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Molecules of Interest

Fujenal, a diterpenoid saga of neighbouring group participation

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ABSTRACT

The chemistry, the biosynthesis and the biotransformations related to fujenal and its analogues are reviewed. Despite the opportunity for free rotation about the C-9:C-10 bond, the chemistry of the ring B of this diterpenoid is dominated by neighbouring group participation between C-6, C-7 and C-19.

1. Isolation and structure

The chemistry of polyfunctional natural products has afforded many examples of neighbouring group participation. There are many well-documented example of transannular participation of hydroxyl groups in the hydrolysis of esters and in acetal formation. Carboxylic acid anhydrides are relatively rare amongst natural products. The diterpenoid aldehyde–anhydride fujenal **1** and the corresponding acid, fujenoic acid **2** (Cross et al., 1963a), are unique in having an anhydride placed so that it can participate in the reactions of an aldehyde or a carboxylic acid. This review brings together a number of scattered observations which relate to the neighbouring group participation of these functional groups in the chemistry and biosynthesis of fujenal.

Fujenal (**1**) was first described as a constituent of the fungus, *Gibberella fujikuroi* (Cross et al., 1963a). Spectroscopic and analytical evidence revealed the presence of a glutaric acid anhydride, an aldehyde and a double bond (Cross et al., 1963b). Ozonolysis of the double bond showed that it comprised a terminal methylene attached to a cyclopentane ring. When fujenal was heated with methanol in a sealed tube at 160° the pseudo-esters **3** and **4** were formed. The formation of these related the anhydride and the aldehyde functions and was the first examples of neighbouring group participation in this series of compounds. Mild acid hydrolysis of the 17-*nor*-16-ketone **5** of the pseudo-ester served to distinguish between the carboxylic acid ester and the methoxy-ketal. Compound **5** was hydrolysed to a lactol which, on oxidation, gave a dicarboxylic acid **6**. This acid had been also obtained by ozonolysis, hydrolysis and oxidation of 7β-hydroxykaurenolide (**7**). The structure and stereochemistry of this kaurenolide, also isolated from *G. fujikuroi*, had been established by a separate degradation (Cross et al., 1963c). This inter-relationship established the structure and stereochemistry of fujenal (**1**) and fujenoic acid (**2**) as kaurenoid diterpenes. The corresponding carboxylic acids **8** and **9** were also isolated from the fungus.

Although diterpenes **1** and **2** were the first examples of ring B *seco*-kaurenoid diterpenoids a very large number, many with tumour inhibitory properties, have subsequently been isolated from Chinese medicinal herbs of the *Rabdosia* (*Isodon*) genus (Fujita and Node, 1984; Sun et al., 2006). Other *seco*-compounds of this type have been found in extracts from the French liverwort *Jungermannia exsertifolia* (Nagashima et al., 1994, 1996). Amygdaloside (**18**) is another ring B *seco*-kaurenoid which has been isolated from almonds (*Prunus amygdalus*) (Sang et al., 2003). A lactol related to fujenal, gibelactol **42**, has also been obtained from *G. fujikuroi* (Barrero et al., 1992).

Cleavage of ring B allows free rotation about the C-9:C-10 bond and leads to structures such as that assigned to enmein (**13**) (Fujita and Node, 1984). This rotation could diminish the opportunities for neighbouring group participation between the anhydride and the 7-aldehyde. A X-ray crystal structure of fujenal (**1**) established that, although some rotation had taken place away from the kaurenoid conformation to relieve interactions

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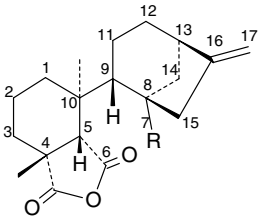
between C-l and C-11, and between C-20 and C-14, fujenal still retained a conformation sufficiently close to that of *ent*-kaurene to allow interactions between C-6 and C-7. Nuclear Overhauser effect enhancements between the 20-H and the 7-H and between the 9-H and the 5-H signals showed that fujenal retained this conformation in solution, i.e. the structure retains a topological relationship between the C-6 carbonyl group and the C-7 aldehyde which dominates the chemistry of fujenal (Avent et al., 1985).

2. Chemistry

The pseudo-esters **3** and **4**, which played a pivotal role in the structure elucidation of fujenal (**1**), were also formed in methanolic solution in the presence of acid catalysts such as hydrochloric acid or tetracyanoethylene (Hanson et al., 2002). The stereochemistry of the pseudo-ester has recently been established by X-ray crystallography. The methoxyl group takes up a β-axial configuration whilst the seven-membered ring B adopts a boat conformation (Hanson



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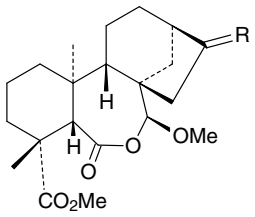
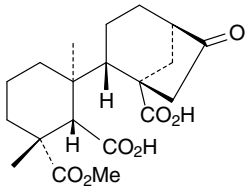
2 R = CO_2H



3 R = CH_2
4 R = α–OMe, β-Me
5 R = O



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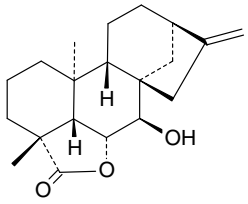

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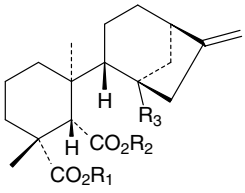
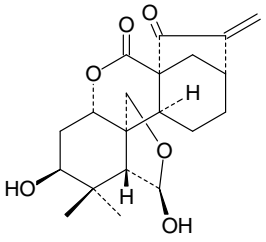


8 $R_1 = R_2 = H$ $R_3 = CHO$
9 $R_1 = R_2 = H$ $R_3 = CO_2H$
10 $R_1 = Me$ $R_2 = H$ $R_3 = CHO$
11 $R_1 = R_2 = Me$ $R_3 = CHO$
12 $R_1 = R_2 = Me$ $R_3 = CH_2OH$



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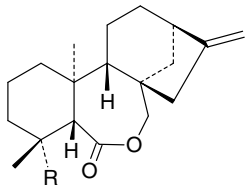
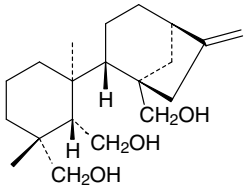


14 R = CO_2H
15 R = CO_2Me
16 R = CH_2OH



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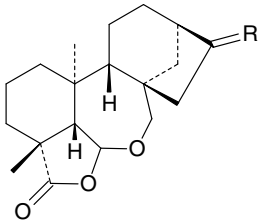
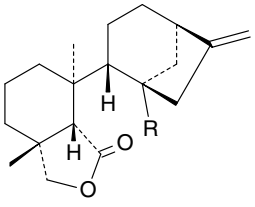
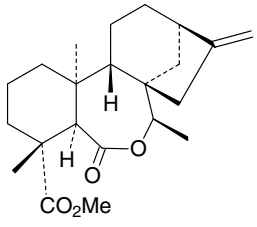


18 R = α-OH, β-CH_2OGlc
19 R = CH_2



20 R = CH_2OH
21 R = CHO



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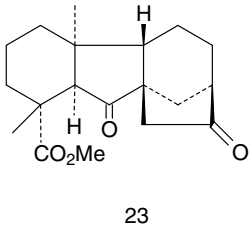

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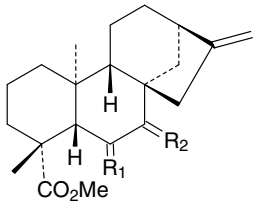
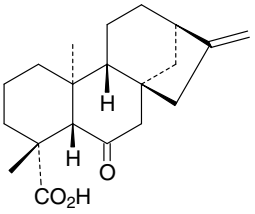


24 R_1 = β-OH, H R_2 = α-OH, H
25 R_1 = β-OH, H R_2 = β-OH, H
26 R_1 = α-OH, H $R_2 = H_2$
27 R_1 = β-OH, H $R_2 = H_2$



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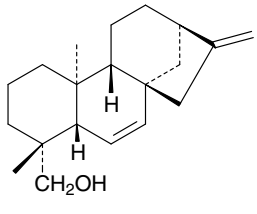

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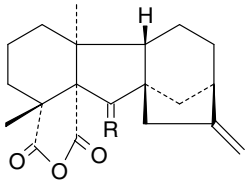
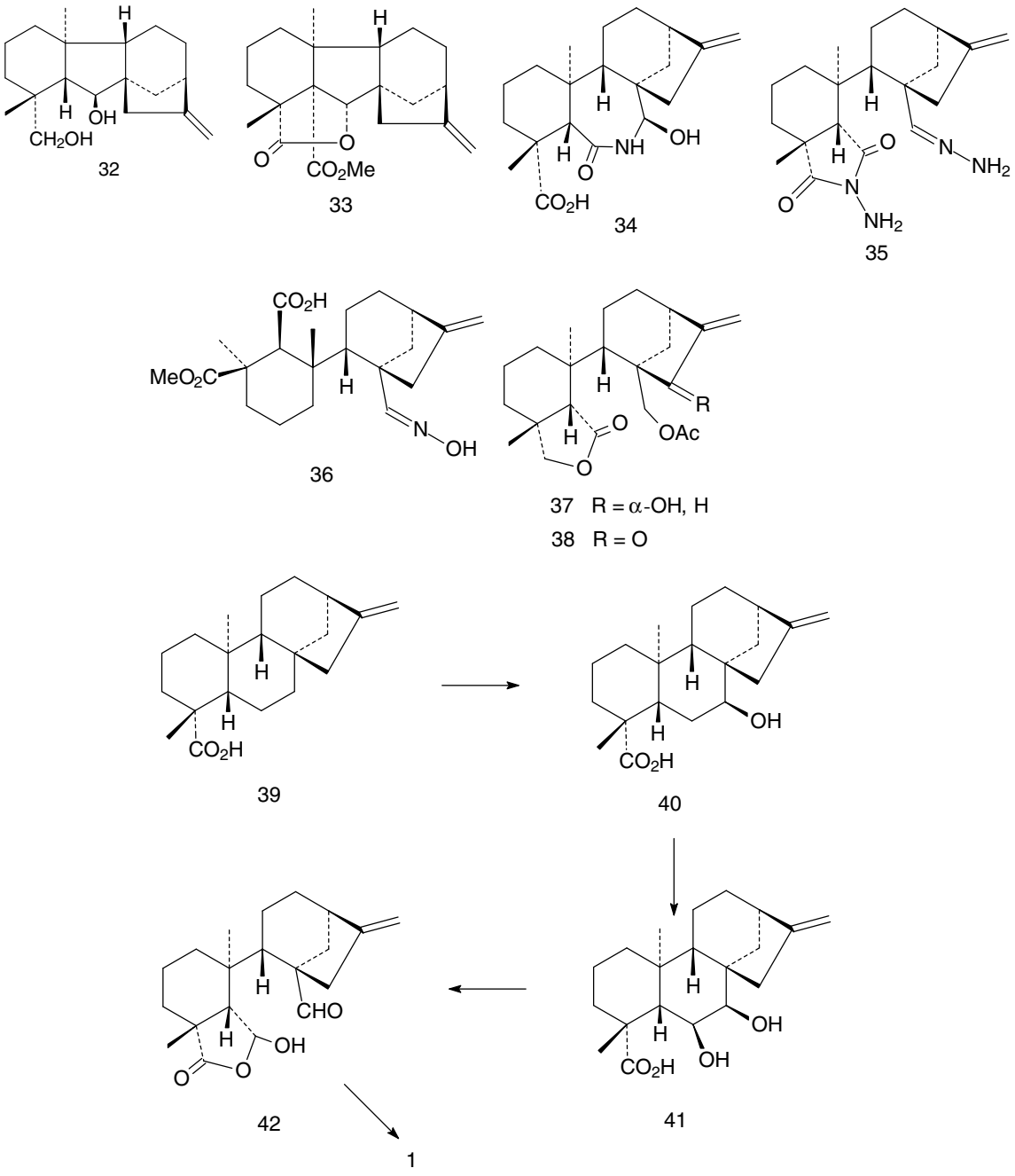


30 R = OH, H
31 R = O

et al., 2002). The configuration at C-7 is determined by the stereoelectronic requirements of the two sets of oxygen lone pairs at C-7. Methanolysis of the anhydride with sodium methoxide gives the 19-monomethyl ester **10**. This was converted to the normal 6,19-dimethyl ester (**11**) with diazomethane (Baynham et al., 1987).

Reduction of fujenal (**1**) with the bulky lithium tri-*t*-butoxyaluminium hydride gave the ε-lactone **14** (Baynham et al., 1987). The structure and stereochemistry of this was established by X-ray crystallography of the methyl ester **15**. The alkoxide formed by reduction of the C-7 aldehyde had participated in the hydrolysis of the anhydride. Reduction of the 19-monomethyl ester **10** with sodium borohydride gave the ε-lactone **15**. Reduction of the normal 6,19-dimethyl ester **11** with sodium borohydride afforded the C-7 alcohol **12**, whilst reduction with lithium hydride gave a 6,7,19-triol **17**. This was also obtained by reduction of the pseudo-ester **3** with lithium aluminium hydride (Hanson and White, 1968).

Reduction of fujenal (**1**) with sodium borohydride in methanol-tetrahydrofuran revealed the participation of the C-7 oxygen function in the reduction of the anhydride (Cross et al., 1963a; Galt and Hanson, 1965; Hanson and White, 1968; Baynham et al., 1987). The minor product was the lactol-ether **19** whilst the major products were the ε- and γ-lactones **16** and **20**, respectively. The ratio of these varied with the solvent. Treatment of the γ-lactone with hydrochloric acid (Hanson and White, 1968) or with tetracyanoethylene in methanol (Hanson et al., 2002) led to isomerization to the ε-lactone. Reduction of fujenal (**1**) with lithium aluminium hydride gave the γ-lactone **20** rather than the 6,7,19-triol **17**.



Scheme 1.

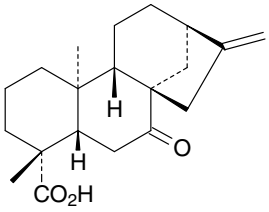
Treatment of fujenal (**1**) with methyl magnesium iodide gave a compound, purified as its methyl ester **22**, in which addition to the aldehyde had taken place, and the resultant alkoxide had cleaved the anhydride ring. X-ray crystallographic analysis showed that epimerization of the ring junction at C-5 had also taken place (Hanson et al., 2002).

Intramolecular reactions which lead to the re-formation of ring B reveal the participation of C-5 and C-6 in reactions at C-7. Thus treatment of the 6,7-dicarboxylic acid **6** with acetic anhydride led to a cyclic anhydride which on pyrolysis formed a cyclopentanone **23** (Cross et al., 1963a).

Despite the possibility of free rotation about the C-9:C-10 bond, the molecular structure of the lactone **20**, established, by X-ray crystallography and by *n*Oe in solution, showed that the C-6 carbonyl group and C-7 were suitably juxtaposed for cyclization (Baynham et al., 1988b).

The acyloin condensation of the aldehyde and anhydride groups of fujenal (**1**) with sodium in liquid ammonia gave a complex mixture of products (Hanson and Triana, 1982). In the majority of these the tetracyclic kaurenoid ring system had been re-formed. The products included the relatively inaccessible kaurenoid 6β,7α and 6β,7β-diol as well as the 6α- and 6β-mono-ols, which in some cases were isolated as their methyl esters (e.g. **24**–**27**). The reductive cyclization of fujenal with the McMurry low-valency titanium reagent leads to the keto-acid **28** (Davis et al., 1989). When the 7-aldehyde of the 6:19-γ-lactone **21** was the substrate, a 6,7-alkene **29** was formed.

The presence of a C-6 carbonyl group in both fujenal (**1**) and the lactone **21** activates C-5 for carbanion formation in the presence of base. This carbanion may then condense with the C-7 aldehyde leading to the formation of a five-membered ring (Galt and Hanson, 1965; Hanson et al., 1981). An internal Perkin condensation



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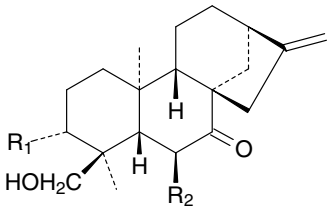
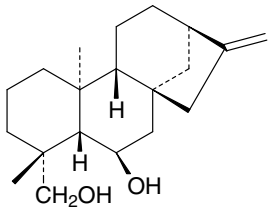


44 $R_1 = R_2 = H$
45 $R_1 = OH$ $R_2 = H$
46 $R_1 = H$ $R_2 = OH$
47 $R_1 = R_2 = OH$



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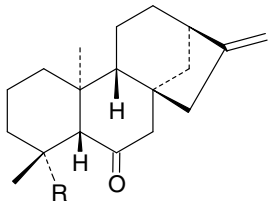
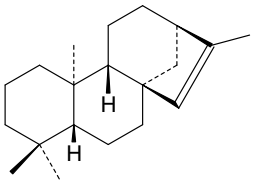


49 R = CHO
50 $R = CO_2H$



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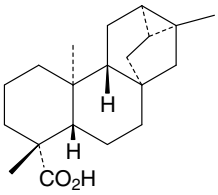

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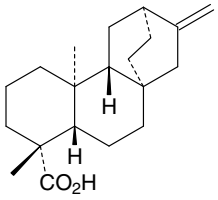

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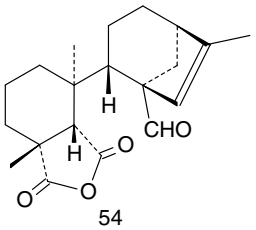

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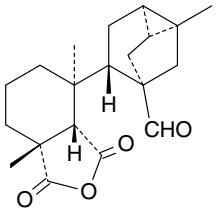

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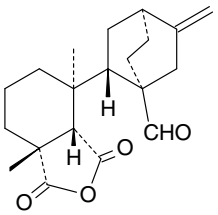

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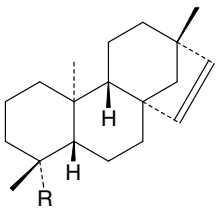
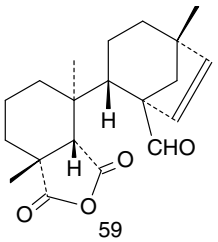


57 R = Me
58 $R = CO_2H$



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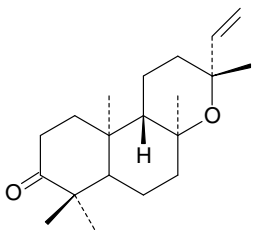

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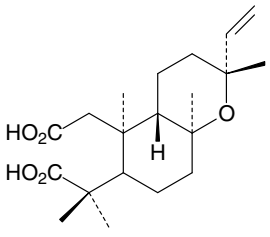

61

of fujenal mediated by sodium hydride in dimethylformamide gave the alcohol **30** (Hanson et al., 1981). When methanol was added to destroy the excess sodium hydride, the monomethyl ester **33** was also obtained suggesting a α-stereochemistry for the alcohol in **30**.

The cyclization products were converted to a series of 5α-gibbanes. Thus, oxidation of the alcohol **30** to a ketone gave β-dicarbonyl compounds **31**, which underwent decarboxylation to generate A/B fused gibbanes. These compounds, particularly the products with a β-hydroxyl group (e.g. **32**), were powerful plant growth inhibitors (Hanson et al., 1982a,b,c, 1983; Hanson and Triana, 1982). They, along with the lactone **20** (Baynham et al., 1988a) acted as mimics of 7β-hydroxy-*ent*-kaurenoic acid (**40**), a key intermediate in the ring-contraction step in gibberellin plant hormone biosynthesis.

The structures of the products which were obtained from the reaction of fujenal (**1**) with ammonia, hydrazine and hydroxylamine reveal further participation between the reactions of the aldehyde and the anhydride (Hanson et al., 2004). On heating with methanolic ammonia fujenal gave a seven-membered lactam **34**. The X-ray crystal structure showed that the C-7 hydroxyl group had taken up an axial conformation comparable to that of the C-7 pseudo-esters. This stereochemistry may be determined by the anomeric interaction between the lone pairs on the amide nitrogen and the C-7 oxygen. However, when fujenal was treated with hydrazine hydrate, the anhydride and the aldehyde reacted separately to give a hydrazide and a hydrazone **35**, respectively. Treatment of fujenal with methanolic hydroxylamine gave an oxime **36**, in which the X-ray crystal structure showed that the anhydride ring had undergone methanolysis and rotation about the 9,10 bond.

Ring D of fujenal (**1**) and its relatives undergo many of the reactions that are typical of the kaurenoid diterpenes. Thus, the 17-*nor*-16-ketone undergoes a Baeyer–Villiger oxidation to form a 16,13-δ-lactone, and it is brominated at C-15. The 16-ene undergoes hydration and it adds hydrogen chloride and methanol (Cross et al., 1963b). The stereochemistry of the addition of methanol was established by X-ray crystallography of the pseudo-ester **4** (Hanson et al., 2002). Allylic oxidation of compounds such as those related to **20**, with selenium dioxide and hydrogen peroxide, gave the 15α-alcohols (e.g. **37**), which were then oxidized to 15-ketones, such as **38**, with chromium trioxide in pyridine (Ali et al., 1991). The 6,7- and 6,19-lactones (e.g. **38**), as analogues of the *Rabdosia* diterpenoids, showed moderate inhibitory activity against HeLa tumour cells.

A characteristic feature of many of these reactions of fujenal (**1**) is the lack of reactivity of the C-6 carbonyl group to attack by external reagents and its participation in intramolecular reactions with C-7. X-ray crystallographic studies of fujenal (**1**) (Avent et al., 1985) and the 6,19-lactone **20** (Baynham et al., 1988b) together with nuclear Overhauser effect enhancement studies in the NMR spectrum suggest that these compounds exist in a conformation in which only a small rotation has occurred about the C-9:C-10 bond. In this conformation the C-20 methyl group hinders the α-face of C-6 to external attack whilst the β-face is hindered to external attack by the C-7 group, which is also suitably placed for internal reactions. These studies also reveal the proximity of C-5 to C-7 allowing for the carbanion cyclization reactions that have been described above. The rotation about the C-9:C-10 bond also exposes C-19 which in the kaurenoid series is normally quite hindered. Hence reduction and methanolysis of the anhydride takes place relatively easily at this centre.

3. Biosynthesis

A complete picture of the biosynthesis of fujenal (**1**) is emerging. This biosynthesis is complicated by two features. Firstly, fujenal is a side product of the *ent*-kaurene:gibberellin biosynthetic pathway in *G. fujikuroi*. Because of the biological importance of the gibberellins these have been the major focus of study. Indeed, fujenal first attracted attention because it was formed in large amounts when some early fermentations of *G. fujikuroi* failed to produce gibberellic acid. Secondly, fujenal (**1**) co-occurs with the corresponding dicarboxylic acid **8**, and it is possible that the anhydride may arise from the latter even in the extraction process.

Fujenal (**1**), and the corresponding 6,19-dicarboxylic acid **8**, lie on a biosynthetic branch of the *ent*-kaurenoid pathway in *G. fujikuroi*. Feeding experiments have demonstrated that *ent*-kaurenoic acid (**39**) was converted into 7β-hydroxy-*ent*-kaurenoic acid (**40**) and then into 6β,7β-dihydroxy-*ent*-kaurenoic acid (**41**). The latter was then oxidatively cleaved to give fujenal (**1**) (Cross et al., 1968, 1970; Hanson et al., 1972; Beale et al., 1982). A possible intermediate in this route is gibelactol (**42**), which has been also isolated from a fermentation of *G. fujikuroi* (Barrero et al., 1992) (Scheme 1). This is the main route, but in a minor pathway fujenal (**1**) can be formed from 7β-hydroxykaurenolide (**7**), via a 6α,7β-diol (Hanson and Sarah, 1979; Beale et al., 1982). On the other way, the facile interconversion of the dicarboxylic acid **8** and the 6,19-anhydride **1** in the fungus is another example of neighbouring group participation in this diterpenoid.

The enzymology of these oxidative steps has been investigated using a mutant of *G. fujikuroi* lacking the entire gibberellin biosynthesis gene cluster but into which one particular gene, *P450-1*, had been re-inserted (Rojas et al., 2004). The key multifunctional oxygenase P450-1 (gibberellin A_{14} synthase) was identified as mediating the steps leading to the ring B *seco*-acids as well as the kaurenolides, both classes of compounds thus being side products of the main gibberellin pathway. The fermentation problems nearly fifty years ago which led to the initial discovery of fujenal may, therefore, have been a consequence of a deficiency in one of the later stages of gibberellic acid biosynthesis.

4. Biotransformations

Microbiological transformations involving analogue biosynthesis in which the substrate bears a formal relationship to a natural fungal metabolite, but differs from it in a significant feature, have shed useful light on aspects of the diterpenoid biosynthetic pathways in *G. fujikuroi*.

An informative biotransformation made use of 7-oxo-*ent*-kaurenes (Fraga et al., 2005). In these substrates, C-7 is at too high an oxidation level to undergo ring contraction to a gibberellin 7-aldehyde. However, 7-oxo-*ent*-kaurenoic acid (**43**) was transformed by *G. fujikuroi* into fujenoic triacid (**9**). The presence of hydroxyl groups at C-3α and C-18 on a kaurenoid substrate inhibits the hydroxylation of C-19 by this fungus. Incubation of 18-hydroxy-7-oxo-*ent*-kaur-16-ene (**44**) and 3α,18-dihydroxy-7-oxo-*ent*-kaur-16-ene (**45**) with *G. fujikuroi* gave the corresponding 6β-hydroxy derivatives, **46** and **47**, without the significant cleavage of ring B suggesting that neighbouring group participation by a C-19 carboxyl group may play a role in this process.

The biotransformation by *G. fujikuroi* of 6α,19-dihydroxy*ent*-kaur-16-ene (**48**), 6,19-dioxo-*ent*-kaur-16-ene (**49**) and 6-oxo-*ent*-kaur-16-en-19-oic acid (**50**), which have not been isolated from this fungus, also afford fujenal (**1**) (Alam et al., 1991). In the two last compounds, C-6 is at a higher oxidation level than C-7 prior to the cleavage of the C-6:C-7 bond to form the aldehyde, which probably imply a different mechanism to form fujenal, than that operating in the natural route. A plausible mechanism has to account for the unsymmetrical fission of the C-6:C-7 bond to generate a C-6 carboxylic acid and a C-7 aldehyde.

The naturally occurring gibberellin plant hormones isolated so far belong to the *ent*-kaur-16-ene series. However, microbiological

transformations of other tetracyclic diterpenes by *G. fujikuroi* have also been studied. Thus, the biotransformation of *ent*-kaur-15-ene (**51**), *ent*-trachyloban-19-oic acid (**52**) and *ent*-atis-16-en-19-ol (**53**) affords gibberellin and fujenal analogues, such as **54**, **55** and **56**, respectively (Beale et al., 1983; Fraga et al., 1987). However, the incubations of beyerane derivatives such us *ent*-beyer-15-ene (**57**) and *ent*-beyera-15-en-19-oic acid (**58**) gave gibberellin analogues, but not fujenal analogues (Díaz et al., 1985; Ali et al., 1992). These facts should be attributed to the presence of the 15,16-bridge in the α-face of the *ent*-beyer-15-ene skeleton, which, although it permits the formation of gibberellins, avoid the cleavage of the B-ring to form a fujenal analogue, such as **59**.

The biotransformation of ribenone (**60**) by *G. fuikuroi* leads to the formation of the 2,3-*seco*-acid **61**, and other metabolites of this type (Fraga et al., 1999). These compounds are very interesting in relation to the substrate specificity of the enzyme involved in the formation in this fungus of fujenal (**1**) and fujenoic acid (**2**) (or their corresponding diacid **8** and triacid **9**, respectively). It has been shown that 7-oxo-*ent*-kaur-16-en-19-oic acid (**43**) was completely metabolized to the triacid **9** by *G. fujikuroi* (Bearder et al., 1975; Fraga et al., 2005). Thus, the formation of the *seco*-acid (**61**) from ribenone (**60**) may occur in a similar manner to the conversion of **43** to the triacid **9**, and may involve the same enzyme.

In this article we have shown how neighbouring group participation, which plays an important part in understanding many aspects of diterpenoid chemistry, determines many of the products of an unusual *seco*-kaurenoid diterpene, fujenal. We have also shown how the use of analogue biosynthetic transformations utilizing the diversity of diterpenoid skeletal, can shed light on the constraints of an interesting biosynthetic pathway.

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