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Progress toward the Total Synthesis of Frondosin C

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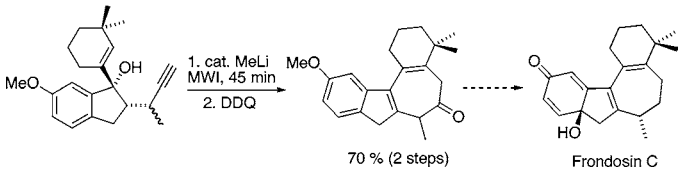
ABSTRACT



A straightforward approach toward the total synthesis of frondosin C is described. This strategy involves a key one-pot, microwave-assisted 5-*exo* cyclization–Claisen rearrangement sequence that was used for the expedient assembly of the frondosic C scaffold. Subsequent manipulation of the tetracyclic core allowed the synthesis of an advanced intermediate bearing the characteristic diene moiety in the B ring.

Five novel sesquiterpene hydroquinone derivatives, frondosins A−E (Figure 1), were recently isolated from the Micronesian marine sponge *Dysidea frondosa*.[1] Frondosins A and D, having opposite optical rotations compared to those present in *Dysidea frondosa*, have also been found in another sponge, *Euryspongia* sp.[2] All members of the frondosin family are antagonists of interleukin-8 (IL-8) and inhibitors of protein kinase C (PKC) in the low micromolar range.[1] IL-8 is a neutrophil-activating peptide, which is produced by several cell types in response to inflammatory stimuli.[3] It is now known to also play an important role in tumor progression and metastasis in several human cancers,[4] including lung cancers.[4b] Thus, IL-8 antagonists hold therapeutic potential as novel anti-inflammatory agents for the treatment of several acute and chronic inflammatory disorders, such as rheumatoid arthritis, psoriasis, and many lung diseases, including acute respiratory distress syndrome, chronic obstructive pulmonary disease, and asthma. In addition, IL-8 represents a potential new target for antiretroviral therapy against HIV-1,[2,4b,5] and inhibitors of IL-8 action may prove useful therapeutic agents against cancer as inhibitors of tumorigenesis and proangiogenesis.[4]

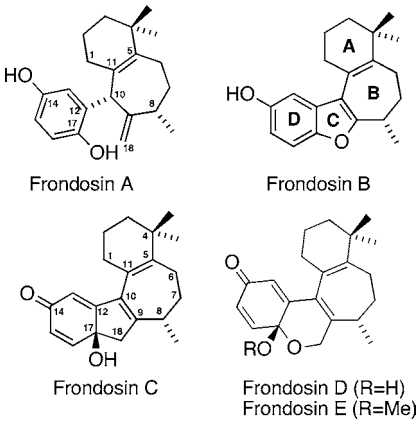


Figure 1. Structures of frondosins A−E.

(1) Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J.; Johnson, R. K. *Tetrahedron* **1997**, *53*, 5047.

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

(3) (a) Seitz, M.; Dewald, B.; Gerber, N.; Baggiolini, M. *J. Clin. Invest.* **1991**, *87*, 463−469. (b) Miller, E. J.; Cohen, A. B.; Nagao, D.; Griffith, R. J.; Maunder, R. J.; Martin, T. R.; Weiner-Kronish, J. P.; Sticherling, M.; Christophers, E.; Matthay, M. A. *Am. Rev. Respir. Dis.* **1992**, *146*, 247.

(4) (a) Brat, D. J.; Bellail, A. C.; Van, Meir, E. G. *Neuro-Oncology* (*Durham, NC, U.S.*) **2005**, *7*, 122. (b) Zhu, Y. M.; Webster, S. J.; Flower, D.; Woll, P. J. *Br. J. Cancer* **2004**, *91*, 1970. (c) Yuan, A.; Chen, J. J.; Yao, P. L.; Yang, P. C. *Front. Biosci.* **2005**, 853.

(5) Lane, B. R.; Lore, K.; Bock, P. J.; Andersson, J.; Coffey, M. J.; Strieter, R. M.; Markovitz, D. M. *J. Virol.* **2001**, *75*, 8195.

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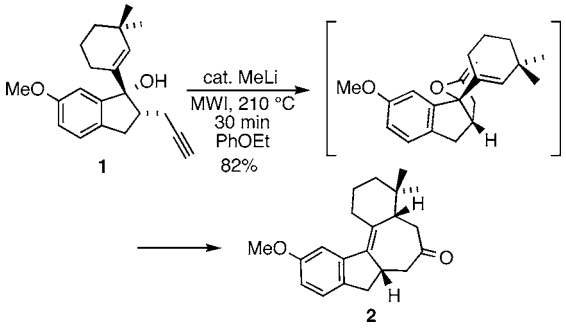
Total synthesis of frondosin B was first achieved by Danishefsky et al.[6] in 2000 and, more recently, by the Trauner[7] and Flynn[8] groups. Other members of the frondosin family, however, have not yet been synthesized.

We recently reported the first known approach to the tetracyclic frondosin C ring system.[9] This approach is based on our ongoing investigations involving a base-catalyzed tandem cyclization/Claisen rearrangement as a convenient route to cycloheptane-containing polycyclic ring structures.[10] The reaction sequence involves an initial 5-*exo* dig cyclization of an appropriately substituted 4-alkyn-1-ol system followed by in situ microwave-assisted Claisen rearrangement of the intermediate 2-alkylidene tetrahydrofuran derivative.[11]

Herein, we wish to report our progress toward the total synthesis of frondosin C. At the outset of the current investigation, it was envisaged that tetracycle **2**, previously synthesized from the tertiary alcohol **1** (Scheme 1),[9] could be

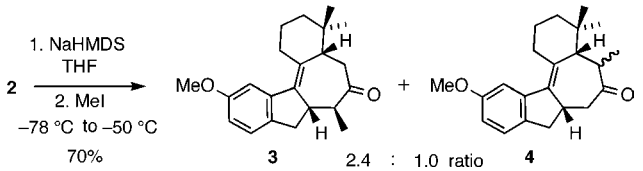
Scheme 1. Synthesis of Frondosin C Tetracyclic Core



manipulated to frondosin C in a sequence of steps involving α-methylation, generation of the requisite B ring diene functionality, demethylation of the methoxy group, and oxidation of the resulting phenol system to the *p*-quinol moiety.

According to this plan, the requisite C8 methyl group was first introduced by treatment of **2** with NaHMDS followed by addition of MeI. It was anticipated that, due to the proximity of the A ring gem dimethyl moiety to C6, methylation at C8 would predominate in this reaction. In fact, this turned out to be the case although the observed regioselectivity was found to be rather modest; the desired ketone **3** and the C8 methylated **4** were formed as a 2.4 to 1 mixture of regioisomers (Scheme 2).[12] It is noteworthy that stereoselectivity of the alkylation affording **3** was high,

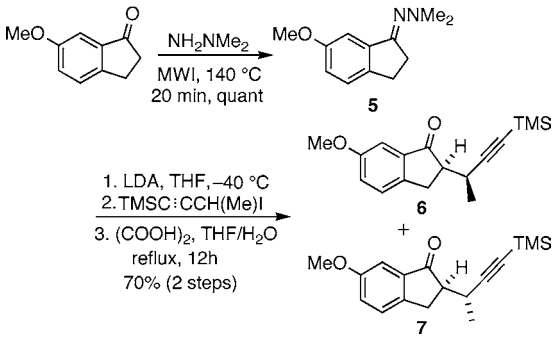
Scheme 2. Methylation of Ketone **2**



consistent with delivery of the electrophile from the less hindered top face of the intermediate enolate anion.

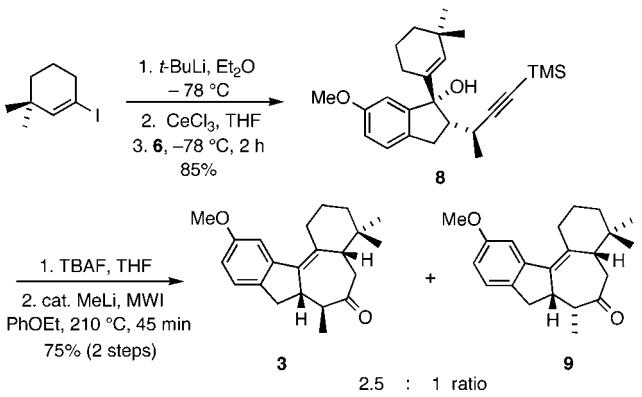
All attempts to improve regioselectivity of the methylation, including through the use of different bases, were unsuccessful and this strategy was ultimately abandoned. Instead, a different approach involving introduction of the requisite methyl group early on in the sequence was implemented. According to this strategy, readily separable isomeric ketones **6** and **7**, each bearing a methyl group at the propargylic position, were prepared in 70% overall yield from commercially available 6-methoxy-1-indanone as shown in Scheme 3.

Scheme 3. Introduction of the C8 Methyl Group



The subsequent coupling reaction involving 1-iodo-3,3-dimethylcyclohexene[10e] and one of the diastereomeric ketones, randomly assigned as **6**, was effected employing our usual protocol[10] to provide tertiary alcohol **8** in 85% yield (Scheme 4).

Scheme 4. Preparation of Tetracyclic Ketones **3** and **9**



(6) (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.

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

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

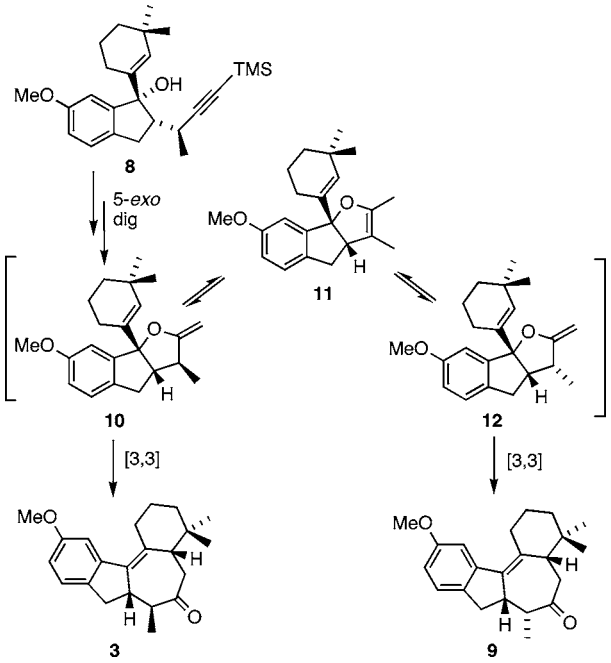
(9) Martinez, I.; Alford, P. E.; Ovaska, T. V. *Org. Lett.* **2005**, *7*, 1133.

(10) (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.

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

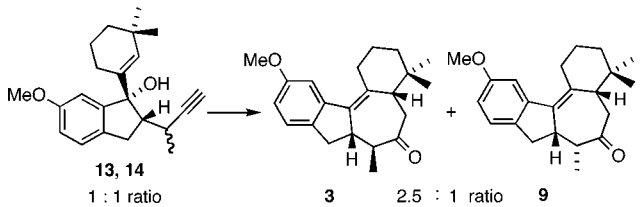
Following treatment with TBAF and exposure to microwave irradiation (MWI) in the presence of catalytic MeLi (~0.1 equiv), **8** was smoothly converted to a 2.5:1 mixture of tetracyclic ketones **3** and **9** (Scheme 4). Given that the cyclization/Claisen rearrangement sequence involves a single diastereomer derived from **8**, the formation of a mixture of isomeric ketones **3** and **9** in the process is intriguing and most likely arises from the interconversion of exocyclic intermediates **10** and **12** via the endocyclic intermediate **11** as depicted in Scheme 5.[13]

Scheme 5. Proposed Interconversion of Intermediates **10** and **12**



Further evidence for the suggested mechanism is provided by the observation that an identical diastereomer ratio of tetracyclic ketones **3** and **9** is obtained when a 1:1 mixture of isomeric alcohols **13** and **14** is subjected to catalytic MeLi and MWI (Scheme 6). Indeed, the entire reaction sequence

Scheme 6. Cyclization/Claisen Rearrangement Sequence Involving a Diastereomeric Mixture of Acetylenic Alcohols **13** and **14**



depicted in Schemes 3 and 4 may be conducted with the same end result starting with hydrazone **5** and performing the subsequent steps without prior separation of the diastereomeric intermediates.

Calculation of minimum energy conformations for compounds **3** and **9** revealed an energy difference of 8.57 kJ/mol in favor of **3**.[14] This being the case, it was envisioned that isomerization of the mixture could provide an opportunity to increase the **3**/**9** ratio further. The initial isomer

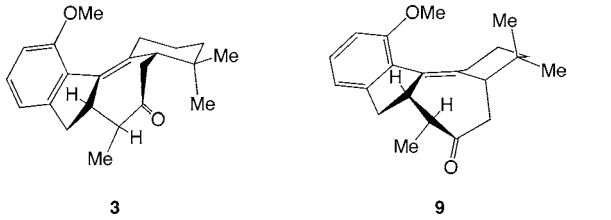


Figure 2. Calculated minimum energy conformations of **3** and **9**.

ratio of 2.5 to 1 was significantly improved in favor of **3** without loss of product material when the mixture was treated with several different bases. The highest observed ratio of 14.6 to 1 (94% de) resulted from refluxing a mixture of **3** and **9** in *t*-BuOK/*t*-BuOH for 3.5 h. Stereochemistry of the major isomer was confirmed by a combination of 2D NMR and 1D NOESY techniques and the experimental observations are in good agreement with the calculated trends.

Removal of the carbonyl functionality was achieved by a three-step sequence involving an initial borohydride reduction, then conversion of the resulting alcohol **15** to the corresponding mesylate and treatment of the mesylate with lithium triethylborohydride (Scheme 7).

It should be noted that several other deoxygenation methods that were attempted, including Ra−Ni reduction of a thioacetal, prepared from **3** and 1,2-ethanedithiol, as well as $NaCNBH_3$ treatment of a tosylhydrazone derived from **3**, were overall less satisfactory in providing **16**.

Somewhat surprisingly, treatment of **16** with PhSeBr in DMF resulted in direct and rapid generation of diene **17** in 86% yield. Although it was anticipated that **17** could be readily converted to the desired diene **18**, this turned out not to be the case (Scheme 7) and all attempts at effecting isomerization of the trisubstituted double bond in **17** failed. However, it was found that **18** could be produced as the major product along with **17** (2.3:1 ratio) in a two-step sequence involving reaction of **16** with *m*-CPBA, followed by treatment of the resulting unstable epoxide **19** with 2.0 equiv of $BF_3 \cdot OEt_2$ (Scheme 7).

In an attempt to find a more reliable method to install the desired diene moiety in the B ring, tetracyclic ketone **3** was

(12) The stereochemistry at C8 of compound **4** could not be determined with certainty.

(13) Rhoads, S. J.; Brandenburg, C. F. *J. Am. Chem. Soc.* **1971**, *93*, 5805.

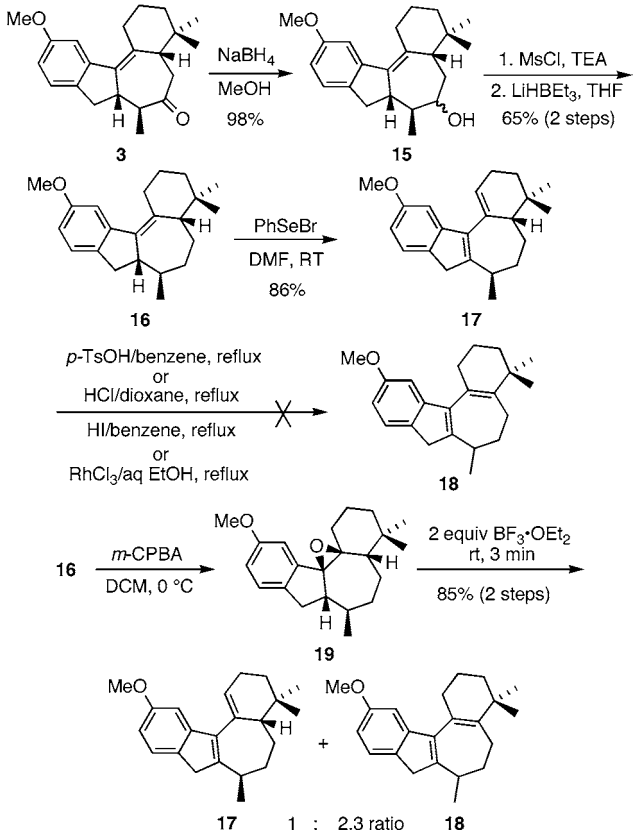
(14) The minimum energy conformations shown were calculated by using MacroModel v. 9.0015 with the MM3* forcefield and a GB/SA chloroform solvent model.[15] Structures were generated by a 10 000-step large-scale low-mode conformational search.[16,17]

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

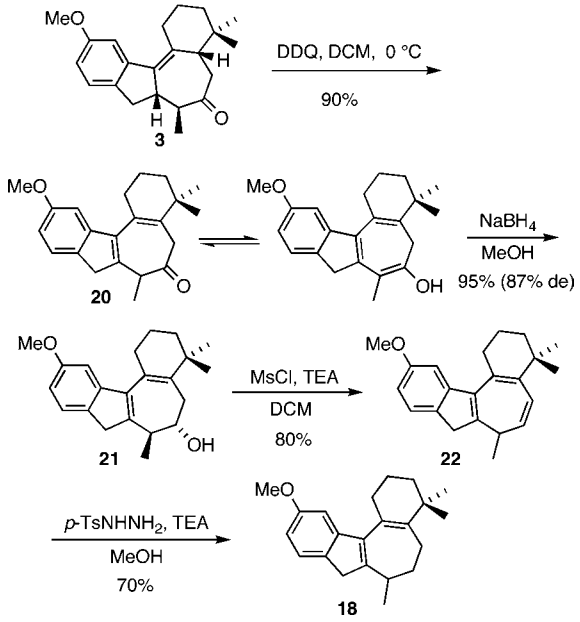
(16) Keseru, G. M.; Kolossvary, I. *J. Am. Chem. Soc.* **2001**, *123*, 12708.

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

Scheme 7. Initial Strategies for the Synthesis of **18**



Scheme 8. Improved Synthesis of **18**



subjected to DDQ oxidation.[18] Gratifyingly, this resulted in direct formation of diene **20** in 90% yield (Scheme 8). Borohydride reduction of the carbonyl group followed by reaction with mesyl chloride and triethylamine resulted in in situ elimination of the intermediate mesylate, affording triene **22** in high yield. Alternatively, **22** could be obtained in a comparable yield by subjecting alcohol **21** to phosphorus oxychloride in pyridine. Finally, diimide reduction of **22** afforded racemic diene **18** in 70% yield.

(18) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628.

In summary, we have achieved the synthesis of an advanced intermediate **18** bearing most of the characteristic structural features of frondosin C. Efforts to complete the total synthesis of this natural product as well as other members of the frondosin family are currently underway in our laboratories.

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Supporting Information Available: Full experimental details and spectroscopic data for compounds **3**−**9**, **15**−**18**, and **20**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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