Structural and Stereochemical Correlations of Polypropionate Metabolites from Marine Pulmonates: Revision of the Relative Stereochemistry of Pectinatone by X-Ray Structure Analysis

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Correlations among polypropionate metabolites isolated from marine pulmonates of the genus *Siphonaria* reveal two major stereochemical types; the relative stereochemistry of pectinatone is revised to (**14**) by X-ray diffraction analysis

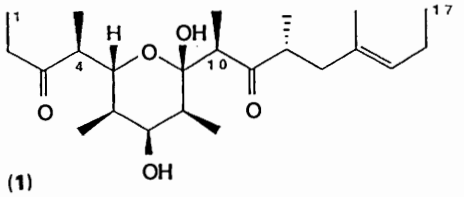
Biosynthetic evidence supported by striking structural and stereochemical correlations within [1] and between [2] members of the polyether and macrolide classes of actinomycete antibiotic suggest that these two classes of antibiotics share a common genetic origin.

Pulmonate limpets of the genus *Siphonaria* contain polypropionate metabolites characterised by the presence of ketal,[3] pyrone,[4] and furanone[4c] entities. Recently, we demonstrated that the denticulatins A (**1**) and B (**2**) from *Siphonaria denticulata* derive *de novo* from propionate[5] and thus share a common biosynthetic origin to actinomycete antibiotics such as the macrolide erythromycin[6] or the polyether monensin.[7] Is this biosynthetic similarity coincidental or are polypropionate metabolites in siphonariids products of bacterial metabolism? Alternatively, the capacity to synthesise polypropionates has evolved following the inclusion of a bacterial genome into siphonariid genetic material. As a preliminary step towards the comparison of structure, stereochemistry, and biosynthetic processes in siphonariids and actinomycetes, we report herein structural and stereochemical trends among the siphonariid metabolites themselves.

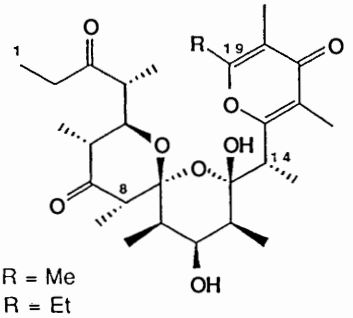
Denticulatin A (**1**),[3b] siphonarins A (**3**) and B (**4**),[3c] and muamvatin (**5**)[3d] all possess a ketal function. The spiroketal portion of siphonarins A and B is reminiscent of the bisdispiroketal skeleton of narasin A (**6**) and other members of the polyether antibiotics. An intriguing stereochemical trend (Scheme) becomes apparent when these four siphonariid molecules are drawn in ring-opened form using the absolute configurations represented for them in the literature; the stereochemistry of (**1**) † from C-3 to C-10 correlates with that of (**3**)–(**4**) from C-7 to C-14, providing that the polycarbonyl-derived precursors of these metabolites are all assembled in the direction shown. Muamvatin (**5**) retains the same stereochemistry as denticulatin A over the chiral centres from C-3 to C-9.

A second group of siphonariid compounds (**7**)–(**12**) are all characterised by an alkenyl chain and often contain an α-pyrone nucleus;[4] structure–activity considerations indicate that this latter functional group is required for antibiotic activity. Stereochemical trends are also apparent; the diemenensins A (**7**) and B (**8**),[4a] siphonarienedione (**9**), and siphonarienolone (**10**)[4e] possess *S* stereochemistry at the contiguous methyl-substituted chiral centres of the alkenyl chain.

Pectinatone (**11**)[4b] and norpectinatone (**12**)[4c] do not fit into this stereochemical pattern; they were determined to have *S,R,S* stereochemistry through oxidative cleavage of the side-chain double bond and correlation of the products with trimethylated fatty acid esters. The relative stereochemistry assigned to (**12**) has been questioned by Oppolzer[8] who synthesised structure (**12**) and a diastereoisomer (**13**); both synthetic products had different physical, spectroscopic and chiroptical properties to those reported for natural norpectinatone. Degradation of pectinatone[4b,c] yields (+)-methyl-2,4,6-trimethylnonanoate. In

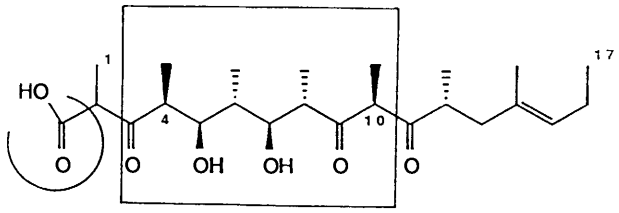


(**1**)
(**2**) epimer at C-10

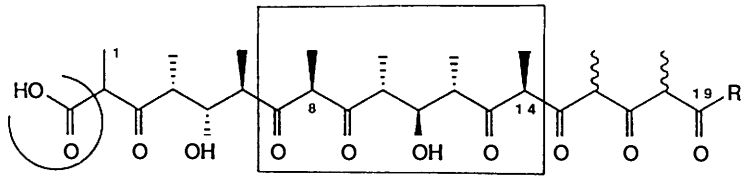


(**3**) R = Me
(**4**) R = Et

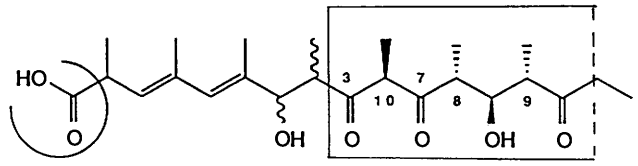
† Denticulatin B (**2**) does not fit into this stereochemical scheme. It is not known which of denticulatins A or B is the natural product; the masked β-diketone system ensures facile epimerisation to an equilibrium mixture of the two isomers.



Denticulatin A precursor



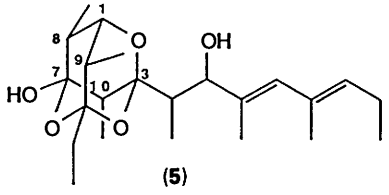
Siphonarin precursor
R=Et or Me.



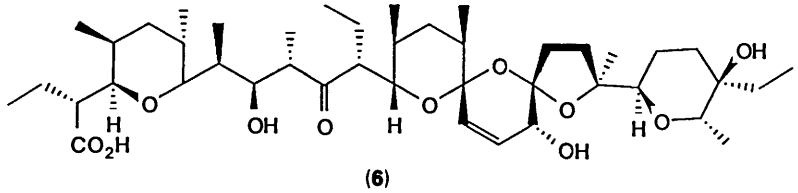
Muamvatin precursor

Direction of chain growth

Scheme.



(5)



(6)

this ester, a large, positive rotation is reliably associated with a 2*S*,6*S* configuration.[4c,9] The stereochemistry at C-4 of methyl 2,4,6-trimethylnonanoate has little influence on the sign and magnitude of the optical rotation shown by the stereoisomers of this compound, so that this centre, corresponding to C-11 of pectinatone, cannot confidently be assigned by the use of optical rotation data alone. These considerations led us to suggest that the stereochemistry at C-11 of pectinatone might be *S*, as in (**14**), rather than the *R* configuration shown in (**11**).

The isolation of crystalline pectinatone together with norpectinatone from the pulmonate *Siphonaria virgulata* provided us with an opportunity to check the relative stereochemistry of thesecompounds.Pectinatone,$[\alpha]_D$ = +61.9°(*c*0.0019,$CHCl_3$), m.p. 126–128 °C ex. hexane (lit., 127–129 °C) gave colourless blades which were the subject of a single crystal X-ray study.*

* Crystals of $C_{21}H_{34}O_3$ are orthorhombic, $P2_12_12_1$ (No. 19), a = 15.79(1), b = 12.800(1), c = 10.403(2) Å, U = 2 103 Å^3, D_c = 1.06 g cm^{-3}. 1 584 Independent diffractometer reflections to $2\theta_{max}$ 45° (monochromatic Mo-K_α radiation, λ = 0.710 69 Å), 848 with $I > 3\sigma(I)$ being refined (full matrix least squares) to R, R_w (on $|F|$) = 0.053, 0.049; no abnormal features other than high thermal motion at the periphery of the pendant tail. C,O atom co-ordinates and anisotropic thermal parameters, (x, y, z, U_{iso})$_H$ (est.) are available from the Cambridge Crystallographic Data Centre. See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1990, Issue 1.

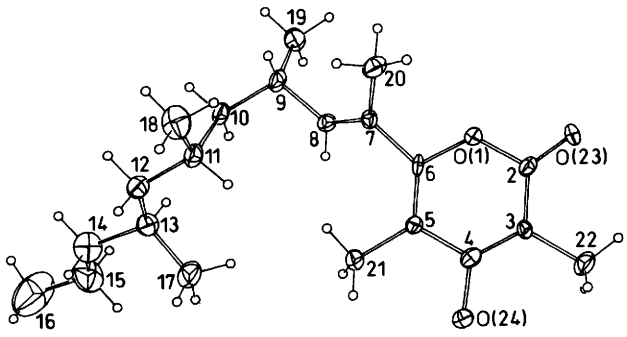
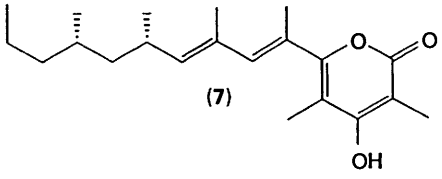
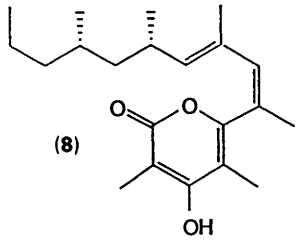


Figure. Molecule of pectinatone projected normal to the ring plane. 20% Probability amplitudes are shown for the non-hydrogen atoms (C,O); hydrogen atoms have arbitrary radii of 0.1 Å.

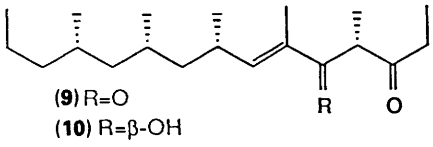
The result (Figure), although consistent with the stoicheiometry and connectivity represented by (**11**), shows clearly that the relative stereochemistry of pectinatone is the same at all three chiral centres; either all *S* or all *R*. Pectinatone is thus shown



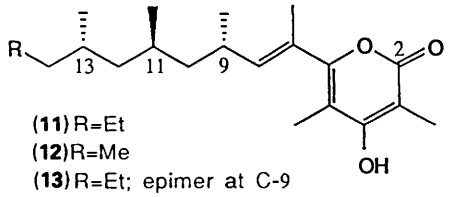
(**7**)



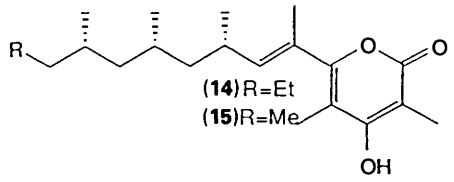
(**8**)



(**9**) R=O
(**10**) R=β-OH



(**11**) R=Et
(**12**) R=Me
(**13**) R=Et; epimer at C-9



(**14**) R=Et
(**15**) R=Me

to have 9*S*, 11*S*, 13*S* stereochemistry, as in (**14**). It is biosynthetically unlikely that *S. virgulata* would generate homologues differing in chirality at only one of three centres, hence we suggest that the relative stereochemistry of norpectinatone be revised to (**15**). The revised stereochemistry now conforms to that shown by other non-ketal metabolites from siphonariids[4] and suggests a common genetic basis for the origin of these compounds.

Our data reinforce the comments of Norte *et al.*[4e] on the difficulty in assigning absolute configuration on the basis of small differences in optical rotation, especially when the yield of degradation product is low.

Experiments designed to determine the extent of biosynthetic and stereochemical similarities between actinomycete and siphonariid metabolites are currently in progress in our laboratory.

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