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THE DERMOCANARINS, UNIQUE MACROCYCLIC LACTONES FROM THE FUNGUS *DERMOCYBE CANARIA*[1]

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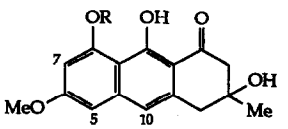
Summary - The dermocanarins I (3) and II (4), unique coupled octaketides containing a nine-membered lactone bridge, have been isolated from the mycelium of the fungus *Dermocybe canaria* and their structures determined by spectroscopic methods.

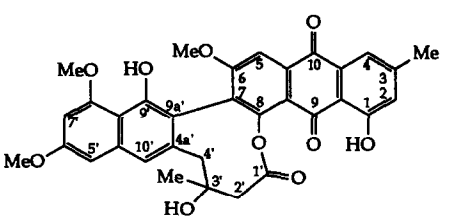
Structurally complex and stereochemically challenging coupled octaketides occur in several toxic[2] and medicinal plants,[3] in molds,[4] and in many fungi.[5] The diversity so far encountered within this group (see below) stems from the capacity of numerous organisms, particularly fungi, to effect regio- and stereo-controlled biaryl coupling between chiral dihydroanthracenones of the types **1** and **2**. We report here the first examples of a new and fundamentally different coupling type in which a chiral biaryl linkage is supplemented by a macrocyclic lactone bridge.



1 R=H
2 R=Me

Coupling	Type
5,5'	Atrovirin
7,7'	Flavomannin
10,10'	Tricolorin
7,10'	Phlegmacin
5,10'	Pseudophlegmacin

The dermocanarins I (3) and II (4) are the major pigments in the bright yellow subterranian mycelium of the Australian toadstool *Dermocybe canaria*.[6,7] The pigments were extracted from the fresh mycelium and purified by extensive chromatography on silica gel and Sephadex LH-20. No reliable estimate of the concentration of the pigments is available since the original sample was heavily and unavoidably contaminated with soil debris.



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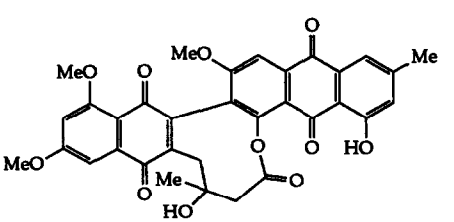

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Dermocanarin I (3) was obtained as an optically active {$[\alpha]_D$ + 27° ($CHCl_3$)} yellow powder, $C_{33}H_{28}O_{10}$ (mass spec.), m.p. 215-218°C, which exhibits electronic (λ_{max} 415 nm) and IR spectra (ν_{max} 1667 and 1633 cm^{-1}) typical of an anthraquinone.[8] The IR spectrum showed a third carbonyl absorption (ν_{max} 1754 cm^{-1}) suggesting

the presence of an ester group or lactone moiety. The nature of the substituents in the anthraquinone portion of dermocanarin I was deduced by NMR spectroscopy. Thus, the ^1H NMR spectrum revealed the presence of three aromatic protons [δ 7.90 (s), 7.65 (br.s), and 7.11 (br.s)], one phenolic hydroxy group (δ 12.54), one methoxyl (δ 4.00), and one C-methyl group (δ 2.47). These atoms and groups were located as shown in formula 3 by a combination of (a) the fully coupled ^{13}C NMR spectrum, (b) selective ^1H-^1H and ^1H-^{13}C decoupling, and (c) n.O.e. experiments. In particular, the site (C-7) at which the anthraquinone portion is directly joined to the rest of the dermocanarin I molecule, and the location (C-8 rather than C-1) of the oxygen bridge were deduced along the following lines. The signal due to 5-H (δ 7.90) appears as a sharp singlet. Irradiation of this proton resulted in simplification of several resonances in the fully coupled ^{13}C NMR spectrum including collapse of a signal at δ 128.5 from a doublet (*J* 6.1 Hz) to a sharp singlet. The magnitude of the coupling constant indicates three bond coupling and, along with other evidence, identifies the nucleus as C-7. The chemical shift of C-7 is not consistent with an oxygenated carbon and implies a link from that nucleus, through carbon, to the remainder of the dermocanarin I molecule. The carbon bearing the free phenolic hydroxy group (C-1) resonates at δ 162.6 as a doublet of doublets (*J* 4.4 and 3.0 Hz). This signal is collapsed to a doublet expressing only the smaller coupling on irradiation of the phenolic proton (δ 12.54). The smaller coupling was traced to 2-H by irradiation at the resonance frequency of that nucleus (δ 7.11), which collapsed the signal at δ 162.6 to a doublet (*J* 4.4 Hz). Consistent with this conclusion, C-8 resonates at δ 152.3 as a sharp singlet.

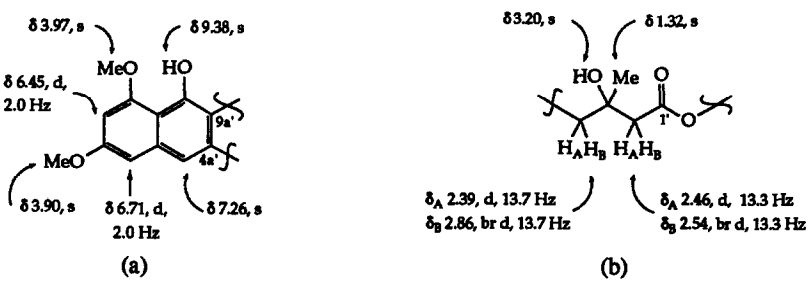


Figure 1. ^1H N.m.r. data ($CDCl_3$) for (a) the naphthalene ring, and (b) the lactone bridge in dermocanarin I.

With the anthraquinone portion of dermocanarin I accounting for a fragment $C_{16}H_{10}O_5$, the remaining elements $C_{17}H_{18}O_5$ were strongly suggestive of a dihydroanthracenone subunit.[9] However, analysis of the residual ^1H and ^{13}C NMR data, together with n.O.e. experiments, identified a substituted naphthalene nucleus (Figure 1a) and an aliphatic C_5 chain (Figure 1b).

A biaryl linkage between C-7 and C-9a' in dermocanarin I was established by n.O.e. experiments. Thus, the C-4' methylene proton at δ 2.86 experiences mutual enhancement with the isolated aromatic proton at C-10' (δ 7.26), thereby placing the side chain at C-4a' and leaving C-9a' as the site of the biaryl bond. Carbon C-9a' resonates at δ 111.6 in accord with its direct attachment to carbon.

Once it is recognised that the carbonyl group at C-1' must be part of a lactone group (δ_C 169.0) the naphthalene, lactone bridge, and anthraquinone subunits of dermocanarin I come together unequivocally in terms of the structure 3. The stereochemical detail implicit in this formulation has not yet been solved, but since the pigment 3 shows only a single set of ^1H and ^{13}C resonances we assume it to be a single stereoisomer.

Dermocanarin II (4) was obtained as a powder, $C_{33}H_{26}O_{11}$, m.p. 235-240°C, $[\alpha]_D$ + 32° ($CHCl_3$). This second yellow pigment displays NMR spectra that reveal the same anthraquinone nucleus and lactone bridge as is present in dermocanarin I (3). In addition, the ^1H NMR spectrum of dermocanarin II exhibits two methoxyl resonances and a pair of *meta* coupled aromatic protons, which must be located in the naphthalene portion of the molecule (Figure 2a). Significantly, the phenolic hydroxy group (δ 9.38) and the isolated aromatic proton (δ 7.26) present in the spectrum of dermocanarin I are absent from the spectrum of the second pigment and are replaced by quinonoid carbonyl groups (Figure 2b). The chemical shift (δ 7.32) of 5'-H in dermocanarin II is consistent with its position *peri* to the C-10' carbonyl. The multiplicities of the carbonyl signals (Figure 2b) are in accord with the location of the biaryl linkage and the lactone bridge at C-9a' and C-4a', respectively, in the naphthoquinone nucleus of dermocanarin II.

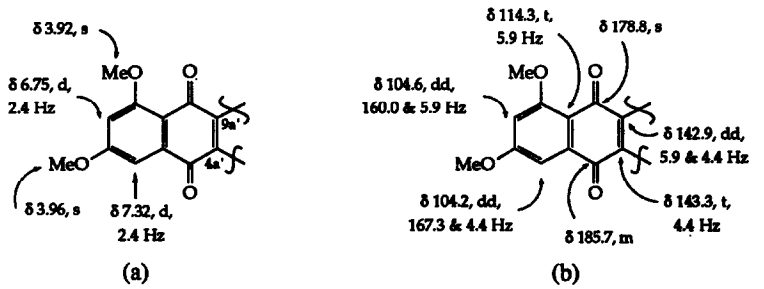
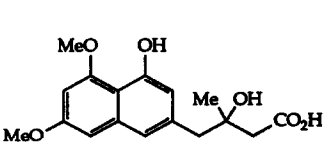


Figure 2. (a) ^1H N.m.r. data ($CDCl_3$), and (b) ^{13}C n.m.r. data ($CDCl_3$) for the napththoquinone nucleus of dermocanarin II.

The dermocanarins I and II represent the first members of a new class of coupled octaketide pigments. The presence of the macrocyclic lactone ring and the nature of the naphthalenoid subunit render them unique among coupled anthraquinones and coupled pre-anthraquinones.[5] In the present case it seems reasonable to suggest that the naphthalene ring and the elements of the lactone bridge arise from a progenitor of the dihydroanthracenone type. For example, retro-Claisen cleavage of torosachrysone-8-*O*-methyl ether (2) could yield the carboxylic acid (5) capable of subsequent esterification and biaryl coupling with physcion (6) to yield dermocanarin I (3). Torosachrysone-8-*O*-methyl ether (2) has been isolated from several toadstools belonging to the genera *Cortinarius*[10,11] and *Tricholoma*,[12] while physcion (6) is the major pigment present in the fruit bodies of *Dermocybe canaria*.[13] Despite the attraction that this mode of biosynthesis holds, at this point an alternative pathway involving formation of a carboxylic acid of the type (5) by malonate attack on a preformed heptaketide cannot be excluded. Experiments designed to shed further light on the biogenesis of the dermocanarins and on their absolute stereochemistry are in progress.



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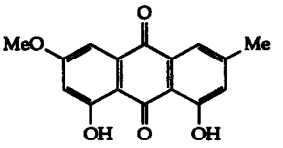

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References and Footnotes

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7. The dermocanarins I and II are also present in the fruit bodies of *Dermocybe canaria* where they are subordinate to physcion (**6**) and physcion-8-*O*-β-D-glucopyranoside as the principal pigments (M. Gill and A. Gimenez, manuscript in preparation).
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