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Studies toward Frondosin A and Its Analogues. Formal Total Synthesis of (±)-Frondosin A

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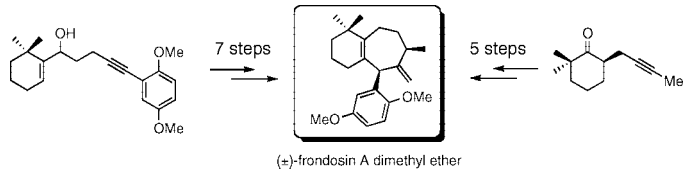
ABSTRACT



Two reaction sequences commencing with different starting materials were successfully employed for the synthesis of frondosin A analogues, including (±)-frondosin A dimethyl ether. Construction of the bicyclo[5.4.0]undecane core in each case was achieved through an expedient microwave-assisted tandem 5-exo cyclization−Claisen rearrangement process.

Investigators at SmithKline Beecham Pharmaceuticals discovered in 1997 that an extract of the Micronesian sponge *Dysidea frondosa* exhibited significant inhibitory activity for the binding of cytokine interleukin-8 to its receptor, CXCLR1/2.[1] This biological activity was subsequently attributed to five structurally novel sesquiterpenes, frondosins A−E, each featuring a unique bicyclo[5.4.0]undecane core with an additional fused (frondosins B−E) or tethered (frondosin A) hydroquinone-derived ring system (Figure 1).

Interleukin-8 is a neutrophil-activating peptide, which is produced by several cell types in response to inflammatory stimuli.[2] Recent studies suggest that IL-8 also plays an important role in tumor progression and metastasis associated with several human cancers.[3] In addition, IL-8 and other chemokines are critically involved in HIV-1 infection, modulating both viral replication and recruitment of target cells to the site of infection.[4] Importantly, it was recently demonstrated that compounds capable of reversing the

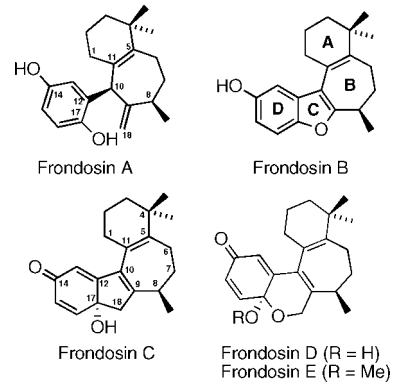


Figure 1. Frondosins A−E.

[†] Currrent address: Shanghai Hengrui Pharmaceuticals Co. Ltd, Shanghai, China.

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

(2) (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.

(3) (a) Brat, D. J.; Bellail, A. C.; Van Meir, E. G. *Neuro-oncol.* **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.

(4) Lane, B. R.; Lore, K.; Bock, P. J.; Andersson, J.; Coffey, M. J.; Strieter, R. M.; Markovitz, D. M. *J. Virol.* **2002**, *76*, 11570.

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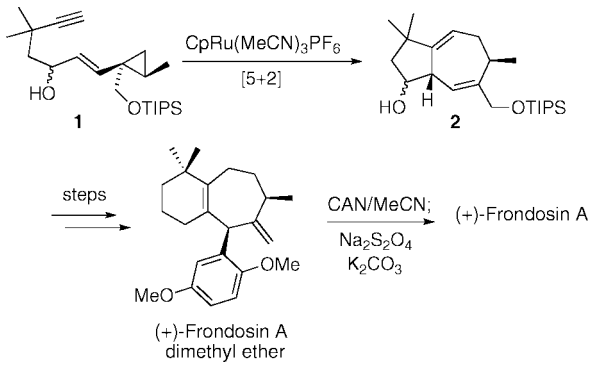
binding of IL-8 also inhibit HIV-1 replication.[5] In fact, the National Cancer Institute's primary anti-HIV assay revealed that frondosins A and D exhibit HIV-inhibitory activity at the low micromolar level.[6]

The unique structural features of the frondosins coupled with their therapeutic potential as lead compounds for the development of novel anti-inflammatory, antitumor, and anti-HIV agents has sparked considerable interest in their total synthesis by several research groups. To date, these efforts have resulted in several published total syntheses of frondosin B,[7–10] one of frondosin C,[11] and a recent total synthesis of (+)-frondosin A by Trost et al.[12] Our own contributions in this area have so far resulted in the total syntheses of (±)-frondosin B[10] and C.[11] Herein, we wish to report our synthetic approaches to frondosin A and its close analogues, including frondosin A dimethyl ether, which is the same advanced frondosin A precursor that Trost et al. previously converted to the natural product through a straightfoward one-pot aryl *O*-demethylation process.[12]

Trost's approach to (+)-frondosin A takes advantage of the Ru-catalyzed [5 + 2] cycloaddition reaction,[13] which was used to assemble a key precursor to the frondosin A bicyclic core from alcohol **1** (Scheme 1). However, this methodology

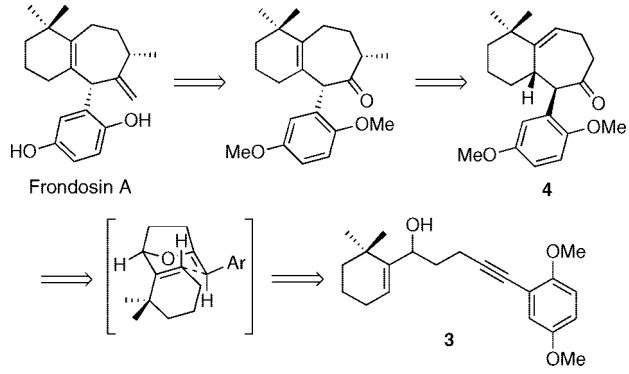
Scheme 1. Trost's Synthesis of (+)-Frondosin A



was not suitable for the direct construction of the desired 6−7 bicyclic ring system. Instead, the 5−7 hydroazulene derivative **2** was synthesized, requiring a late stage ring expansion sequence to generate the correct A ring moiety. With use of these strategies, the target natural product was prepared in 21 total steps and 7% overall yield.

We imagined that frondosin A could be readily assembled using the retrosynthetic strategy outlined in Scheme 2. The

Scheme 2. Retrosynthesis of Frondosin A



key 6−7 bicyclic intermediate **4** in this scheme is derived from alcohol **3** through a one-pot base-catalyzed tandem cyclization/Claisen rearrangement[14] sequence, a strategy that we have previously exploited for the synthesis of a variety of cycloheptene-containing ring systems,[15] including frondosins B[10] and C.[11]

It was further envisioned that the misplaced C5−C6 double bond in ketone **4** could be isomerized to the desired tetrasubstituted position, and that the B ring carbonyl group would provide a convenient site for installation of the requisite exocyclic double bond.

The bicyclic ketone **5** was assembled in a short sequence of steps as described previously.[10] The desired olefination of the hindered B ring carbonyl carbon was then effected by applying the bimetallic $TiCl_4$−Mg promoted methylene transfer reaction developed by Yan et al.[16] to afford compound **6** in 75% yield (Scheme 3). A close analogue of frondosin A (**8**) was subsequently prepared via a two-step oxidative demethylation/reduction sequence.[10]

Surprisingly, the trisubstituted C5−C6 double bond in **5** was resistant to isomerization under a variety of conditions investigated (e.g., *p*-TsOH/benzene, HI/benzene, $RhCl_3$/EtOH). As a result, a slightly more circuitous approach was developed to effect this transformation.

As shown in Scheme 4, it was found that the desired double bond "shift" could be achieved indirectly by exploiting the Saegusa oxidation[17] as the key transformation in the overall 3-step sequence. Thus, on exposure to $Pd(OAc)_2$, the

(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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(14) For an early example of this sequence, see: Marvell, E. N.; Titterington, D. *Tetrahedron Lett.* **1980**, 2123.
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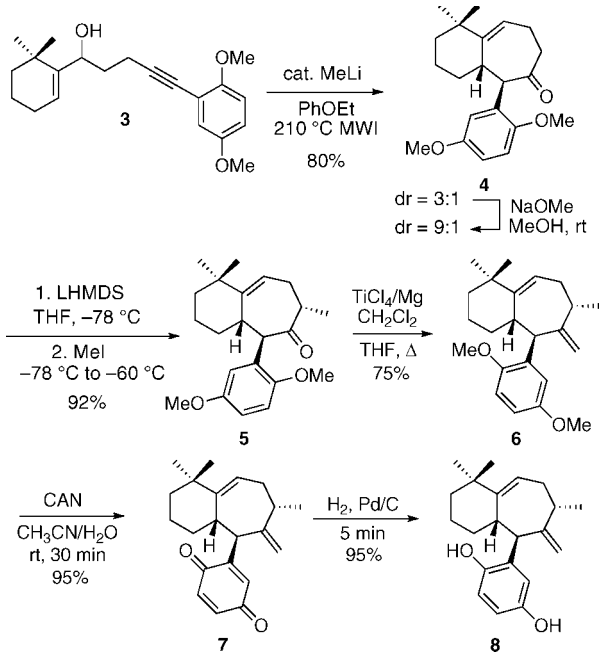
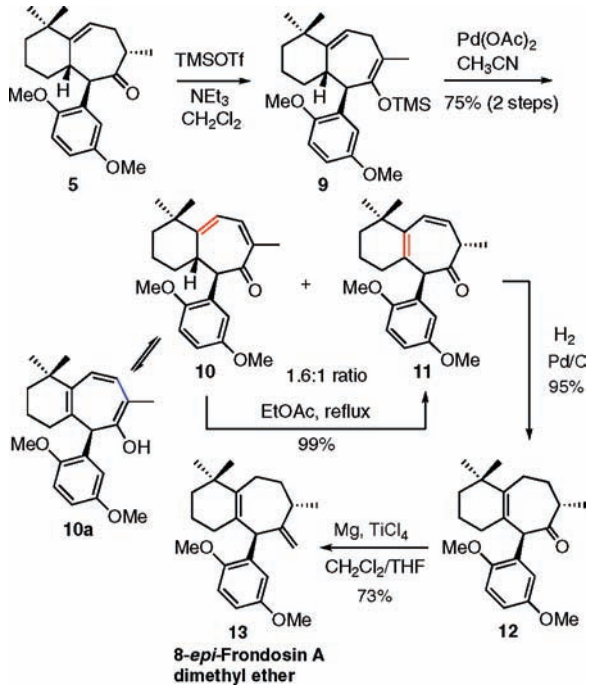
Scheme 3. Synthesis of Frondosin A Analogue **8**



TMS enol ether **9**—prepared from **5**—was smoothly converted to a mixture of isomeric dienones **10** and **11** in an initial ratio of 1.6 to 1, the minor isomer having the desired C5−C11 double bond in place. Gratifyingly, **10** could be quantitatively converted to the less conjugated isomer **11**—most likely via the fully conjugated enol tautomer **10a**—on simple heating in refluxing ethyl acetate.[18] It is of interest to note that the diene isomerization was accompanied by complete reconstitution of the original *trans* stereochemistry between the two α substitutents on the B ring.

Brief exposure of diene **11** to catalytic hydrogenation conditions provided ketone **12** in 95% yield and subsequent olefination of the hindered ketone afforded the epimer of frondosin A as its dimethyl ether derivative **13** in 73% yield (Scheme 4). The molecular structure of **12**, confirming the location of the tetrasubstituted double bond as well as the *trans* relationship of the two B ring substitutents, was unequivocally established by X-ray crystallography (Figure 2).[19]

Scheme 4. Double Bond Isomerization via the Saegusa Oxidation Strategy



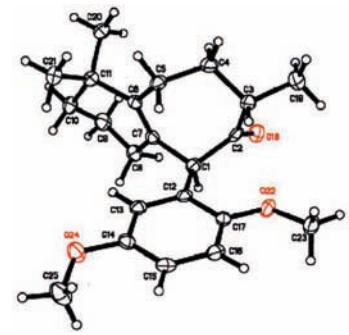


Figure 2. ORTEP drawing of compound **12** derived from a single-crystal X-ray analysis (arbitrary numbering of atoms).

Subsequent treatment of **12** with KHMDS at room temperature for 30 min, followed by protonation with HOAc, resulted in the formation of a readily separable mixture of **14** and **12** in 1.6 to 1 ratio, respectively. Finally, the synthesis of (±)-frondosin A dimethyl ether **15** was achieved from **14** by employing the $TiCl_4$−Mg promoted olefination protocol described above (Scheme 5).

On the basis of our earlier investigations[15] utilizing 3° acetylenic alcohols as starting materials for the synthesis of seven-membered-ring systems by the tandem cyclization/Claisen rearrangement strategy, we also considered the possibility of constructing the bicyclo[5.4.0]undecane core of frondosin A through a different route. The key intermediate for this sequence was readily assembled from commercially available 2,2-dimethylcyclohexanone in two straightforward steps as depicted in Scheme 6. Although the major diastereomer of **17** (shown) was initially separated and used for the subsequent cyclization/Claisen rearrangement process, it was discovered that even the corresponding minor stereoisomer could be converted to the same bicyclic product **18**, albeit more slowly, under the same conditions.

Unlike ketone **5**, which could not be transformed to **12** through a direct double bond shift, the analogous bicyclic

(17) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

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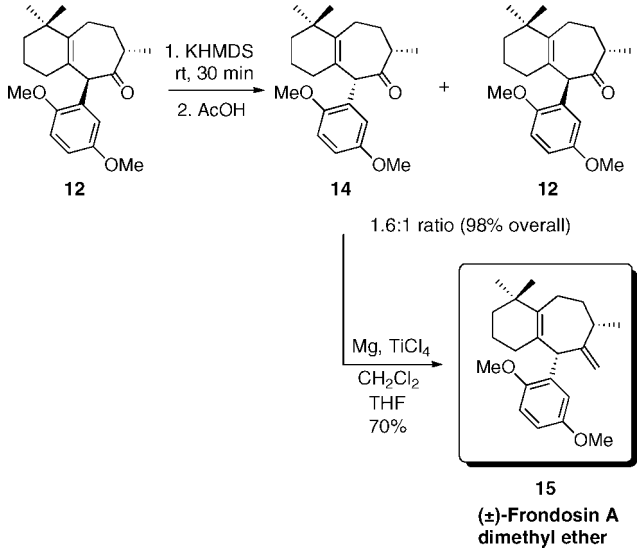
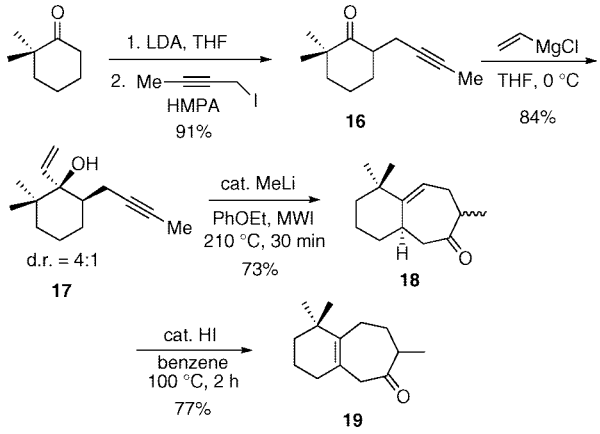
(19) The crystallographic data for compound **12** have been deposited with the Cambridge Crystallographic Data Center (CCDC 687989).

Scheme 5. Preparation of (±)-Frondosin A Dimethyl Ether



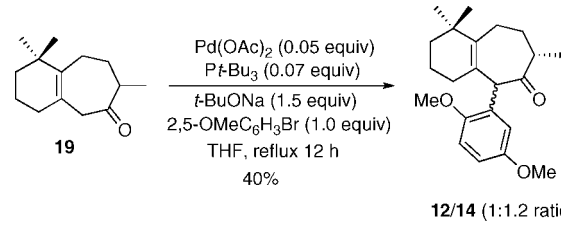
Scheme 6. Alternative Construction of the Frondosin A Core



ketone **18** was readily isomerized with catalytic HI in benzene[20] at 100 °C to afford **19** in good yield (Scheme 6). Interestingly, no formation of the analogous fully conjugated α,β-unsaturated ketone was detected under these conditions.

When ketone **19** was reacted with sodium *tert*-butoxide and 2,5-dimethoxybromobenzene in the presence of catalytic $Pd(OAc)_2$ and P*t*-Bu_3, the expected α-arylated product was formed as a mixture of *cis* and *trans* isomers in a 1.2 to 1 ratio, respectively, in 40% overall yield (Scheme 7).[21] Notably, these are the same diastereomeric products (**12** and **14**) that were produced via a diffferent route described in Scheme 5.

Scheme 7. α-Arylation of Ketone **19**



Although the yield for the α-arylation step was rather modest, the synthesis of the carbon core of frondosin A with an attached aromatic moiety was achieved through this strategy in only five steps from 2,2-dimethylcyclohexanone. As shown earlier, the *cis* isomer **14** serves as an advanced intermediate that can be converted to (±)-frondosin A in just two steps.[12]

In conclusion, the formal total synthesis of (±)-frondosin A and several of its close analogues was achieved by two different strategies. Both approaches enabled the rapid assembly of the requisite bicyclo[5.4.0]undecane scaffold through the tandem 5-exo dig cyclization/Claisen rearrangement process. Investigations toward the total syntheses of the remaining members of the frondosin family as well as other related natural products are currently ongoing in our laboratories.

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

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