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Synthesis of a Liphagal–Frondosin C Hybrid and Speculation on the Biosynthesis of the Frondosins

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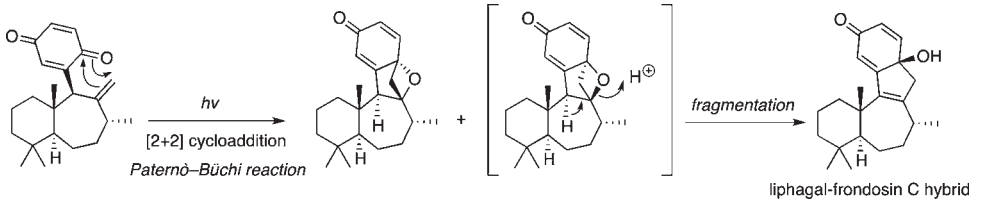
ABSTRACT



A hypothesis for the biosynthesis of the frondosins A–E is presented. Synthesis of a liphagal–frondosin C hybrid molecule has been achieved, with the frondosin C 6–7–5–6 ring system being constructed by a photochemical process that follows an intramolecular Paternò–Büchi reaction/fragmentation pathway.

Marine sponges provide a rich source of natural products with unusual molecular structures and potentially useful biological activities.[1] Liphagal (**1**)[2] and frondosins A–E (**2**–**6**)[3] are marine sponge-derived meroterpenoids with 6–7 carbocyclic ring systems that are fused or attached to benzofuran, hydroquinone, or quinone groups (Figure 1). Liphagal was isolated in 2006 by Andersen from *Aka coralliphaga*, and it was found to be a potent inhibitor of the PI3K cell signaling pathway.[2] We recently synthesized liphagal via a biomimetic ring-expansion strategy,[4] and routes to the compound have also been published by the groups of Andersen,[1] Mehta,[5] Alvarez-Manzaneda,[6] and Stoltz.[7] The frondosins have also attracted significant attention from the synthetic community since their initial isolation in 1997 from *Dysidea frondosa* and their reported inhibition of the binding of interleukin-8 to its receptor in the low micromolar range.[8]

Despite the close similarity between the structures of the frondosins A–E, there has been no synthetic work on the biosynthetic relationships between these compounds. As part of our continuing interest in biomimetic reactions of *o*-quinone methides,[9] we were interested in investigating the formation of some of the unusual frondosin quinone systems using a 6–7 carbocyclic scaffold generated during

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our previous liphagal work.[4] This would give insight into the biosynthesis of the frondosins, as well as generating liphagal–frondosin hybrid molecules for further biological evaluation.

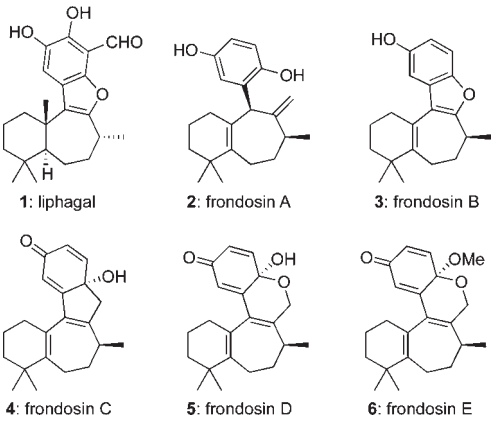


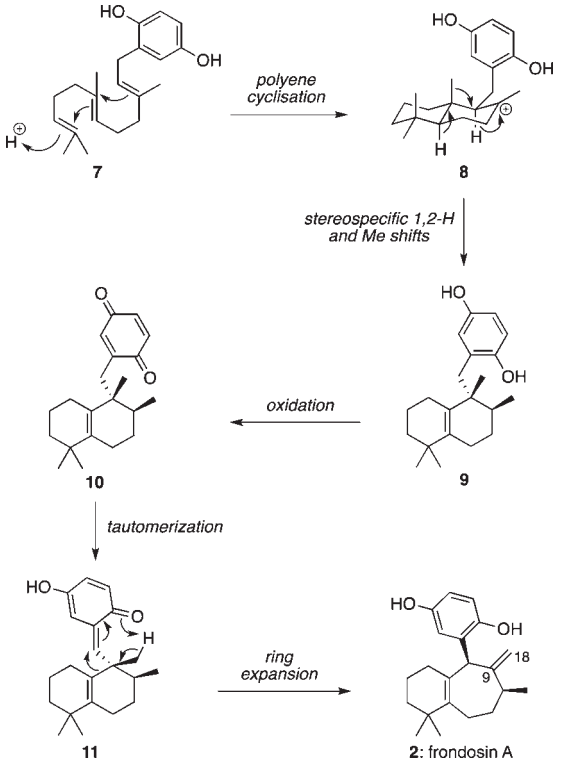
Figure 1. Liphagal and the frondosins.

Frondosin A is presumably derived from initial union of farnesyl pyrophosphate and hydroquinone to give the polyene **7**, which could cyclize to give the drimane carbocation **8** (Scheme 1). Rearrangement of carbocation **8** via sequential 1,2-hydride and methyl shifts would then form **9**.[10] The hydroquinone moiety of **9** could readily undergo oxidation to give the quinone **10**. Tautomerization of quinone **10** could then form *o*-quinone methide[11] **11**, which might undergo a ring-expansion to generate the 6,7-ring system of frondosin A (**2**), with concomitant reformation of the aromatic hydroquinone ring as the reaction driving force. This reaction may possess a degree of synchronicity which ensures the formation of the exocyclic $\Delta^{9,18}$ methylene group, as the mechanism drawn in Scheme 1 suggests.

We propose that quinones and *o*-quinone methide intermediates are further involved in the biosynthetic conversion of frondosin A into frondosins B–E (similar ideas have been presented by Pettus[12] in a recent book chapter). Oxidation of the hydroquinone of frondosin A would give quinone **12**, which would possess a relatively acidic proton at C-10 (Scheme 2).

Deprotonation at C-10 would generate the *o*-quinone methide **13**, which could perhaps undergo an intramolecular vinylogous aldol reaction to give frondosin C (**4**), although stereoelectronic considerations might appear to disfavor such a transformation. Later experiments in this paper will indicate that an alternative mechanism is more likely for the biogenetic origin of frondosin C. A more

Scheme 1. Proposed Biosynthesis of Frondosin A via an Intramolecular Vinylogous Aldol Reaction



obvious fate for the *o*-quinone methide **13** might be a 6π-electrocyclic reaction to form **14**.[13] A third and final oxidation in the biosynthetic sequence would then give a quinone cation that could be trapped by water at C-17 to give frondosin D (**5**) or by methanol to give frondosin E (**6**). Finally, the biosynthesis of frondosin B (**3**) requires a one-carbon dehomologation, which could occur from frondosin D (**5**) via an intramolecular 1,6-conjugate addition to give **15**, followed by deformylation by a retro [4 + 2] cycloaddition mechanism.[12]

Our intention was to model some of the biosynthetic processes outlined in Schemes 1 and 2 using a readily accessible liphagal-type scaffold. As such, the known aldehyde **17**[14] was obtained from (+)-sclareolide[15] (**16**) in eight steps (Scheme 3). Addition of 2,5-dimethoxymagnesium bromide to **17** generated **18** in 87% yield, which was treated with $LiAlH_4$ to give diol **19**. Pinacol rearrangement of **19** by treatment with TFA then gave the ring-expanded product **20** as a single diastereoisomer in 61% yield over two steps, presumably via a benzylic carbocation. The relative stereochemistry of **20** was assigned by analysis of

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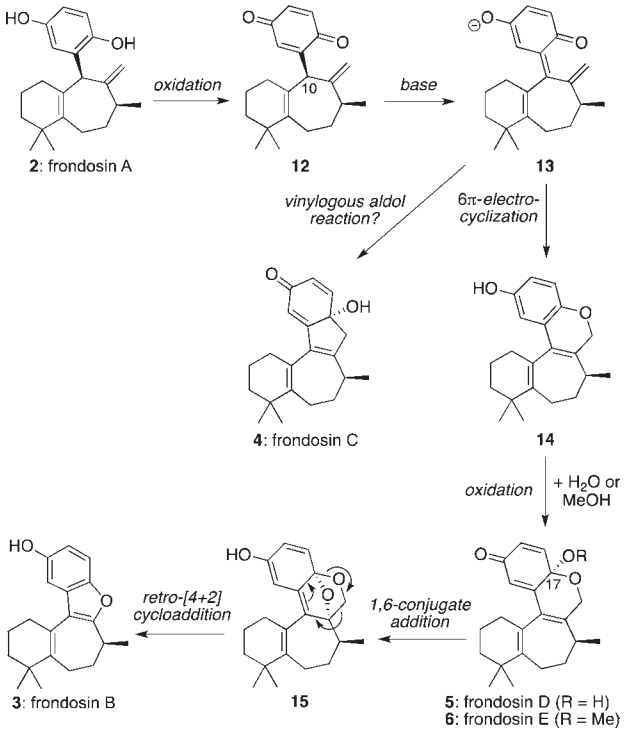
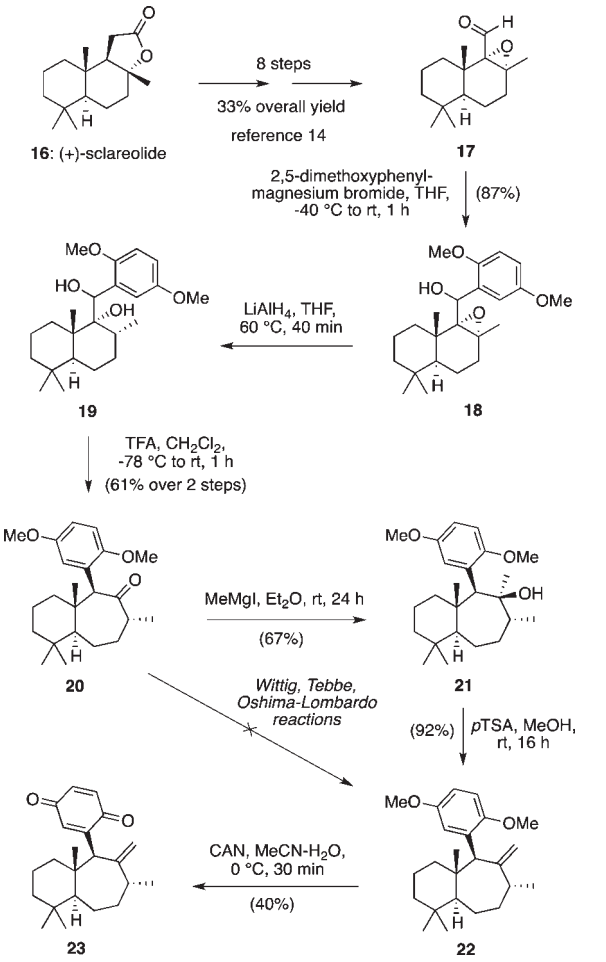
Scheme 2. Proposed Biosynthesis of Frondosins B–E via *o*-Quinone Methide Rearrangements



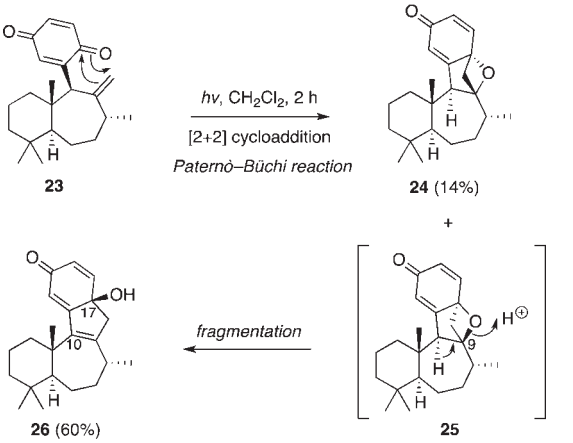
a NOESY NMR spectrum. Attempts to directly methylenate ketone **20** under a variety of conditions failed to give more than trace quantities of alkene **22**, so a two step strategy was employed instead. Stereoselective addition of methylmagnesium iodide to **20** gave tertiary alcohol **21** as a single diastereoisomer. Screening of a variety of reaction conditions initially failed to selectively dehydrate **21** to **22**, with a mixture of tetra-substituted alkenes generally being formed. However, the use of *p*TSA in MeOH gave exocyclic alkene **22** as the sole reaction product in 92% yield; we are unable to explain this unusual selectivity. Oxidation of **22** with CAN then gave quinone **23**, albeit in a modest isolated yield of 40% due to significant decomposition of the starting material under the reaction conditions.

A sample of quinone **23** in $CDCl_3$ was found to undergo slow conversion into two new products, **26** and **24**, in a 5:1 ratio as observed by ^1H NMR, with the reaction taking 10 days to reach completion (Scheme 4). Compound **26** was immediately recognized as having a frondosin C-type carbocyclic framework, and **24** was later characterized as possessing a highly strained bicyclic oxetane ring system. Attempts to speed up the formation of **26** using acid or base catalysis failed, but exposure of a CH_2Cl_2 solution of **23** to sunlight resulted in a complete reaction in 30 min, as observed by TLC analysis. The optimized final procedure involved exposure of a solution of quinone **23** to a 500W lamp for 2 h. Presumably a photochemical [2 + 2] cycloaddition between the exocylic alkene and the adjacent quinone carbonyl group of **23** (a Paternò–Büchi reaction)

Scheme 3. Synthesis of Quinone **23**



Scheme 4. Synthesis of Liphagal–Frondosin C Hybrid **26** via an Intramolecular Paternò–Büchi Reaction

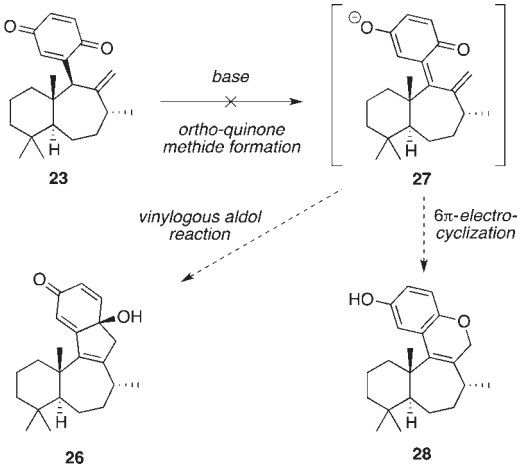


initially gives a mixture of diastereomeric oxetanes **24** and **25** with unusual 6-oxabicyclo[2.2.1]hexane ring systems. Bicyclic oxetane **24** is stable under the reaction conditions

(and is indeed stable at elevated temperatures), but the presumed intermediate **25** could readily undergo fragmentation to give **26** due to the antiperiplanar relationship between the proton at C(10) and the C(9)-O bond that is broken. The relative stereochemistry of **24** was determined by NOE spectroscopy. The configuration of the C-17 stereocenter of **26** was also determined by NOE spectroscopy.

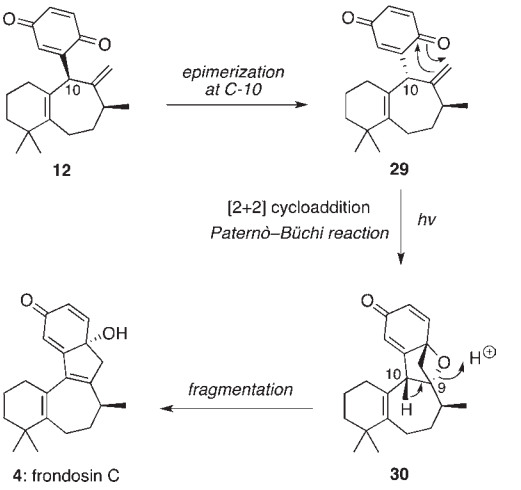
Attempts to form an *o*-quinone methide intermediate from **23**, and thus give **26** via a vinylogous aldol reaction, or 28 via a 6π-electrocyclization, failed under a variety of conditions (Scheme 5).

Scheme 5. Attempted *o*-Quinone Methide Formation from **23**



The ease of the photochemical transformation of **23** into **26** suggests that a similar process might occur in the biosynthesis of frondosin C (**4**). Epimerization at C-10 of the reactive quinone **12** might first be required to give **29**, which could undergo an intramolecular Paternò–Büchi reaction to give the 6-oxabicyclo[2.2.1]hexane ring system of **30** (Scheme 6). The bicyclic oxetane ring system of **30** would then possess the correct relative stereochemistry at C-9 and C-10 for a stereoelectronically favorable fragmentation to occur to give **4**.

Scheme 6. Revised Biosynthesis of Frondosin C via an Intramolecular Paternò–Büchi Reaction



In conclusion, we have developed an efficient synthesis of the 6–7–5–6 ring system of frondosin C via an intramolecular [2 + 2] cycloaddition/fragmentation strategy. It is probable that this reaction sequence mirrors the biosynthesis of frondosin C. Furthermore, we have presented a biosynthetic origin for the whole frondosin family. Efforts to mimic these reactions in a synthesis of all the frondosins are underway and will be reported in due course.

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Supporting Information Available. Experimental procedures and spectral data for compounds **18**–**24** and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.