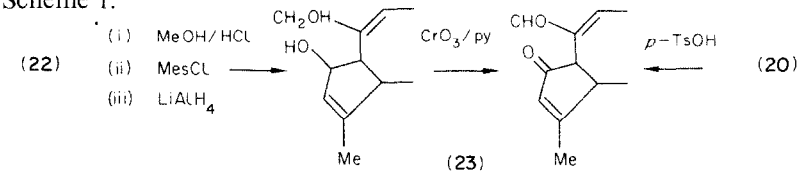
(21) Anhydroophiobolin *A*



(22) Ophiobolin *D*

The third compound obtained[16] was proved to be anhydroophiobolin *A* (**22**),[26] but no further details are available. The same compound was obtained as a degradation product by Canonica.[21]

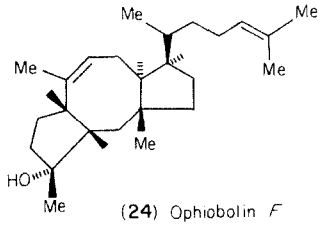
A further example of this structure type was isolated by Nozoe *et al.*[28] from *Cephalosporium caerulens*. Cephalonic acid was obtained by ethyl acetate extraction of the culture broth at pH 3, followed by silica gel chromatography. X-ray crystallographic analysis of the bromoacetyl derivative of methyl cephalonate indicated a structure (**22**) for the parent compound. The name ophiobolin *D* has been suggested for this compound.[14] The structures of **20** and **22** were confirmed by chemical correlation with anhydroophiobolin *C* (**23**) as shown in Scheme 1.[29]



(23)

SCHEME 1. CORRELATION OF OPHIOBOLIN *C* (**20**) AND *D* (**22**).

A less complex ophiobolin derivative is ophiobolin *F* ($C_{25}H_{42}O$) obtained by Nozoe *et al.*, from *Cochliobolus heterostrophus*. Catalytic hydrogenation afforded a tetrahydroderivative ($C_{25}H_{46}O$) confirming the presence of three rings. Six C-methyl groups were observed in the NMR spectrum of the parent compound and two vinylic protons. This evidence, together with MS data and biosynthetic considerations, suggested structure **24** for this compound.

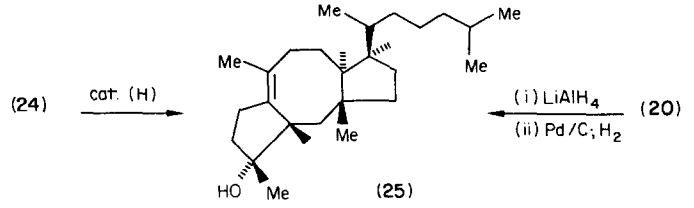


(24) Ophiobolin *F*

Chemical confirmation of this structure came from correlation with ophiobolin *C* (**20**)[30] through the common reduction product (**25**) as shown in Scheme 2.

[27] FIECCHI, A. (1968) *Corsi Semin. Chim.* **11**, 57; *Chem. Abstr.* **72**, 21795q.
[28] ITAI, A., NOZOE, S., TSUDA, K., OKUDA, S., IITAKA, Y. and NAKAYAMA, Y. (1967) *Tetrahedron Letters* 4111.
[29] NOZOE, S., ITAI, A., TSUDA, K. and OKUDA, S. (1967) *Tetrahedron Letters* 4113.
[30] NOZOE, S. and MORISAKI, M. (1969) *Chem. Commun.* 1319.

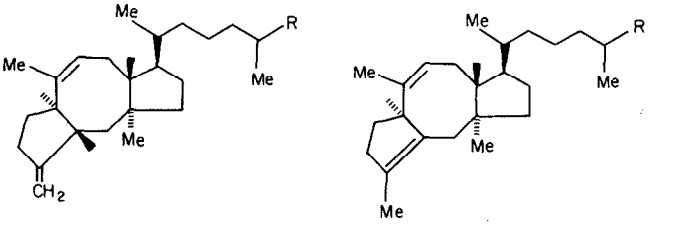
A number of ophiobolane derivatives have been isolated from the wax of the insect *Ceroplastes albolineatus* which infest the shrub *Senecio praecox*. Silica-gel chromatography of the unsaponifiable lipid portion of the wax of the female insects, followed by derivatization gave three 3,5-dinitro-benzoate derivatives.[31] Saponification afforded two compounds ceroplastol I and ceroplastol II having the molecular formula $C_{25}H_{40}O$.



SCHEME 2. CONFIRMATION OF STRUCTURE OF OPHIOBOLIN *F* (**24**).

Ceroplastol I was shown, by hydrogenation, to contain three olefinic bonds and by ozonolysis two of these were placed in terminal methylene and $-CH{=}C(Me)CH_2OH$ functions, the third contained a vinylic function. Chromium trioxide–pyridine oxidation confirmed the presence of an allylic alcohol. Because of the similarities of the IR and NMR spectra of ceroplastols I and II, they were thought to be structural isomers.[31]

In 1968 Iitaka *et al.*, isolated from *C. albolineatus* the carboxylic acid corresponding to ceroplastol I, ceroplasteric acid.[32] The structural relationship was confirmed by hydride reduction of ceroplasteric acid. Repetition of the degradative work confirmed the previous results and dehydrogenation indicated the absence of 6-membered rings, although the molecule was tricyclic. X-ray crystallographic analysis of the 4-bromo-benzoate derivative of ceroplastol I afforded the structure and absolute configuration of **26** for ceroplastol **1** and **27** for ceroplasteric acid.



(**26**) Ceroplastol *I* R = CH_2OH (**28**) Ceroplastol *II* R = CH_2OH

(**27**) Ceroplasteric acid R = COOH (**29**) Albolic acid R = COOH

The structure of ceroplastol II was then deduced[33] by chemical correlation with ceroplastol I. Acetylation of ceroplastol I with acetic anhydride/pyridine, isomerization with *p*-toluene sulphonic acid and hydrolysis afforded ceroplastol II. The latter thus contains a $\Delta^{2,3}$-olefinic linkage rather than one at $\Delta^{3,20}$ and has the structure (**28**).

Ceroplasteric acid (**27**) was re-isolated from *C. albolineatus* together with a new sesterterpenic acid, albolic acid.[34] Isomerization of ceroplasteric acid methyl ester with *p*-toluene sulphonic acid afforded a compound identical with albolic acid methyl ester. Albolic acid therefore has the structure **29.**

[31] RIOS, T. and COLUNGA, F. (1965) *Chem. Ind.* (*Lond.*) 1184.
[32] IITAKA, Y., WATANABE, I., HARRISON, I. T. and HARRISON, S. (1968) *J. Am. Chem. Soc.* **90**, 1092.
[33] RIOS, T. and QUIJANO, L. (1969) *Tetrahedron Letters* 1317.
[34] RIOS, T. and GOMEZ, G. F. (1969) *Tetrahedron Letters* 2929.

The NMR spectra of ceroplastol I (**26**), ceroplasteric acid (**27**), ceroplastol II (**28**) and albolic acid (**29**) confirm the structural assignments (Table 3).

It should be noted that the *A/B* and *B/C* ring junctions are both *trans* in this series but *cis/trans* in the ophiobolane series. In addition the absolute configurations at C_6,C_{10} and C_{11} in this series are opposite to the corresponding ones in the ophiobolane series. The significance of these observations remains to be determined.

TABLE 3. NMR SPECTRA OF CEROPLASTERIC ACID DERIVATIVES

(ppm)	Multiplicity* coupling constant (Hz)	Assignment	(ppm)	Multiplicity, coupling constant (Hz)	Assignment
	Ceroplastol I (**26**)			Ceroplasteric acid (**27**)	
			0·80	*d*, *J* 6·5	C-15 Me
			0·90	*s*	C-11 Me
			1·63	*s*	C-7 CH
			1·84	*s*	C-19 Me
4·83		C-3 CH_2	4·88	*d*, *J* 8	C-3 CH_2
5·50	*m*	C-8 CH and	5·52	*t*, *J* 8	C-8 CH
		C-18 CH	6·92	*t*, *J* 8	C-18 CH
	Ceroplastol II (**28**)			Albolic acid (**29**)	
0·70	*s*	C-11 Me	0·70	*s*	C-11 Me
0·79	*d*, *J* 6·5	C-15 Me	0·80	*d*, *J* 6·5	C-15 Me
1·55	*s*	C-7 Me	1·60	*s*	C-8 Me
1·65	*s*	C-3 Me	1·66	*s*	C-3 Me
3·65	*b*	C-6 CH	1·86	*s*	C-19 Me
3·86	*s*	C-25 CH_2	3·65	*b*	C-6 CH
5·30	*m*	C-8 CH and	5·41	*t*, *J* 8	C-8 CH
		C-18 CH	6·86	*t*, *J* 8	C-18 CH

* *s*—Singlet; *d*—doublet; *t*—triplet; *b*—broad singlet; *m*—multiplet.

From a petroleum ether extract of the lip fern, *Cheilanthes farinosa*, a compound cheilarinosin ($C_{25}H_{42}O_2$) was obtained.[35] The IR spectrum indicated the presence of hydroxyl, terminal methylene and trisubstituted olefin linkages. Hydrogenation afforded a monoacetate which still contained a tertiary hydroxyl group. That the acetylatable hydroxyl group was secondary was shown by the NMR spectrum of the acetate derivative and its oxidation to a ketone. MS evidence indicated that the hydroxyl group was located at C-17. Comparison with the NMR spectra of the ophiobolane derivatives indicated an overall similarity. The locations of the remaining functional groups with the appropriate methyl group was confirmed by dehydration of the acetylated tetrahydroderivative. Ozonolysis afforded a ketone which, by its IR absorption was not 5-membered so that the initial hydroxyl group in cheilarinosin was located at either C-7 or C-15. That the former was correct was proved by Oppenhauer oxidation which afforded an α,β-unsaturated ketone so that the vinylic group was located at C-15, 23. The gross structure **30** was thus proposed for cheilarinosin, no stereochemical assignments being possible.

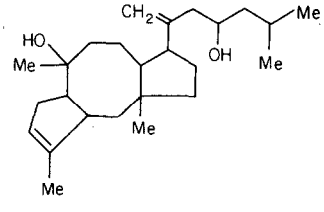
Sesterterpenes of the cheilanthatriol type

A second compound from *Cheilanthes farinosa*, cheilanthatriol, was also obtained from the petroleum ether extract.[36] The compound furnished a monoacetate and a diacetate

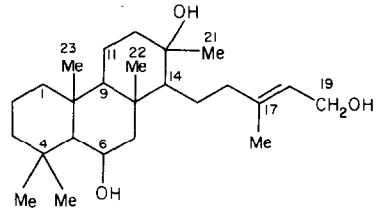
[35] THANU IYER, R., AYENGAR, K. N. N. and RANGASWAMI, S. (1972) *Ind. J. Chem.* **10**, 482.
[36] KHAN, H., ZAMAN, A., CHETTY, G. L., GUPTA, A. S. and DEV, S. (1971) *Tetrahedron Letters* 4443.

indicating the presence of two types of acetylatable alcohol function. Manganese dioxide oxidation gave an α,β-unsaturated aldehyde; an allylic primary hydroxyl group was therefore present in the parent compound. The remaining oxygen function indicated by the molecular formula ($C_{25}H_{44}O_3$) was found to be a tertiary hydroxyl group from the IR and NMR spectra of the diacetate derivative.

Only one olefinic proton was observed in the NMR spectrum of the parent compound and this was suggested to be part of the allylic alcohol. On catalytic hydrogenation cheilanthatriol consumed two equivalents of hydrogen to give a saturated diol with loss of the primary hydroxyl group. Cheilanthatriol is therefore tricarbocyclic. Biogenetic considerations and the dissimilarity to the ophiobolane type suggested a perhydrophenanthrene skeleton which was confirmed by Se dehydrogenation to give 1,7,8-trimethylphenanthrene as the major product. This evidence, together with a study of the mass spectrum, indicated a partial structure leaving only one secondary hydroxyl group to be placed on a ring.

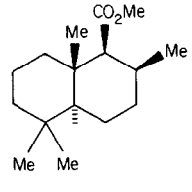


(30) Cheilanosin

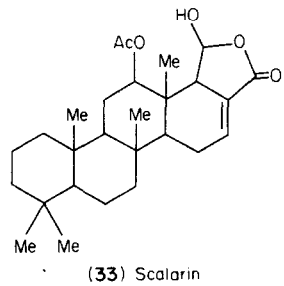


(31) Cheilanthatriol

NMR data indicated that this OH group was surrounded by *three* protons. Only two positions are therefore possible, namely C-6 and C-11. Oxidation of the saturated diol gave a ketoalcohol which was stable in alkali. The secondary hydroxyl group can only be located at C-6 and the gross structure of cheilanthatriol is therefore **31**.



(32)



(33) Scalarin

From the ether-soluble fraction of the marine sponge *Cacospongia scalaris*, a white crystalline compound, scalarin, was obtained.[37] IR and NMR spectroscopy indicated the presence of a secondary acetate and UV and NMR data supported a 5-membered lactol moiety with an exocyclic double bond. A series of chemical reactions afforded a saturated ketolactone which exchanged three hydrogens confirming the presence of the secondary acetoxy group adjacent to a methylene group. Extensive degradation eventually afforded **32**, identified by comparison with an authentic sample. On the basis of this and mass and NMR spectral evidence the structure (**33**) was suggested for scalarin.

[37] FATTORUSSO, E., MAGNO, S., SANTACROCE, C. and SICA, D. (1972) *Tetrahedron* **28**, 5993.

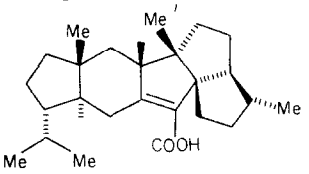
Sesterterpenes of the retigeranic acid type

Shibata *et al.*[38] isolated from the lichens *Lobaria retigera*, *L. subretigera* and *L. isidiosa* var. *subisidiosa* a compound whose physical properties resembled those of a compound obtained previously by Seshadri *et al.* from *Lobaria* spp.,[39] *L. retigera*[40] and *L. subretigera*[41] which they had called retigeranic acid.[41]

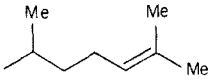
Spectral data indicated a molecular formula $C_{25}H_{38}O_2$,[38] the presence of five C-methyl groups and an α,β-unsaturated carboxyl group.[38,40] The *p*-bromo-anilide of retigeranic acid was subjected to X-ray crystallographic analysis which indicated the novel pentacyclic structure **34** for retigeranic acid.[38]

Sesterterpenes of the gascardic acid type

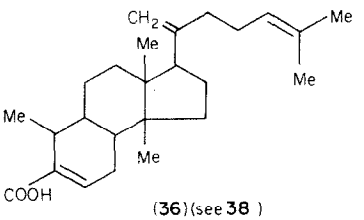
Only one example of this structure type is known, namely gascardic acid, isolated from secretions of the insect *Gascardia madagascariensis*.[42] Elegant and extensive degradative work by Arigoni's group in Zurich[43,44] succeeded in elucidating the correct structure of this molecule, including absolute stereochemistry, and showed it to be another novel sesterterpene skeleton.



(34) Retigeranic acid



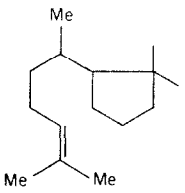
(35)



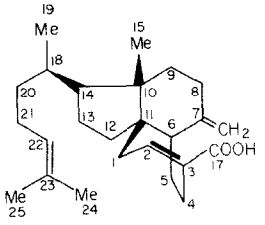
(36) (see 38)

Early work[42] had shown the presence of an α,β-unsaturated carboxylic acid and a geminal olefin. Three olefinic bonds were found and the molecular formula of the hexahydro derivative indicated it to be tricyclic. Modified Kuhn Roth oxidation indicated a side chain **35** and a structure **36** was proposed, based on the oxidation of the *A* ring of an assumed triterpenoid precursor.

The NMR spectrum, however, supported a structure containing only two methyl groups attached to saturated carbon atoms so that further work was clearly required. Degradation[43,44] afforded a tricyclic 5-membered ketone which exchanged only two hydrogens and a partial structure **37** was proposed.



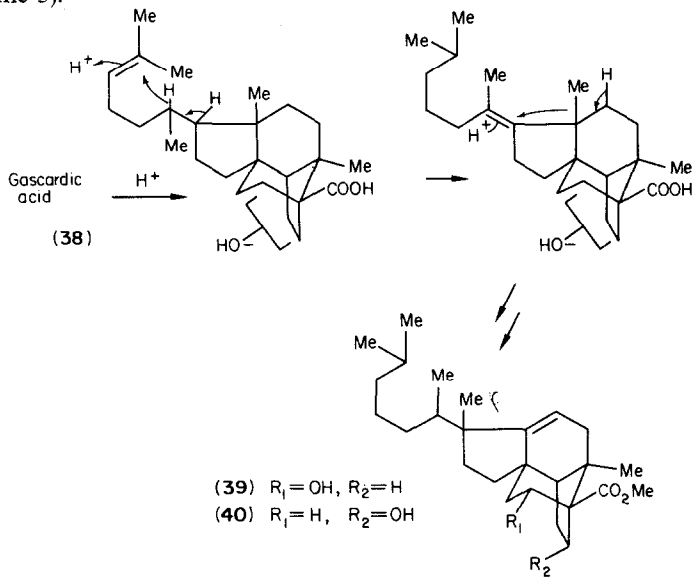
(37)



(38) Gascardic acid

[38] KANEDA, M., TAKAHASHI, R., IITAKA, Y. and SHIBATA, S. (1972) *Tetrahedron Letters* 4609.
[39] AGARWAL, S. C., AGHORAMURTY, K., SARMA, K. G. and SESHADRI, T. R. (1961) *J. Sci. Ind. Res.* **20B**, 613.
[40] RAO, P. S., SARMA, K. G. and SESHADRI, T. R. (1965) *Current Sci.* **34**, 9.
[41] RAO, P. S., SARMA, K. G. and SESHADRI, T. R. (1966) *Current Sci.* **35**, 147.
[42] BROCHERE, G. and POLONSKY, J. (1960) *Bull. Soc. Chim. France* 963.
[43] SCARTAZZINI, R. (1966) Ph.D. Thesis, ETH Zurich. Diss. Nr. 3899.
[44] SCARTAZZINI, R., WOLF, G., SETTIMI, G. and ARIGONI, D. (1966) Unpublished results.

Oxidative degradation to remove the carboxyl group gave a tricyclic ketone in which the functional group was located in a 7-membered ring and exchanged four hydrogens. Oxidative reactions in the ring containing the geminal olefin, and combination of the above results gave a formula **38** for gascardic acid, with α,β-unsaturated acid located at either Δ^2 or Δ^3. Treatment of gascardic acid with a mixture of acetic acid, formic acid and conc H_2SO_4, followed by treatment with diazomethane gave a β-hydroxyester containing a single olefinic bond. The latter was not, however, located at Δ^{22} as expected but at $\Delta^{9,10}$. An elaborate 1,5-hydride shift and subsequent methyl group migration from C-10 to C-14 was suggested. The expected closure of the α,β-unsaturated acid and the geminal olefin was observed. The product was therefore either **39** or **40**, produced by the mechanism shown (Scheme 3).



SCHEME 3. CONFIRMATION OF POSITION OF DOUBLE BOND (Δ^2 OR Δ^3) IN GASCARDIC ACID (**38**).

Epimerization of the hydroxyl group by oxidation and reduction and subsequent cyclization with lead tetracetate gave a mixture of cyclopropyl ethers, indicating that the correct hydroxyester structure was **39**. Gascardic acid therefore has the structure **38**, including absolute configuration.

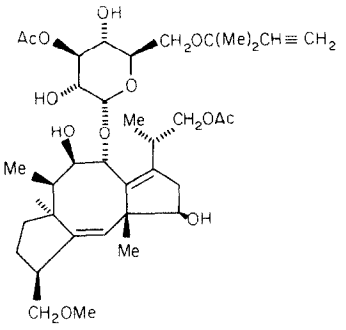
Other compounds related to sesterterpenes

Although this concludes the summary of the compounds isolated as sesterterpenoids, one other group of compounds should be mentioned at this point which may be related to the sesterterpenoids but for which additional evidence is lacking. This group of compounds is represented by fusicoccin A (**41**),[45] the toxin producing the wilting of almond trees (*Prunus amygdalus*) and isolated from the fungus *Fusicoccum amygdali*. The *A*, *B* and *C* rings of this compound bear a close structural and stereochemical resemblance to the corresponding rings in the ophiobolane series. The only difference being a change in the stereochemistry at C-6. However, **41** is only a diterpenoid-compound based on the central carbon skeleton. There are no other diterpenoid compounds with this carbon skeleton and

[45] BALLIO, A., CHAIN, E. B., DE LEO, P., ERLANGER, B. F., MAURI, M. and TONOLO, A. (1964) *Nature* **203**, 297.

one wonders if the isoprene unit attached at C-6 of the sugar unit were not once part of the main carbon skeleton.[2]

The isolation and physical properties of the sesterterpenoids are summarized in Table 4.



(41) Fusicoccin *A*

BIOGENESIS AND BIOSYNTHESIS OF THE SESTERTERPENES

The subtleties of terpenoid biosynthesis in plants and microorganisms are still being elucidated and appreciated. The discovery of the sesterterpenes has brought forth another area of possible experimentation and investigators quickly realised this. Indeed knowledge of the biosynthesis of the sesterterpenes is surprisingly advanced for such a rare group of compounds. Clearly, the fact that many of these compounds can be isolated from culture media has been of significant value. In the discussion which follows each skeletal type is considered individually.

Sesterterpenes of the linear type

The linear sesterterpenes have been considered to be derived from five isoprene units linked head-to-tail[6] or from a phytyl residue by addition of a *cis*-isoprene unit.[3] Surprisingly, no biosynthetic data are available, but circumstantial evidence suggests that the former proposal is more likely.

Sesterterpenes of the ophiobolane type

In 1965 a novel two-step cyclization of *trans, trans, cis*-geranylfarnesol pyrophosphate (**42**) was suggested[16] to lead to ophiobolin *A* (**16**) as shown in Scheme 4. The initial product of this cyclization, ophiobolin *F* (**24**), was later isolated,[5] but has not been examined as a precursor of ophiobolin *A* (**16**) or its congeners. It should be noted that geranylfarnesol (**2**) co-occurs with the ceroplastols **26** and **28** and their corresponding acids **27** and **29**.[6]

In 1966 Canonica *et al.*[46] reported the first biosynthetic experiments on sesterterpenoids. [2-^{14}C]-mevalonic acid was fed to growing *Cochliobolus miyabeanus*. After 3·5 days ophiobolin *B* (**19**) was isolated and after 6 days ophiobolin *A* (**16**) was obtained. Incorporations were 0·42 and 2·48% respectively. Degradation indicated the isoprenoid nature of the ring system and confirmed the labelling expected of the cyclization mechanism of Scheme 4. In addition, ophiobolin *B* (**19**) was efficiently (9·9%) incorporated into ophiobolin *A* (**16**), indicating that as with many secondary metabolites, oxidative ela-

[46] CANONICA, L., FIECCHI, A., GALLI KIENLE, M., RANZI, B. M. and SCALA, A. (1966) *Tetrahedron Letters* 3035.

TABLE 4. PHYSICAL PROPERTIES OF THE SESTERTERPENES

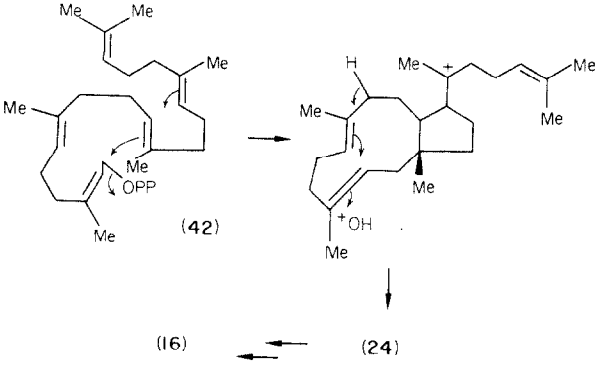
Compound (synonyms)	Isolation	Structure	Molecular formula	m.p.	IR (cm^{-1})	UV (nm)	Mass spec.	NMR
3,7,11,15,19-Pentamethyl -2-*cis*-6-*trans*-eicosadien -1-ol (**1**)	*Solanum tuberosum*[3]	(3)	$C_{25}H_{48}O$ (3)		3310, 1660 (3)		(3)	(3)
All-*trans*-geranyl farnesol (**2**)	*Cereoplastes albolineatus*[6]	(6)	$C_{25}H_{42}O$ (5)		3290, 828 (6)		(6)	(6)
All-*trans*-geranyl nerolidol (**3**)	*Cochliobolus heterostrophus*[5]	(5)	$C_{25}H_{42}O$ (5)		3600, 925 (5)		(5)	(5)
Ircinin-1 (**6**) and ircinin-2 (**7**)	*Ircinia oros*[7]	(7)	$C_{25}H_{30}O_5$ (7)		3150, 1735 (7)	260 (7)	(7)	(7)
Fasciculatin (**10**)	*Ircinia fasciculata*[8]	(8)	$C_{25}H_{34}O_4$ (8)		3600, 1720, 1625 (8)	232, 241 250, 268 (8)	(8)	(8)
Furospongin-3 (**11**) and furospongin-4 (**12**)	*Spongia officinalis*[9]	(9)	$C_{26}H_{36}O_5$ (9)		3500, 1710, 1685 (9)	220 (9)	(9)	(9)
Variabilin (**15**)	*Ircinia variabilis*[10]	(10)	$C_{25}H_{34}O_4$ (10)		1730, 1630, 880 (10)	255 (10)	(10)	(10)
Ophiobolin A[14]	*Cochliobolus*				3450, 1742, 1673	238		
Cochliobolin[15,21]	*Miyabeanus*[17,18]	(21)	$C_{25}H_{36}O_4$ (16)(21)	181–2° (17)(18)(19) (15)(20)(21)	(16)(18) (19)(21)	(15)(16) (18)(19) (20)(21)	(16)(21)	(16)(21)
Ophiobolin[16,17,18,19]	*Helminthosporium*							
Cochliobolin *A* (**16**)	*oryzae*[15,25]	X-ray (16)						
	H. turcicum[19]			(16)				
	H. leersii[20]							
	H. panici-miliacei[20]							
	H. zizaniae[20]							
	C. heterostrophus[20]							
Ophiobolin B[14] (**19**)	*H. zizaniae*[24,16,23,26]		$C_{25}H_{38}O_4$	173–5°	3500, 1745, 1675	239		
Zizanin[24,25] (**19**)	*H. oryzae*[25]	(25)	(16)(23)(25)	(16)(23) (24)	(16)	(16)(23)	(16)(23)	(16)(25)
Ophiobolosin A[22,23]	*C. miyabeanus*[23]	(26)	(26)	(25)(26)	(23)(25)	(24)(25)	(25)	
Zizanin B[16,26]	*C. heterostrophus*[16]							
Cochliobolin B[25]								
Ophioblin C (**20**)	*H. zizaniae*[16,26]	(26)	$C_{25}H_{38}O_3$	121°	3500, 1742, 1670	240		
Zizanin A[16,26]	*C. heterostrophus*[16]	(26)	(16)(26)	(16)(26)	(26)	(26)	(26)	(26)
Anhydroophiobolin A (**21**)	*H. zizaniae*[16]	(26)	$C_{25}H_{34}O_3$	135°	1695, 1675	232		
	C. heterostrophus[16]		(16)	(16)(21)	(21)	(21)	(21)	(21)
Ophiobolin D (**22**)	*C. caerulens*[28]	X-ray (28)	$C_{25}H_{36}O_4$	139°	1680, 1610	259		
Cephalonic acid[28,29]		(29)	(28)(29)	(28)(29)	(28)(29)	(28)(29)		(29)
Ophiobolin F (**24**)	*C. heterostrophus*[5]	(5)	$C_{25}H_{42}O$ (5)	80–1° (5)	3500 (5)		(5)	(5)
Ceroplastol I (**26**)	*Ceroplastes albolineatus*[31]	X-ray (32)	$C_{25}H_{40}O$ (31)		865 (31)		(31)	(31)
Ceroplasteric acid (**27**)	*C. albolineatus*[32]	(32)	$C_{25}H_{38}O_2$ (32)		874 (32)			(32)
Ceroplastol II (**28**)	*C. albolineatus*[31]	(33)	$C_{25}H_{40}O$ (31)		3350, 1670 (31)(33)			(33)
Albolic acid (**29**)	*C. albolineatus*[34]	(34)	$C_{25}H_{38}O_2$ (34)		1680, 925 (34)	(34)		(34)
Cheilarinosin (**30**)	*Cheilanthes farinosa*[35]	(35)	$C_{25}H_{42}O_2$ (35)	177° (35)	3425, 893 (35)		(35)	(35)
Cheilanthatriol (**31**)	*Cheilanthes farinosa*[36]	(36)	$C_{25}H_{44}O_3$ (36)	182–3° (36)	3450, 990 (36)		(36)	(36)
Scalarin (**33**)	*Cacospongia scalaris*[37]	(37)	$C_{27}H_{40}O_5$ (37)	133–5° (37)	3350, 1755, 1733 (37)	220 (37)	(37)	(37)
Retigeranic acid (**34**)	*Lobaria* spp.[39]			218–222	1667	242		
	L. retigera[40]	X-ray (38)	$C_{25}H_{38}O_2$	(38)(40)	(38)(40)	(38)(40)	(38)	(38)
	L. subretigera[38,41]		(38)	225–7°				
	L. isidiosa[38]			(39)				
Gascardic acid (**38**)	*Gascardia madagascariensis*[42,43]	(43)	$C_{25}H_{38}O_2$ (42)(43)	123–4° (42)(43)	1675, 888 (42)(43)	227 (42)(43)	(42)(43)	(42)(43)

boration takes place after cyclizations to the appropriate skeleton have taken place, rather than at some intermediate stage.

Nozoe[47] also studied the biosynthesis of this structure type in an effort to establish the origin of the two oxygen atoms in ophiobolin *A* (**16**). After incubation of *C. heterostrophus* in the presence of ^{18}O enriched oxygen, ophiobolin *A* (**16**) was isolated and converted to anhydroophiobolin *A* (**21**). The results demonstrated that the oxygen atom at C_{14} was de-

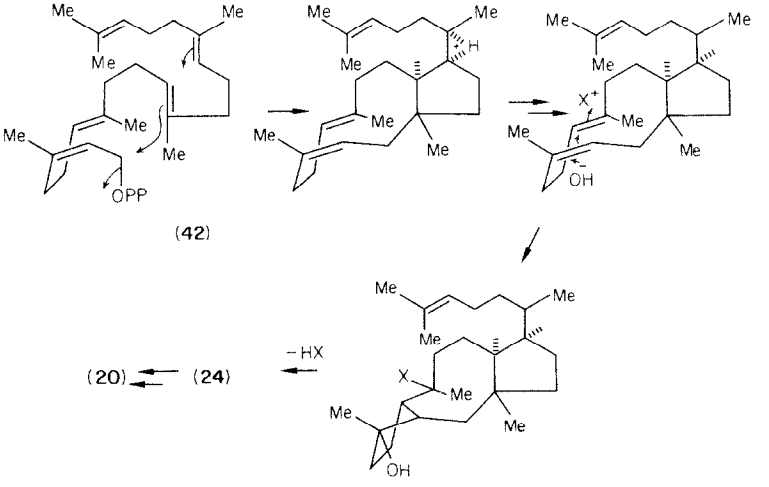
[47] NOZOE, S., MORISAKI, M., TSUDA, K. and OKUDA, S. (1967) *Tetrahedron Letters* 3505.

rived from atmospheric oxygen, whereas the hydroxyl group at C-3 was not derived from this source. Initiation of cyclization by hydroxylation at this position was therefore excluded. Identical results were obtained by Canonica's group.[48] In addition it was demonstrated that (**16**) was produced from ophiobolin *C* (**20**) probably via ophiobolin *B* (**19**).[47] Scheme 5 was proposed to explain the formation of ophiobolin *C* (**20**).



SCHEME 4. SUGGESTED BIOSYNTHESIS OF OPHIOBOLIN *A* (**16**) VIA OPHIOBOLIN *F* (**24**).

Additional information on the transfer of tritium from C-8 to C-15 was gained when [2-^{3}H]-2*S*- and 2*R*-mevalonic acids were separately added to cultures of *Cochliobolus miyabeanus*.[49] Ophiobolins *A* (**16**) and *B* (**19**) were isolated and degraded. In one case (from 2*S*-labelled mevalonate) tritium was not transfered, so that the 8β-hydrogen not involved. In the other case, (from 2*R*-labelled mevalonate), tritium *was* transfered and retained, indicating stereospecific transfer of the C-8 α-hydrogen to C-15 during biosynthesis.

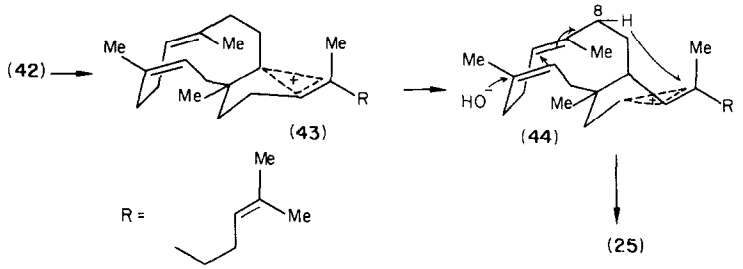


SCHEME 5. PROPOSED BIOSYNTHESIS OF OPHIOBOLIN *C* (**20**).

The nature of the labelling of ophiobolin *A* (**16**) and ophiobolin *B* (**19**) after feeding [2-^{3}H]-mevalonic acid lactone has also been examined.[48] Excellent and extensive degradation work indicated that nine tritium atoms were located as expected, two each on carbon

[48] CANONICA, L., FIECCHI, A., GALLI KIENLE, M., RANZI, B. M., SCALA, A., SALVATORI, T. and PELLA, E. (1967) *Tetrahedron Letters* 3371.
[49] CANONICA, L., FIECCHI, A., GALLI KIENLE, M., RANZI, B. M. and SCALA, A. (1967) *Tetrahedron Letters* 4657.

atoms 4, 12, 24, and/or 25 and 16, and one tritium on C-8. However, an additional tritium label was found unexpectedly at C-15* and it was speculated[48] that a transfer of hydrogen (tritium) from C-8 to C-15 occurred at some stage. On the basis of Scheme 6 a loss of tritium would be expected at C-8. Canonica therefore postulated[48] a non-classical ion 43 as the initial cyclization product. Rearrangement of **43** affords an ion **44** which undergoes nucleophilic attack at C-3 and hydride transfer from C-8 to C-15 to give **24.** In addition, it was found[48] that one tritium was lost from C-24 (25) during the biosynthesis of ophiobolin *A* (**16**) from ophiobolin *B* (**19**) and the mechanism shown in Scheme 7 was proposed for this process.



SCHEME 6. PROPOSED MECHANISM OF HYDROGEN TRANSFER IN THE BIOSYNTHESIS OF OPHIOBOLIN *A*.

Further work by the same groups[50,51] was aimed at studying the stereochemistry of hydrogen elimination at C-4 of mevalonate. As expected and corresponding to the biosynthesis of many terpenoid-derived compounds,[52–63] the 4*S*-proton was specifically lost in the biosynthesis of the linear sesterterpene chain. In a molecule such as ophiobolin *C* (**20**) therefore, five tritium atoms are present, whereas in ophiobolin *A* (**16**) and *B* (**19**), where no C-14 proton is present only four tritium atoms are observed. The tritium present in labelled ophiobolin *C* are at C_2, C_6, C_{10}, C_{14} and C_{18} (see **17**).

It was concluded that all-*trans*-geranylfarnesyl pyrophosphate (**3**) is the precursor of the ophiobolins.[50] However, the most facile cyclization of the acyclic precursor occurs with *trans, trans, cis*-geranylfarnesyl pyrophosphate (**42**) in order to avoid the formation of a *trans* double bond in the initially-formed 11-membered ring of **43**[48,49] Although isomerization can take place along this pathway (with possible loss of stereochemical integrity at C-3), Scheme 5 is favoured. The only modification suggested[50] is that the initial intermediate may be an enzyme-bound carbonium ion **45** which suffers nucleophilic attack at

* The importance of degrading a labelled secondary metabolite cannot be over-emphasized, too often regiospecificity in a labelled product is assumed, rather than demonstrated.

[50] CANONICA, L., FIECCHI, A., GALLI KIENLE, M., RANZI, B. M. and SCALA, A. (1968) *Tetrahedron Letters* 275.
[51] NOZOE, S., MORISAKI, M., OKUDA, S. and TSUDA, L. (1968) *Tetrahedron Letters* 2347.
[52] BATTERSBY, A. R., BYRNE, T. C., KAPIL, R. S., MARTIN, J. A., PAYNE, T. G., ARIGONI, D. and LOEW, P. (1968) *Chem. Commun.* 951.
[53] COSCIA, C. J., BOTTA, L. and GUARNACCIA, R. (1970) *Arch. Biochem. Biophys.* **136,** 498.
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[55] CORNFORTH, J. W. and POPJAK, G. (1966) *Biochem. J.* **101,** 553.
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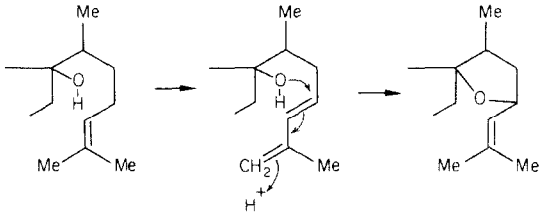
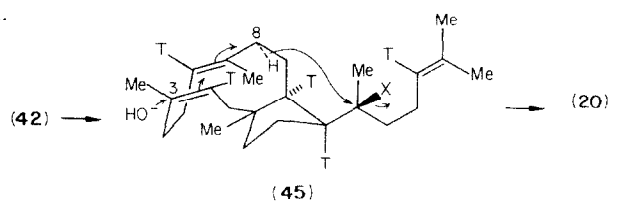
[57] ACHILLADELIS, B., ADAMS, P. M. and HANSON, J. R. (1970) *Chem. Commun.* 511.
[58] ACHILLADELIS, B. and HANSON, J. R. (1968) *Tetrahedron Letters* 4397.
[59] CORNFORTH, J. W., CORNFORTH, R. H., POPJAK, G. and YENGOYAN, L. (1966) *J. Biol. Chem.* **241,** 3970.
[60] NOZOE, S., MORISAKI, M. and MATSUMOTO, H. (1970) *Chem. Commun.* 926.
[61] CORNFORTH, J. W., CORNFORTH, R. H., DONNINGER, C. and POPJAK, G. (1966) *Proc. Roy. Soc. Ser. B* **163,** 492.
[62] RANDALL, P. J., REES, H. H. and GOODWIN, T. W. (1972) *Chem. Commun.* 1295.
[63] CORBELLA, A., GARIBOLDI, P. and JOMMI, G. (1972) *Chem. Commun.* 600.

C-3, ring closure of C-2 to C-6 and stereospecific hydride transfer from C-8α to C-15, with concomitant displacement of the enzyme (Scheme 8). A somewhat similar hydride transfer has been observed in the biosynthesis of the sesquiterpene alkaloid dendrobine[64] and the tricothecane derivatives helicobasidin and trichodermol.[65,66]



SCHEME 7. PROPOSED MECHANISM FOR LOSS OF HYDROGEN FROM C24(25) DURING BIOSYNTHESIS OF OPHIOBOLIN *B*.

Nozoe has more recently studied the biosynthesis of this structure-type using a cell-free system from *C. heterostrophus*.[30] Incubation with [2-^{14}C]-mevalonate for 3 hr at 37° produced ophiobolin *F* (**24**) containing an amazing 56% of the added radioactivity. [1,1-$^{3}H_2$]-All-*trans* geranylfarnesyl pyrophosphate (**3**) incorporated into **24** to the extent of 20% under the same conditions. [1,1-$^{3}H_2$]-All-*cis* geranylfarnesyl pyrophosphate and [1,1-$^{3}H_2$]-all-*trans* geranylfarnesol itself, were inactive. No degradative results were presented but this was the first incorporation of a linear C_{25} unit to a C_{25}-cyclized molecule. In a cell-free supernatant of *C. heterostrophus* after centrifugation at 105000 *g* Nozoe *et al.*[67] found enzyme activity capable of converting isopentenyl pyrophosphate and farnesyl pyrophosphate into ophiobolin *F* (**24**) with essentially no simultaneous sterol formation. The same supernatant converted geranylfarnesyl pyrophosphate (**42**) into ophiobolin *F* (**24**). The phosphorylating properties of the system were in the pellet rather than the supernatant after centrifugation, and hence the non-incorporation of all-*trans*-geranylfarnesol itself (**3**) may be explained.



SCHEME 8. PROPOSED INTERMEDIATES IN THE BIOSYNTHESIS OPHIOBOLIN *C* (SEE SCHEME 5).

Glycine has been shown to be a moderate but specific precursor of the monoterpene unit in a number of alkaloids[68-71] and of carotene.[72] Bose *et al.* have studied the biosynthetic utility of glycine as a precursor of ophiobolin *B* (**19**) in *Cochliobolus miyabeanus*.[73]

[64] CORBELLA, A., GARIBOLDI, P. and JOMMI, G. (1973) *Chem. Commun.* 729.
[65] ADAMS, P. M. and HANSON, J. R. (1971) *Chem. Commun.* 1414.
[66] ACHILLADELIS, B. A., ADAMS, P. M. and HANSON, J. R. (1972) *J. Chem. Soc. Perkin Trans. I* 1425.
[67] KAWAGUCHI, A., NOZOE, S. and OKUDA, S. (1973) *Biochim. Biophys. Acta.* **296**, 615.
[68] GARG, A. K. and GEAR, J. R. (1969) *Chem. Commun.* 1447.
[69] GARG, A. K. and GEAR, J. R. (1972) *Phytochemistry* **11**, 689.
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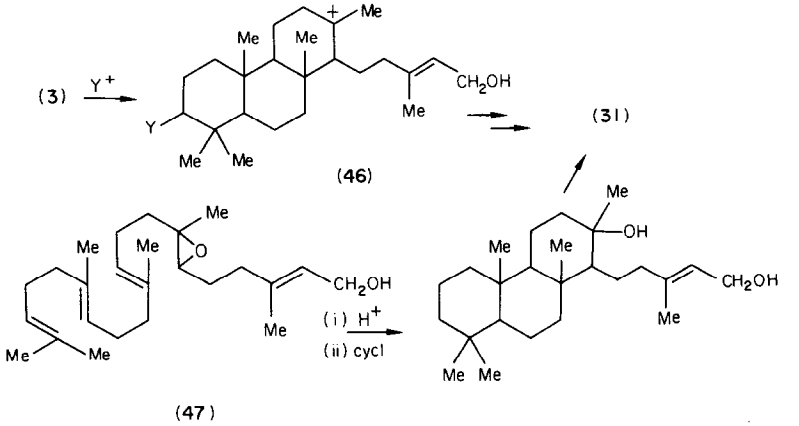
[71] MAREKOV, N., ARNANDOV, M. and POPOV, S. (1970) *Dokl. Bolg. Akad. Nauk.* **23**, 169.
[72] SHETTY, A. S. and MILLER, G. W. (1966) *Plant Physiol.* **41**, 415.
[73] BOSE, A. K., KHANCHANDANI, K. S. and HUNGUND, B. L. (1971) *Experientia* **27**, 1403.

Although [1-^{14}C]-glycine was poorly incorporated, [2-^{14}C]-glycine was specifically incorporated into ophiobolin *B* in a manner corresponding to labelling by [2-^{14}C]-acetate. [3-^{14}C]-Serine was also well incorporated, labelling being specific and corresponding to that expected from [1-^{14}C]-acetate. [1-^{14}C]-Serine was poorly utilized, but [^{14}C-methyl]-sarcosine and [2- and 3-^{14}C]-pyruvate efficiently labelled (**19**). The specificity was not, however, determined. The routes from amino acids to precursors of isoprene units have not been well investigated.

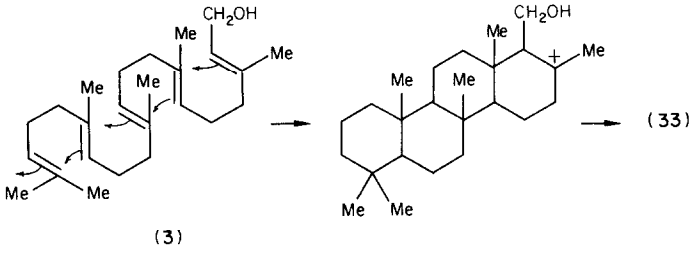


SCHEME 9. PROPOSED BIOSYNTHESIS OF CHEILANTHATRIOL.

Cheilanthatriol and scalarin

The biosynthesis of cheilanthatriol (**31**) is speculated[36] to take place from geranylfarnesol (**3**) by a standard steroid-type cyclization to give the cation **46** which picks up hydroxyl ion. An alternative cyclization may begin with the epoxy-geranylfarnesol derivative **47** which spontaneously cyclizes upon protonation.

No biosynthetic scheme has been proposed for scalarin (**33**), but is suggested here that formation of all four rings takes place in a concerted fashion from all-*trans*-geranylfarnesol (**3**). Oxidation then affords scalarin (Scheme 10).



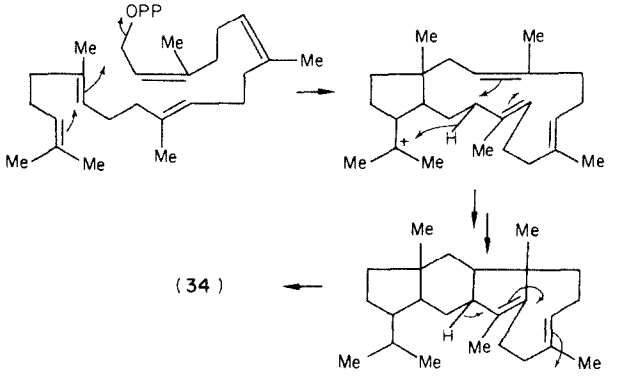
SCHEME 10. PROPOSED BIOSYNTHESIS OF SCALARIN.

Retigeranic and gascardic acids

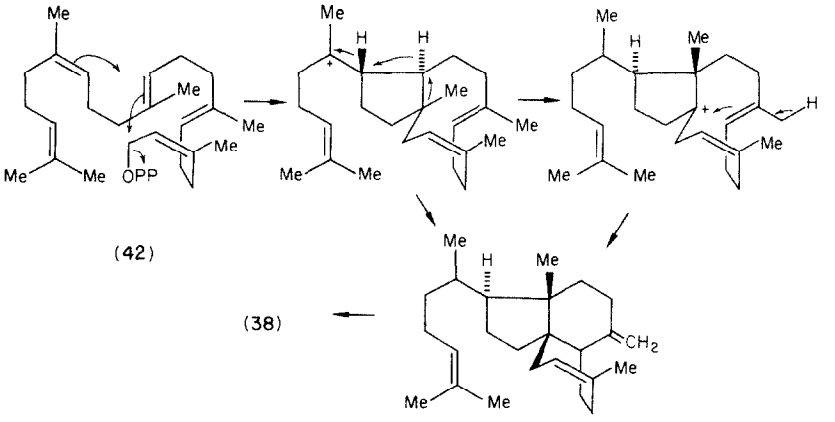
A very interesting scheme has been postulated[37] for the biosynthesis of the retigeranic acid (**34**) (Scheme 11), building each ring sequentially. The scheme has not been the subject of experimental work.

A further fascinating scheme was proposed[43] for gascardic acid (**38**) (Scheme 12), starting from *trans, trans, cis*-geranylfarnesyl pyrophosphate (**42**). The methyl group at C-10

of **38** is thought to arise by migration from C-11, possibly with a concerted loss of the C-16 proton. No experimental work has been reported.



SCHEME 11. PROPOSED BIOSYNTHESIS OF RETIGERANIC ACID.



SCHEME 12. PROPOSED BIOSYNTHESIS OF GASCARDIC ACID.

Fusicoccin

A recent result[74] suggests that the fusicoccin type compounds are produced from a diterpene precursor. However, the result only showed that a compound having the ophiobolane ring system but lacking the isoprenyl group in the sugar moiety *could* be isoprenylated (from an external source) and oxidized. It did *not* rule out the possibility of intact intramolecular isoprenylation[2] or degradation of a sesterterpene with subsequent isoprenylation from an external source. Further biosynthetic experimentation is clearly required.

The biosynthetic results for the sesterterpenes are summarized in Table 5.

CONCLUSIONS

Surprisingly there has been no systematic effort to determine if the sesterterpenoids are ubiquitous or are sparsely distributed in Nature. Nothing is known about their taxonomic distribution in plants or phytopathogenic fungi or their role in the life cycle of a plant. Their discovery to date has essentially been by chance observation rather than by design.

[74] BARROW, K. D., BARTON, D. H. R., CHAIN, E., OHNSORGE, U. F. W. and SHARMA, R. P. (1973) *J. Chem. Soc. Perkin Trans I* 1590.

TABLE 5. BIOSYNTHETIC RESULTS FOR THE SESTERTERPENES

Precursor	Compound labelled	Organism	Incorporation (%)	Degradative result	Reference
$^{18}O_2$	Ophiobolin *A*	*C. heterostrophus*		Oxygen at C-14 derived from O_2 but not O at C-3	47
$^{18}O_2$	Ophiobolin *B*	*C. miyabeanus*			48
[1-^{14}C]-acetate	Ophiobolin *B*	*C. miyabeanus*	0·4		73
[2-^{14}C]-acetate	Ophiobolin *B*	*C. miyabeanus*	1·6, 2·7*, 1·1†		73
[2-^{14}C]-pyruvate	Ophiobolin *B*	*C. miyabeanus*	4·1*		73
[3-^{14}C]-pyruvate	Ophiobolin *B*	*C. miyabeanus*	6·8*		73
[1-^{14}C]-glycine	Ophiobolin *B*	*C. miyabeanus*	0·063		73
[2-^{14}C]-glycine	Ophiobolin *B*	*C. miyabeanus*	2·4, 1·7*	Specific	73
[1-^{14}C]-serine	Ophiobolin *B*	*C. miyabeanus*	0·03		73
[3-^{14}C]-serine	Ophiobolin *B*	*C. miyabeanus*	1·5, 4·2,* 3·3‡	Specific	73
[^{14}C-methyl]-methionine	Ophiobolin *B*	*C. miyabeanus*	1·5*		73
[^{14}C-methyl]-sarcosine	Ophiobolin *B*	*C. miyabeanus*	2·9*		73
[^{14}C]-formate	Ophiobolin *B*	*C. miyabeanus*	0·3		73
[2-^{14}C]-mevalonic acid lactone	Ophiobolin *A*	*C. miyabeanus*	2·48	Specific	46
	Ophiobolin *B*	*C. miyabeanus*	0·42	Specific	46
	Ophiobolin *F*	*C. heterostrophus*	56§		30
[2-^{3}H]-mevalonic acid lactone	Ophiobolin *A*	*C. miyabeanus*	2·56	Specific one additional ^{3}H found at C-15	48
	Ophiobolin *B*	*C. miyabeanus*	14·42		48
[2-^{3}H]-2*S*-mevalonic acid	Ophiobolin *A*	*C. miyabeanus*	1·4		49
	Ophiobolin *B*	*C. miyabeanus*	6·2	No ^{3}H migration	49
[2-^{3}H]-2*R*-mevalonic acid	Ophiobolin *A*	*C. miyabeanus*	2·26		49
	Ophiobolin *B*	*C. miyabeanus*	4·94	^{3}H migration C-8α to C-15	49
[2-^{14}C, 4-^{3}H]-4*S*-mevalonic acid lactone	Ophiobolin *B*	*C. miyabeanus*	0·52	0·8% ^{3}H retention	50
	Ophiobolin *C*	*C. miyabeanus*	0·54		50
[2-^{14}C, 4-^{3}H]-4*R*-mevalonic acid lactone	Ophiobolin *A*	*C. miyabeanus*	3·83	104% of predicted ^{3}H retention	50, 51
	Ophiobolin *B*	*C. miyabeanus*	3·71	103% of predicted ^{3}H retention	50, 51
	Ophiobolin *C*	*C. miyabeanus*	0·22	101% ^{3}H retention	50, 51
[1-^{14}C]-isopentenyl pyrophosphate	Ophiobolin *F*	*C. heterostrophus*	10·8§‖		65
[^{14}C]-farnesyl pyrophosphate¶	Ophiobolin *F*	*C. heterostrophus*	6·0§‖		65
[1,1-$^{3}H_2$]-all-*trans*-geranylfarnesyl pyrophosphate	Ophiobolin *F*	*C. heterostrophus*	20§		30
			8·9§‖		65
[1,1-$^{3}H_2$]-all-*trans*-geranylfarnesol	Ophiobolin *F*	*C. heterostrophus*	very low§		30
[1,1-$^{3}H_2$]-all-*cis*-geranylfarnesyl pyrophosphate	Ophiobolin *F*	*C. heterostrophus*	very low§		30
[^{14}C]-ophiobolin *B*	Ophiobolin *A*	*C. miyabeanus*	9·9		46
	Ophiobolin *B*	*C. miyabeanus*	10·2		46
[^{3}H]-17-18-epoxy-ophiobolin *B*	Ophiobolin *A*	*C. miyabeanus*	0		48
[^{3}H]-ophiobolin *C*	Ophiobolin *A*	*C. heterostrophus*	0·008		47
	Ophiobolin *B*	*C. heterostrophus*	0·005		47

* In the presence of glycine.
† In the presence of [2-^{13}C]-acetate.
‡ In the presence of L-serine.
§ Enzyme preparation.
‖ Per 15 mg/min protein.
¶ From [2-^{14}C]-mevalonate.

and unfortunately their structure diversity seems to preclude the possibility of a single phytochemical screening test to detect their presence. The pharmacological properties[10,15,23,24] of the products discovered to date however suggest that it may be well worth investigating plants and phytopathogenic fungi for their sesterterpenoid content in order to find pharmacologically active phytoconstituents.

The area of sesterterpenoid chemistry has been reviewed. It highlights some excellent structure elucidation and biosynthetic work. Further reports of new structure types and of more advanced biosynthetic precursors are anticipated.

Acknowledgements—The author would like to thank Professor N. R. Farnsworth for his encouragement and provision of facilities and Professor D. Arigoni for kindly supplying unpublished results on the structure of gascardic acid.