The Biosynthesis of C_5—C_{20} Terpenoid Compounds

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Reviewing the literature published during 1982 and 1983
(Continuing the coverage of literature in *Biosynthesis*, Vol. 7, p. 85)

1 Introduction

This report follows the pattern of those on the C_5—C_{20} terpenoids which appeared in the Specialist Periodical Reports on Biosynthesis.[1] It covers the years 1982 and 1983. Several textbooks and reviews have appeared[2] which contain chapters or articles on general terpenoid biosynthesis.

The use of stable isotopes, detected by n.m.r., has continued to provide biosynthetic information, and a number of instances have been reported in which the amounts of material that were biosynthesized by cell-free systems have been adequate for Fourier-transform n.m.r. studies.

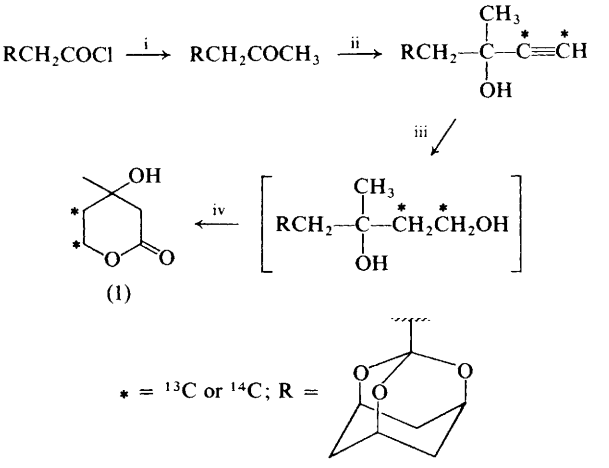
A series of syntheses of [^{13}C]- and [^{14}C]-(*RS*)-mevalonolactones (1), labelled on the methyl group and at C-4 and C-5, have been described.[3] They are particularly noteworthy for the use of the 2,4,10-trioxa-adamantyl group as a blocking group for the carboxyl and are exemplified in Scheme 1. A re-investigation of an earlier synthesis[4] of [3′-^{13}C]-(*RS*)-mevalonolactone, which could not be reproduced, has been reported.[5] A synthesis of (3*S*)-homomevalonolactone from quinic acid has been described.[6] *Gluconobacter scleroideus* converts 3-methylpentane-1,3,5-triol into the unnatural (3*S*)-mevalonolactone.[7] A diastereoselective synthesis of mercaptomethylmevalonolactone (a potential inhibitor of hydroxymethylglutaryl-CoA reductase) has been reported.[8] The properties of HMG-CoA reductase from the latex of *Hevea brasiliensis* have been studied.[9] The biosynthesis of allylic isoprenoid pyrophosphates by enzyme preparations from the flavedo of *Citrus paradisi* (grapefruit) has revealed that whereas *C. sinensis* (orange) contains a large excess of *E*-prenyltransferases, *C. paradisi* contains a higher proportion of *Z*-transferases. The role of metal ions in this context has been discussed.[10]

2 Hemiterpenoids

The origin of the diastereotopic methyl groups in the 1,1-dimethylallyl residues that are found in a number of fungal metabolites has been investigated. In the case of echinulin (2), the *pro-S* methyl group is derived[11] predominantly from the methyl group of mevalonate. On the other hand, ^{13}C n.m.r. studies show[12] that there is a loss of regiospecific identity in the biosynthesis of roquefortine (3). The latter is a precursor of oxaline in cultures of *Penicillium oxalicum*.[13] Bakuchiol (4), which is a compound possessing insect juvenile hormone activity and which is obtained from *Psoralea corylifolia*, has been shown[14] to incorporate mevalonate.

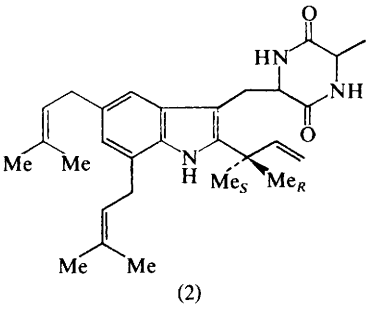
3 Monoterpenoids

Tracer studies have shown[15] that the extractable activity of geranyl pyrophosphate synthetase from *Pelargonium graveolens*



Reagents: i, $LiCH(CO_2SiMe_3)_2$, Et_2O, DME; ii, $LiC{\equiv}CH$; iii, 9-borabicyclononane, H_2O_2, OH^-; iv, CF_3CO_2H

Scheme 1



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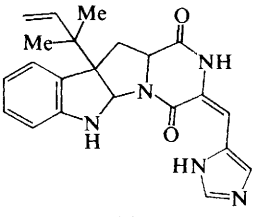

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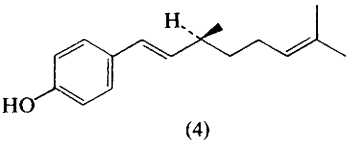
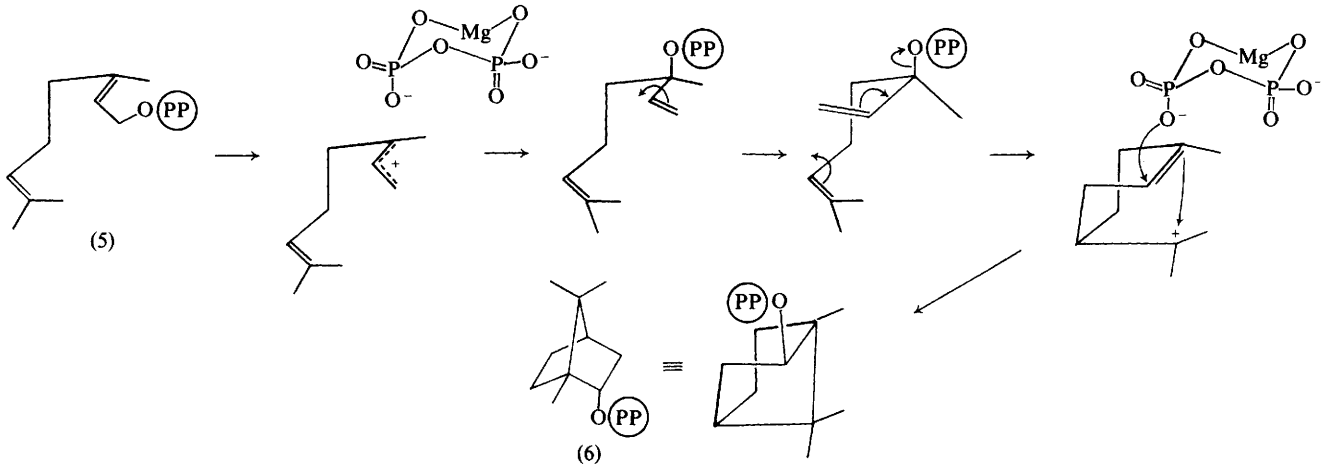


(4)

passes through a sharp maximum in July, and it is then some 390 times greater than in winter. Under conditions of optimum incorporation, both C_5 moieties of geraniol were equally labelled by [^{14}C]isopentenyl pyrophosphate. Although the effectiveness of the incorporation of radioactivity from [^{14}C]-linaloyl pyrophosphate, -neryl pyrophosphate, and -geranyl pyrophosphate by *Artemisia annua* into isothujone, 1,8-cineole, and α-pinene was in that order, it was suggested[16] that this may also reflect the activity of endogenous phosphatases.

Two reviews[17,18] describe recent progress in the application of enzymological methods to monoterpenoid cyclizations. An enzyme system from *Salvia officinalis* that mediates the formation of *d*-bornyl pyrophosphate (6) from geranyl pyrophosphate (5) has been described.[19] This has been used to study



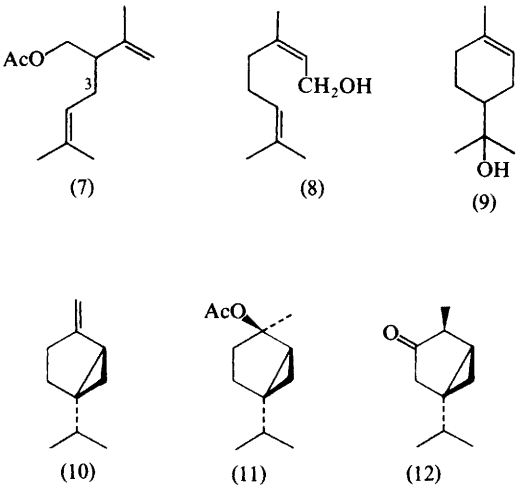
Scheme 2

the cyclization. Evidence has been provided to show that the two ends of the pyrophosphate moiety in the biosynthesis of *d*-bornyl pyrophosphate by *S. officinalis* and of *l*-bornyl pyrophosphate by *Tanacetum vulgare* do not become equivalent during their formation from geranyl pyrophosphate. Separate incubations of [1,1-$^3H_2$]geranyl [α-^{32}P]- and [β-^{32}P]-pyrophosphates gave samples of bornyl pyrophosphates which were hydrolysed to bornyl phosphate. Only the monophosphates from the α-labelled geranyl pyrophosphates retained the $^3H/^{32}P$ ratio of the starting material. Experiments with [1-^{18}O, 8,9-$^{14}C_2$]geranyl pyrophosphate established that the original pyrophosphate oxygen of the precursor is the exclusive source of the pyrophosphate ester oxygen of the product. These results imply a very tight restriction on the motion of the transiently generated inorganic pyrophosphate in the cyclization, as exemplified in Scheme 2.

Several model studies on the biosynthesis of monoterpenoids have been reported. Labelling studies have shown[20] that the biomimetic intermolecular 1′–2 electrophilic condensation of 3-methylbut-2-enyl acetate to form lavandulyl acetate (7) is a stereorandom process at C-3. The stereospecific cyclization of *N*-methyl-(*S*)-4-([1′-^{2}H]neryloxy)pyridinium methyl sulphate to form α-terpineol (9) proceeds[21] with inversion of configuration at C-1. The spectrum of products that is obtained in the solvolysis of a series of methanesulphonates of nerol and its fluorinated analogues has been interpreted[22] in terms of a stepwise cyclization of nerol (8) to α-terpineol (9). It has been observed[23] that phosphoric ester groups influence the elimination of sulphonium salts to afford allylic alcohols rather than their βγ-isomers.

Biosynthesis of monoterpenes in callus tissues and suspension cells of species of the genus *Perilla* has been observed[24] and may form a suitable system for further work. The metabolism of *l*-menthone in *Mentha piperita* is highly compartmentalized.[25] The biosynthetic implications of the co-occurrence of monoterpenes in clones of *Pinus contorta* have been discussed[26] in terms of biosynthesis of monoterpenes proceeding *via* groups of similar enzyme systems. Radioactivity from $^{14}CO_2$ feeding experiments with *Pinus pinaster* was shown[27] to accumulate in β-myrcene and in β-ocimene prior to the α- and β-pinenes, suggesting a stepwise cyclization. Genetic variations have been recorded[28] in the content of volatile terpenoids of various inbred lines and F_1 hybrids of cultivars of *Daucus carota*.

[1-^{3}H]Geraniol is converted[29] into sabinyl acetate (11) in the leaves of *Artemisia absinthium*. However, under conditions of oxygen restriction, much more sabinene (10) is formed. [10-^{3}H]Sabinene is converted into the acetate and into 3-thujone (12) – a step also observed in *Tanacetum vulgare*. The stereoselectivity of the reduction of carvone (13) by suspension cells of *Nicotiana tabacum* has been examined.[30] The double-bond is reduced from the *si*-face to give (14) and the carbonyl group from the *re*-face to form (15), as shown in Scheme 3.

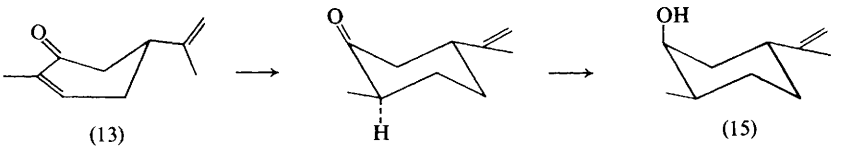


The biosynthesis of the iridoids has continued to attract attention. The synthesis of [4-^{13}C]- and [9-^{13}C]-10-hydroxygeraniol and of [10-^{3}H]iridotrial has been reported.[31] 10-Hydroxycitronellol (16) is a precursor of dolichodial (17) in *Teucrium marum*.[32] The effect of metabolic period, dose, and method of application on the incorporation of deoxyloganin (18) into dihydrocornin (19) and thence into cornin (20) and hastatoside (21) by *Verbena officinalis* has been detailed.[33,34] The biosynthesis of the iridoids aucubin (23) in *Plantago major* and antirrinoside (24) in *Antirrhinum majus* has been shown[35] to involve 8-*epi*-deoxyloganic acid (22) rather than deoxyloganic acid (25). The taxonomic aspects of this differentiation between the utilization of the 8-epimers have been noted.

A number of studies have been reported[36] on the microbial oxidation and degradation of various monoterpenes and their derivatives. This work has been reviewed.

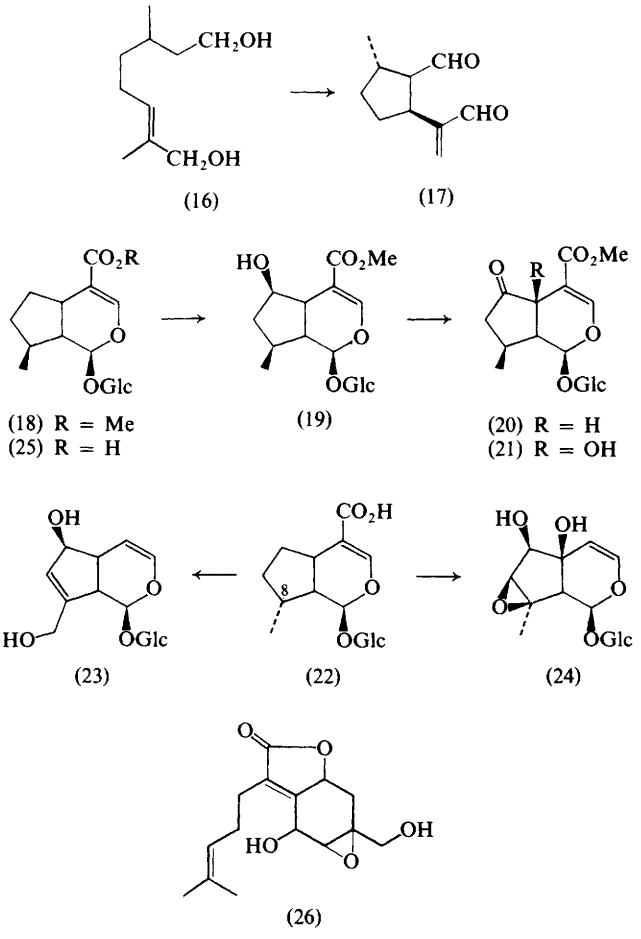
4 Sesquiterpenoids

There have been a number of advances in sesquiterpenoid biosynthesis. The role of the amino-acid leucine in the biosynthesis of terpenoids has been the subject of a number of studies. Although hydroxymethylglutaryl-coenzyme A (HMG-CoA) stands at the intersection of two metabolic pathways – the breakdown of leucine into acetoacetate and acetate and the synthesis of mevalonate – labelling studies with tissue cultures of *Andrographis paniculata* have shown[37] that HMG-CoA that is derived from leucine is broken down before re-synthesis into the sesquiterpenoid paniculide (26). These tissue cultures have been shown[38] to transform *trans,trans*-[1,1-$^3H_2$, 12,13-$^{14}C_2$]farnesyl pyrophosphate (28) and both (3*R*,5*R*)- and (3*R*,5*S*)-[5-

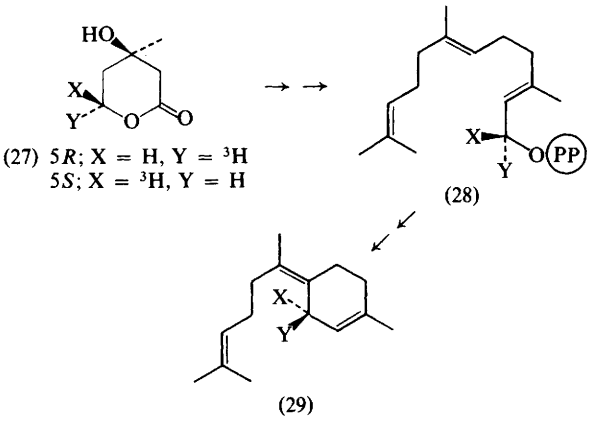


(13) (14) (15)

Scheme 3

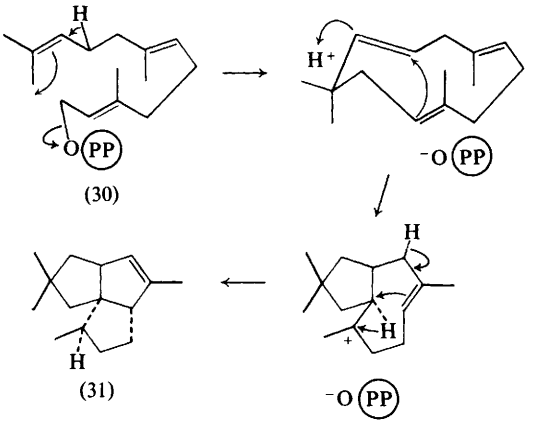


(16) (17) (18) R = Me (25) R = H (19) (20) R = H (21) R = OH (23) (22) (24) (26)



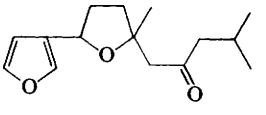
(27) 5*R*; X = H, Y = ^{3}H 5*S*; X = ^{3}H, Y = H (28) (29)

Scheme 4



(30) (31)

Scheme 5



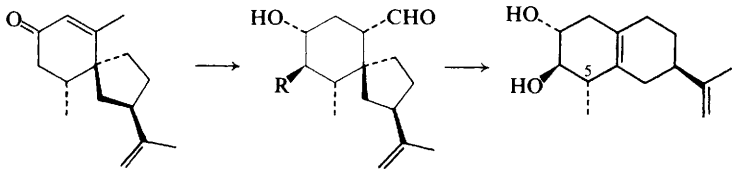
(32)

^{3}H]mevalonates (27) into (*Z*)-γ-bisabolene (29) without the loss of tritium, contrary to previous reports (see Scheme 4). A cell-free preparation from a culture of *Streptomyces* UC5319 has been obtained[39] that mediates the cyclization of farnesyl pyrophosphate (30) to pentalenene (31) (see Scheme 5), which is a precursor of the pentalenolactones. This work has been reviewed.[17]

The production and metabolism of sesquiterpenoid phytoalexins has been reviewed.[40] Oxygen-18 studies have shown[41] that all three oxygen atoms of ipomeamarone (32), produced by *Ipomoea batatas*, are derived from molecular oxygen and not water. The postulated migration of hydrogen from C-5 and C-4 in the biosynthesis of the potato phytoalexins lubimin, 3-hydroxylubimin, and rishitin has been confirmed[42] by the incorporation of [2-$^2H_3$, 2-^{13}C]acetate and direct observation of the predicted β-shift of the ^{13}C n.m.r. signal of C-5 due to a deuterium label at C-4 – the so-called β-hop. The biosynthesis of rishitin (36) from solavetivone (33) *via* lubimin (34) and 3-hydroxylubimin (35) (see Scheme 6) has been established[43] on the basis of feeding experiments with [8,8-$^2H_2$]solavetivone. A similar hydride shift (see Scheme 7) has been established[44] in the biosynthesis of PR toxin (37) by *Penicillium roqueforti*, using [4,4-$^2H_2$]mevalonate as a substrate.

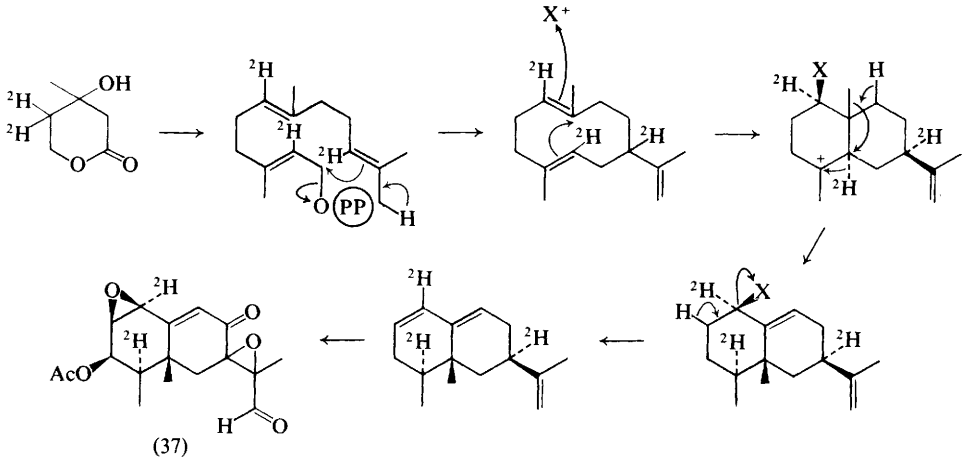
The full paper on the mevalonoid origin of the hydrogen atoms of the phytotoxin dihydrobotrydial (38), produced by *Botrytis cinerea*, has appeared.[45] The acetate and mevalonate labelling patterns of alliacolide (39), produced by *Marasmius alliaceus*, suggest that its carbon skeleton can be dissected[46] into isoprene units as shown in (40). Feeding experiments with [2-$^2H_3$]acetate and [2,2-$^2H_2$]-, [4,4-$^2H_2$]-, and [5,5-$^2H_2$]-mevalonate revealed[47] the occurrence of hydrogen rearrangements to C-1 and from C-5 to C-6 during the biosynthesis. This adds to the number of instances in which a secondary methyl group of a terpenoid has been shown to be derived from a hydrogen rearrangement. Furthermore, many sesquiterpenoids that are obtained from the Basidiomycetes contain a cyclopentane ring bearing a methylene group which is derived from C-4 of mevalonate. This result suggests that these methylene groups might also be generated by a hydrogen shift.

The labelling pattern of illudin M (41) when it is biosynthesized by *Clitocybe illudens* from [1,2-$^{13}C_2$]acetate is in accord with previous dissections into isoprene units.[48] The enrichment from [2-$^2H_3$]acetate and [2,2-$^2H_2$]mevalonate shows that one hydrogen atom is lost from C-12 during the biosynthesis whilst the retention of a ^{2}H–^{13}C coupling at C-6 in material that is biosynthesized from [5,5-$^2H_2$,5-^{13}C]mevalonate shows that there is no hydride rearrangement involving this centre, contrary to previous reports.



(33) (34) R = H (35) R = OH (36)

Scheme 6



(37)

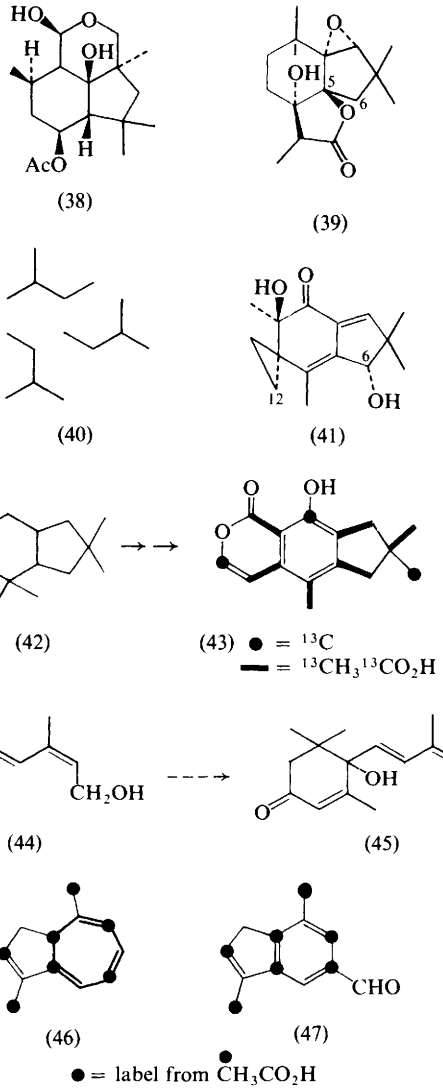
Scheme 7

The incorporation of [1-^{13}C]-, [2-^{13}C]-, and [1,2-$^{13}C_2$]-acetate into fomajorin D (43) by *Fomes annosus* generated a labelling pattern consistent with its biosynthesis from farnesyl pyrophosphate *via* a protoilludyl cation (42).[49]

The biosynthesis of abscisic acid (45) has been reviewed.[50] The production of relatively large amounts of abscisic acid by the plant pathogen *Cercospora rosicola* has facilitated these studies. α-Ionylidene-ethanol (44) and the corresponding acid have been shown[51] to be precursors whilst the insertion of the 1′-hydroxy-group is the last step.[52]

3,10-Dihydro-1,4-dimethylazulene (46) is an unusual product of cultured cells of the liverwort *Calypogeia granulata*. Biosynthetic studies using [2-^{13}C]acetate have established[53] its terpenoid origin and that of a congener, 3,7-dimethylindene-5-carbaldehyde (47).

Cantharidin (49) forms part of the defensive secretion of the blister beetle, *Lytta vesicatoria*. Evidence has been provided[54] for the incorporation of C-4 and C-11 of farnesol as shown in (48). The biosynthesis of a number of meroterpenoids which, like the austalides (produced by *Aspergillus ustus*), contain triprenyl units has been examined[55] and is reviewed in the report on polyketides (see *Nat. Prod. Rep.*, 1984, **1**, 281).

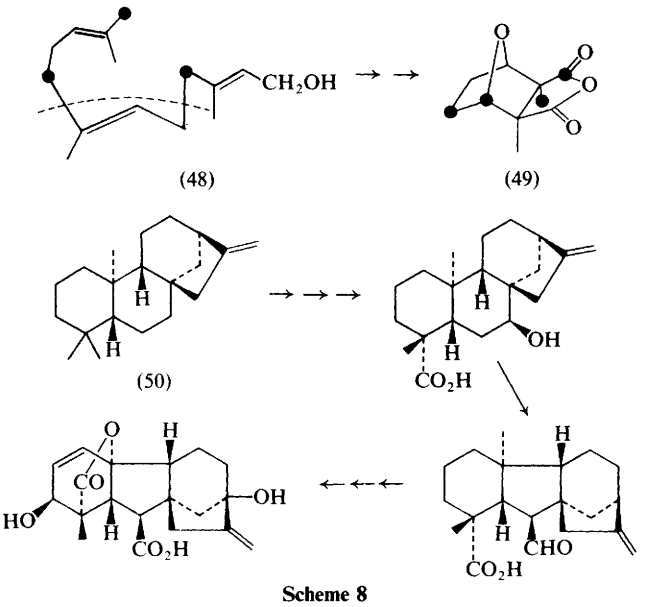


(38) (39) (40) (41) (42) (43) ● = ^{13}C ▬ = $^{13}CH_3{}^{13}CO_2H$ (44) (45) (46) (47) ● = label from CH_3CO_2H

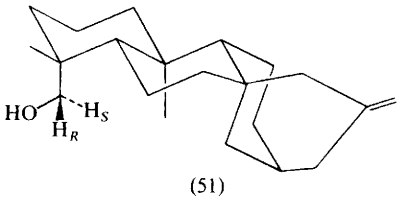
5 Diterpenoids

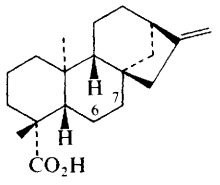
Most of the advances in the biosynthesis of diterpenoids have been concerned with the gibberellin plant-growth hormones. The biosynthesis of the gibberellins and related diterpenoids by the fungus *Gibberella fujikuroi*[56] and in higher plants[57] has been reviewed. The biosynthesis falls into a number of stages (see Scheme 8) involving the formation of *ent*-kaurene (50), its oxidation, the contraction of ring B, the loss of C-20, and the formation of the various gibberellins. The stereospecificity of the oxidation of *ent*-kauren-19-ol (51) to the aldehyde has been investigated.[58] A microsomal enzyme preparation from *Marah macrocarpus* removes the *pro*-19*R* hydrogen atom. A cell-free system which mediates the oxidation of *ent*-kaurene to the 19-aldehyde has also been obtained[59] from seedling shoots of maize.

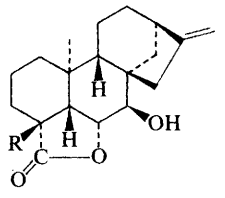
Apart from the gibberellins, the fungus *Gibberella fujikuroi* also produces a series of lactones, known as the kaurenolides,

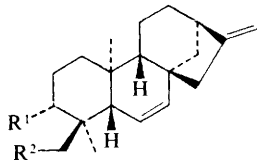


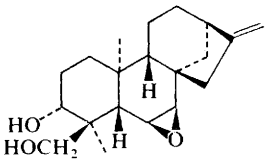
Scheme 8

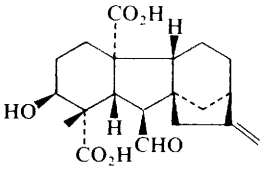


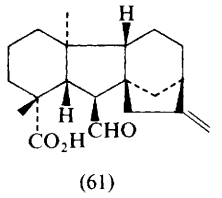












e.g. (54). In their biosynthesis from *ent*-kaur-16-en-19-oic acid (52), both oxygen atoms from C-19 are retained.[60] The implication of *ent*-kaura-6,16-dien-19-oic acid (53) in this step suggests that a 6β,7β-epoxide may be formed and then opened, with participation of the carboxyl group in a *trans* diaxial manner. Possibly because of its high reactivity, this epoxide has not been detected. However, a 3α-hydroxy-group is known to block oxidation at C-19. Hence, although *ent*-kaura-6,16-diene (55) and *ent*-18-hydroxykaura-6,16-diene (56) were efficiently transformed into 7-hydroxy- (54) and 7,18-dihydroxy-kauren-olides (57), respectively, *ent*-3β,18-dihydroxykaura-6,16-diene (58) gave the *ent*-6α,7α-epoxide (59).[61]

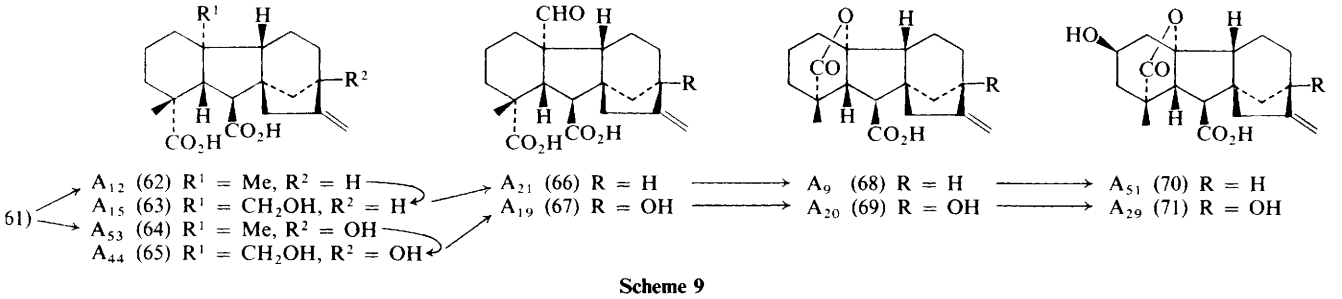
At one time, gibberellin A_{13} 7-aldehyde was proposed as an intermediate in the biosynthesis of gibberellic acid. However, its partial synthesis and non-incorporation has led to this being discounted.[62] The cofactors, including 2-oxoglutarate and Fe^{2+}, that are required for the oxidation of gibberellin A_{12} aldehyde (61) by an oxidase from *Cucurbita maxima* have been established.[63] The biosynthetic relationships (see Scheme 9) between all the major gibberellins of *Pisum sativum* have been established,[64] using a soluble cell-free system. The C_{20} open lactones and lactols play an important role in this metabolic pathway (see Scheme 9), which has also been established by very thorough studies, over a number of years, on the intact developing seeds of *P. sativum*.[57]

[1,2-$^3H_2$]Gibberellin A_4 (72) is converted into gibberellins A_1 (73) and A_8 (74) and various glucosides by cell cultures derived from anise[65] and carrot.[66] The biosynthesis of gibberellins A_4 (72) and A_9 (68) from [2-^{14}C]mevalonic acid and ^{14}C-labelled *ent*-kaur-16-ene in the seeds of *Sechium edule* has also been studied.[67]

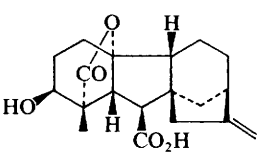
ent-Kaurenoid diterpenoids are one of several biosynthetically closely related diterpenoid skeleta. Although the naturally occurring gibberellins all belong to the *ent*-kaurene series, there is nothing yet known about the biosynthesis of gibberellins which would preclude the occurrence of gibberellin-like substances that are derived from these other diterpenoid skeleta. The fungal biosynthetic pathway is relatively non-structure-specific. The metabolism of the diterpenoid hydrocarbon *ent*-trachylobane (75) to the C_{19} gibberellin analogue trachylobagibberellin A_{40} (76) has been observed,[68] although it is interesting to note the predominance of 2α-hydroxylation rather than 3β-hydroxylation in this transformation. The corresponding 19-acid, trachylobanic acid (77), obtained from species of the genus *Helianthus*, was also transformed[69] into the 12,16-cyclogibberellins A_9 and A_{12}. The hydrocarbon beyer-15-ene (78) was transformed[70] into beyergibberellin A_9 (79) in a similar manner. The microbiological transformation of ^{2}H-labelled steviols by *Gibberella fujikuroi* has been used to prepare[71] some 13-hydroxylated ^{2}H-labelled gibberellins.

The inhibition of the biosynthesis of gibberellins has been studied in the context of the development of novel plant-growth regulators. Compactin, which is an inhibitor of hydroxymethylglutaryl-CoA reductase, not only reduces the incorporation of acetate into gibberellic acid by *G. fujikuroi* but also affects the incorporation of mevalonate.[72] A number of synthetic growth retardants also affect the biosynthesis of sterols in *Nicotiana tabacum*.[73]

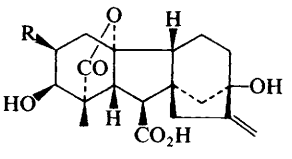
ent-6α-Hydroxy-5β(H)-7-norgibberell-16-en-19-oic acid (80) and the corresponding diol, but not the *ent*-6β-epimer, have



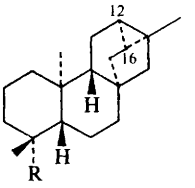
Scheme 9



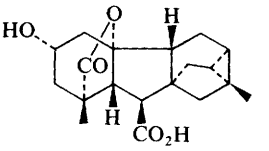
Gibberellin A_4 (72)



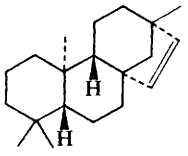
Gibberellin A_1 (73) R = H
Gibberellin A_8 (74) R = OH



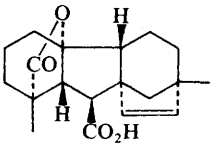
(75) R = Me
(77) R = CO_2H



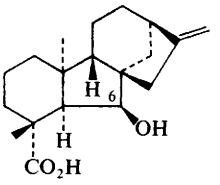
(76)



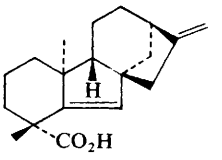
(78)



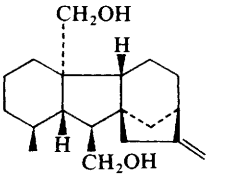
(79)



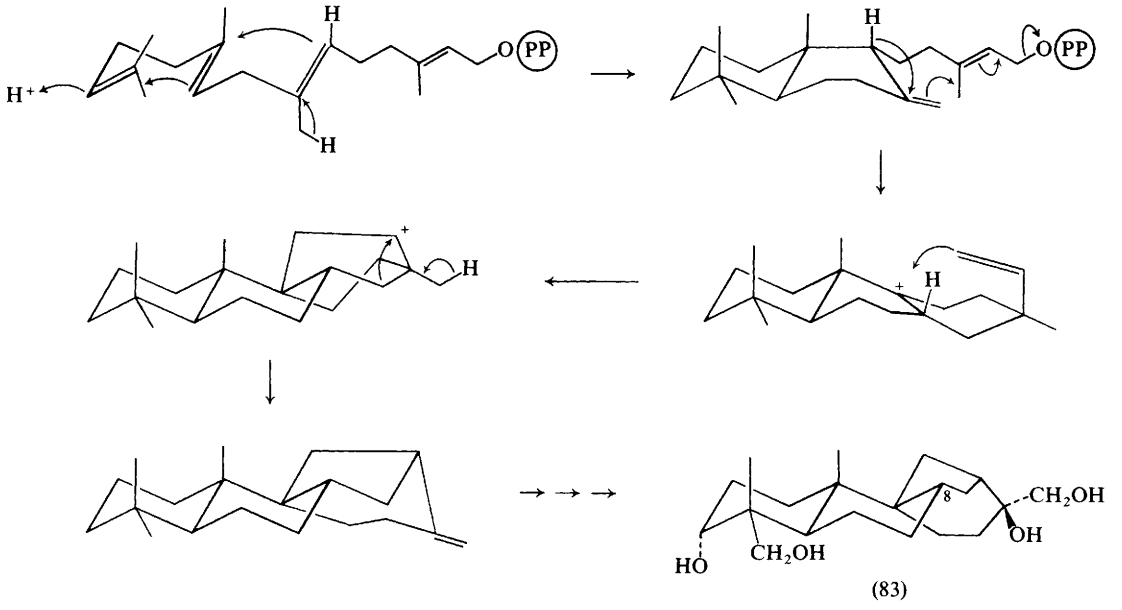
(80)



(81)

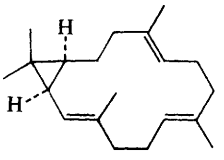


(82)



(83)

Scheme 10



(84)

been shown[74] to inhibit the biosynthesis of gibberellic acid in *G. fujikuroi* at the ring-contraction stage and to act as regulators of plant growth. The corresponding 6-ketones[75] and 5,16-dienes, *e.g.* (81),[76] have also been shown to act as inhibitors, although the stage at which they function has not been clarified. Some 19-nor-gibberellenes, *e.g.* (82), were also observed[77] to inhibit the biosynthesis of gibberellic acid and again they appeared to act at the ring-contraction step.

The diterpenoid aphidicolin (83) has attracted a lot of interest as an antiviral and tumour-inhibitory substance. The appearance of a ^2H–^{13}C coupling in the ^2H n.m.r. spectrum of a sample of aphidicolin that was biosynthesized from [4,4-$^2H_2$,3-^{13}C]mevalonate established[78] that a β-hydrogen atom at C-9 migrated to C-8 during the biosynthesis (see Scheme 10). This has led to the suggestion that those cyclic diterpenoids in which the initial cyclization involves a bicyclic intermediate should be divided into two groups, based on the different (chair-chair or chair-boat) conformations of geranylgeranyl pyrophosphate in this initial step in the biosynthesis.

An increasing number of diterpenoids have been isolated in which the initial cyclization involves an attack of the pyrophosphate group at C-1 of geranylgeranyl pyrophosphate on the distal double-bond. The *pro*-1*S* hydrogen atom of geranylgeranyl pyrophosphate has been shown[79] to be eliminated in the cyclization to form casbene (84) whilst studies with [2-^{14}C]mevalonate have shown that the cyclopropane ring is formed on the *re*:*re* face of the 14–15 double-bond of geranylgeranyl pyrophosphate.

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