# The Acyloin Condensation of the Diterpenoid Fujenal

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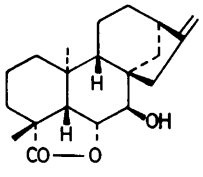
The reaction of the *B*-seco-diterpenoid fujenal with sodium in liquid ammonia affords two 6-monohydroxy- and two 6,7-dihydroxy-kaurenes.

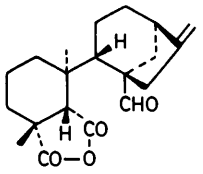
OUR biosynthetic studies have made use of a number of *ent*-kaurenoid diterpenes which are hydroxylated in ring *B*.[1] The kaurenolide lactones [*e.g.* (1)] [2] which were obtained from commercial gibberellin fermentation residues made convenient starting materials for the partial synthesis of some of these compounds.[3-5] However the kaurenolide biosynthetic pathway diverges from the gibberellin pathway at a relatively early stage, probably in the immediate metabolism of *ent*-kaur-16-en-19-oic acid.[6] Recent industrial mutants which provide a good yield of gibberellic acid do not appear to produce substantial quantities of the kaurenolides. Consequently we have sought alternative sources of the biosynthetically useful hydroxylated kaurenes. Although diterpenoids with an *ent*-kaurenoid skeleton are common in higher plants, there are few that possess a C-6 oxygen function. The *B*-seco-aldehyde–anhydride fujenal (2) is also produced [7] by *G. fujikuroi*. We describe here a reconstruction of ring *B* of fujenal which leads to useful hydroxylated kaurenoids.

As part of the proof of its structure,[8,9] the bitter principle enmein (3) was converted into *ent*-kaurane by a route which involved the acyloin condensation of the lactone–ester (4) to afford the alcohol (5) as the major product. Fujenal (2), which possesses an aldehyde–anhydride system, should in principle undergo a similar reaction. Fujenal was treated with sodium in dried liquid ammonia [10] under similar conditions and the complex mixture of products was separated by chromatography on silica.

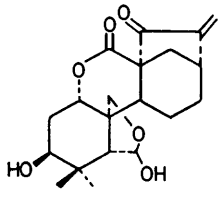
The first, minor product, $C_{20}H_{28}O_3$ (6) [$\nu_{max.}$ 3 510 (OH) and 1 745 $cm^{-1}$ ($\gamma$-lactone)], showed an AB doublet ($\delta$ 3.65 and 4.15, $J$ 9 Hz), in the $^1H$ n.m.r. spectrum typical of a C–$CH_2$–O grouping and a singlet ($\delta$ 4.25) assigned to the methine hydrogen in a C–CH(OH)–C grouping. On oxidation it gave the known ketone (7),[11] identified by its n.m.r. spectrum. The alcohol (6) was assigned the stereochemistry at C-6 epimeric to that of the known compound (8) [11] on the basis of their $^1H$ n.m.r. spectra. In the former (6), the 18-$H_3$ signal appears at $\delta$ 1.40 whilst in the latter (8), it appears at $\delta$ 1.23. Hence in compound (6) the hydroxy-group is *syn* to C-18 (*i.e.* $\beta$). This minor compound probably arises through partial reduction of the anhydride and a base-catalysed internal aldol condensation between C-5 and C-7. The second, dimeric, minor product, $C_{40}H_{54}O_8$ (9), retained the anhydride i.r. absorption ($\nu_{max.}$ 1 855 and 1 775 $cm^{-1}$) and possessed two secondary alcohol groups [$\nu_{max.}$ 3 500 $cm^{-1}$, $\delta$ 4.02 (s, 2 H)]. On oxidation with chromium trioxide, fujenal (2) was regenerated, and the compound was therefore assigned the dimeric structure (9). The third product was a hydroxy-acid, $C_{20}H_{30}O_3$ (10) ($\nu_{max.}$ 3 390, 3 000br, and 1 705 $cm^{-1}$), which gave a monomethyl ester (11) with diazomethane. On oxidation with



(1)



(2)



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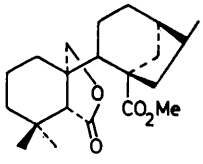

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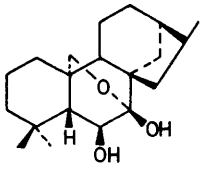

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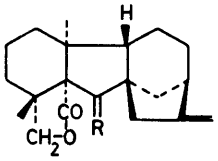
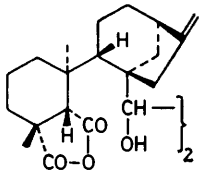


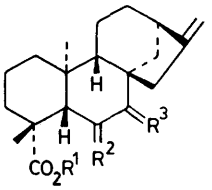
(6) R = α-H, β-OH
(7) R = O
(8) R = α-OH, β-H

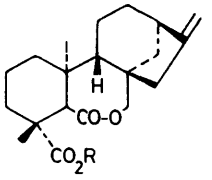


(9)

chromium trioxide, the acid gave the known 6-oxo-acid (12).[2] The stereochemistry of the 6-alcohol was assigned from the multiplicity of the 6-H resonance ($\delta$ 4.32) (see Table), which appeared as a triplet ($J$ 10.5 Hz) of doublets ($J$ 4.5 Hz) indicative of two diaxial and one axial–equatorial coupling. As expected for an equatorial 6$\beta$-alcohol, the 18-$H_3$ resonance was at lower field ($\delta$

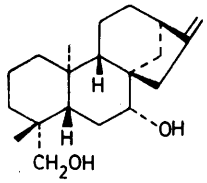
1.52), and the 20-$H_3$ resonance (δ 0.90) was comparable with that in *ent*-kaur-16-en-19-oic acid (δ 1.18 and 0.90, respectively). The fourth product, $C_{20}H_{28}O_4$ (13) [$\nu_{max.}$ 2 900br, 1 695 ($CO_2H$), and 1 730 $cm^{-1}$ (lactone)], was identical with a by-product of the reaction of fujenal with





(10) $R^1$ = H, $R^2$ = α-H, β-OH, $R^3$ = $H_2$
(11) $R^1$ = Me, $R^2$ = α-H, β-OH, $R^3$ = $H_2$
(12) $R^1$ = H, $R^2$ = O, $R^3$ = $H_2$
(15) $R^1$ = Me, $R^2$ = α-OH, β-H, $R^3$ = $H_2$
(16) $R^1$ = Me, $R^2$ = α-H, β-OH, $R^3$ = α-OH, β-H
(17) $R^1$ = Me, $R^2$ = α-H, β-OH, $R^3$ = α-H, β-OH
(18) $R^1$ = Me, $R^2$ = α-OH, β-H, $R^3$ = α-H, β-OH
(19) $R^1$ = Me, $R^2$ = α-OH, β-H, $R^3$ = α-H, β-OAc
(20) $R^1$ = Me, $R^2$ = H, $R^3$ = O
(22) $R^1$ = Me, $R^2$ = α-H, β-OH, $R^3$ = α-OTs, β-H

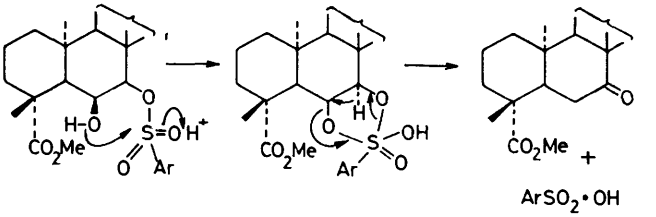
(13) R = H
(14) R = Me



(21)

sodium hydride.[12] On treatment with diazomethane, the compound formed a monomethyl ester (14) ($\nu_{max.}$ 1 730br $cm^{-1}$). The $^1H$ n.m.r. spectra of both the acid and the ester contained an AB doublet (δ 3.90 and 4.60; 3.75 and 4.48, respectively, $J$ 13 Hz) assigned to the system C–$CH_2$OC(O), and a singlet (δ 2.95) assigned to 5-H. These features can be accommodated by the structure (13).

10% each) of the acyloin condensation, were diols, $C_{21}H_{32}O_4$ (16) and (17). Their structures and stereochemistry followed from their $^1H$ n.m.r. spectra (see Table). In that of compound (16), the 6-H resonance appeared as a triplet (δ 4.05) in which the magnitudes (10 Hz) of the coupling constants $J_{5.6}$ and $J_{6.7}$ showed that the compound possessed a diequatorial diol system. In the spectrum of the other ester (17), the coupling constants $J_{5,6}$ (11 Hz) and $J_{6.7}$ (2 Hz) were indicative of an equatorial–axial diol. These relationships were established by decoupling studies. The position of the



SCHEME

5-H resonance clearly reflects the diaxial interaction with the 7β-hydroxy-group. This is also revealed by a comparison of the diaxial diol (18) with the corresponding 7β-acetate (19). Comparison of the position of the 13-methyl resonances in (16) and (17) with those of the 6-epimer (18) reflects the interaction with an equatorial 6β-hydroxy-group, whilst the position of the 10-methyl resonance in the spectra of (18) and (19) reflects the diaxial interaction with the 6α-hydroxy-group. These features have an obvious diagnostic value in the determination of stereochemistry at C-6.

The formation of the hitherto relatively inaccessible 6β,7β-diol (17) afforded an opportunity to attempt the ring-contraction of the kaurene to the gibberellin ring system. However in an effort to form a mono-toluene-*p*-sulphonate, treatment of the diol (17) with toluene-*p*-sulphonyl chloride gave the known 7-oxo-ester (20),[13] identified by comparison with an authentic sample. This reaction is unusual in that it apparently utilizes an equatorial leaving group with the elimination of an equatorial hydrogen atom. A possible alternative mechanism (see Scheme) involving acylation at the less

$^1H$ N.m.r. spectra determined for solutions in $CDCl_3$ at 220 MHz †

| Compound | 5-H | 6-H | 7-H | 17-$H_2$ | 18-$H_3$ | 20-$H_3$ | OMe |
|---|---|---|---|---|---|---|---|
| (10) | 1.23 | 4.32 | N.a. | 4.83, 4.88 | 1.52 | 0.98 | |
| (15) | N.a. | 4.55 | N.a. | 4.81, 4.86 | 1.30 | 1.09 | 3.79 |
| (16) | 1.23 | 4.05 | 3.40 | 4.81, 4.88 | 1.45 | 0.89 | 3.77 |
| (17) | 1.95 | 4.32 | 3.64 | 4.87 | 1.42 | 0.85 | 3.76 |
| (18) | 1.67 | 4.32 | 3.71 | 4.88 | 1.31 | 1.09 | 3.81 |
| (19) | 1.40 | 4.26 | 4.96 | 4.81, 4.84 | 1.23 | 1.09 | 3.80 |

† N.a. = not assigned. The multiplicities of the 6-H and 7-H signals were determined after treatment with $^2H_2O$.

Further elution gave a mixture of acids which were methylated with diazomethane and then separated (as their esters) by chromatography on silica. The first product from this chromatography was the known hydroxy-ester (15),[3] which was epimeric at C-6 to the ester (11). The second and third products from this chromatography, which formed the major products (*ca.*

hindered 7-position, followed by cyclic sulphonate formation, would alter the conformation of ring *B*. Elimination to reduce the C-6,C-18 interaction and ketonization by a 1,2-hydrogen shift then affords the 7-oxo-ester. Reduction of the oxo-ester with lithium aluminium hydride gave the 7α,19-diol (21) (*cf.* ref. 4). In contrast, the diol (16) gave a 7α-mono-toluene-*p*-

sulphonate (22). The location of the *p*-tolylsulphonyloxy-group at C-7 was demonstrated by the downfield shift of the 7-H doublet ($\Delta\delta$ 1.22 p.p.m.) in comparison with the parent alcohol. The angle strain inherent in the formation of a diequatorial cyclic sulphonate possibly precludes ready ketonization in this instance.

In conclusion, the acyloin condensation of fujenal affords a simple method of preparing some hitherto relatively inaccessible kaurenoid C-6 and C-7 mono-ols and diols.

## EXPERIMENTAL

Silica for chromatography was Merck 7734. $^1$H N.m.r. spectra were determined at 90 MHz with a Perkin-Elmer R32 or at 220 MHz with a Perkin-Elmer R34 instrument (PCMU); i.r. spectra were for Nujol mulls. Light petroleum refers to the fraction of b.p. 60—80 °C.

*Acyloin Condensation of Fujenal* (2).—The fujenal was dried over phosphorus pentaoxide *in vacuo* at room temperature for 3 days. Liquid ammonia was dried over sodium and distilled. Small pieces of sodium (1 g) were added under dry nitrogen to the liquid ammonia (160 ml) and anhydrous ether (140 ml) in a three necked flask fitted with a solid $CO_2$ condenser and protected from atmospheric moisture by potassium hydroxide and silica gel drying tubes. Fujenal (2 g) in dry ether (100 ml) was added over 2 h. Methanol (10 ml) in ether (100 ml) was then added and the ammonia allowed to evaporate. The solution was acidified with dil. hydrochloric acid and the products were recovered in ether. The combined extracts were washed with water, dried ($Na_2SO_4$), and evaporated. The reaction was repeated with a further 2 g of fujenal and the combined products were chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave the *hydroxylactone* (6), which crystallized from ethyl acetate–light petroleum as prisms (25 mg), m.p. 206—207 °C (Found: C, 76.3; H, 8.75. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%); $\nu_{max.}$ 3 510, 3 060, 1 745, 1 660, and 870 cm$^{-1}$; $\delta$ 1.10 (3 H, s), 1.40 (3 H, s), 3.65 and 4.15 (each 1 H, d, *J* 9 Hz), 4.25 (1 H, s), and 4.90 (2 H, br, s). Elution with 15% ethyl acetate–light petroleum gave the *dimer* (9), which crystallized from acetone–light petroleum as prisms (38 mg), m.p. 240—243 °C (Found: C, 72.9; H, 8.05. $C_{40}H_{54}O_8$ requires C, 72.5; H, 8.2%); $\nu_{max.}$ 3 500, 1 855, 1 775, 1 660, and 900 cm$^{-1}$; $\delta$ 1.30 (6 H, s), 1.40 (6 H, s), 4.02 (2 H, s), and 4.90 (4 H, s). Elution with 30% ethyl acetate–light petroleum gave ent-6$\alpha$-*hydroxykaur*-16-*en*-19-*oic acid* (10), which crystallized from ethyl acetate–light petroleum as needles (140 mg), m.p. 193—195 °C (Found: C, 75.7; H, 8.8. $C_{20}H_{30}O_3$ requires C, 75.4; H, 9.5%); $\nu_{max.}$ 3 390br, 3 000br, 1 705, 1 658, and 885 cm$^{-1}$; for $^1$H n.m.r. see Table. The methyl ester (11), prepared with diazomethane, was a gum, $\nu_{max.}$ 3 540, 1 722, 1 660, and 875 cm$^{-1}$; $\delta$ 0.92 (3 H, s), 1.53 (3 H, s), 3.80 (3 H, s), 4.22 (1 H, m), and 4.83 (2 H, br, s). Further elution with 15% ethyl acetate–light petroleum gave *ent*-7-hydroxy-6,7-secokaur-16-ene-6,19-dioic acid 6,7-lactone (275 mg) which crystallized from ethyl acetate–light petroleum as plates, m.p. 268—271 °C, identical (i.r. and n.m.r.) with the material obtained [12] from the action of sodium hydride on fujenal. Elution with 40% ethyl acetate–light petroleum gave a white solid (1.36 g), which was methylated with diazomethane and rechromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave methyl *ent*-6$\beta$-hydroxykaur-16-en-19-oate (15), which crystallized from methanol as needles (60 mg), m.p. 155—157 °C (lit.,[3] 158—159 °C) (Found: C, 76.3; H, 9.2. Calc. for $C_{21}H_{32}O_3$: C, 75.8; H, 9.7%), identical (i.r., n.m.r. and mixed m.p.) with an authentic sample. Elution with 15% ethyl acetate–light petroleum gave *methyl* ent-6$\alpha$,7$\beta$-*dihydroxykaur*-16-*en*-19-*oate* (16) (440 mg), which crystallized from light petroleum as needles, m.p. 95—96 °C (Found: C, 72.5; H, 9.0. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.3%), $\nu_{max.}$ 3 340br, 1 730, 1 660, and 875 cm$^{-1}$; for $^1$H n.m.r. see Table. Further elution gave *methyl* ent-6$\alpha$,7$\alpha$-*dihydroxykaur*-16-*en*-19-*oate* (17) (410 mg), which crystallized from light petroleum as needles, m.p. 111—113 °C (Found: C, 72.5; H, 9.2. $C_{21}H_{32}O_4$ requires C, 72.4; H, 9.3%); $\nu_{max.}$ 3 500, 3 350br, 1 727, 1 655, and 868 cm$^{-1}$; for $^1$H n.m.r. see Table.

*Oxidation of the Hydroxy-lactone* (6).—The hydroxy-lactone (6) (15 mg) in acetone (3 ml) was treated with an excess of 8N-chromium trioxide for 1 h, at room temperature. Methanol was added and the mixture concentrated. The product was recovered in ethyl acetate and the solvent evaporated off to afford the oxo-lactone (7), which crystallized from aqueous methanol as plates, m.p. 90—93 °C (lit.,[11] 142—143 °C) (Found: C, 76.9; H, 8.3. Calc. for $C_{20}H_{26}O_3$: C, 76.4; H, 8.3%), identical ($^1$H n.m.r.) with authentic material.

*Oxidation of the Dimer* (9).—The dimer (25 mg) in acetone (3 ml) was treated with 8N-chromium trioxide reagent at room temperature for 1 h. The product was recovered as above and chromatographed on silica. Elution with 10% ethyl acetate–light petroleum gave fujenal (14 mg), m.p. 164—167 °C, identified by its i.r. and n.m.r. spectra.

*Oxidation of the Acid* (10).—The acid (25 mg) in acetone (3 ml) was treated with 8N-chromium trioxide reagent at room temperature for 1 h. The product was recovered as above and chromatographed on silica. Elution with 15% ethyl acetate–light petroleum gave *ent*-6-oxokaur-16-en-19-oic acid (12) (12 mg), m.p. 261—262 °C (lit.,[2] 264—265 °C), identified by its i.r. spectrum.

*Treatment of the Diols* (16) *and* (17) *with Toluene*-p-*sulphonyl Chloride*.—(*a*) The diol (16) (100 mg) in pyridine (3 ml) was treated with toluene-*p*-sulphonyl chloride (150 mg) for 48 h at room temperature. The mixture was poured into dil. hydrochloric acid and recovered in ethyl acetate. It was purified by t.l.c. in 40% ethyl acetate–light petroleum on silica. The ent-7$\beta$-*toluene*-p-*sulphonate* (22) (45 mg) crystallized from ethyl acetate–light petroleum as needles, m.p. 137—139 °C (decomp.) (Found: C, 67.5; H, 7.6. $C_{28}H_{38}O_6S$ requires C, 67.2; H, 7.25%); $\nu_{max.}$ 3 565, 1 712, 1 660, 1 600, and 905 cm$^{-1}$; $\delta$ 0.86 (3 H, s), 1.44 (3 H, s), 2.38 (3 H, s), 3.63 (3 H, s), 4.25 (1 H, t, *J* 11 Hz), 4.62 (1 H, d, *J* 11 Hz), 4.72 (2 H, br, s), and 7.27 and 7.84 (each 2 H, d, *J* 9 Hz).

(*b*) The diol (17) (100 mg) in pyridine (3 ml) was treated with toluene-*p*-sulphonyl chloride (150 mg) for 48 h at room temperature. The solution was poured into dil. hydrochloric acid and the product recovered in ethyl acetate and chromatographed on silica. Elution with 5% ethyl acetate–light petroleum gave methyl *ent*-7-oxokaur-16-en-19-oate (20) (47 mg), which crystallized from light petroleum as needles, m.p. 113—114 °C (lit.,[13] 110—112 °C) (Found: C, 76.3; H, 8.9. Calc. for $C_{21}H_{30}O_3$: C, 76.3; H, 9.15%); $\nu_{max.}$ 1 712, 1 702, 1 658, and 873 cm$^{-1}$; $\delta$ 1.03 (3 H, s), 1.15 (3 H, s), 3.70 (3 H, s), and 4.85 (2 H, br, s), identical (i.r. and mixed m.p.) with an authentic sample.

*Reduction of the Oxo-ester* (20).—The ester (20) (30 mg) in ether (40 ml) was treated with lithium aluminium hydride (75 mg) for 6 h under reflux. The suspension was treated with moist ether and the product recovered in ether to afford ent-7β,19-*dihydroxykaur*-16-*ene* (21) (18 mg), which crystallized from ethyl acetate–light petroleum as needles, m.p. 199—202 °C (Found: C, 78.6; H, 10.6. $C_{20}H_{32}O_2$ requires C, 78.9; H, 10.6%); $\nu_{max.}$ 3 418br, 1 660, and 882 $cm^{-1}$, δ [($^2H_5$)pyridine] 1.0 (3 H, s), 1.15 (3 H, s), 3.58 (1 H, m), 3.95 (2 H, ABq, *J* 10 Hz), and 4.80 (2 H, br, s).

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REFERENCES

[1] J. R. Hanson, J. Hawker, and A. F. White, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1892.
[2] B. E. Cross, R. H. B. Galt, and J. R. Hanson, *J. Chem. Soc.*, 1963, 2944.
[3] J. R. Hanson, *Tetrahedron*, 1966, **22**, 2877.
[4] J. R. Hanson and A. F. White, *Tetrahedron*, 1969, **25**, 2743.
[5] J. R. Hanson and J. Hawker, *Tetrahedron*, 1972, **28**, 2521.
[6] P. Hedden and J. E. Graebe, *Phytochemistry*, 1981, **20**, 1011.
[7] B. E. Cross, R. H. B. Galt, and J. R. Hanson, *J. Chem. Soc.*, 1963, 5052.
[8] K. Shudo, M. Natsume, and T. Okamoto, *Chem. Pharm. Bull.*, 1965, **13**, 1019.
[9] E. Fujita, T. Fujita, K. Fuji, and N. Ito, *Chem. Pharm. Bull.*, 1965, **13**, 1023; *Tetrahedron*, 1966, **22**, 3423.
[10] E. E. van Tamelen, T. A. Spencer, jun., D. S. Allen, jun., and R. L. Orvis, *Tetrahedron*, 1961, **14**, 8.
[11] R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.*, 1965, 1565.
[12] J. R. Hanson, K. H. Parry, J. Triana, and C. Willis, unpublished work.
[13] R. H. B. Galt and J. R. Hanson, *Tetrahedron*, 1966, **22**, 3185.