Synthesis of the Fusicoccin H Aglycone. Construction of the Carbon Framework

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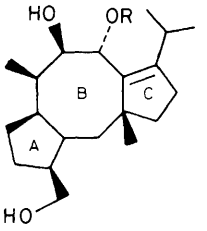
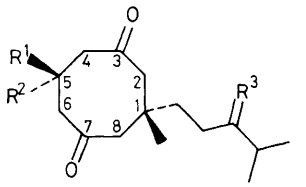
The symmetrical cyclo-octanedione (**4**) has been synthesised and its stereochemistry determined; cyclisation of the derived triketone (**5**) led to the functionalised bicyclo[6.3.0]undecene (**12**) which embodies the B/C ring system of the fusicoccin structure, and regiospecific alkylation of (**4**) with 4-iodobutyl benzoate to give (**13**) was followed by appropriate transformations to yield the A/B fragment (**16**).

Fusicoccin H (**1**) is a minor phytotoxic metabolite[1] of the pathogenic fungus *Fusicoccum amygdali* Del. which adversely affects almond and peach trees in the Mediterranean area. It is one of a relatively uncommon group of natural products having linearly fused five- and eight-membered rings. An attractive intermediate for a total synthesis of the corresponding aglycone (**2**) would be the symmetrical cyclo-octanedione (**3**). We now report a photochemical route to the epimeric compound (**4**), together with some preliminary observations on its chemistry.

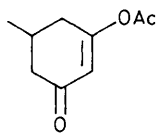
A solution of the enol acetate (**6**)[2] in excess of the olefin (**8**)† was irradiated through a Pyrex filter using a Hanovia 250 W medium-pressure mercury lamp. Surplus (**8**) was distilled from the reaction mixture and the residue, which contained (*vide infra*) the photoadduct (**7**), was hydrolysed and retro-aldolised with aqueous lithium hydroxide. The solid product thus obtained [20% based on (**6**)] was shown by n.m.r. and further evidence detailed below to be substantially the dione (**4**). Recrystallisation yielded the pure *trans*-dimethyl compound (**4**), m.p. 112 °C, directly; the *cis*-isomer (**3**) has not yet



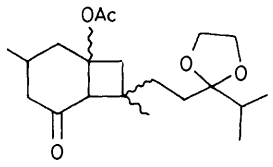
(**1**) R = α-D-glucopyranosyl
(**2**) R = H



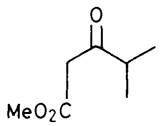
(**3**) R^1 = Me; R^2 = H, R^3 = ⟩
(**4**) R^1 = H, R^2 = Me, R^3 = ⟩ 
(**5**) R^1 = H, R^2 = Me, R^3 = O



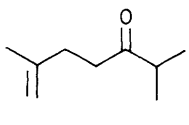
(**6**)



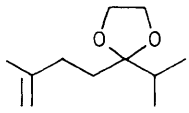
(**7**)



a,b,c



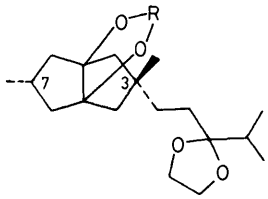
d



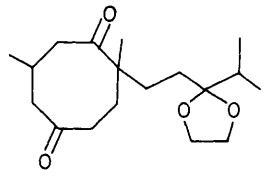
(**8**)

Reagents: a, NaOEt, 3-chloro-2-methylprop-1-ene; b, HO^-; c, H_3O^+; d, $HOCH_2CH_2OH$, *p*-$MeC_6H_4SO_3H$, benzene, azeotrope.

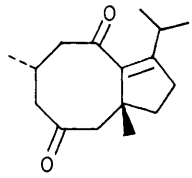
† Satisfactory analytical and spectral data were obtained for the new compounds, all of which are racemates.



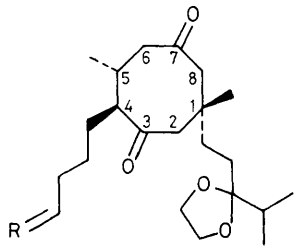
(**9**) R = H, H
(**10**) R = BPh



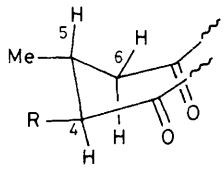
(**11**)



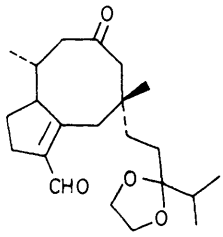
(**12**)



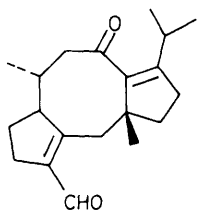
(**13**) R = H, OCOPh
(**14**) R = H, OH
(**15**) R = O



(**14a**)



(**16**)



(**17**)

Table 1. Lanthanide-induced shifts (p.p.m.) for the methyl groups of (**9**).[a]

Molar ratio Eu(dpm)$_3$[b]/(**9**)	δ(3-Me)	Induced shift	δ(7-Me)	Induced shift
0.0	1.133	—	1.034	—
0.156	1.589	0.456	1.133	0.099
0.611	3.259	2.126	1.549	0.515
0.955	4.4—4.7	3.3—3.6	1.835	0.801

[a] In $CDCl_3$. [b] dpm = dipivaloylmethanato.

been isolated from this reaction. The dione (**4**) had *m/z* 267 ($M^+ - C_3H_7$), and formed an octadeuterio-derivative having *m/z* 275 ($M^+ - C_3H_7$) when treated with MeOD–MeONa. The symmetry of (**4**) was evident from its n.m.r. spectrum which exhibited an AB quartet (δ 2.1 and 2.7; *J* 12 Hz), absent from that of the [$^2H_8$]-derivative, for the methylene protons on C-2 and C-8. Furthermore, the proton-decoupled ^{13}C n.m.r. spectrum of (**4**) consisted of only 13 resonances. These data clearly distinguish the dione (**4**) from the alternative possibility (**11**) which would have resulted from inverse orientation during the photoreaction between (**6**) and (**8**).

The relative stereochemistry of (**4**) was determined in the following way. Irradiation of the dione in propan-2-ol solution (Hanovia PCR 1L 100 W lamp, quartz filter) gave the photopinacol (**9**). Precedent[3] suggested that (**9**) would be a *cis* vicinal diol, and this was confirmed by its facile transformation [PhB(OH)$_2$,benzene,azeotrope] to the phenylboronate (**10**). Application of the lanthanide shift reagent Eu(dpm)$_3$ to (**9**) led to very substantial induced n.m.r. shifts (Table 1) for the C-3 tertiary methyl group, while the doublet due to the C-7 methyl group remained close to its original position. The stereostructure which uniquely accommodates these results is that shown for (**9**).

When the acetal group of (**4**) was removed by acid-catalysed exchange with propanone, the triketone (**5**), m.p. 96 °C, was obtained in 93% yield. This could be cyclized to the α,β-unsaturated ketone (**12**), $\lambda_{max.}$ 263 nm, either by heating with aqueous ethanolic lithium hydroxide (59% yield), or on brief treatment with Bu^{t}OK in cold Bu^{t}OH (72%).

Alternatively, the lithium enolate of (**4**) [lithium diisopropylamide in tetrahydrofuran (THF), −78 °C] could be regiospecifically alkylated with 4-iodobutyl benzoate to yield (**13**). The n.m.r. spectrum of (**13**) showed an AB quartet pattern for the protons on C-2 and C-8 which was similar to that for (**4**), but the signals were doubled owing to the newly introduced asymmetry. Hydrolysis of (**13**) gave the primary alcohol (**14**) [98% yield from (**4**)]. We assign the stereochemistry of (**14**) on the basis of a spin-decoupling experiment at 360 MHz, where irradiation of the C-5 secondary methyl resonance at δ 1.07 revealed the C-5 methine proton at δ 2.41. This exhibited two *trans*-diaxial vicinal coupling constants of 11.5 Hz to the adjacent protons on C-4 and C-6, while $J_{5ax-6eq}$ was 2.0 Hz. These results are only compatible with a *trans*-diequatorial disposition for the substituents on C-4 and C-5 (**14a**). Oxidation of (**14**) by pyridinium chlorochromate gave the aldehyde (**15**) (92%) which could be cyclised (Bu^{t}OK, Bu^{t}OH) under carefully controlled conditions to yield the bicyclic unsaturated aldehyde (**16**) (30%).

These successful syntheses of (**12**) and (**16**) provide an effective methodology for construction of the fused A/B and B/C ring systems of the fusicoccin nucleus. We expect that stepwise or simultaneous double cyclization of an appropriate derivative of (**16**) will yield a tricyclic compound (**17**) which is suitably functionalised for conversion into the C-7 epimer of the target molecule (**2**).

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