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A Configurational Model for Siphonariid Polypropionates Derived from Structural and Biosynthetic Considerations.

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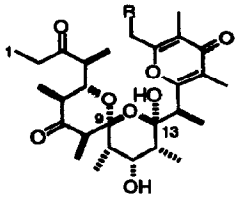
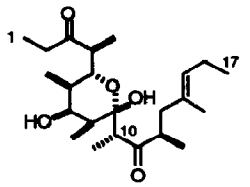
Abstract: The energies of the acetal ring systems in siphonarin B (**2**), muamvatin (**5**), and caloundrin B (**7**) are compared. A configurational model for siphonariid metabolites is proposed which rationalises the stereochemistry of their acyclic precursors. It contains a tetrapropionate unit common to the Cane-Celmer-Westley PAPA model for polyether antibiotics of bacterial origin.

Recent experiments[1,2] on the biosynthesis of polypropionate and polyacetate metabolites of bacterial origin support a processive mechanism, where each chain extension unit introduced into the growing polyketide chain is correctly functionalised prior to addition of the next chain building unit. These chemical studies, complemented by important advances in the biochemistry and genetics of macrolide and polyether biosynthesis, provide a fascinating comparison between polyketide and fatty acyl synthases.[3]

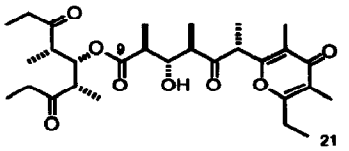
Marine molluscs of the genus *Siphonaria* (false limpets) have been found to produce diverse cyclic acetals (see **Scheme 1**),[4,5] which have a high degree of methylation and oxygenation. These polypropionate metabolites include siphonarin A (**1**) and B (**2**) isolated from *S. zelandica*,[4a] denticulatin A (**3**) and B (**4**) from *S. denticulata*,[4b] and muamvatin (**5**) from *S. normalis*.[4c] Baconipyrone C (**6**), isolated from *S. baconi*,[4d] is unusual in that it lacks a contiguous carbon skeleton. More recently, a collection of *S. zelandica* yielded caloundrin B (**7**) as a minor component,[5] which is isomeric to siphonarin B and arises by a muamvatin-like cyclisation.



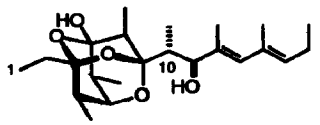
siphonarin A, R = H (**1**)
siphonarin B, R = Me (**2**)



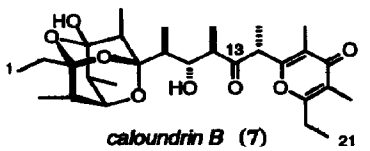
denticulatin A (**3**)
denticulatin B, C10-epimer (**4**)



baconipyrone C (**6**)



muamvatin (**5**)

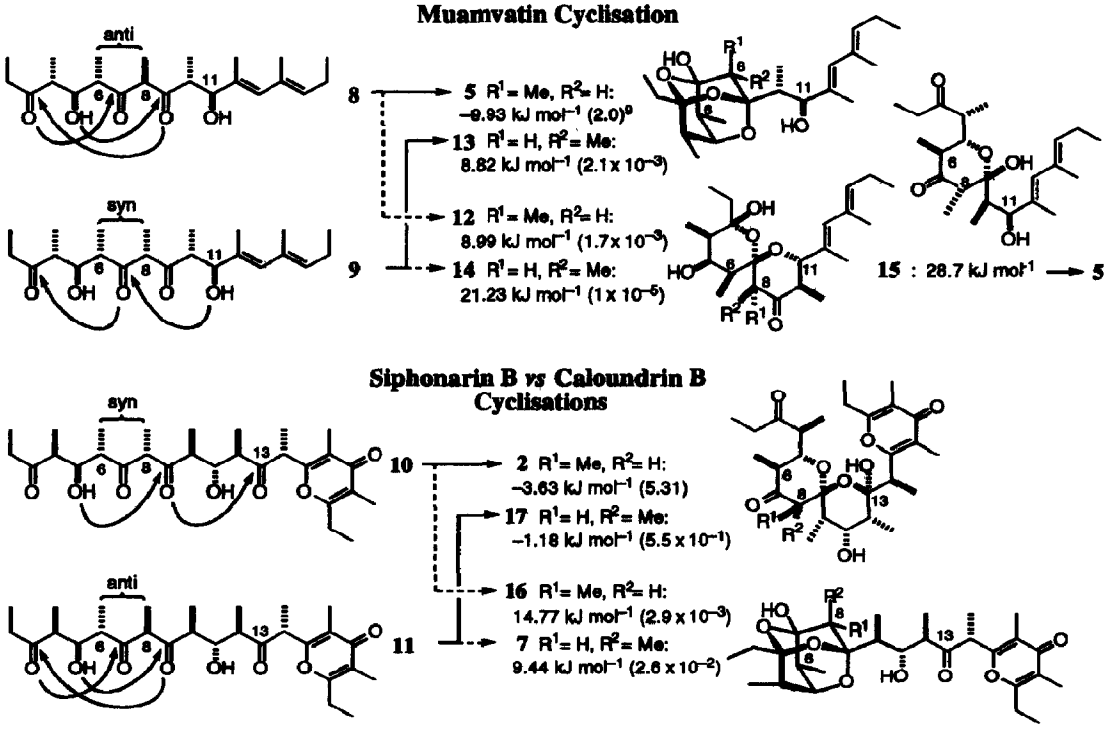


caloundrin B (**7**)

Scheme 1

In previous papers, we have provided structural, biosynthetic[6] and synthetic evidence[7] leading to the assignment of the absolute configuration of the siphonarins to be that shown in **Scheme 1**, together with a model for their biosynthesis. In this model, the γ-pyrone / spiroacetal ring system arises from decarboxylation and cyclisation of a linear polypropionate precursor. Here we analyse the structural and stereochemical relationships between the siphonariid metabolites **1** – **7** and propose a general configurational model which overlaps with the Cane-Celmer-Westley PAPA model for polyether antibiotics of bacterial origin.

Previously, we have proposed[8] that the formation of muamvatin and the siphonarins is determined by thermodynamic factors, where the preferred acetal ring system is related to the oxidation state of the carbons and the configuration of the hydroxyl and methyl groups in the acyclic precursor. Moreover, these and related compounds isolated from siphonariid molluscs may represent thermodynamic, *i.e.* non-enzymic, cyclisation products of unstable acyclic polypropionate metabolites. The available cyclisation modes for **8** and **9**, likely acyclic precursors for muamvatin, and **10** and **11**, plausible precursors for siphonarin B and caloundrin B, were considered by comparing the calculated energies[9,10] of the isomeric acetal ring systems (**Scheme 2**). Since the C_8 stereocentre is readily epimerisable by its relationship with a β-diketone (*cf.* C_{10} in denticulatin A and B), two precursors are available in each case.



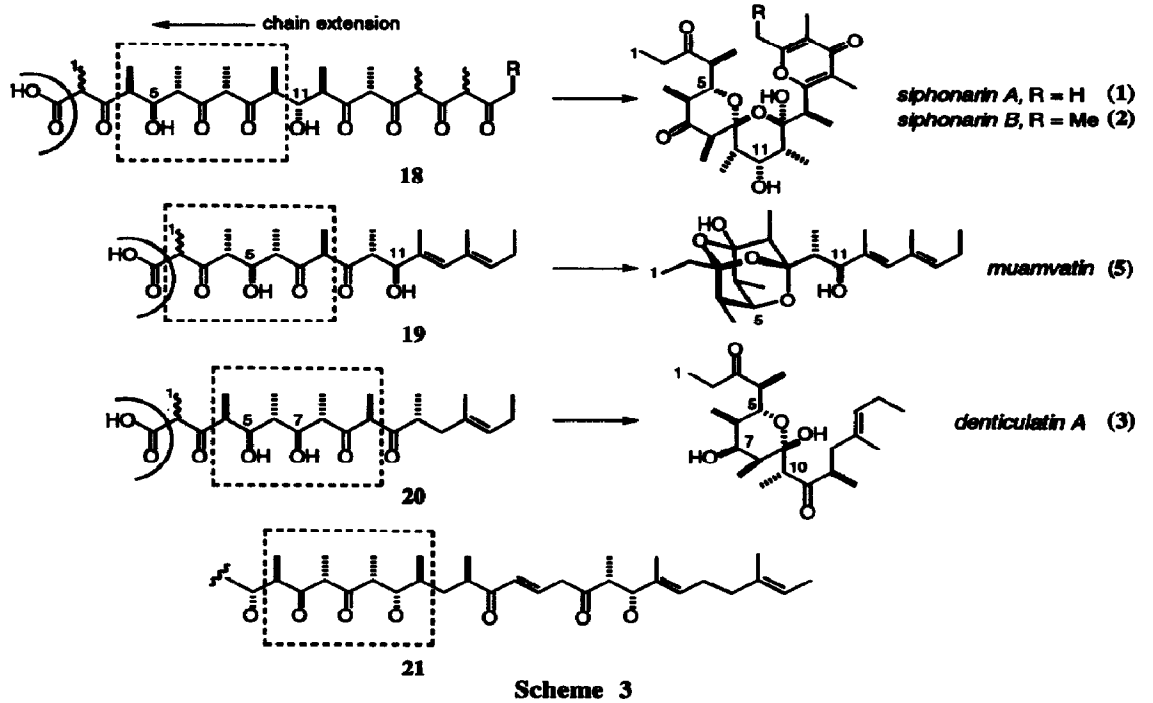
Scheme 2

For the acyclic precursor **8** (6,8-anti) to muamvatin, calculations showed the derived trioxaadamantyl structure **5** to be significantly more stable relative to the corresponding spiroacetal **12**. For the 8-*epi* precursor **9** (6,8-syn), however, the preference for **13** over **14** was less pronounced. We have previously speculated that the muamvatin structure **5** is an artifact of the isolation process.[8] The true natural product may be the less stable hemiacetal **15** (*cf.* denticulatin A and B) formed by partial cyclisation of **8**, or conceivably an unstable acyclic system related to **8**, which rearranges on isolation and silica gel chromatography to give the thermodyamically preferred, trioxaadamantyl ring system in **5**.

Repeating these calculations for the two alternative cyclisation modes of the acyclic precursors **10** (6,8-syn) and **11** (6,8-anti) led to a preference for the spiroacetal structure **2** in siphonarin B relative to the trioxaadamantyl isomer **16**. Note that the trioxaadamantyl structures **13** and **16** are destabilised by a 1,3-diaxial interaction between the methyl groups attached to C_6 and C_8. Hence formation of the minor isomer caloundrin B requires epimerisation at C_8 of **10** to give **11**, which is more likely than **10** to follow the trioxaadamantyl cyclisation mode giving **7** over that producing **17** (= 8-*epi*-siphonarin B). The thermodynamic cyclisation

preference in these systems thus seems to be affected by the syn *vs* anti relationship between the C_6 and C_8 methyl groups in the acyclic precursors **8** – **11**.

The siphonarin group of metabolites are derived from the linear combination of ten propionate units (siphonarin B), or one acetate and nine propionate units (siphonarin A), where the terminal carboxyl group is lost after completion of the chain assembly. In the absence of any experimental evidence to the contrary, it is assumed that the assembly process is processive rather than non-processive. In the processively-modified, polyketide precursor **18** (**Scheme 3**), the majority of the carbons derived from C_1 of propionate retain their original oxidation level, while C_5 and C_{11} are reduced giving hydroxyl-bearing stereocentres of opposite configuration. The stereochemistry of ketoreductase enzymes involved in fatty acid biosynthesis is exclusively *R*.[3a,11] This stereochemistry of reduction is also frequently,[1,2b,c,12] but not exclusively,[2a,13] shown by polyketide ketoreductases. The baconipyrones, *e.g.* **6** in **Scheme 1**, are non-contiguous polypropionate metabolites from *S. baconi*, which are assumed to arise either by rearrangement of the siphonarin skeleton[4d] or from the precursor polypropionate **18** itself.



Scheme 3

Although the absolute configuration of denticulatin A (**3**) and B (**4**),[14] and muamvatin (**5**)[8,15] has been confirmed by synthesis, there is no experimental evidence for the direction of chain growth in their associated polypropionate precursors. Extension of the above siphonarin biosynthetic model **18** to encompass these other siphonariid metabolites[8,16] was made by assuming: (*i*) the maximum number of secondary hydroxyl centres with configuration corresponding to that demonstrated for fatty acids; (*ii*) any structural variation occurs predominantly at the beginning of the polypropionate chain; and (*iii*) a β-keto acid chain terminus is preferred. This results in octapropionate precursors **19**, leading to muamvatin, and **20** leading to denticulatin A. An intriguing feature, which emerges when **18** – **20** are compared with each other, is that they all share a common tetrapropionate unit as shown by the dashed boxes.

Biosynthetic models which correlate known polyether[17a] or macrolide[17b] antibiotics and which highlight stereochemical homology[18] between polyethers and macrolides have been previously proposed. A comparison of our general siphonariid model with the PAPA model **21** of Cane, Celmer and Westley[17a] for polyethers is shown in **Scheme 3**. Significant structural and stereochemical homology exists, where notably the tetrapropionate unit common to **18**–**20** is also present in the PAPA model **21**. The occurrence of common structural motifs in bacterial and siphonariid polypropionates points to a common genetic origin.[18b] We are currently probing the proteins of *S. zelandica* and related siphonariids to search for large proteins resembling polyketide or fatty acyl synthases.

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