A Route, *via* Tetraquinane, to the 5-8-5 Carbocyclic Nucleus of Fusicoccins and Ophiobolins

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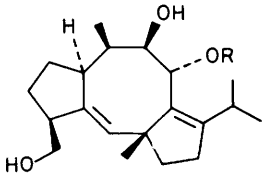
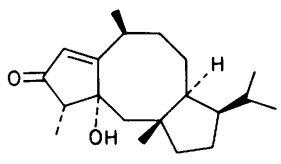
Short, stereoselective syntheses of dicyclopenta[*a,d*]cyclo-octane-based diones (**14**) and (+)-(**22**) *via* a 5-5-5-5→5-8-5 strategy are reported; our approach constitutes an effective methodology for constructing fusicoccane and ophiobolane-type natural products.

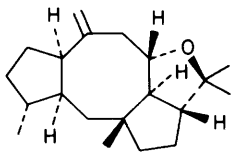
The dicyclopenta[*a,d*]cyclo-octane ring system, thought to be prevalent among the di- and sester-terpenes of fungal origin only, has recently been located among higher plants and marine flora.[1—4] Prominent natural products bearing this fundamental carbon framework are diterpenoids fusicoccin-H (**1**),[1] anadensin (**2**),[2] epoxydictymene (**3**),[3] and the sesterterpenoids of ophiobolane–ceroplastol type, *e.g.*, ophiobolin-F (**4**).[4] The presence of the uncommon 5-8-5 tricarbocyclic ring system with extensive functionalisation and many stereogenic centres, as well as the wide ranging biological activity attributed to members of this family, make them challenging targets of synthesis. Consequently, considerable effort has been mounted in this direction but to date no successful synthesis of a natural product of this family has yet been achieved.[5] We report here a new and general approach to the dicyclopenta[*a,d*]cyclo-octane ring system which has the potential for ready adaptation to the targets (**1**)—(**4**).



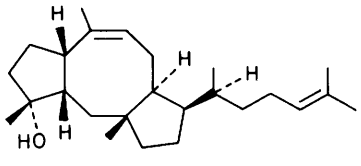
(**1**) R = α-D-glucopyranosyl



(**2**)



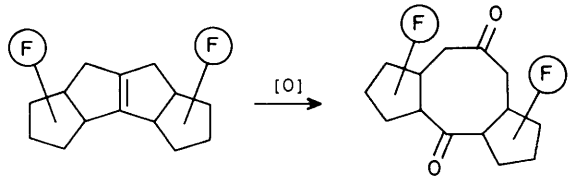
(**3**)



(**4**)

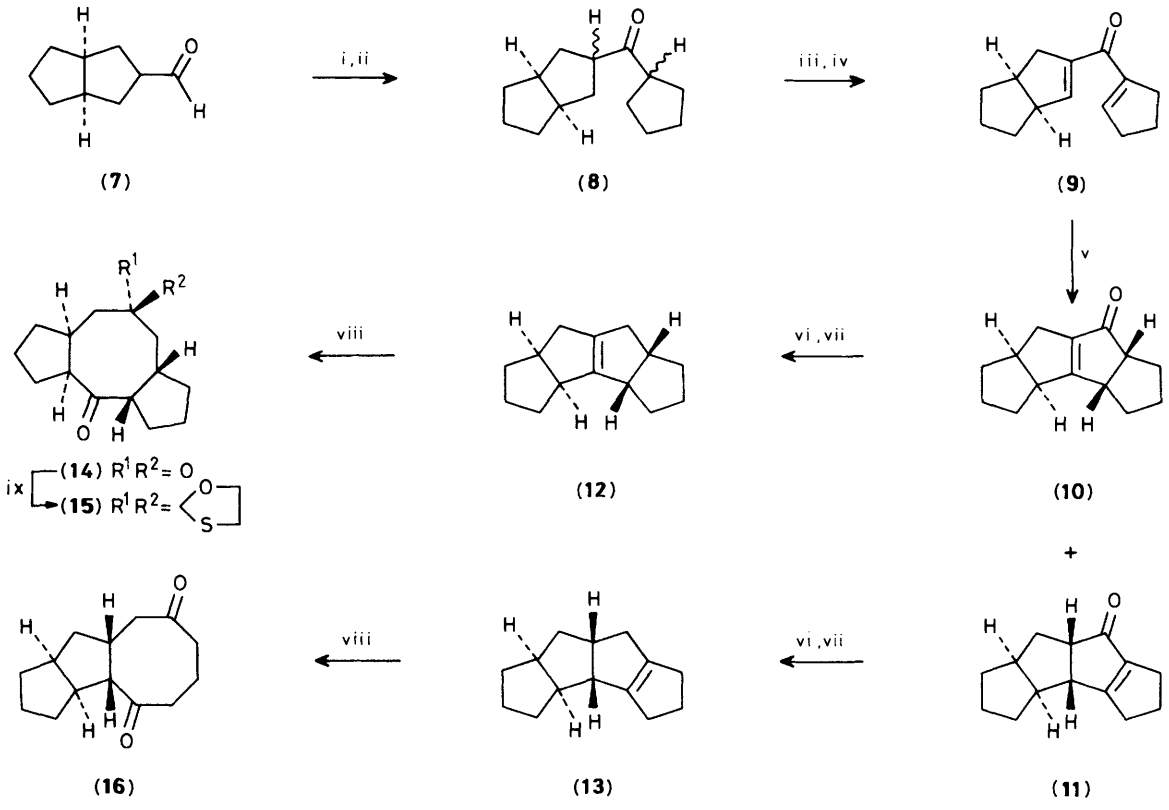
The conceptual basis of our route to the 5-8-5 ring system resides in the recognition that the bicyclo[3.3.0]oct-1(5)-ene moiety can serve as a masked cyclo-octane-1,5-dione equivalent, (**5**)→(**6**).[6] Since polyquinanes prefer the stable *cis,anti,cis*-type pattern and exhibit *exo*-selectivity, these stereochemical controls can be transcribed into the dicyclopenta[*a,d*]cyclo-octane system during the unravelling step.[7] Therefore, the design of (**5**) became our primary objective and a new approach was envisaged towards this end.[8]

Scheme 1 summarises our successful approach to the C_2 tetracyclo[6.6.0.0^{2,6}.0^{10,14}]tetradec-1(8)-ene (**12**) from readily available bicyclo[3.3.0]octane-3-carboxaldehyde (**7**).† Ultra-



(**5**) (**6**)

† Prepared from bicyclo[3.3.0]octan-3-one *via* Wittig reaction with methoxymethyltriphenylphosphonium chloride and aqueous acid hydrolysis.

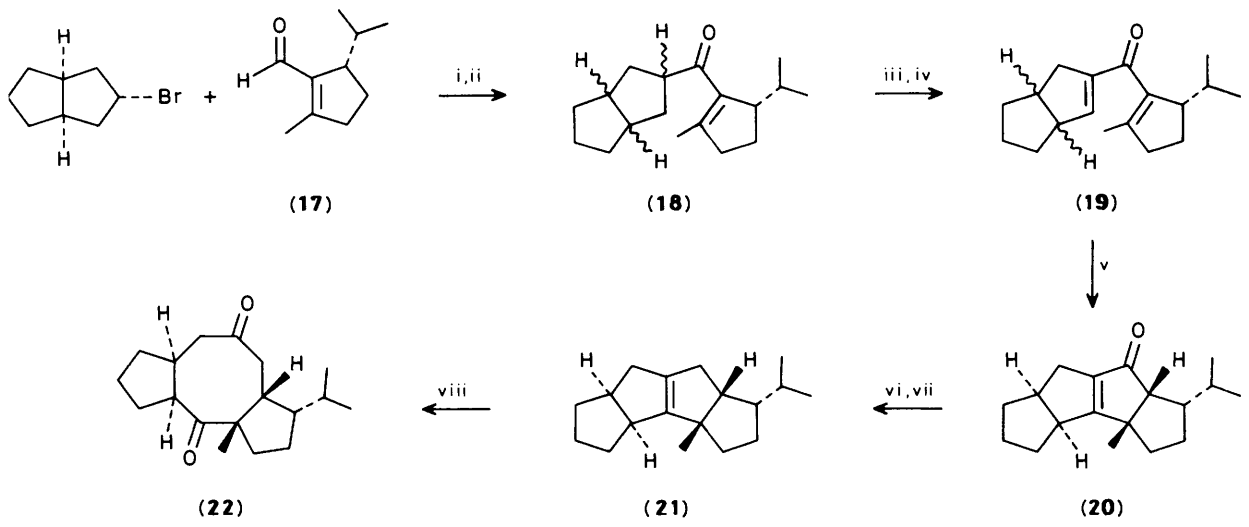


Scheme 1. *Reagents and conditions:* i, Li, chlorocyclopentane, ultrasound, tetrahydrofuran (THF), 35%; ii, pyridinium chlorochromate–molecular sieves 4 Å, CH_2Cl_2, 85%; iii, Br_2, CCl_4, 91%; iv, Li_2CO_3–LiBr, dimethylformamide (DMF), 80 °C, 70%; v, polyphosphoric acid (PPA), 100 °C, 60%; vi, $HSCH_2CH_2SH$, $MeC_6H_4SO_3H$, C_6H_6, 87%; vii, Na, liq. NH_3, 74%; viii, RuO_2–$NaIO_4$–CCl_4–MeCN–H_2O, 92%; ix, $HSCH_2CH_2OH$, pyridinium toluene-*p*-sulphonate (PPTS), C_6H_6, 76%.

sound promoted condensation of (**7**) with cyclopentyl-lithium, and pyridinium chlorochromate oxidation furnished a diastereoisomeric mixture of ketones (**8**) which was directly transformed into a single dienone (**9**) *via* an α-bromination–dehydrobromination sequence. The $\nu_{C=O}$ (neat) 1610 cm^{-1}, ^1H n.m.r. (100 MHz): δ 6.6 (1H, br. s), 6.4 (1H, br. s), and ^{13}C n.m.r. (25 MHz): δ 190.6, 145.0, 144.7, 142.9, 141.6 were features that firmly secured the formulation (**9**). Nazarov cyclisation of (**9**) with polyphosphoric acid gave a 4 : 1 mixture of tetraquinane-based enones (**10**) and (**11**). While these could be separated by h.p.l.c. and characterised, it was more convenient to carry the mixture through deoxygenation *via* the thioacetalisation–desulphurisation sequence to the tetracyclic hydrocarbons (**12**) and (**13**), respectively. These could be separated readily on $AgNO_3$–SiO_2 gel and were fully characterised. The required C_{14}-tetraquinene hydrocarbon (**12**) of C_2-symmetry exhibited the expected 8-line ^{13}C n.m.r. spectrum with diagnostic resonances at δ 150.23, 142.7, 47.4, 45.4, 37.6, 35.9, 30.2, 26.1. On the other hand, (**13**) had 14 resonances at δ 148.3, 142.4, 55.1, 48.1, 47.0, 44.5, 40.7, 35.7, 33.9, 32.1, 29.12, 27.7, 27.4, 25.8. On RuO_2–$NaIO_4$ oxidation, according to Sharpless' procedure,[9] (**12**) was transformed into the tricyclic dione (**14**), m.p. 66 °C, in near quantitative yield. The $\nu_{C=O}$ (KBr) 1680 cm^{-1} and 8-line ^{13}C n.m.r. signals at δ 216.01, 211.8, 53.6, 45.0, 40.5, 33.9, 28.0, 24.0 were fully consonant with its structure. The C_2-symmetry and *cis,anti,cis*-stereochemical disposition in (**14**) were further secured through its conversion into the mono-1,3-oxathiolane derivative (**15**), m.p. 91 °C, which was devoid of any symmetry and exhibited a 16-line ^{13}C n.m.r. spectrum (*cf. cis,syn,cis*-isomer of C_s-symmetry would have 10-line spectrum). The isomeric olefin (**13**) was likewise oxidised with RuO_2–$NaIO_4$ to furnish the interesting ring sytem (**16**), m.p. 129 °C, $\nu_{C=O}$ (KBr) 1680 cm^{-1}, ^{13}C n.m.r.: δ 213.8, 212.9, 62.29, 45.2 (2 × C), 43.6, 42.7, 41.7, 40.09, 33.9, 33.5, 26.1, 23.9.

In order to extend the scope of the above approach to the enantioselective construction of the fusicoccane-type diterpenoids, we identified (**17**),[10] readily available from (+)-limonene and having the methyl and isopropyl groups correctly positioned, as the chiron for elaboration into the tetraquinane system. Reaction between (**17**), *exo*-3-bromobicyclo[3.3.0]octane,‡ and lithium chips under ultrasound irradiation led to the diasteroisomeric mixture of allylic alcohols which was oxidised with barium manganate to give the enone (**18**) (60 : 40 mixture). Carefully controlled monobromination α to the carbonyl group with 2,4,4,6-tetrabromocyclohexa-2,5-dienone and dehydrobromination furnished the dienone (**19**), $\nu_{C=O}$ (KBr) 1620 cm^{-1}, ^1H n.m.r. (100 MHz): δ 6.4 (1H, br. s), 1.8 (3H, s). Nazarov-type cyclisation on (**19**) presented considerable difficulties but eventually toluene-*p*-sulphonic acid in refluxing toluene provided the required tetracyclic enone (**20**), $\nu_{C=O}$ (neat) 1700, 1640 cm^{-1}, ^1H n.m.r. (100 MHz): δ 1.25 (3H, s), 0.95 (3H, d, *J* 7 Hz), 0.85 (3H, d, *J* 7 Hz) in *ca.* 20% yield. The stereochemistry of (**20**)

‡ Prepared from bicyclo[3.3.0]octan-3-one *via* $LiAlH_4$ reduction and PBr_3 bromination.



Scheme 2. *Reagents and conditions:* i, Li, THF, ultrasound, 40%; ii, $BaMnO_4$, CH_2Cl_2, 55%; iii, 2,4,4,6-tetrabromocyclohexa-2,5-dienone; iv, Li_2CO_3–LiBr, DMF, 80 °C, 26% [from (**18**)]; v, *p*-$MeC_6H_4SO_3H$, toluene, 110 °C, 20%; vi, $HSCH_2CH_2SH$, *p*-$MeC_6H_4SO_3H$, C_6H_6, 90%; vii, Na, liq. NH_3; viii, RuO_2, $NaIO_4$–CCl_4–MeCN–H_2O, 82% [from (**20**)].

was derived on the basis of previous analogy and close correlation of its ^{13}C n.m.r. parameters with the enone (**10**) and model substituted bicyclo[3.3.0]octanes.[11] Deoxygenation of (**20**) *via* thioacetalisation–desulphurisation gave the labile olefin (**21**) and was directly subjected to RuO_2–$NaIO_4$ oxidation to give (+)-dione (**22**), m.p. 61 °C, $[\alpha]_D$ + 15° (*c* 2.0), $\nu_{C=O}$ (KBr) 1680 cm^{-1}, ^1H n.m.r. (100 MHz): δ 1.2 (3H, s), 0.95 (3H, d, *J* 7 Hz), 0.8 (3H, d, *J* 7 Hz).

N. K. thanks C.S.I.R. for the award of a Junior Research Fellowship. This research was supported by U.G.C. in the form of a Special Assistance Programme in Organic Chemistry and COSIST programme in Organic Synthesis.

Received, 16th May 1986; Com. 657

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