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Total Synthesis of (±)-Frondosin B

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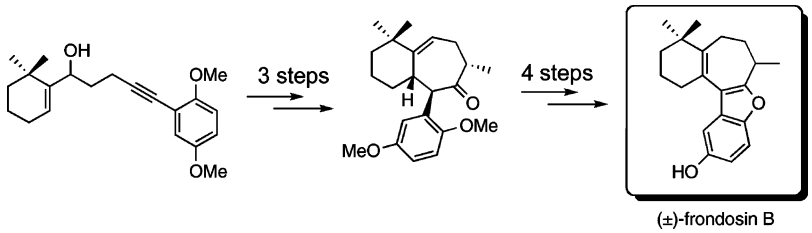
ABSTRACT



An expeditious reaction sequence featuring a microwave-assisted tandem 5-*exo* cyclization–Claisen rearrangement process was used to assemble the A/B ring system of frondosin B. Completion of the target natural product was achieved in 38.2% yield over an eight-step linear sequence.

Five structurally related sesquiterpene hydroquinones, frondosins A−E (Figure 1), were isolated in 1997 from the Micronesian marine sponge *Dysidea frondosa* by Freyer et al.[1] Shortly thereafter, investigators at the National Cancer Institute extracted frondosins A and D from another sponge, *Euryspongia* sp.[2] Interestingly, this organism apparently manufactures the two frondosins as complementary enantiomers with opposite optical rotations compared to those present in *Dysidea frondosa*.[2]

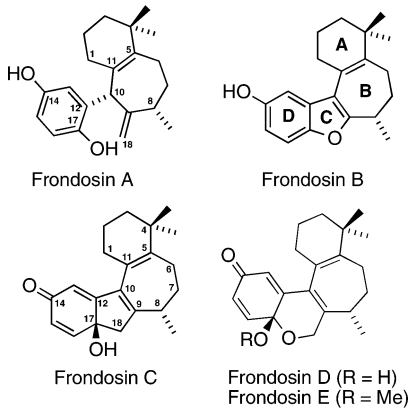


Figure 1. Frondosins A−E.

All members of the frondosin family have been found to exhibit biological activity as antagonists of interleukin-8 (IL-8) and inhibitors of protein kinase C in the low micromolar range.[2] Interleukin-8 is a neutrophil-activating peptide, which is produced by several cell types in response to inflammatory stimuli,[3] and it is now known to also play an important role in tumor progression and metastasis in several human cancers,[4] including lung cancers.[4b]

Importantly, it was recently demonstrated that compounds which inhibit the actions of IL-8 also inhibit HIV-1 replication.[5] In fact, frondosins A and D have been found to exhibit

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HIV-inhibitory activity in the National Cancer Institute's primary anti-HIV assay[2] through an unknown mechanism.

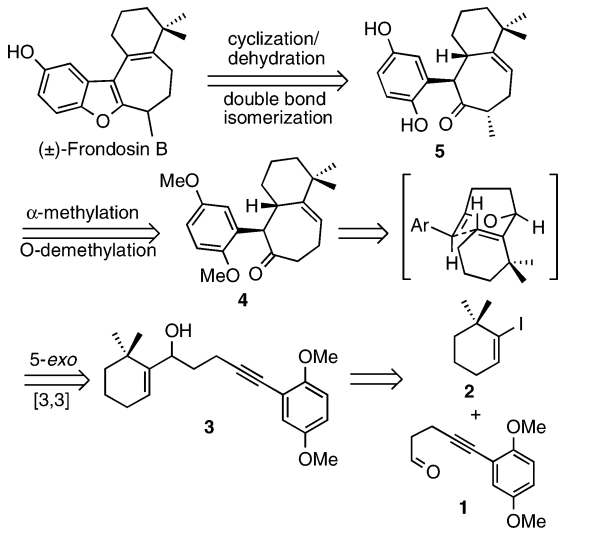
Structurally, the frondosins feature a unique bicyclo[5.4.0]-undecane sesquiterpene core which, with the exception of frondosin A, is part of a fused tetracyclic framework. Although the bicyclo[5.4.0]undecane (A−B ring system) fragment is nearly identical in all members of this class, the principal structural variation between them lies in the constitution of the C−D ring fragment.

The unique structural features of the frondosins coupled with their therapeutic potential as novel anti-inflammatory, anti-tumor, and anti-HIV agents have sparked considerable interest in their total synthesis by several research groups. As a result of these efforts, (±)-frondosin C was recently synthesized by Ovaska et al.,[6] and total syntheses of frondosin B have been reported by three groups: Danishefsky and co-workers[7] achieved the synthesis of the (+)-enantiomer of frondosin B in 0.8% overall yield over 18 steps; Trauner's group prepared (−)-frondosin B in 7.3% overall yield over a 20-step sequence;[8] and Flynn et al.[9] recently disclosed their elegant synthesis of racemic frondosin B in 32% overall yield over a six-step sequence.

In this communication, we wish to report a novel and efficient total synthesis of (±)-frondosin B. The sequence compares favorably with existing strategies and highlights the synthetic utility of a tandem 5-*exo* cyclization/Claisen rearrangement process, first observed by Marvell et al.[10] and developed further in our laboratory, as a convenient general route to seven-membered ring-containing ring systems.[6,11] This methodology involves a base-catalyzed intramolecular oxyanionic cyclization of appropriately substituted 4-pentyn-1-ols, followed by in situ Claisen rearrangement of the intermediate 2-alkylidenetetrahydrofurans. We anticipated this methodology to be particularly well suited for the construction of frondosin B, which incorporates a seven-membered ring at the core of the tetracyclic ring system.

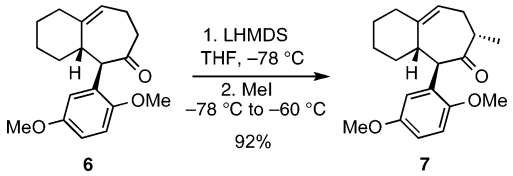
As shown retrosynthetically in Scheme 1, it was envisioned that the key bicyclo[5.4.0]undecanyl system **4** could be assembled in a single operation from alcohol **3**, which, in turn, would be available through a simple coupling reaction involving vinyl iodide **2**[12] and aldehyde **1**, prepared in a single step from the corresponding known alcohol.[13] It was expected that the synthesis of the benzofuran precursor **5** could be achieved in potentially two additional steps from **4** through regioselective α-methylation and subsequent O-demethylation of the *para*-dimethoxy-substituted aromatic ring.

Scheme 1. Retrosynthetic Analysis for the Synthesis of Frondosin B



We have recently demonstrated that the bicyclo[5.4.0]-undecane system **6** lacking the requisite *gem*-dimethyl moiety on the A ring is readily prepared via the cyclization/Claisen rearrangement strategy analogous to that shown in Scheme 1.[14] However, considering that the more substituted α position of the cycloheptenone ring is benzylic and presumably more acidic, it was not obvious that this compound could be regioselectively methylated at the less substituted carbon. Pleasingly, it was found that on treatment with LHMDS followed by the addition of MeI under kinetic conditions, **6** was smoothly converted to **7** with complete regio- and stereocontrol in excellent yield (Scheme 2). With this encouraging result, the applicability of this strategy to the total synthesis of frondosin B could be explored.

Scheme 2. Synthesis of a Bicyclic Ketone Model System



The requisite alkynol precursor **3** for this sequence was prepared in a straightforward manner in 93% yield from 1-iodo-6,6-dimethylcyclohex-1-ene[12] and aldehyde **1** as shown in Scheme 3. On exposure to catalytic MeLi and microwave irradiation, **3** was readily converted to the expected 6−7 bicyclic ring system **4** in 80% yield. Notably,

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(7) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878.
(8) (a) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569. (b) Hughes, C. C.; Trauner, D. *Tetrahedron* **2004**, *60*, 9675.
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(11) (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. (f) Martinez, I.; Alford, P. E.; Ovaska, T. V. *Org. Lett.* **2005**, *7*, 1133. (g) Li, X.; Kyne, R. E.; Ovaska, T. V. *Org. Lett.* **2006**, *8*, 5153.
(12) Barton, D. H. R.; Bashiardes, G.; Fourrey, J.-L. *Tetrahedron Lett.* **1983**, *24*, 1605.
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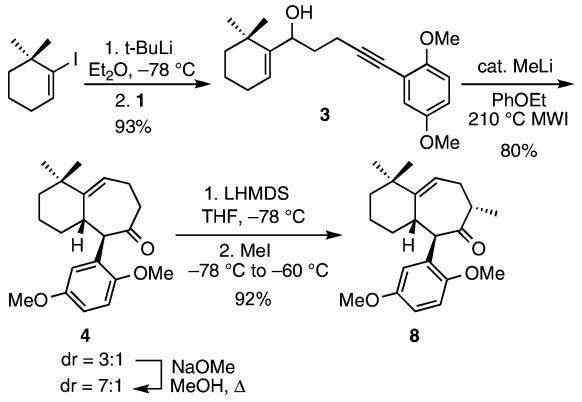
(14) Li, X.; Ovaska, T. V. *J. Org. Chem.* **2007**, *72*, 6624.

Scheme 3. Synthesis of Bicyclic Ketone **8**



the initially observed 3:1 diastereomer ratio could be improved significantly (7:1) simply by exposing the mixture to MeONa in refluxing methanol, allowing the preparation of the desired isomer of **4** in 70% yield from **3**.

Upon methylation under kinetic conditions using LHMDS as the base, ketone **4** was converted to the bicyclic ketone **8** in a regiospecific manner as a single diastereomer in 92% isolated yield. The relative stereochemistry of this key intermediate was unequivocally established by single-crystal X-ray analysis (Figure 2).[15]

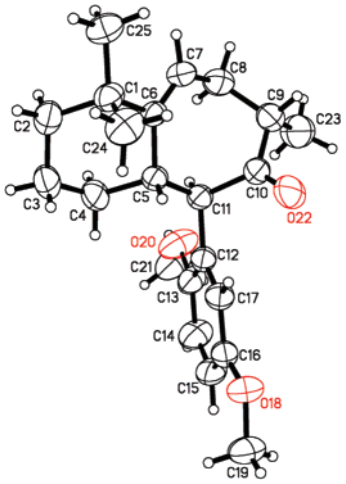
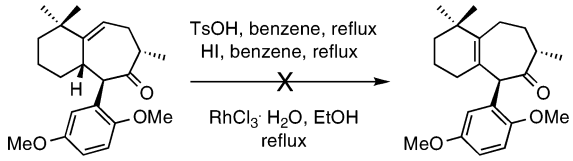


Figure 2. ORTEP drawing of compound **8** derived from a single-crystal X-ray analysis (arbitrary numbering of atoms).

To install the necessary tetrasubstituted double bond at the A/B ring junction, it was envisioned that the trisubstituted double bond in **8** could be readily isomerized under a variety of conditions to provide compound **9**. However, all attempts to achieve this transformation were unsuccessful, and in most cases, the starting material was recovered unchanged (Scheme 4). It is reasonable to assume that the observed resistance of

Scheme 4. Attempted Isomerization of **8** to **9**

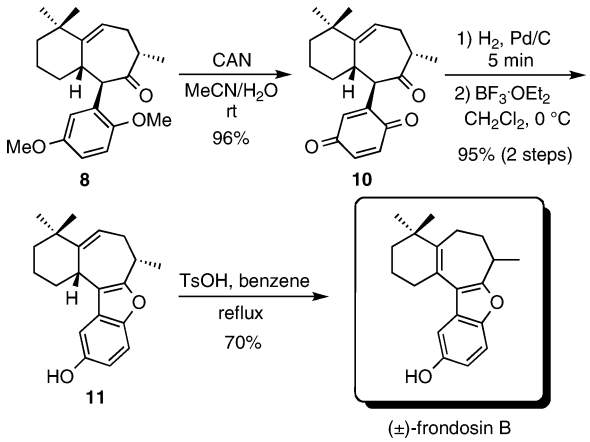


8 to isomerization stems, in part, from the sterically congested environment near the double bond (Figure 2).

As an alternative strategy, it was envisaged that double bond isomerization could also be achieved at the end of the synthetic sequence following installation of the benzofuran moiety. It was reasoned that, with the tetracyclic system in place, the overall ring geometry would be considerably more planar and, additionally, the formation of a more conjugated system through a double bond shift should be energetically favored.

As outlined in the retrosynthetic analysis (Scheme 1), it was envisioned that formation of the key benzofuran system could be achieved through a straightforward acid-catalyzed intramolecular cyclization reaction involving one of the OH groups of the benzene-1,4-diol moiety in **5** and the proximal B ring carbonyl carbon.[16] However, our initial efforts to generate the requisite benzene-1,4-diol precursor **5** through a simple deprotection reaction involving both methoxy groups met with failure (Scheme 4). Consequently, the direct deprotection strategy was abandoned in favor of a highly efficient two-step sequence involving standard oxidative demethylation of **8** with ceric ammonium nitrate[17] and reduction of the resulting *para*-quinone derivative **10** by catalytic hydrogenation (Scheme 5). Upon exposure to BF_3·

Scheme 5. Completion of the Total Synthesis of Frondosin B



Et_2O at 0 °C, the hydroquinone intermediate **5** cyclized readily to provide the complete frondosin B ring system **11** in 91% yield over three steps.

(15) The crystallographic data for compound **8** have been deposited with the Cambridge Crystallographic Data Center (CCDC 656193).

(16) Kang, W.-B.; Sekiya, T.; Toru, T.; Ueno, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3752.

The final double bond isomerization was achieved according to the plan simply by treating **11** with catalytic TsOH in refluxing benzene. In addition to the desired (±)-frondosin B, the product mixture consisted of a small quantity of unidentified impurities; however, these were readily removed from the desired product by standard column chromatography. Comparison of the ^{1}H and ^{13}C NMR spectra of the synthetic product with those of the naturally occurring frondosin B[1] unambiguously confirmed that the target structure had indeed been synthesized.

In conclusion, the total synthesis of (±)-frondosin B was achieved in 38.2% overall yield over eight linear steps. The key operation in the sequence is the efficient formation of intermediate **8** bearing the 6−7 core of frondosin B. Studies toward the total syntheses of other members of the frondosin family as well as other cycloheptanoid natural products are currently ongoing in our laboratories.

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Supporting Information Available: Full experimental details, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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