SHORT PAPER

J. Chem. Research (S),
2002, 647–648

Interactions between the aldehyde and anhydride groups in the diterpenoid fujenal[†]

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Methanolysis of the diterpenoid aldehyde:anhydride, fujenal, catalysed by tetracyanoethylene afforded C-6:C-7 methoxylactones whilst the addition of methyl magnesium bromide to fujenal afforded a 6,7-lactone but with an *cis* A/B ring junction; the structures of these products were established by X-ray crystallography.

Keywords: Gibberella fujikuroi, fujenal, tetracyanoethylene

The diterpenoid aldehyde:anhydride fujenal **1** is a metabolite of the fungus, *Gibberella fujikuroi*.[1,2] It is unusual, but not unique, amongst natural products in possessing a five-membered cyclic anhydride. Although ring B of the tetracyclic diterpenoid skeleton has been cleaved to form the C-7 aldehyde and the C-6:C-19 anhydride, a number of the reactions of fujenal reveal interactions between these functional groups. In this paper, we report two examples of these interactions.

When fujenal **1** was heated with methanol in a sealed tube at 160° for 4 days, it gave[2] two methoxy-lactones **2** and **3**. The methoxy-lactone **2** played a key role in the elucidation of the structure of fujenal and its correlation with the tetracyclic kaurenolide diterpenoid metabolites of *Gibberella fujikuroi*. However, the stereochemistry of **2** at C-7 and that of **3** at C-7 and C-16, which were not crucial to the interrelationship with the kaurenolides, were not established at the time.

Tetracyanoethylene (TCNE) is a mild π-acid catalyst which has been used for the methanolysis of a number of oxygen functions.[3,4] In continuation of our studies[3] on the scope of tetracyanoethylene catalysed reactions, we have examined its use as a catalyst in the methanolysis of the anhydride ring of fujenal. Treatment of fujenal **1** in refluxing methanol with TCNE for 3 hours gave a separable mixture of the methoxy-lactones **2** and **3**.[2] The X-ray crystal structure of the methoxy-lactone **3** established its full stereochemistry (Fig. 1). The methoxyl group at C-7 has taken up the C-7β axial conformation. This position is analogous to the anomeric position of an acetal in which the stereo-electronic effect of the oxygen lone pairs plays a major role in determining the axial stereochemistry of ethers.[5] In the case of **2** and **3** the interaction between the lone pairs of 04 and 05 leads to the axial C-7β conformation for the methoxyl group. The configuration at C-16 parallels that of the hydration of ent-kaurene to give ent-kauranol.[6]

The γ-lactone **4** was obtained[7] by the reduction of fujenal **1** with lithium aluminium hydride or sodium borohydride. When **4** was treated with tetracyanoethylene in methanol, isomerisation rather than methanolysis of the lactone ring took place and the product was the ε-lactone **5**.[8]

Both the formation of the pseudo-ester and the isomerisation of the lactone ring may be rationalised in terms of single-electron transfer catalysis by the TCNE. They reveal the participation of C-7 functional groups in the reactions of C-6 of these 6,7-seco diterpenes.

Treatment of fujenal **1** with methyl magnesium bromide gave a lactonic acid which was purified as its methyl ester **6**. The alkoxide formed by the addition of the methyl magnesium bromide to the aldehyde, had cleaved the anhydride ring. The stereochemistry of the methyl group at C-7 was established by X-ray crystallography (Fig. 2). This also revealed that C-5 had unexpectedly undergone epimerization to form the unusual *cis* A/B ring junction and that ring B had taken up a boat type of conformation. These changes relieve the interactions between the C-4 substituents and C-6 and, unlike the methoxy-lactone **3** where stereo-electronic features involving the interaction of the oxygen lone pairs control the stereochemistry at C-7, it allows the methyl group at C-7 to occupy a sterically more favourable equatorial conformation.

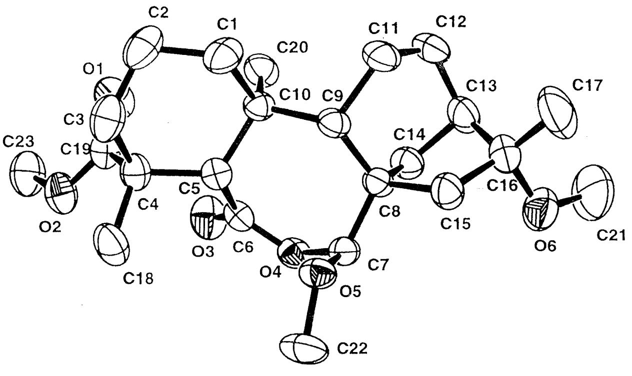

Fig.1 X-Ray crystal structure of the pseudo-ester **3**.

Experimental

^{1}H NMR spectra were determined at 300 MHz for solutions in deuteriochloroform. IR spectra were determined as nujol mulls. Silica for chromatography was BDH silica for flash chromatography. Light petroleum refers to the fraction b.p. 60–80°C.

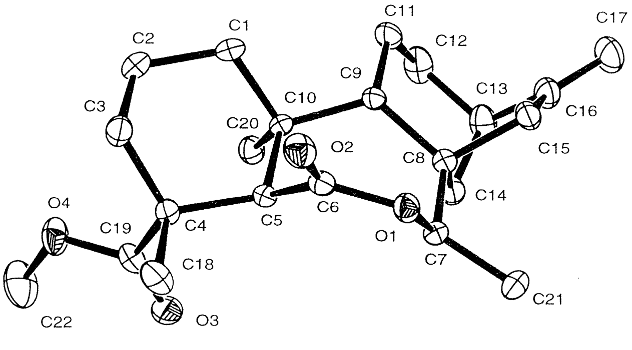

Fig.2 X-Ray crystal structure of the Grignard adduct **6**.

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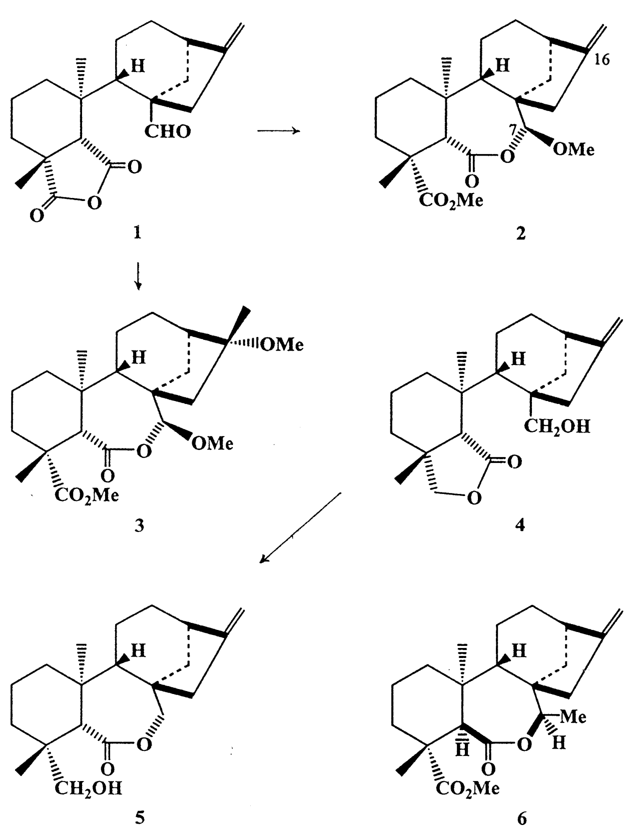
[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 1

Methanolysis of fujenal: Fujenal **1** (500 mg) in methanol (25 cm^3) containing tetracyanoethylene (100 mg) was heated under reflux for 3 h. The solvent was evaporated to give a residue which was chromatographed on silica. Elution with 20% ethyl acetate: light petroleum gave ent-7β-hydroxy-7α-methoxy-6, 7-secokaur-16-ene-6,19-dioic acid 19-methyl ester 6,7-lactone **2** (155 mg) which crystallized from acetone as cubes, m.p. 182–184°C, (lit.,[2] 190°C), υ_{max}/cm^{-1} 1735,1723,1655; δ_H 1.23 and 1.35 (each 3H, s, H-18 and H-20), 3.49 (3H, s, 7-OMe), 3.67 (3H, s, 19-OMe), 4.50 (1H, s, H-7), 4.76 and 4.84 (each IH,s,H-17). Further elution with 30% ethyl acetate:light petroleum gave ent-7 α, 16 β-dimethoxy-7 β-hydroxy-6, 7-secokaurane-6, 19-dioic acid 19-methyl ester 6,7-lactone **3** (280 mg) which crystallized from ethyl acetate as plates, m.p. 180–182°C (lit.,[2] 190°C), υ_{max}/cm^{-1} 1721; δ_H (acetone-d$_6$) 1.21,1.27 and 1.33 (each 3 Hs, H-17, H-18 and H-20), 3.11 (3H, s, 16-OMe), 3.48 (3H, s, 7-OMe), 3.68 (3H, s, 19-OMe), 4.50 (1H, s, H-7).

*Reaction of the lactone **4** with TCNE and methanol*: The lactone **4**[8] (250 mg) was dissolved in methanol (10 cm^3) containing TCNE (50 mg) and stirred at room temperature for 3 h. The solvent was evaporated and the residue was chromatographed on silica. Elution with 20% ethyl acetate:light petroleum gave ent-7, 19-dihydroxy-6,7-secokaur-16-en-6-oic acid 6,7-lactone 5[8] (205 mg), m.p.132–135°C [lit.,[8] 210–211.5°C(polymorphic form)], υ_{max}/cm^{-1} 3420, 1720; δ_H (acetone-d$_6$) l.10 (3H, s, H-20), 1.20 ((3H, s, H-18), 3.20 and 4.14 (each 1H, d, *J* 8.8 Hz, H-19), 3.74 and 3.97 (each 1H, s, H-7), 4.69 and 4.77 (each IH, s, H-17).

Reaction of fujenal with methyl magnesium bromide: Fujenal (1 g) in dry tetrahydrofuran (45 cm^3) was treated with methyl magnesium bromide in ether (3M, 1.5 cm^3) under nitrogen at 0°C. The mixture was left to stir overnight and then treated with saturated aqueous ammonium chloride. The solution was extracted with dichloromethane. The extract was washed with water, dried and the solvent evaporated to give a residue which was chromatographed on silica. Elution with 25% ethyl acetate:light petroleum gave fujenal (150 mg) and then crude 7-hydroxy-7methyl-6, 7-secokaur-16-en-6, 19-dioic acid 6-7 lactone (640 mg), m.p.228–230°C. The crude acid was dissolved in methanol (50 cm^3) and methylated with excess ethereal diazomethane. The solvent was evaporated and the residue purified by chromatography on alumina. Elution with 10% ethyl acetate:light petroleum gave ent-7β-hydroxy-7α-methyl-6, 7-seco-5β(H) -kaur-16-en-6, 19-dioic acid 6-7 lactone 19-methyl ester (500 mg), m.p. 118–120°C, (Found: M$^+$ 360.227 $C_{22}H_{32}O_4$ requires M$^+$ 360.230), υ_{max}/cm^{-1} 1732,1660; δ_H 1.03 (3H, s, H-20), l.23 (3H, s, H-18), 1.34 (3H, d, *J* 6.2 Hz, 7-Me), 3,73 (3H, s, OMe), 4.79 and 4.85 (each lH, br.s. H-17), 4.98 (lH,q, *J* 6.2 Hz, H-7).

X-Ray crystallographic data and structure determinations: (a) $C_{23}H_{36}0_6$, M 408.5, orthorhombic, space group $P2_12_12_1$ (No.19), *a* = 6.2668(2), *b* = 17.6525(8), *c* = 19.9568(8)Å, α = β = γ = 90° V = 2207.7(2) Å^3, Z = 4, D$_{calc}$ 1.23 g/cm^3, μ = 0.09 mm^{-1} F(000) 888, Data were collected using a crystal of size 0.4 × 0.2 × 0.1 mm^3. A total of 10,487 reflections were collected for 4.12<θ<27.90° and -8<=*h*<=8, -23<=*k*<=23,-26<=*l*<=26. There were 5,195 independent reflections and 3,542 reflections with *I*>2σ(*I*) that were used in the refinement. There was no crystal decay and no absorption correction was applied. The structure was solved by direct methods using SHELXL-97 and refined by full matrix least squares on F^2. The final R indices were R$_1$ = 0.061, wR$_2$ = 0.125 and (all data), R$_1$ = 0.104 and wR$_2$ = 0.147. The goodness-of-fit on F^2 was 1.031 and the largest difference peak and hole was 0.22 and –0.22 eÅ^{-3}.

(b) $C_{22}H_{32}O_4$, M 360.48, monoclinic, space group $p2_1$(no.4), *a* = 6.7594(6), *b* = 20.3909(16), *c* = 7.4852(4)Å, α = γ = 90° = β = 106.195(5)^0, V = 990.75(13) Å^3, Z = 2, D$_{calc}$ 1.21 g/cm^3, μ = 0.08 mm^{-1}, F(000) 392, Data were collected using a crystal of size 0.4 × 0.4 × 0.1 mm^3. A total of 3829 reflections were collected for 3.73<θ<25.05° and –7<=*h*<=8, –21<=*k*<=24, –8<=*l*<=8. There were 2753 independent reflections and 2403 reflections with I>2σ(I) that were used in the refinement. There was no crystal decay and no absorption correction was applied The structure was solved by direct methods using SHELXL-97 and refined by full matrix least squares on F^2. The final R indices were R$_1$ = 0.056, wR2 = 0.146 and (all data), R$_1$ = 0.066 and wR$_2$ = 0.162. The goodness-of-fit on F^2 was 1.065 and the largest difference peak and hole was 0.22 and –0.14 eÅ^{-3}.

The crystallographic data have been deposited at the Cambridge Crystallographic Data Centre.

C.U. wishes to thank the Royal Society of Chemistry for a travel grant.

Received 20 February 2002; accepted 19 September 2002
Paper 02/1256

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