Quinolinone Cycloaddition as a Potential Synthetic Route to Dimeric Quinoline Alkaloids[1]

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Acid-catalysed dehydration of the quinolinone allylic alcohol **24** and concomitant Diels–Alder cycloaddition of the resulting diene **25** under acid conditions, followed by further intramolecular cyclization, led to the isolation of isomeric tetracyclic compounds containing one quinolin-2-one and one quinolin-4-one ring (dimer A, **27** and dimer C, **30**). Further intramolecular cyclization of dimer A **27** yielded the heptacyclic product (dimer B, **28**) having a ring structure of similar type to the dimeric quinoline alkaloids (paraensidimerins). The structures of the cyclization products (dimer A, dimer B and dimer C) have been determined by spectroscopic and X-ray diffraction methods. Mechanistic pathways for the chemical synthesis of polycyclic quinolinone products and their relevance in the biosynthesis of dimeric quinoline alkaloids are discussed.

Since the first isolation of a dimeric quinoline alkaloid in 1978,[2] a further 18 dimers have been identified from Rutaceous plant species to date.[3,4]

The largest group of these compounds are the structurally similar paraensidimerins and vepridimerines. Paraensidimerins A, C, E and F, **1–4** were isolated from *Euxylophora paraensis*[5] and vepridimerines A, B, C and D, **5–8**, from *Vepris louisii* and *Oricia renieri*.[6] Alkaloids **1–6** may be derived from the dimerization of two quinolin-2-one units to produce a characteristic XYZ ring system, Scheme 1, while alkaloids **7** and **8** may be formed from one quinolin-2-one and one quinolin-4-one unit.

Paraensidimerins A, C, E and F are isomeric and differ only in the stereochemistry of the protons H_d and H_e about the XY ring junction. Vepridimerines A and B can also be considered as the tetramethoxy derivatives of paraensidimerins A and C, respectively.

The postulated[7] biosynthetic route to these dimers involves the Diels–Alder cycloaddition of two molecules of diene *e.g.* **9**, to give an adduct with a *cis* relationship between protons H_d and H_e. Ring closure by intramolecular addition of the oxygen functions either at position 2 or 4 would yield the *cis* products (**1**, **3**, **5** or **7**). Formation of the *trans* isomers is more difficult to rationalize but it has been proposed[3,7] that they could arise by isomerization of cyclohexenes **11** and **13**. Epimerization of the doubly allylic proton H_e in compound **13**, either by a homolytic or heterolytic mechanism, would occur readily. Subsequent ring closure would yield the *trans* isomers (**2**, **4**, **6** or **8**), Scheme 1. Dimerization of the dienes *e.g.* **9** ⟶ **11**, appears to compete with cyclization *e.g.* **16** ⟶ **14**, as both *N*-methylflindersine **14** and veprisine **15** have been isolated along with the appropriate dimers from the plants.

Examples of other alkaloids formed *via* Diels–Alder cycloadditions appear to be relatively uncommon and to our knowledge there are no documented examples of pure enzymes having been isolated which catalyse these pericyclic cycloadditions.[8] Although many dimeric quinoline alkaloids have been isolated, evidence for enzyme-catalysis of this cycloaddition is currently unavailable. Examples of the catalysis of the Diels–Alder reaction by antibodies[9,10] and by a trimeric porphyrin host,[11] have recently been reported.

A total synthesis of any of these dimers has yet to be achieved although a partial synthesis of the paraensidimerins[12] and vepridimerines[13,14] was reported by Ayafor and co-workers. This 'biogenetic type' synthesis involved the thermolysis of *N*-methylflindersine **14** and veprisine **15** respectively; presumably *via* the sequences **14** ⟶ **16** ⟶ **9** ⟶ **11** ⟶ **1–4** and **15** ⟶ **17** ⟶ **10** ⟶ **12** ⟶ **5–8** (*cf.* Scheme 1). In all cases this route led to a complex mixture of dimeric products in low yield. The nature of the dimeric products was also difficult to control and was found to be dependent on the temperature applied in the reaction. Novel paraensidimerins containing both a quinolin-2- and -4-one moiety were also isolated.[12]

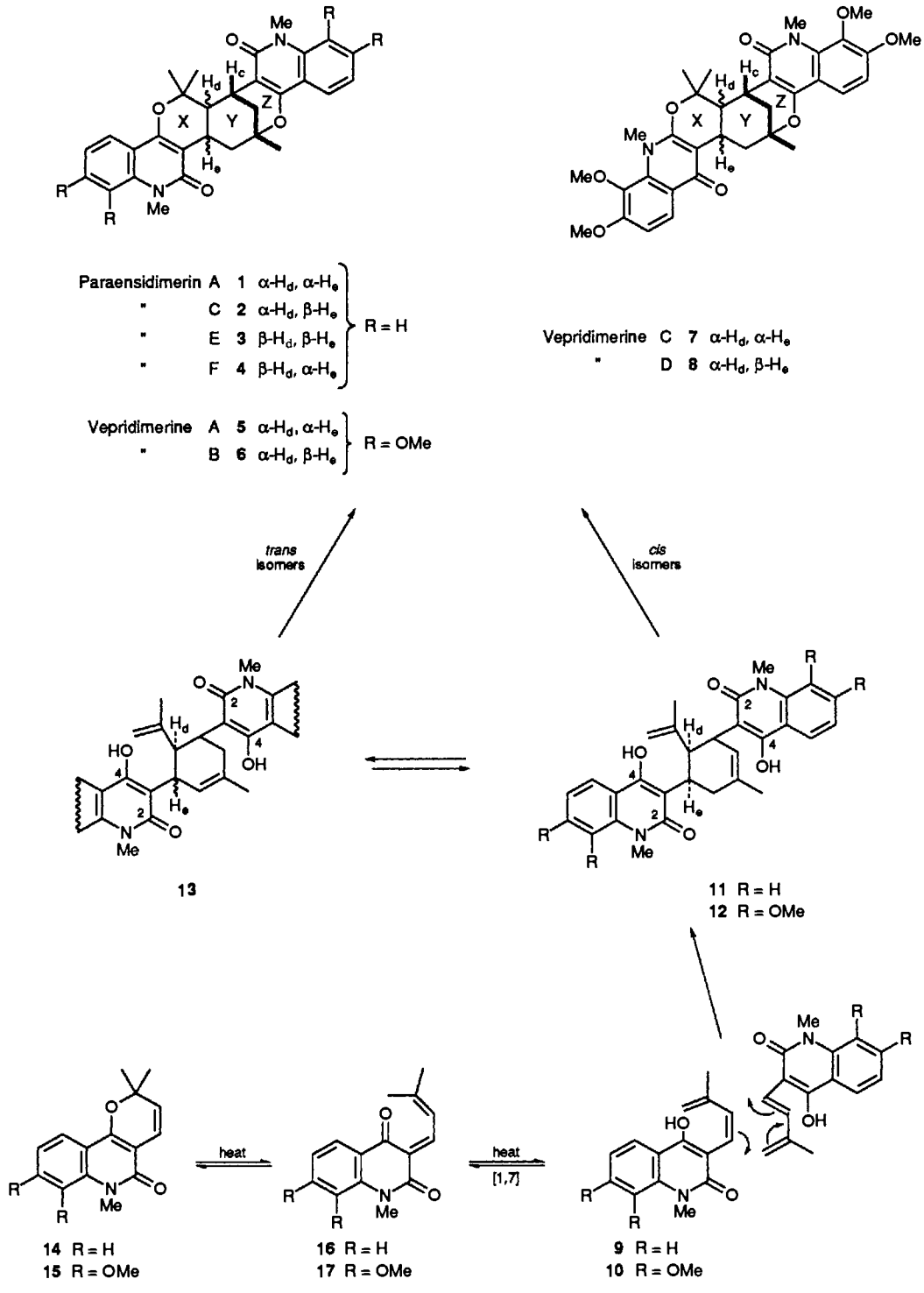
In the present studies, which concentrated on the unsubstituted paraensidimerin series, our attempts to develop total stereospecific routes of biomimetic design for these dimeric compounds are reported.

Results and Discussion

Preliminary studies in our laboratories showed that conjugated dienes of the type **9** were unsuitable starting compounds since they were found to be unstable and proved difficult to isolate and purify. An alternative methodology was thus sought.

Barnes *et al.*[15] reported that acid treatment of the allylic alcohol **18** yielded the dimeric benzopyran **20**, presumably *via* dimerization and cyclization of the phenolic diene **19**, Scheme 2. This reaction sequence was confirmed by Ngadjui and co-workers.[12] As the ring system found in the product was similar to that found in the paraensidimerins it was recognised that a quinolinone allylic alcohol of the type **24** (*cf.* Scheme 3) was a potential precursor and therefore its synthesis was undertaken. The desired quinolinone allylic alcohol **24** was prepared in three steps, in an overall yield of 42%, from the commercially available hydroxy quinolin-2-one **21** as outlined in Scheme 3. The final and key step in the synthesis involved arylation of 2-methylbut-3-en-2-ol to form the desired product **24**.

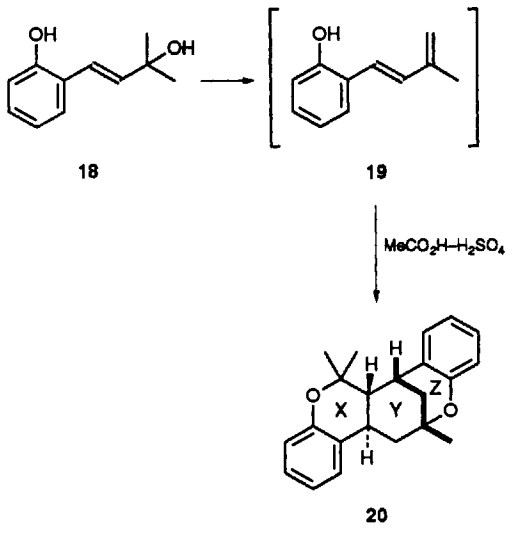
Palladium-catalysed 'Heck' reactions[16] which have previously been used to introduce 2-methylbut-3-enyl moieties into coumarin[17] and acridone[18] molecules, have thus now been extended to quinolinones. Temperature control during the reaction was found to be crucial in maintaining a low level of by-products. The optimal yield of the desired product **24** was achieved when a large excess of the alcohol (6 mol dm^{-3} excess) was added to a solution of **23** in dimethylformamide (DMF) containing triethylamine, the palladium catalyst bis(triphenylphosphine)palladium(II) chloride, copper(I) iodide (which is



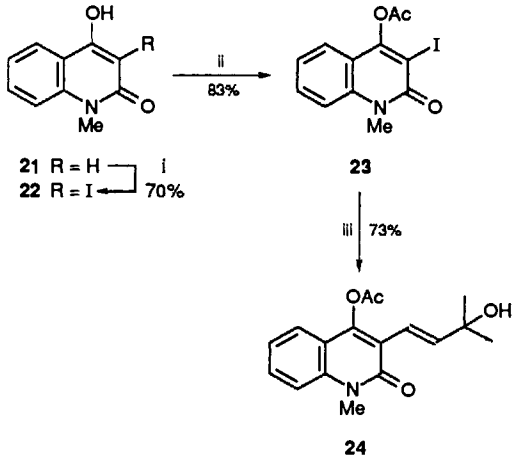
Scheme 1

thought to act as co-catalyst to assist in the regeneration of the catalyst[19]) and when the temperature was maintained in the range 85–90 °C for 3 h. Satisfactory ^{1}H and ^{13}C NMR, IRMS and elemental microanalytical data confirmed the structure of **24**. A coupling constant of 16.2 Hz between 1'-H and 2'-H was consistent with a *trans* relationship. The two major by-products of the reaction were identified as the diene **25** and *N*-methylflindersine **14**. Diene by-products have previously[20] been obtained from 'Heck' reactions of this type and are thought to arise due to the dehydrating influence of the amine hydroiodide (*e.g.* $Et_3HN^+I^-$) formed in the reaction, or the small amount of acid that may be in equilibrium with it.

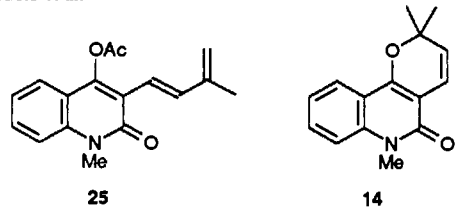
Dehydration of the quinolinone allylic alcohol **24** was achieved by dissolution in glacial acetic acid, containing a few drops of concentrated sulfuric acid, and stirring the mixture at room temperature. TLC analysis of the reaction mixture showed diene **25** to be present. Addition of a few more drops of conc. H_2SO_4 followed by stirring the mixture for a further 48 h gave a product mixture which contained none of the anticipated diacetate cycloadduct **26** (*cf.* Scheme 4). Purification by PLC yielded a major product as a white solid **28** (dimer B) which was found to have the empirical formula $C_{30}H_{30}N_2O_4$ on mass spectral analysis and elemental microanalysis. The ^{1}H NMR spectrum showed eight aromatic, two *N*-methyl, three *C*-methyl



Scheme 2



By-products of iii:



Scheme 3 *Reagents and conditions:* i, I_2 in dioxan, reflux 10 min; ii, Ac_2O, pyridine, room temp. 2 h; iii, 2-methylbut-3-en-2-ol, $[Pd\{P(C_6H_5)_3\}Cl_2]$ CuI, Et_3N, DMF at 85–90 °C under N_2, 3 h

signals and a complex pattern associated with seven other protons in the range δ 3.86–1.55 confirming that dimerization had occurred. These signals were similar to those quoted for the paraensidimerins.[5] Using a number of NMR techniques (δ_C/δ_H correlation. COSY and DEPT) the ^1H and ^{13}C NMR signals of dimer B, listed in Table 1, were found to be consistent with the structure **28** (*cf.* Scheme 4). In view of the complexity of the suspected product **28** a suitable crystal of dimer B for X-ray structure analysis was obtained, in the form of its methanol (2 mol) solvate. To avoid loss of solvent of crystallization during X-ray data collection it was necessary to seal a crystal inside a capillary containing some methanol. The structure is shown in Fig. 1 and confirmed the earlier structure and stereochemical assignment based on spectral data.

Dimer B **28** contained the desired XYZ ring system found in the paraensidimerins **1**–**4**. The cyclohexane ring Y adopted a

Table 1 ^1H NMR (COSY, DEPT, δ_C/δ_H) and ^{13}C NMR data for dimer **28**

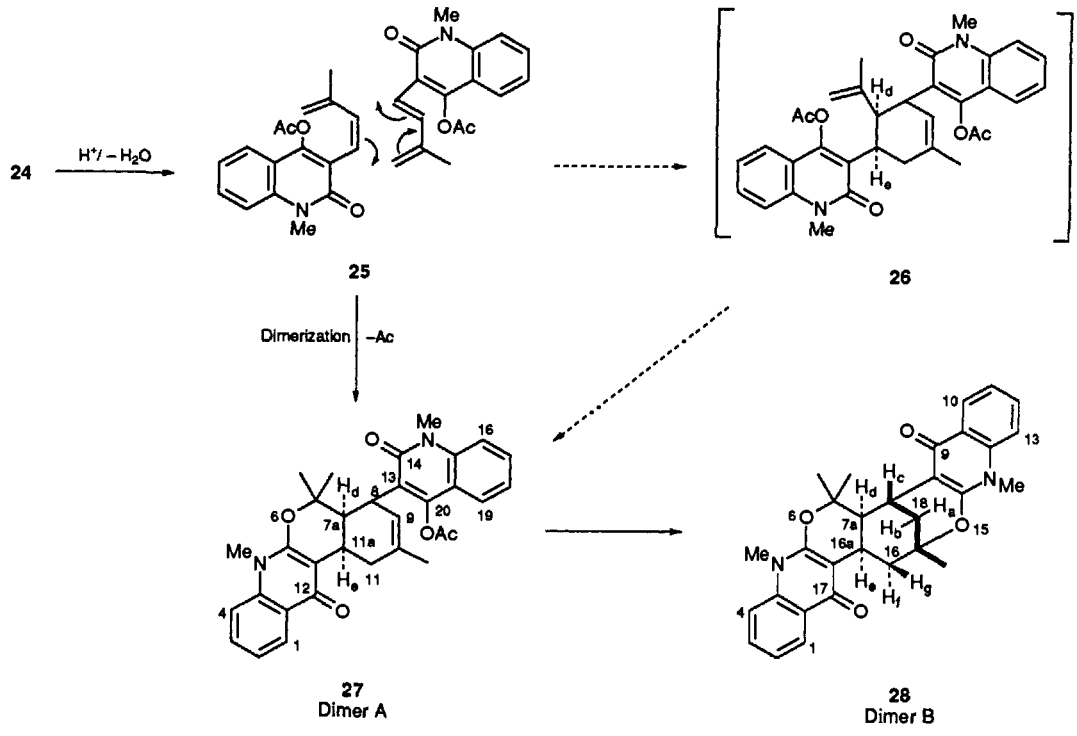
Protons	δ_H[a]	Carbons	δ_C
1-H, 10-H	8.35, 8.39	Me	25.35
	(2 × dd, *J* 8.0, 1.4)	CH-16a	25.53
		CH-8	26.29
2-H, 11-H	7.27–7.31 (m)	Me	28.72
		NMe	30.39
3-H, 12-H	7.56–7.62 (m)	NMe	30.47
		CH_2-18	32.28
4-H, 13-H	7.37–7.44 (m)	CH_2-16	39.17
		CH-7a	43.45
7a-H (H_d)	2.27 (d, *J* 6.9)	C-7	80.93
		C-15a	83.55
8-H (H_c)	3.86 (s)	C-16b	101.31
		C-8a	103.70
18-H (H_a)	1.75 (dt, *J* 13.7, 2.75)	C-4	114.38
		C-13	114.52
18-H (H_b)	2.14 (dd, *J* 13.7, 2.75)	C-2, C-12	122.56
		C-17a	124.13
16-H (H_f)	3.36 (ddd, *J* 14.5, 5.7, 2.75)	C-9a	124.33
		C-1	126.23
16-H (H_g)	1.55–1.59 (m)	C-10	126.27
		C-3, C-11	131.44
16a-H (H_e)	3.24 (m)	C-4a, C-13a	138.99
		C-5a	154.93
NMe	3.66, 3.76 (2 × s)	C-14a	157.32
		C-9	174.46
Me	1.55, 1.59, 1.90 (3 × s)	C-17	176.59

[a] ^1H NMR multiplicities and coupling constants (in Hz) are given in parentheses.

chair conformation and thus long range *W* coupling (*J* 2.75 Hz) was observed between the two equatorial protons at C-16 (H_f) and C-18 (H_a). The XY ring fusion protons H_d and H_e as expected showed a *cis* relationship (*J* 6.9 Hz), while H_e and H_d had a *trans* diequatorial relationship with a dihedral angle of 76° which accounted for their very small coupling constant (*J* < 1 Hz). The latter spectral characteristics were consistent with the heptacyclic structure reported for paraensidimerin A[5] **1**. The only structural difference between the new dimer **28** and paraensidimerin A **1** was that the former contained two quinolin-4-one moieties instead of two quinolin-2-one moieties. The two deshielded aromatic resonances at δ 8.35 and 8.39 for 1-H and 10-H, as well as the carbonyl signals in the ^{13}C NMR spectrum at δ 174.46 and 176.59 are characteristic of quinolin-4-one units.[21]

When the reaction was repeated using a smaller quantity of conc. H_2SO_4 and a shorter reaction time, in an attempt to obtain the required adduct **26** (a diacetate derivative of the proposed biosynthetic intermediate **11**), a different dimeric product **27** (dimer A) was isolated. Dimer A had the molecular mass m/z = 524 and the constitution $C_{32}H_{32}N_2O_5$, which was equivalent to the molecular mass of dimer B **28** plus C_2H_2O, indicative of a partially cyclized monoacetylated derivative. Although both the ^1H and ^{13}C NMR spectra were poorly resolved at a number of temperatures, the NMR data taken together with the significant fragmentation pattern in the mass spectrum allowed assignment of the partially cyclized dimeric structure **27** to dimer A, Scheme 4, and showed that it contained both quinolin-2- and -4-one moieties. Dimer A **27** proved to be an intermediate in the synthesis of dimer B **28**. Thus, it was quantitatively converted into dimer B **28** on prolonged treatment under the acidic reaction conditions. Base-catalysed hydrolysis and cyclization of dimer A **27** (NaOH in MeOH) to give dimer B **28** was also achieved.

As the diacetate cycloadduct **26** could not be isolated using these conditions, it is assumed to be present only as a transient intermediate which subsequently undergoes rapid acid catalysed deacetylation and cyclization to form **27**. (Scheme 4).



Scheme 4

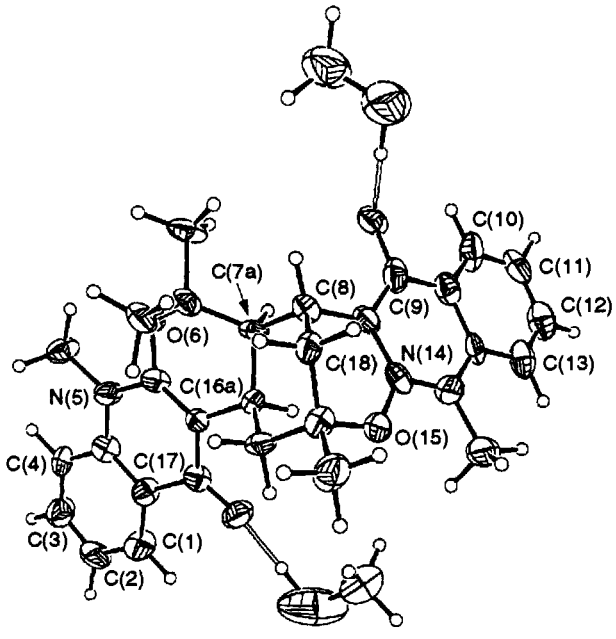


Fig. 1 An ORTEP projection of dimer B **28**

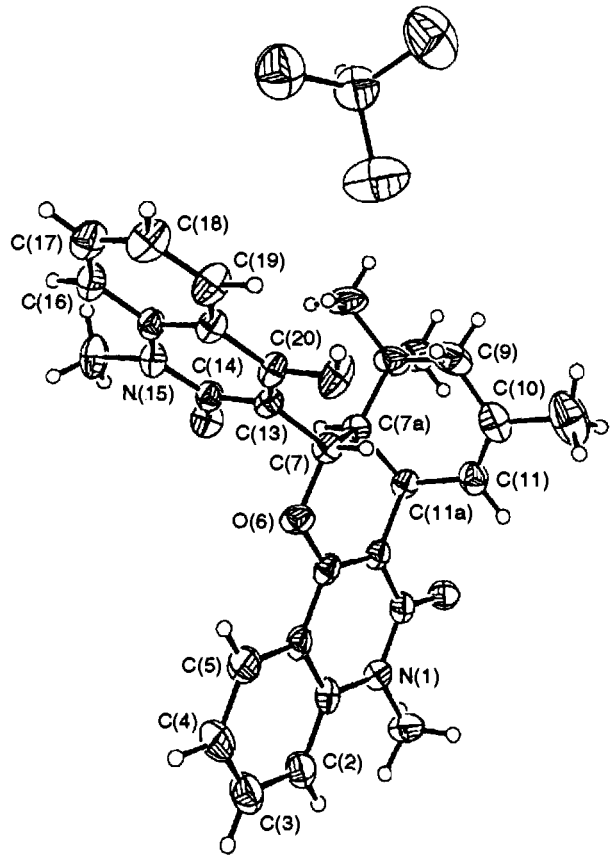
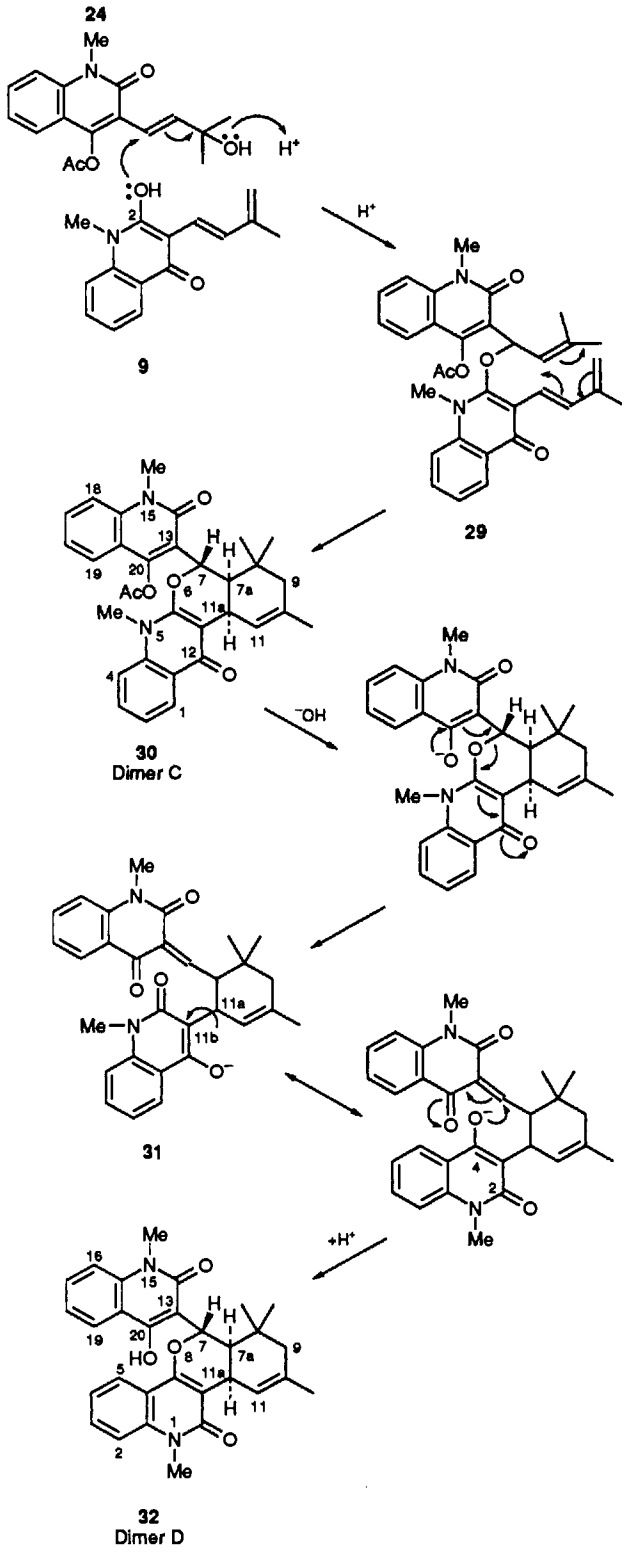


Fig. 2 An ORTEP projection of dimer D **32**

During the synthesis of both dimer A **27** and dimer B **28** a further dimeric product **30** (dimer C) was also isolated. Dimer C was found to to be isomeric with dimer A **27** with an empirical formula of $C_{32}H_{32}N_2O_5$ from high resolution mass spectral analysis. The ^1H and ^{13}C NMR spectra of dimer C were again poorly resolved at room temperature, but a marked improvement in the spectral resolution was achieved at lower temperature (−50 °C) in $CDCl_3$. The ^{13}C NMR spectrum confirmed that 32 carbon atoms were present and the ^1H NMR showed eight aromatic, two *N*-methyl, one acetyl and three *C*-methyl resonances similar to dimer A **27**. Attempts to obtain a suitable crystal of dimer C **30** for X-ray crystallographic analysis were unsuccessful.

Treatment of dimer C **30** with sodium hydroxide gave an almost quantitative yield (97%) of the deacetylated dimer **32** (dimer D) as a white solid. A suitable crystal of dimer D **32** was obtained, as its chloroform solvate, and the structure obtained by X-ray crystallography is shown in Fig. 2. An unequivocal assignment of the ^1H NMR signals to structure **32** (*cf.* Scheme 5) was thus possible.



Scheme 5

As the ^{1}H NMR spectrum of dimer D **32** was quite similar to that of dimer C **30**, the structure of the latter compound could thus also be deduced. The key signals were a 1 H doublet at δ 5.87 for 7-H and a 1 H singlet at δ 5.55 for 11-H in dimer D **32** (the equivalent signals occurred at δ 5.99 and 5.50, respectively in dimer C **30**). The dihedral angle of 79° between 11-H and 11a-H in dimer D **32** accounted for their near zero coupling (a similar angle is expected between the equivalent protons in dimer C **30**). The ring junction protons 7a-H and 11a-H in both dimers exhibited small coupling constants (J 3.9 Hz in dimer D **32** and 4.4 Hz in dimer C **30**) characteristic of a *cis* relationship as expected from a Diels–Alder type addition. Protons 7-H and 7a-H adopted a *trans* relationship in dimer D **32** and the same stereochemistry is assumed for the equivalent protons in dimer C **30** due to the close similarity in the coupling constants ($J_{7,7a}$ 10.3 Hz in dimer D **32** and $J_{7,7a}$ 11.0 Hz in dimer C **30**). Proton 11a-H also occurred downfield due to deshielding from the adjacent quinolinone carbonyl at C-12 in both cases (δ 3.88 in dimer D **32** and δ 4.12 in dimer C **30**). One significant difference though was apparent from the ^{1}H and ^{13}C NMR spectra of the two dimers. In dimer C **30** a signal was observed at δ 8.51 for a deshielded aromatic proton, characteristic of a quinolin-4-one unit, which was confirmed as the ^{13}C NMR showed a signal at δ 175.96. Thus, dimer C could be assigned structure **30** (*cf.* Scheme 5) and was made up of quinolin-2- and -4-one moieties.

Dimers with structures analogous to **30** and **32** have not yet been isolated as naturally occurring compounds. A tentative mechanism for the formation of dimers C **30** and D **32** is outlined in Scheme 5. Reaction of the diene **9** with the allylic alcohol **24** may occur by nucleophilic attack of the oxygen atom at C-2 to yield the intermediate **29** which could undergo Diels–Alder cyclization to yield dimer C **30**. The diene **9** was also proposed as an intermediate resulting from the pyrolysis of *N*-methylflindersine **14** (*cf.* Scheme 1), and also apparently accounted for the co-occurrence[5] of **14** in plant species containing dimeric quinolinones. It is noteworthy that a small amount of alkaloid **14** was also isolated during the acid-catalysed dimerizations and this is consistent with the intermediacy of the diene **9** in the reaction media.

Treatment of dimer C **30** with base not only achieved the desired deacetylation but also must have allowed ring opening to occur, followed by ring closure through the oxygen at C-4 to give a quinolin-2-one unit. The 'phenoxide' resulting from the ester cleavage might allow ring opening by β-elimination to give compound **31**. Rotation at bond 11a–11b and subsequent recyclization by a Michael type addition would enable formation of dimer D **32**. Base-catalysed rearrangements of linear quinolinones to form their more stable angular forms are known.[22,23]

In conclusion, acid-catalysed dehydration of the quinolinone allylic alcohol **24** and concomitant dimerization of the resulting diene **25** did not permit isolation of the anticipated diacetylated adduct **26**, but instead afforded two isomeric tetracyclic monoacetates **27** (dimer A) and **30** (dimer C) containing one quinolin-2-one ring and one quinolin-4-one ring. When the reaction was carried out in the presence of additional acid and for a longer period (or when **27** was treated with base) dimer A **27** underwent further deacetylation and cyclization to yield the quinolinone dimer **28** (dimer B). This dimer contained the desired XYZ fused ring system with similar stereochemistry to that found in paraensidimerin A **1**, but contained two quinolin-4-one moieties instead of the desired quinolin-2-one moieties. The remaining monoacetate **30** (dimer C) was unaffected by further treatment with acid but underwent deacetylation, ring opening and rearrangement to give **32** (dimer D) when treated with base. This represents the first known isolation of dimers of these types. Further studies into the effect of differing reaction conditions on the nature of the products are currently under investigation.

Although none of the known paraensidimerins **1**–**4** was isolated in these studies the formation of dimer B **28** provides experimental evidence in support of the biosynthetic pathway outlined in Scheme 1 and of the role of an intermediate of a similar type to compound **11** (as dimer B, **28**, is presumably formed *via* the intermediate **26**). The results also support the

proposal that dimers of this type are indeed true alkaloids and not merely artefacts formed during isolation. If the latter were the case dimers of the type isolated in these studies would also have been expected to be isolated.

Experimental

M.p.s were recorded on a Reichert block and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 983 G instrument coupled to a Perkin-Elmer 3700 data station. ^{1}H NMR (500 and 300 MHz) and ^{13}C NMR (125 MHz) spectra were recorded with General Electric GE 500 and GE 300 instruments with solutions in $CDCl_3$, containing Me_4Si as internal standard, unless otherwise stated. *J* Values are given in Hz. Mass spectra were recorded at 70 eV on an AEI-MS 902 instrument updated by VG Autospec Instruments. Accurate molecular weights were determined by the peak-matching method using perfluorokerosene as standard reference and were accurate to within ±0.000 006 amu. Elemental microanalyses were carried out by the Butterworth Microanalytical Consultancy Ltd., Middlesex, UK.

Analytical TLC was carried out on Merck Kieselgel 60_{254} plates, preparative TLC on Merck Kieselgel $PF_{254+366}$ (Type 60) and flash chromatography on Merck Kieselgel 60 (230–400) mesh.

4-Hydroxy-3-iodo-1-methyl-1,2-dihydroquinolin-2-one **22**.—A solution of iodine (1.8 g, 7.1 mmol) in warm dioxane (10 cm^3) was added in portions during 2 min to a refluxing solution of the commercially available or synthesised[24] 4-hydroxy-1-methyl-1,2-dihydroquinolin-2-one **21** (1.0 g, 5.7 mmol) and sodium hydrogen carbonate (1.3 g, 15.5 mmol) in water (25 cm^3). After refluxing for a further 5 min the solution was cooled to 5 °C and acidified with acetic acid. The precipitate was collected by filtration, dried and recrystallized to give the pure title compound **22** (1.20 g, 70%), R_f 0.60 (2% MeOH in $CHCl_3$), m.p. 171–173 °C (from methanol as yellow needles) (lit.,[25] m.p. 170–172 °C); ν_{max}(KBr)/cm^{-1} 3427 (OH) and 1596 (quinolin-2-one); δ_H(300 MHz; $CDCl_3$) 3.79 (3 H, s, NCH_3), 6.35 (1 H, br s, OH), 7.24–7.29 (1 H, m, 7-H), 7.38 (1 H, d, *J* 8.5, 5-H), 7.62–7.68 (1 H, m, 6-H) and 8.05 (1 H, d, *J* 8.1, 8-H); *m/z* 301 (M$^+$, 100%) and 175 (45).

4-Acetoxy-3-iodo-1-methyl-1,2-dihydroquinolin-2-one **23**.—The iodo compound **22** (5.0 g, 16.6 mmol), acetic anhydride (20 cm^{-3}) and pyridine (1 cm^{-3}) were stirred together for 2 h at room temperature. The cream coloured precipitate that formed was collected and recrystallized to give the title compound **23** (4.74 g, 83.2%), R_f 0.83 (2% MeOH in $CHCl_3$), m.p. 178–181 °C (from chloroform as a yellow crystalline solid) (Found: C, 41.9; H, 3.0; N, 4.0. $C_{12}H_{10}INO_3$ requires C, 42.0; H, 2.9; N, 4.1%); ν_{max}(KBr)/cm^{-1} 1758 (OAc) and 1635 (quinolin-2-one); δ_H(300 MHz; $CDCl_3$) 2.52 (3 H, s, $OCOCH_3$), 3.82 (3 H, s, NCH_3), 7.24–7.29 (1 H, m, 7-H), 7.42 (1 H, d, *J* 8.5, 5-H), 7.59 (1 H, d, *J* 8.1, 8-H) and 7.63–7.68 (1 H, m, 6-H); *m/z* 343 (M$^+$, 30%) and 301 (M$^+$ − C_2H_3O, 100).

(E)-4-Acetoxy-1-methyl-3-(3'-methyl-3'-hydroxybut-1'-enyl)-1,2-dihydroquinolin-2-one **24**.—The iodo acetate **23** (2.0 g, 5.8 mmol), triethylamine (0.886 g, 1.5 mol equiv.) and bis(triphenylphosphine)palladium(II) chloride (200 mg) were stirred in dimethylformamide (100 cm^3) under nitrogen. 2-Methylbut-3-en-2-ol (0.753 g, 1.5 mol equiv.) was added in one portion and the temperature of the mixture was slowly raised to 70 °C over a period of 6 h and then to 90 °C where it was kept for a further 4–5 h. The progress of the reaction was followed by TLC, and the desired product **24** was observed as a fluorescent spot, R_f 0.33 (2% MeOH in $CHCl_3$).

Water (300 cm^3) was added to the reaction mixture and the solution was thoroughly extracted with ethyl acetate (6 × 300 cm^3). The organic extracts were washed with aqueous sodium thiosulfate (5%, 3 × 500 cm^3) and water (3 × 500 cm^3) and then dried over magnesium sulfate. The extracts were evaporated to dryness under reduced pressure to yield the crude products. Purification by flash chromatography ($CHCl_3$) gave the pure title alcohol **24** as a viscous brown oil which solidified to a light brown solid (1.016 g, 60%), m.p. 166–168 °C (from Et_2O–MeOH as colourless crystals) (Found: C, 67.9; H, 6.3; N, 4.7%; M$^+$, 301.1356. $C_{17}H_{19}NO_4$ requires C, 67.7; H, 6.35; N, 4.65%; *M*$^+$, 301.1314); ν_{max}(KBr)/cm^{-1} 3480 (OH), 1760 (OAc) and 1635 (quinolin-2-one); δ_H(500 MHz; $CDCl_3$) 1.43 [6 H, s, $C(CH_3)_2$], 2.47 (3 H, s, $OCOCH_3$), 3.75 (3 H, s, NCH_3), 6.60 (1 H, d, *J* 16.2, 2'-H), 7.15 (1 H, d, *J* 16.2, 1'-H), 7.24–7.27 (1 H, m, 7-H), 7.39 (1 H, d, *J* 8.4, 5-H) and 7.54–7.59 (2 H, m, 6-H, 8-H); δ_C(125 MHz; $CDCl_3$) 19.71 (1 C, $OCOCH_3$), 28.85 (3 C, 2 × CH_3 + NCH_3), 70.37 (1 C, C-2'), 113.24 (1 C, C-8), 115.04 (1 C, C-2'), 118.25 (1 C, C-4a), 121.42 (1 C, C-6), 122.01 (1 C, C-5), 129.95 (1 C, C-7), 137.40, 137.81 (2 C, C-8a, C-3), 144.33 (1 C, C-1'), 149.95 (1 C, C-4), 160.88 (1 C, C-2) and 166.52 (1 C, $OCOCH_3$); *m/z* 301 (M$^+$, 7.7%), 283 (M$^+$ − H_2O, 2.4), 226 (M$^+$ − $C_3H_7O_2$, 27.0) and 200 (M$^+$ − C_5H_9O, 100).

A second product of the reaction was obtained and purified by preparative TLC. This was obtained as a light brown solid (165 mg, 10%) and identified as (*E*)-4-acetoxy-1-methyl-3-(3'-methylbuta-1',3'-dienyl)-1,2-dihydroquinolin-2-one **25**, R_f 0.90 (2% MeOH in $CHCl_3$), m.p. 142–144 °C (from Pr^i_2O–MeOH as colourless crystals which became coloured on standing for a number of weeks) (Found: M$^+$, 283.1205. $C_{17}H_{17}NO_3$ requires *M*$^+$, 283, 1208); ν_{max}(KBr)/cm^{-1} 1770 (OAc) and 1640 (quinolin-2-one); δ_H(90 MHz; $CDCl_3$) 1.95 (3 H, s, CH_3), 2.40 (3 H, s, $OCOCH_3$), 3.68 (3 H, s, NCH_3), 5.10 (2 H, s, C=CH_2), 6.45 (1 H, d, $J_{3',4'}$ 16, 3'-H) and 6.90–7.70 (5 H, m, Ar-H + 4'-H); *m/z* 283 (M$^+$, 64.7%), 241 (M$^+$ − C_2H_2O, 82.2) and 226 (M$^+$ − C_3H_5O, 100).

Finally, a third compound was identified as *N*-methylflindersine (2,2,6-trimethyl-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinolin-5-one) **14** and was obtained as a crystalline solid (70 mg, 5%), R_f 0.74 (2% MeOH in $CHCl_3$) identical both by ^{1}H NMR and TLC analysis with an authentic sample;[26] ν_{max}(KBr)/cm^{-1} 1645 (quinolin-2-one); δ_H(300 MHz; $CDCl_3$) 1.51 [6 H, s, $C(CH_3)_2$], 3.68 (3 H, s, NCH_3), 5.53 (1 H, d, $J_{3,4}$ 10.0, 3-H), 6.75 (1 H, d, $J_{4,3}$ 10.0, 4-H), 7.20–7.32 (2 H, m, Ar-H), 7.51–7.57 (1 H, m, Ar-H) and 7.96 (1 H, d, $J_{7,8}$ 7.9, 7-H); *m/z* 241 (M$^+$, 22%) and 226 (M$^+$ − CH_3, 100).

[When the above reaction was repeated using iodo acetate **23** (2.0 g, 6.0 mmol), the palladium catalyst (50 mg), copper(I) iodide (15 mg), triethylamine (0.76 g, 7.5 mmol), 2-methylbut-3-en-2-ol (3.0 g, 34 mmol) and the temperature maintained between 85–90 °C for 3 h, the desired alcohol **24** separated from the ethyl acetate extracts as a white solid (1.28 g, 73%).]

Dehydration of Allylic Alcohol **24** *and Dimerization of Diene* **25**. *Method* 1.—The alcohol **24** (892 mg, 2.96 mmol) was dissolved in glacial acetic acid (40 cm^3) containing a few drops of concentrated sulfuric acid. The solution was stirred at room temperature for 2 h and monitored by TLC (2% MeOH in $CHCl_3$). The reaction was found to be complete after 2 h. The solution was stirred overnight and then poured into aqueous sodium carbonate (1 mol dm^{-3} 100 cm^3) and the resulting mixture thoroughly extracted with ethyl acetate (4 × 70 cm^3). The combined organic extracts were washed briefly with water (3 × 100 cm^3), dried over magnesium sulfate and evaporated to yield the crude products as a semi-solid gum. Purification by flash chromatography ($CHCl_3$) firstly gave two isomeric dimeric products. Dimer C **30** was obtained as a white solid

(265 mg, 34%), R_f 0.39 (2% MeOH in $CHCl_3$), m.p. 242–243 °C (from MeOH) (Found: M^+, 524.2303. $C_{32}H_{32}N_2O_5$ requires M^+, 524.2311); ν_{max}(KBr)/cm^{-1} 1760 (OAc) and 1630 (quinolin-2- and -4-one); δ_H(500 MHz; $CDCl_3$; −50 °C) 0.72 (3 H, s, CH_3), 1.19 (3 H, s, CH_3), 1.60 (1 H, d, $J_{9^A,9^B}$ 18.0, 9-H^A), 1.70 (3 H, s, CH_3), 2.19 (4 H, br s, 9-H^B, $OCOCH_3$), 2.56 (1 H, dd, $J_{7a,7}$ 11.0, $J_{7a,11a}$ 4.4, 7a-H), 3.52 (3 H, s, NCH_3), 3.86 (3 H, s, NCH_3), 4.12 (1 H, m, 11a-H), 5.50 (1 H, br s, 11-H), 5.99 (1 H, d, $J_{7,7a}$ 11.0, 7-H), 7.38–7.76 (7 H, m, Ar-H) and 8.51 (1 H, d, $J_{1,2}$ 8.1, 1-H); δ_C(125 MHz; $CDCl_3$; −50 °C) 20.77 (1 C, $OCOCH_3$), 23.36 (1 C, CH_3), 29.44 (1 C, CH_3), 28.28 (2 C, NCH_3, C-11a), 30.41 (1 C, CH_3), 30.55 (1 C, NCH_3), 32.34 (1 C, C-8), 39.82 (1 C, C-9), 41.18 (1 C, C-7a), 74.04 (1 C, C-7), 102.12 (1 C), 114.46 (1 C, Ar-C) 114.72 (1 C, Ar-C), 115.66 (1 C), 120.89 (1 C, C-11), 121.94 (1 C), 122.56, 122.95, 123.32 (3 C, 3 × Ar-C), 123.84 (1 C), 126.13 (1 C, C-1), 130.93 (1 C), 131.53, 132.29 (2 C, 2 × Ar-C), 138.25, 138.87 (2 C, C-4a, C-15a), 154.48, 154.80 (2 C, C-5a, C-20), 161.84 (1 C, C-14), 168.36 (1 C, $OCOCH_3$) and 175.96 (1 C, C-12); m/z 524 (M^+, 42%), 308 ($M^+ - C_{12}H_{10}NO_3$, 30) and 294 (100).

Dimer A **27** was obtained as a white solid (208 mg, 27%), R_f 0.30 (2% MeOH in $CHCl_3$), m.p. 244–246 °C (from MeOH) (Found: M^+, 524.2311. $C_{32}H_{32}N_2O_5$ requires M^+, 524.2311); ν_{max}(KBr)/cm^{-1} 1750 (OAc) and 1635 (quinolin-2- and -4-one); δ_H(360 MHz; $CDCl_3$; 57 °C) 1.29 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 1.73 (3 H, s, CH_3), 1.96–2.05 (1 H, m, 11-H^A),* 2.40 (1 H, s, $OCOCH_3$), 2.45–2.67 (2 H, m, 7a-H, 11-H^B),* 3.29–3.41 (1 H, m, 11a-H),* 3.61 (3 H, s, NCH_3), 3.73 (3 H, s, NCH_3), 3.88–3.92 (1 H, m, 8-H), 5.90 (1 H, br s, 9-H), 7.19–7.30 (2 H, m, Ar-H), 7.35–7.39 (3 H, m, Ar-H), 7.51–7.59 (2 H, m, Ar-H) and 8.45 (1 H, dd, $J_{1,2}$ 8.0, $J_{1,3}$ 1.5, 1-H); δ_C(125 MHz; $CDCl_3$; 50 °C) 20.75 (1 C, $OCOCH_3$), 22.53 (1 C, CH_3), 22.82 (1 C, CH_3), 27.66 (1 C, CH_3), 30.10 (2 C, 2 × NCH_3), 30.81, 32.83, 44.60, 77.20, 83.60, 102.35 (6 C), 114.14, 114.25 (2 C, 2 × Ar-C), 116.60 (1 C), 122.25, 122.31 (2 C, 2 × Ar-C), 122.98 (1 C, Ar-C), 124.64 (1 C), 125.85 (1 C, C-9), 126.67 (1 C, C-1), 128.56 (1 C), 130.64, 131.23 (2 C, 2 × Ar-C), 133.83, 138.66, 139.22, 152.05, 154.41 (5 C), 162.49 (1 C, C-14), 167.99 (1 C, $OCOCH_3$) and 176.44 (1 C, C-12); m/z 524 (M^+, 44%), 481 ($M^+ - C_2H_3O$, 13), 308 ($M^+ - C_{12}H_{10}NO_3$, 24) and 226 (100).

Finally, *N*-methylflindersine **14** was also obtained as a crystalline solid (89 mg, 12%), R_f 0.74 (2% MeOH in $CHCl_3$) identical both by ^{1}H NMR and TLC analysis with an authentic sample.[26] (See earlier for spectral details.)

Method 2.—The alcohol **24** (400 mg, 1.33 mmol) was dissolved in glacial acetic acid (20 cm^3) and a few drops of concentrated sulfuric acid were added. The solution was stirred at room temperature for 2 days and then a few more drops of sulfuric acid were added and the mixture was stirred for a further 2 days. The reaction was then worked up exactly as described previously (method 1) and gave a number of products. The two major products were isolated by multiple elution preparative TLC (2% MeOH in $CHCl_3$). One, R_f 0.39 (2% MeOH in $CHCl_3$), isolated as a white solid (120 mg, 34.5%) was identified as dimer C **30** described previously. The other named dimer B **28** was isolated as a white solid (107 mg, 33%), R_f 0.15 (2% MeOH in $CHCl_3$), m.p. 231–233 °C (from MeOH as cubic crystals) (Found: C, 69.75; H, 7.4; N, 4.6. $C_{30}H_{30}N_2O_4 \cdot 2CH_3OH$ requires C, 70.3; H, 7.0; N, 5.1%); ν_{max}(KBr)/cm^{-1} 1611 (quinolin-4-one); m/z 482 (M^+, 58%), 308 ($M^+ - C_{10}H_8NO_2$, 46) and 226 (100); ^{1}H NMR and ^{13}C NMR as depicted in Table 1.

(Treatment of dimer A **27** with glacial acetic acid containing a few drops of concentrated H_2SO_4 for 1 day gave a quantitative yield of dimer B **28**. On one occasion treatment of dimer A **27** with 1 mol dm^{-3} sodium hydroxide also gave dimer B **28**.)

Base Treatment of Dimer C **30**.—Dimer C **30** (270 mg, 0.52 mmol) was dissolved in ethanol (60 cm^3), aqueous sodium hydroxide (1 mol dm^{-3}, 60 cm^3) was added and the solution was stirred at room temperature overnight. Acidification using concentrated hydrochloric acid and addition of some water gave a precipitate which was extracted with chloroform (3 × 30 cm^3). The combined organic extracts were dried over $MgSO_4$ and reduced to give the crude products as a solid. Purification by preparative TLC (2% MeOH in $CHCl_3$) gave the product dimer D **32** as a white solid (242 mg, 97%), R_f 0.40 (2% MeOH in $CHCl_3$), m.p. 229–234 °C (from Pr^{i}OH–MeOH as glassy cubic crystals) (Found: M^+, 482.2217. $C_{30}H_{30}N_2O_4$ requires M^+, 482.2206); ν_{max}(KBr)/cm^{-1} 3410 (OH) and 1630 (quinolin-2-one); δ_H(500 MHz; $CDCl_3$; 57 °C) 0.75 (3 H, s, CH_3), 1.14 (3 H, s, CH_3), 1.53 (1 H, d, $J_{9^A,9^B}$ 17.9, 9-H^A), 1.74 (3 H, s, CH_3), 2.39 (1 H, dd, $J_{7a,7}$ 10.3, $J_{7a,11a}$ 3.9, 7a-H), 2.46 (1 H, d, $J_{9^B,9^A}$ 17.8, 9-H^B), 3.66 (3 H, s, NCH_3), 3.73 (3 H, s, NCH_3), 3.88 (1 H, m, 11a-H), 5.55 (1 H, br s, 11-H), 5.87 (1 H, d, $J_{7,7a}$ 10.4, 7-H), 7.12–7.76 (7 H, m, Ar-H) and 8.10 (1 H, dd, J 8.0 and 1.4, Ar-H); δ_C(125 MHz; $CDCl_3$; 57 °C) 23.52 (1 C, CH_3), 24.12 (1 C, CH_3), 30.00 (1 C, NCH_3), 30.21 (1 C, CH_3), 30.52 (1 C, NCH_3), 33.42 (1 C, C-8), 33.60 (1 C, C-11a), 41.10 (1 C, C-9), 44.39 (1 C, C-7a), 75.99 (1 C, C-7), 111.08, 111.88 (2 C), 114.55, 114.63 (2 C, 2 × Ar-C), 116.01, 116.80 (2 C), 120.77 (1 C, C-11), 122.37, 122.58 (2 C, 2 × Ar-C), 123.23, 124.64 (2 C, 2 × Ar-C), 131.08, 132.29 (2 C, 2 × Ar-C), 133.04, 139.10, 140.27, 155.80, 159.80 (5C), 163.22 and 163.33 (2 C, C-12, C-14); m/z 482 (M^+, 1.3%) and 307 (100).

Crystal Data for Dimer B **28**.—$C_{30}H_{30}O_4N_2 \cdot 2CH_3OH$, M = 546.66, monoclinic, space group $P2_1/n$ (No. 14), a = 9.525(4), b = 32.026(10), c = 9.816(4) Å, β = 108.68(3)°, U = 2836(1) Å^3, Z = 4, μ(Mo-Kα) = 0.07 cm^{-1}, λ(Mo-Kα) = 0.710 73 Å, D_c = 1.28 g cm^{-3}, F(000) = 1168, crystal size 0.52 × 0.54 × 0.88 mm, scan width 1.0°, scan range $3 < 2\theta < 50°$.

Data collection, analysis and refinement. Siemens P3/V2000 diffractometer; 5009 unique reflections; 1657 observed with $I > 2\sigma(I)$; direct methods solution (SHELXS-86); full-matrix least-squares refinement (SHELX-76); anisotropic vibration parameters for non-hydrogen atoms; hydrogens included at geometrically calculated positions with common isotropic temperature factors for benzene, methyl, methylene, tertiary and hydroxy hydrogens refining to U = 0.10(2), 0.13(2), 0.06(2), 0.05(2) and 0.29(7) Å^2, respectively. In the final cycles 1280 data with $I > 3\sigma(I)$ yielded R = 0.099 and R_w = 0.099; weighting scheme adopted $w = 2.96/[\sigma^2(F_o) + 0.003\,81F_o^2]$. Maximum residual electron density was 0.25 e Å^{-3}.

The crystal was air sensitive and the data had to be collected with the crystal sealed in a glass capillary with solvent.

Crystal Data for Dimer D **32**.—$C_{30}H_{30}O_4N_2 \cdot CHCl_3$, M = 601.96, monoclinic, space group $P2_1/n$ (No. 14), a = 12.955(4), b = 13.482(6), c = 17.101(3) Å, β = 91.80(2)°, U = 2985(1) Å^3, Z = 4, μ(Cu-Kα) = 3.14 cm^{-1}, λ(Cu-Kα) = 1.541 78 Å, D_c = 1.34 g cm^{-3}, F(000) = 1256, crystal size 0.64 × 0.49 × 0.53 mm, scan width 1.2°, scan range $3 < 2\theta < 110°$.

Data collection, analysis and refinement. Siemens P3/V2000 diffractometer; 3755 unique reflections; 2712 observed with $I > 2\sigma(I)$; Patterson and Fourier solution (SHELXS-86); full-matrix least-squares refinement (SHELXL-93); anisotropic vibration parameters for non-hydrogen atoms; all hydrogens except the chloroform hydrogens and the hydroxy hydrogen included at geometrically calculated positions with common isotropic temperature factors for benzene, methyl, methylene and tertiary hydrogens refining to U = 0.07(1), 0.15(1),

* Tentative assignment based on broad, unresolved signals.

0.07(1) and 0.04(1) Å^2, respectively. The chloroform hydrogen refined to U = 0.14(3) Å^2 and the hydroxy hydrogen to U = 0.04(1) Å^2. In the final cycles all data yielded R = 0.088; data with $I > 2\sigma(I)$ yielded R = 0.064; w$R2$ = 0.168. Maximum residual electron density was 0.40 e Å^{-3}.

Tables of atomic coordinates, temperature factors, bond lengths and angles for both structures have been deposited with the Cambridge Crystallographic Data Centre.*

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* For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1995, Issue 1.

References

1 Preliminary report: C. F. Neville, S. A. Barr and M. F. Grundon, *Tetrahedron Lett.*, 1992, **33**, 5995.
2 J. Reisch, I. Mester, J. Korosi and K. Szendrei, *Tetrahedron Lett.*, 1978, 3681.
3 M. F. Grundon, in *The Alkaloids; Quinoline Alkaloids Related to Anthranilic Acid*, Academic Press, London, 1988, vol. 32, ch. 5, p. 341.
4 Ref. 3, p. 386; M. F. Grundon, *Nat. Prod. Rep.*, 1990, 7, 131; J. P. Michael, *Nat. Prod. Rep.*, 1991, **8**, 63; 1992, **9**, 30; 1993, **10**, 98; 1994, **11**, 163.
5 L. Jurd, R. Y. Wong and M. Benson, *Aust. J. Chem.*, 1982, **35**, 2505; 1983, **36**, 759.
6 B. T. Ngadjui, J. F. Ayafor, B. L. Sondengam, J. D. Connolly, D. S. Rycroft, S. A. Khalid, P. G. Waterman and (in part) N. M. D. Brown, M. F. Grundon and V. N. Ramachandran, *Tetrahedron Lett.*, 1982, 2041.
7 M. F. Grundon, in *Chemistry and Chemical Taxonomy of the Rutales*, Phytochemical Society of Europe Symposia Series No. 22, Academic Press, London, 1983, ch. 2.
8 The existence of a Diels–Alderase has been inferred from the formation of optically active Diels–Alder adducts in cell cultures although the isolation and characterization of such an enzyme has not been reported: Y. Hano, T. Nomura and S. Ueda, *J. Chem. Soc., Chem. Commun.*, 1990, 610; H. Oikawa, T. Yokota, T. Abe, A. Ichihara, S. Sakamura, Y. Yoshizawa and J. C. Vederas, *J. Chem. Soc., Chem. Commun.*, 1989, 1282.
9 D. Hilvert, K. W. Hill, K. D. Nared znd M.-T. M. Auditor, *J. Am. Chem. Soc.*, 1989, **111**, 9261.
10 A. C. Braisted and P. G. Schultz, *J. Am. Chem. Soc.*, 1990, **112**, 7430.
11 C. J. Walter, H. L. Anderson and J. K. M. Sanders, *J. Chem. Soc., Chem. Commun.*, 1993, 458.
12 B. T. Ngadjui, J. F. Ayafor, S. Mitaku, A.-L. Skaltsounis, F. Tillequin and M. Koch, *J. Nat. Prod.*, 1989, **52**, 300.
13 J. F. Ayafor, B. L. Sondengam, J. D. Connolly and D. S. Rycroft, *Tetrahedron Lett.*, 1985, **26**, 4529.
14 B. T. Ngadjui, J. F. Ayafor, A. E. Ngo Bilon, B. L. Sondengam, J. D. Connolly and D. S. Rycroft, *Tetrahedron*, 1992, **48**, 8711.
15 C. S. Barnes, M. I. Strong and J. L. Occolowitz, *Tetrahedron*, 1963, **19**, 839.
16 R. F. Heck and J. P. Nolley, Jr., *J. Org. Chem.*, 1972, **37**, 2320; H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.*, 1974, **96**, 1133; R. F. Heck, in *Organic Reactions: Palladium Catalysed Vinylation of Organic Halides*, Wiley, New York, 1982, vol. 27, ch. 2, p. 345.
17 J. Reisch, H. M. T. B. Herath and N. S. Kumar, *Liebigs Ann. Chem.*, 1990, 931.
18 J. Reisch, H. M. T. B. Herath and N. S. Kumar, *Liebigs Ann. Chem.*, 1991, 685.
19 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467.
20 J. B. Melpolder and R. F. Heck, *J. Org. Chem.*, 1976, **41**, 265; A. J. Chalk and S. A. Magennis, *J. Org. Chem.*, 1976, **41**, 273.
21 N. M. D. Brown, M. F. Grundon, D. M. Harrison and S. A. Surgenor, *Tetrahedron*, 1980, **36**, 3579.
22 H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.*, 1959, **81**, 3739; 1960, **82**, 4395.
23 K. J. James and M. F. Grundon, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1467; *J. Chem. Soc., Chem. Commun.*, 1970, 337.
24 J. A. Bosson, M. Ramussen, E. Ritchie, A. V. Robertson and W. C. Taylor, *Aust. J. Chem.*, 1963, **16**, 480.
25 J. L. Gaston, R. J. Greer and M. F. Grundon, *J. Chem. Res. (S)*, 1985, 135.
26 R. C. Anand and A. K. Sinha, *Indian J. Chem.*, 1991, **30**, 604.

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