

First Approach to the Frondosin C Ring System via a Tandem Cyclization/Claisen Rearrangement Sequence

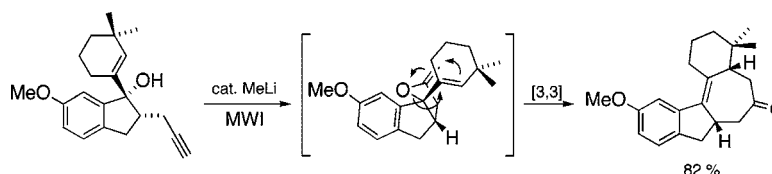
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ABSTRACT



A one-pot tandem 5-exo cyclization/Claisen rearrangement strategy is utilized as the key step in the straightforward construction of the tetracyclic ring system of frondosin C. This reaction is done under microwave irradiation in the presence of catalytic MeLi.

Five novel sesquiterpene hydroquinone derivatives, frondosins A–E (Figure 1), were recently isolated from the

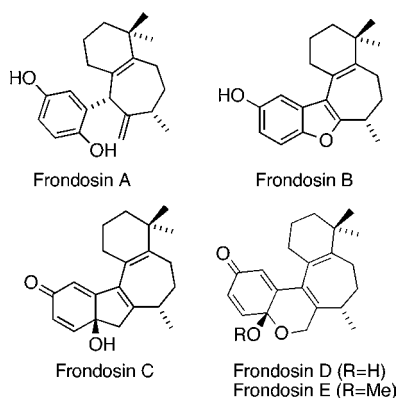


Figure 1. Structures of frondosins A–E.

Micronesian marine sponge *Dysidea frondosa*.¹ These compounds were found to be antagonists of interleukin-8 (IL-8), a neutrophil-activating peptide, which is produced by various cell types in response to inflammation.¹ Thus, IL-8 antagonists such as the frondosins hold therapeutic potential

as novel antiinflammatory agents. Additionally, some members of the frondosin family were found to exhibit anti-HIV activity.²

The total synthesis of frondosin B was first achieved by Danishefsky et al.³ in 2000 and, more recently, by the Trauner⁴ and Flynn⁵ groups. The other members of the frondosin family, however, have not yet been synthesized. Herein, we describe the first approach to the frondosin C ring system. This approach is based on our recent investigations involving a base-catalyzed tandem cyclization/Claisen rearrangement as a route to cycloheptane-containing polycyclic ring structures.⁶ The reaction sequence involves an initial 5-exo dig cyclization of an appropriately substituted

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(2) Hallock, Y. F.; Cardellina, J. H.; Boyd, M. R. *Nat. Prod. Lett.* **1998**, *11*, 153.

(3) (a) Danishefsky, S. J.; Inoue, M.; Frontier, A. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 761. (b) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878.

(4) (a) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569. (b) Hughes, C. C.; Trauner, D. *Tetrahedron* **2004**, *60*, 9675.

(5) Kerr, D. J.; Willis, A. C.; Flynn, B. L. *Org. Lett.* **2004**, *6*, 457.

(6) (a) Ovaska, T. V.; Roark, J. L.; Shoemaker, C. M. *Tetrahedron Lett.* **1998**, *39*, 5705. (b) Ovaska, T. V.; Roses, J. B. *Org. Lett.* **2000**, *2*, 2361.

(c) Ovaska, T. V.; Reisman, S. E.; Flynn, M. A. *Org. Lett.* **2001**, *3*, 115.

(d) Ovaska, T. V.; Ravi Kumar, J. S.; Hulford, C. A.; O'Sullivan, M. F.; Reisman, S. E. *Tetrahedron Lett.* **2002**, *43*, 1939. (e) McIntosh, C. E.; Martinez, I.; Ovaska, T. V. *Synlett* **2004**, 2579.

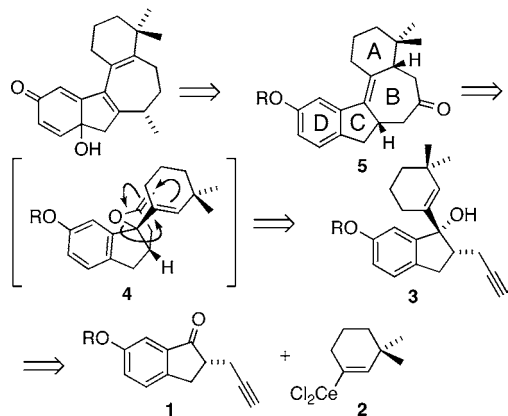
4-alkyn-1-ol system followed by in situ Claisen rearrangement of the intermediate 2-alkylidene tetrahydrofuran derivative (Scheme 1).⁷

Scheme 1. Tandem Cyclization/Claisen Rearrangement as a Route to Cycloheptane-Containing Polycyclic Ring Structures



It was envisioned that the tetracyclic frondosin C carbon skeleton **5** might be constructed through a Claisen rearrangement involving intermediate **4**, which, in turn, would be accessible via a base-catalyzed cyclization of acetylenic alcohol **3** (Scheme 2). Formation of the requisite tertiary alcohol would be effected by coupling the 6-alkoxy-2-propargylindanone **1** with the vinylcerium derivative **2**.

Scheme 2. Retrosynthetic Analysis for the Construction of an Advanced Intermediate in the Synthesis of Frondosin C



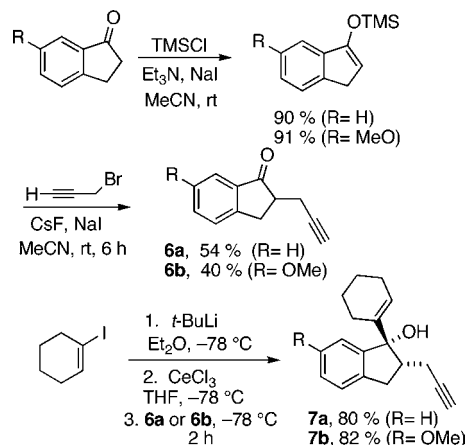
To test the proposed strategy, two model systems were prepared as shown in Scheme 3. Thus, commercially available indanone and 6-methoxyindanone were converted to the corresponding TMS silyl enol ethers and alkylated with propargyl bromide under mild conditions in the presence of cesium fluoride.⁸ The balance of the product mixture in each case consisted of dialkylated material (typically 20–30%) and hydrolyzed starting material. The latter undoubtedly resulted from premature quenching of the intermediate enolate anion under the reaction conditions employed.⁹ Reaction of ketones **6a** and **6b** with 1-cyclohexenylcerium dichloride, generated in situ from the corresponding vinyl-lithium species, produced the acetylenic alcohols **7a** and **7b** in 80 and 82% yields, respectively.

(7) For an early report of this sequence, see: Marvell, E. N.; Titterton, D. *Tetrahedron Lett.* **1980**, 2123.

(8) For a general procedure, see: Kita, Y.; Segawa, J.; Haruta, J.; Yasuda, H.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1099.

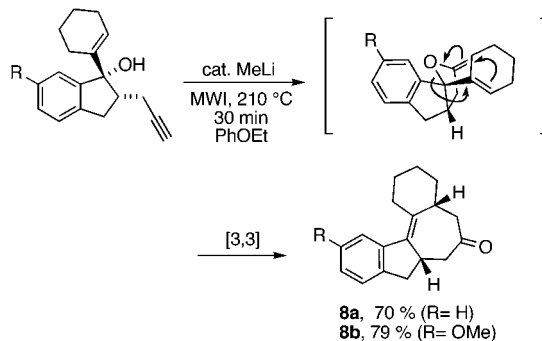
(9) Conditions for the alkylation step have not been optimized. A more direct alkylation using LDA for the initial α -deprotonation resulted in the formation of even greater amounts of dialkylated products.

Scheme 3



At this point, the stage was set for the key 5-exo cyclization/Claisen rearrangement sequence, which proceeded smoothly in the presence of catalytic MeLi (~10 mol %) in phenetole following 30 min of heating in a microwave oven (Scheme 4). The tetracyclic ketone products **8a** and **8b** were produced in 70 and 79% yields, respectively, after purification by column chromatography.

Scheme 4



Installation of the requisite *gem*-dimethyl moiety on the A ring of the frondosin C core required a slight modification of the sequence depicted in Scheme 3 and involved the use of 1-iodo-2,2-dimethylcyclohexene rather than 1-iodocyclohexene¹⁰ as the starting material (Scheme 5). The synthesis of this material was achieved in a few steps starting with commercially available 3-methylcyclohexen-2-one as shown in Scheme 5.

With vinyl iodide **9** in hand, preparation of the requisite acetylenic alcohol **10** was achieved in a straightforward

(10) Barton, D. H. R.; Bashiardes, G.; Fourrey, J. L. *Tetrahedron* **1988**, 44, 147.

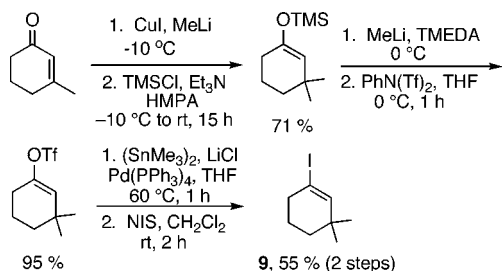
(11) Minimum energy conformation shown was calculated using MacroModel v. 8.5 with the MM3* forcefield and a GB/SA chloroform solvent model.¹² Structures were generated by a 5000 step low-mode conformational search.^{13,14}

(12) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, 112, 6127.

(13) Keseru, G. M.; Kolossvary, I. *J. Am. Chem. Soc.* **2001**, 123, 12708.

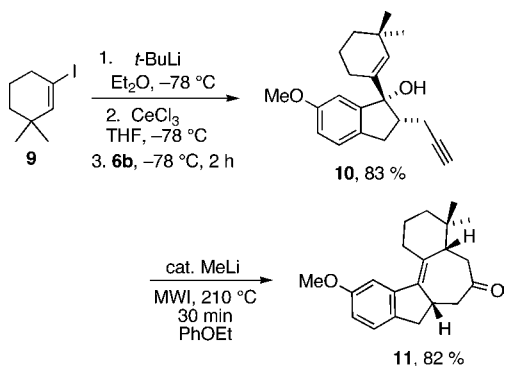
(14) Keseru, G. M.; Kolossvary, I. *J. Comput. Chem.* **2001**, 22, 21.

Scheme 5



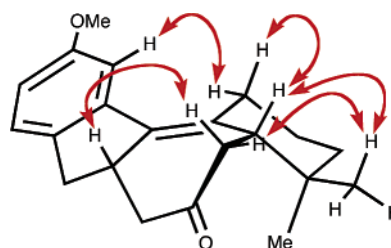
fashion and in high yield following metalation of **9** and reaction of the resulting organocerium species **2** with ketone **6b** (Scheme 6). Upon 30 min of microwave irradiation in the presence of catalytic MeLi , **10** was smoothly converted to the desired tetracyclic frondosin C analogue **11** in 82% isolated yield.

Scheme 6



The molecular structure of **11** was confirmed by a combination of standard two-dimensional NMR techniques (gradient COSY, gradient HSQC, gradient HMBC), and the

ring stereochemistry was secured by a series of one-dimensional NOESY experiments (Figure 2).

Figure 2. Diagnostic nuclear Overhauser enhancements in **11**.¹¹

In conclusion, we have demonstrated that construction of the tetracyclic frondosin C framework may be achieved in a straightforward manner using a tandem 5-exo cyclization/Claisen rearrangement strategy as the key ring-forming operation in the overall sequence. Further studies employing this methodology for the total synthesis of frondosin C as well as other members of the frondosin family are currently in progress in our laboratory. Results from these investigations will be communicated in due course.

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Supporting Information Available: Full experimental details and spectroscopic data on all previously unreported compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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