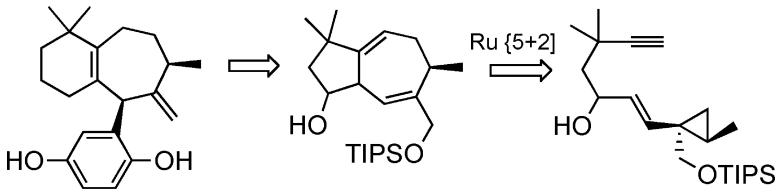
Article

Total Synthesis of (+)-Frondosin A. Application of the Ru-Catalyzed [5+2] Cycloaddition

Barry M. Trost, Yimin Hu, and Daniel B. Horne

J. Am. Chem. Soc., **2007**, 129 (38), 11781-11790• DOI: 10.1021/ja073272b • Publication Date (Web): 31 August 2007



Frondosin A

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 15 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 08/31/2007

Total Synthesis of (+)-Frondosin A. Application of the Ru-Catalyzed [5+2] Cycloaddition

Barry M. Trost,* Yimin Hu, and Daniel B. Horne

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received May 8, 2007; E-mail: bmtrost@stanford.edu

Abstract: The first total synthesis of (+)-frondosin A was accomplished in 19 longest linear and 21 total steps from commercially available materials. The key features of the synthesis include a Ru-catalyzed [5+2] cycloaddition, a Claisen rearrangement, and a ring expansion to construct the core of the frondosin A in a diastereoselective and regioselective fashion. This is the first application of a Ru-catalyzed [5+2] cycloaddition in the total synthesis of a natural product. Through this synthesis, the absolute configuration of (+)-frondosin A was established.

Introduction

Frondosin A (**1**) is a member of a family of five norsesquiterpenoid (14-carbon) natural products, frondosins A−E, which were originally extracted from the marine sponge *Dysidea frondosa*, collected in Pohnpei, Federated States of Micronesia.[1] Researchers at the National Cancer Institute (NCI) later isolated (−)-frondosins A and D from the HIV-inhibitory extract of *Euryspongia* sp.[2] Interestingly, the frondosins isolated at the NCI were of optical rotation different from and opposite those of the frondosins first isolated, so both enantiomers of these natural products appear to be produced by different species of sponge, and both are biologically active.

The frondosins inhibit the binding of interleukin-8 (IL-8), a chemokine which is produced by macrophages, fibroblasts, and epithelial and endothelial cells, and which has been implicated in a wide range of acute and chronic inflammatory disorders, including psoriasis and rheumatoid arthritis. IL-8 has been identified as a principal factor directing neutrophil (white blood cell) recruitment to the inflammatory focus, and as such the IL-8 receptor antagonist is a promising target for development of novel anti-inflammatory agents. Frondosin A was found to be the most potent of the frondosins, with IL-8α, IL-8β, and protein kinase C (PKC) activites all in the low micromolar range. In addition, the frondosins have been shown to exhibit anti-HIV activity.

To date there have been several reported syntheses of frondosin B and one of frondosin C.[3] As the most biologically potent compound in its class, frondosin A, for which there are no reported syntheses, was of particular interest to us as a synthetic target. The proposed structure of frondosin A rests upon spectroscopic data that were used to assign the relative stereochemistry, although the absolute configuration remains unknown. The reported syntheses for other frondosins started from the assembly of the C and D rings and constructed the A and B ring systems at a late stage. For frondosin A, we envisioned that the Rh-catalyzed[4] and Ru-catalyzed[5] [5+2] cycloaddition would provide an opportunity to quickly access the bicyclo[5.4.0] structure corresponding to the A−B ring system of the norsesquiterpene carbon framework present in frondosin A. This strategy would allow installation of what we anticipated to be a sensitive exocyclic olefin and the readily oxidizable hydroquinone at a late stage of the synthesis. In addition to confirming the structural assignment, an enantioselective synthesis would also establish the absolute stereochemistry of frondosin A.

Results and Discussion

The first-generation synthetic plan, based on the Ru-catalyzed [5+2] cycloaddition as the key step, is summarized in Scheme 1. The aromatic functionality in frondosin A could be incorporated using a cross-coupling reaction, followed by a Claisen rearrangement. The advanced intermediate **7**, in which the bicyclo[5.4.0] core structure has been constructed, could derive from a 1,7-enyne (**8**) utilizing the Ru-catalyzed [5+2] cycloaddition. The cyclopropyl functionality in compound **8** could be

(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.; Boyd, M. R. *Nat. Prod. Lett.* **1998**, *11*, 153.
(3) (a) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878. (b) Inoue, M.; Frontier, A. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 761. (c) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569. (d) Hughes, C. C.; Trauner, D. *Tetrahedron* **2004**, *60*, 9675. (e) Chaplin, J. H.; Flynn, B. L. *Chem. Commun.* **2001**, 1594. (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.
(4) (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *112*, 4720. (b) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; Pleuss, N.; *Tetrahedron* **1998**, *54*, 7203. (c) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A.; Rieck, H. *J. Am. Chem. Soc.* **1999**, *121*, 10442. (d) Wender, P. A.; Haustedt, L. O.; Lim, J.; Love, J. A.; Williams, T. J.; Yoon, J.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 6302.
(5) (a) Trost, B. M.; Shen, H. C.; Horne, D. B.; Toste, F. D.; Steinmetz, B. G.; Koradin, C. *Chem.—Eur. J.* **2005**, *11*, 2577. (b) Trost, B. M.; Shen, H. C.; Schulz, T.; Koradin, C.; Schirok, H. *Org. Lett.* **2003**, *5*, 4149. (c) Trost, B. M.; Shen, H. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2313. (d) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379. (e) Trost, B. M.; Shen. H. *Org. Lett.* **2000**, *2*, 2523.

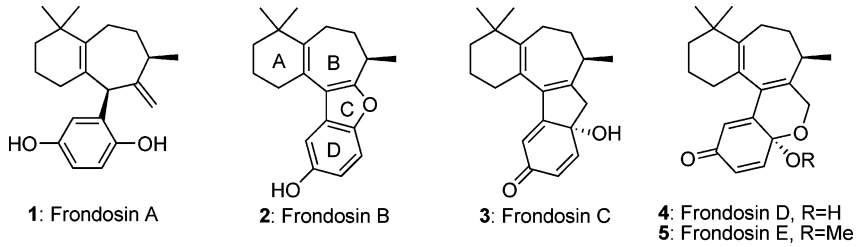
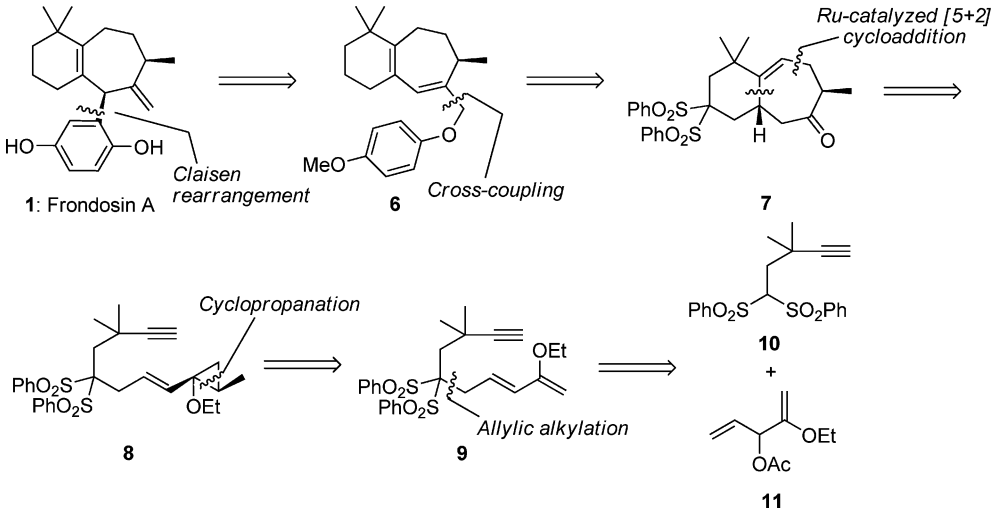
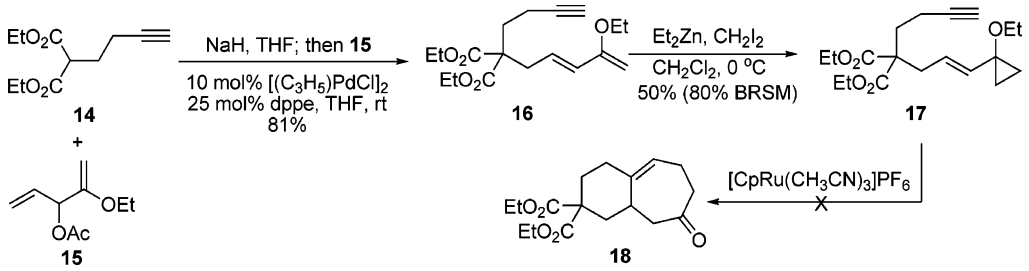


Figure 1. Frondosins A−E.

Scheme 1. Retrosynthesis of Frondosin A by the Ru-Catalyzed [5+2] Cycloaddition

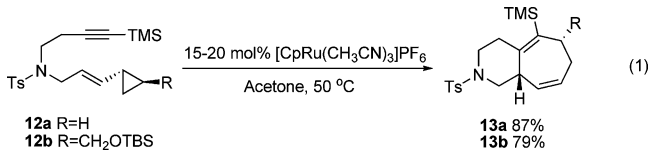


Scheme 2. Synthesis of 1,7-Enyne Model System **17**



installed employing an asymmetric cyclopropanation. Dienyne **9** could be synthesized from compounds **10** and **11** via an allylic alkylation reaction.

One goal of this route was to examine the feasibility of using 1,7-enynes in Ru-catalyzed [5+2] cycloadditions. The use of 1,6-enynes in Ru-catalyzed [5+2] reactions to access bicyclo-[5.3.0] ring systems was previously described by our group.[5] Only one example of a 1,7-enyne participating in a [5+2] cycloaddition exists, an amino-tethered system, wherein a [5+2] reaction occurred using either Ru or Rh catalysts (eq 1).[5d]



(1)

To test whether other 1,7-enynes would participate in a [5+2] reaction, a simplified model system (**17**) was prepared as shown in Scheme 2. Alkyne **14**[6] was reacted with allyl acetate **15**[4c] in a Pd-catalyzed allylic alkylation to afford dienyne **16**. Chemoselective cyclopropanation of the more electron rich olefin in compound **16** gave the desired model substrate **17**.

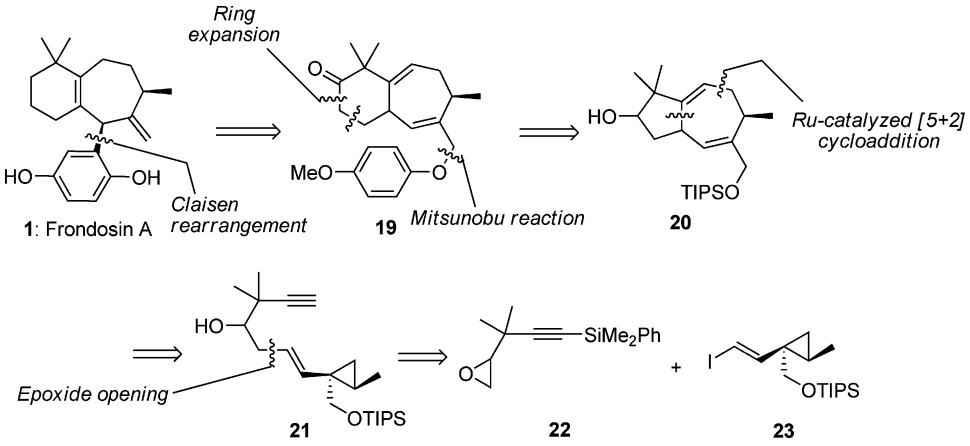
Unfortunately, when enyne substrate **17** was subjected to the standard [5+2] cyclization conditions (10% $[CpRu(CH_3CN)_3]PF_6$, acetone, room temperature), none of the desired product **18** could be detected. Attempts to facilitate the reaction by heating and the examination of different solvents (acetone, DMF, CH_2Cl_2) led only to no reaction or to decomposition at higher temperatures.

It was at this point that we decided to revise our synthetic strategy to utilize a 1,6-enyne substrate in the [5+2] cycloaddition. A retrosynthesis based on the new strategy is shown in Scheme 3. The key intermediate **19**, which bears a bicyclo-[5.4.0] ring system, could derive from compound **20**, which has a bicyclo[5.3.0] ring system. A 1,6-enyne (**21**) could be employed to build the bicyclo[5.3.0] ring system via a Ru-catalyzed [5+2] cycloaddition. The 1,6-enyne **21** could be obtained by metalation of vinyl iodide **23** and addition to alkynyl epoxide **22**.

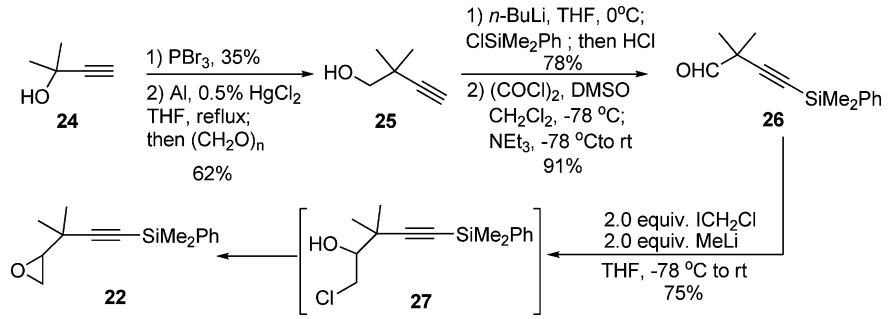
The synthesis of alkynyl epoxide **22** was achieved as described in Scheme 4. From commercially available 2-methyl-

(6) Taylor, E. C.; Macor, J. E.; French, L. G. *J. Org. Chem.* **1991**, *56*, 1807.

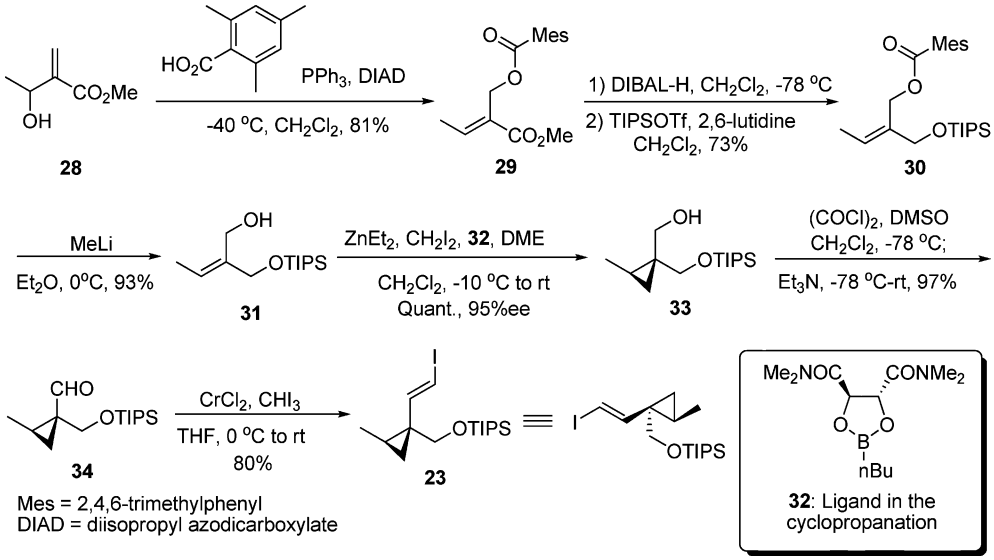
Scheme 3. Second-Generation Retrosynthesis for Frondosin A



Scheme 4. Synthesis of Alkynyl Epoxide **22**



Scheme 5. Synthesis of Vinyl Iodide **23**



3-butyn-2-ol (**24**), bromination with phosphorus tribromide afforded a propargyl bromide. An aluminum-mediated addition to formaldehyde yielded the desired homopropargyl alcohol **25**. Formation of the (dimethylphenylsilyl)alkyne was performed to reduce the volatility of intermediates in subsequent steps as well as protection of the alkyne for the subsequent addition reaction to the epoxide. A Moffatt−Swern oxidation of the resulting primary alcohol gave the aldehyde **26**, which was then converted to epoxide **22** through the reaction with (chloromethyl)lithium.[7]

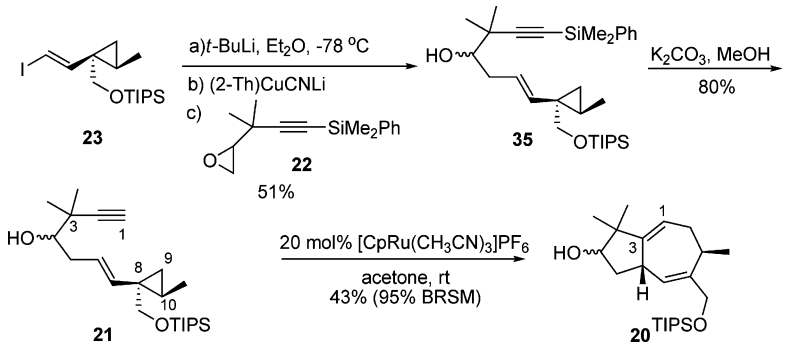
Synthesis of vinyl iodide **23** was accomplished by cyclopropanation of allylic alcohol **31** (Scheme 5). The preparation of allylic alcohol **31** was adopted from the procedure of Charette with a similar substrate.[8] The enantioselective cyclopropanation of alcohol **31** was achieved with chiral oxaborolane ligand **32**.[9] Alcohol **33** was assigned to be of *R*,*R*-configuration on the basis of Charette's model for asymmetric cyclopropanation of allylic alcohols. This assignment was later confirmed by synthesis of a compound with a known optical rotation (Scheme 16). Alcohol

(7) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795.

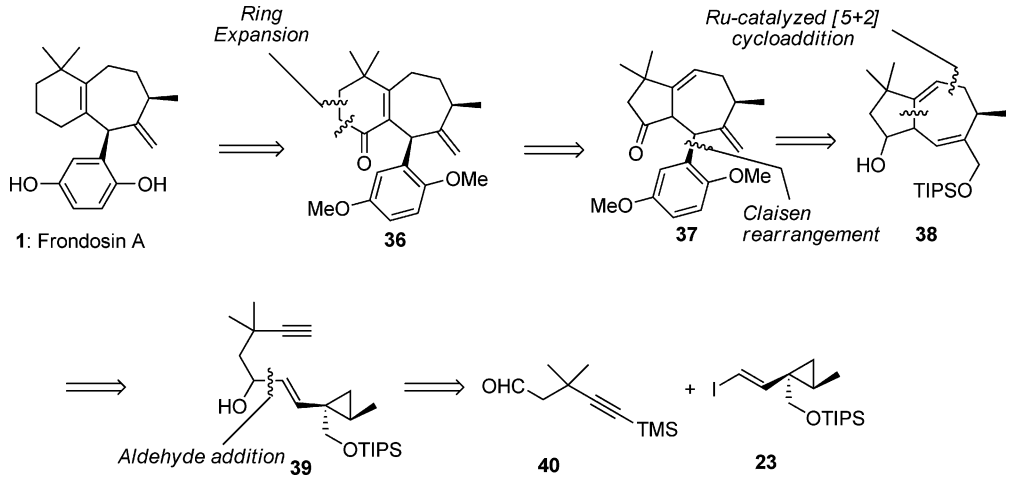
(8) Charette, A. B.; Cote, B.; Monroc, S.; Prescott, S. *J. Org. Chem.* **1995**, *60*, 6888.

(9) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651.

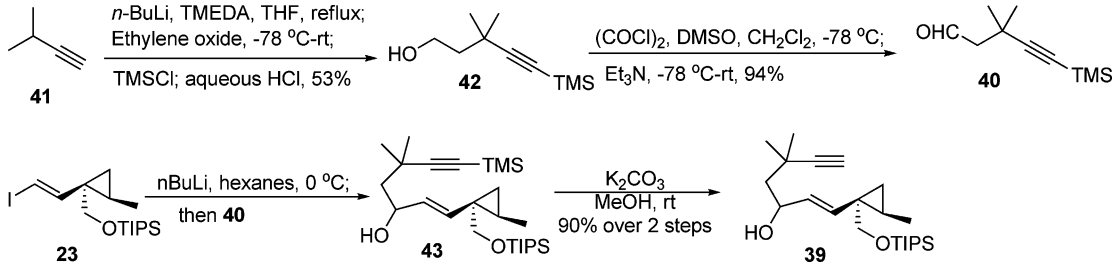
Scheme 6. Completion of the Bicyclo[5.3.0] Ring



Scheme 7. Third-Generation Retrosynthesis for Frondosin A



Scheme 8. Preparation of [5+2] Cycloaddition Precursor **39**



33 was then oxidized by the Moffatt−Swern reaction, and the resulting aldehyde **34** was transformed into vinyl iodide **23** by the Takai conditions.[10]

The coupling of the vinyl iodide **23** and the epoxide **22** was achieved by a copper-mediated process (Scheme 6). The deprotection of the alkyne in **35** afforded the cyclization substrate **21**. Finally, the standard ruthenium [5+2] conditions were applied to the enyne **21** to successfully yield the cyclized product **20**.

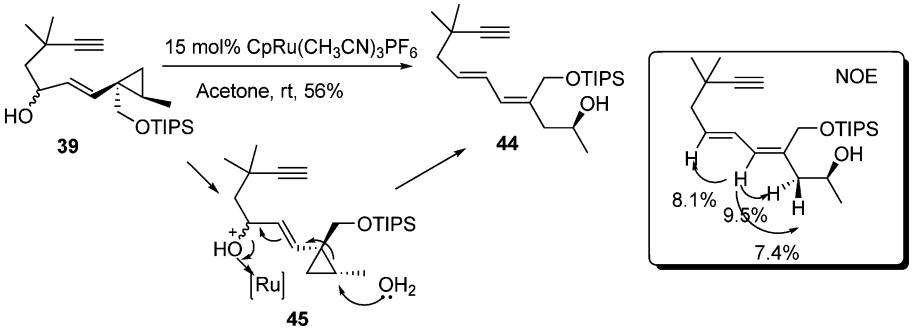
It is at this stage that several problems were realized. The Ru-catalyzed [5+2] cycloaddition reaction was problematic. In addition to the high catalyst loadings required to achieve modest conversions, one of the alcohol diastereomers is much less reactive than the other. More importantly, initial experiments suggested that several difficulties for the ring expansion and double bond migration in later stages of the synthesis would present themselves.

To address the problems above, a third strategy was proposed (Scheme 7). Compared to the plan in Scheme 3, the major change is the use of allylic alcohol **39**, instead of homoallylic alcohol **21**, for the Ru-catalyzed [5+2] cycloaddition. The cycloaddition product **38** could be converted to compound **37** through a sequence of steps involving the Claisen rearrangement. The position of the carbonyl functionality in compound **37** was anticipated to facilitate a base-mediated double bond migration into conjugation with the ketone.

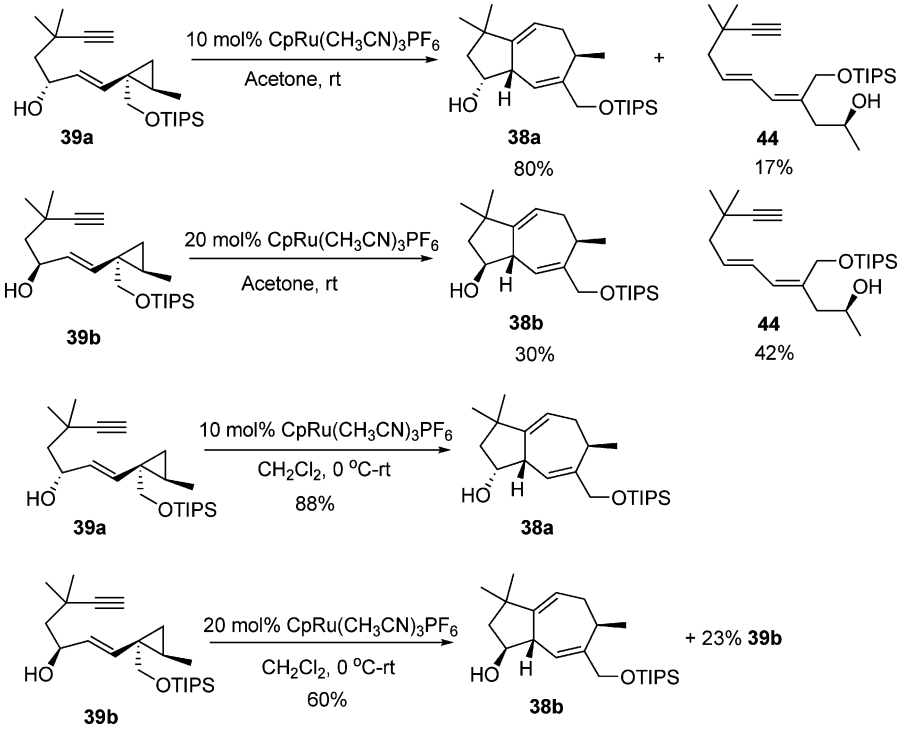
Enyne **39** was prepared through a sequence of steps shown in Scheme 8. Aldehyde **40**[11] was prepared in two steps from commercially available 3-methylbutyne (**41**). Vinyl iodide **23** was then coupled with aldehyde **40**, employing *n*-butyllithium in the lithium−halogen exchange and addition reaction. Compound **43** was used without purification in the subsequent deprotection reaction to afford cyclopropyl enyne **39** as the precursor for the key [5+2] cycloaddition. Compound **39** is an approximately 1:1 mixture of two diatereomers with respect to the newly formed stereogenic center.

(10) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
(11) Marco-Contelles, J.; Ruiz-Caro, J.; Mainetti, E.; Devin, P.; Fensterbank, L.; Malacria, M. *Tetrahedron* **2002**, *58*, 1147.

Scheme 9. Unexpected Diene Formation under the [5+2] Cycloaddition Condition



Scheme 10. Different Reactivities in the [5+2] Cycloaddition Reactions with **39a** and **39b**

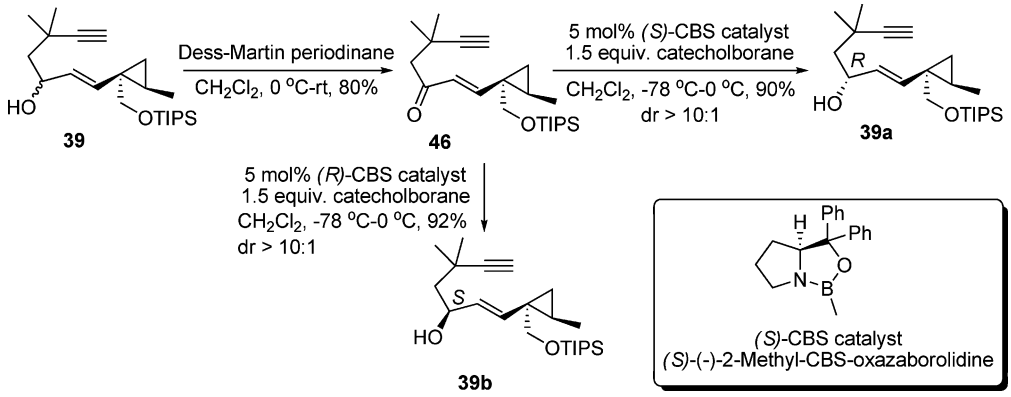


The stage was now set to attempt the [5+2] cycloaddition reaction. Under standard conditions, no desired products were observed. Instead, dienyne **44** was isolated as the major product (Scheme 9). The geometry of the double bonds was determined by an NOE experiment. It is also interesting to note that compound **44** seems to be a single enantiomer since derivatizing this compound with (*R*)- or (*S*)-α-methoxyphenylacetic acid afforded one diastereoisomer in each case. The absolute stereochemistry of the stereogenic center in compound **44** was determined by comparing the ^{1}H NMR data of the two diastereomeric esters.[12] The mechanism for the formation of this diene **44** was proposed as a solvolysis process. The cationic ruthenium catalyst could complex to the hydroxyl group to activate the vinylcyclopropane functionality in intermediate **45**. Trace amounts of water present in the solvent may well facilitate the ring opening to yield diene **44** with an inversion of the stereochemistry. The same stereochemical outcome was observed in a similar acid-catalyzed solvolysis of cyclopropanes.[13]

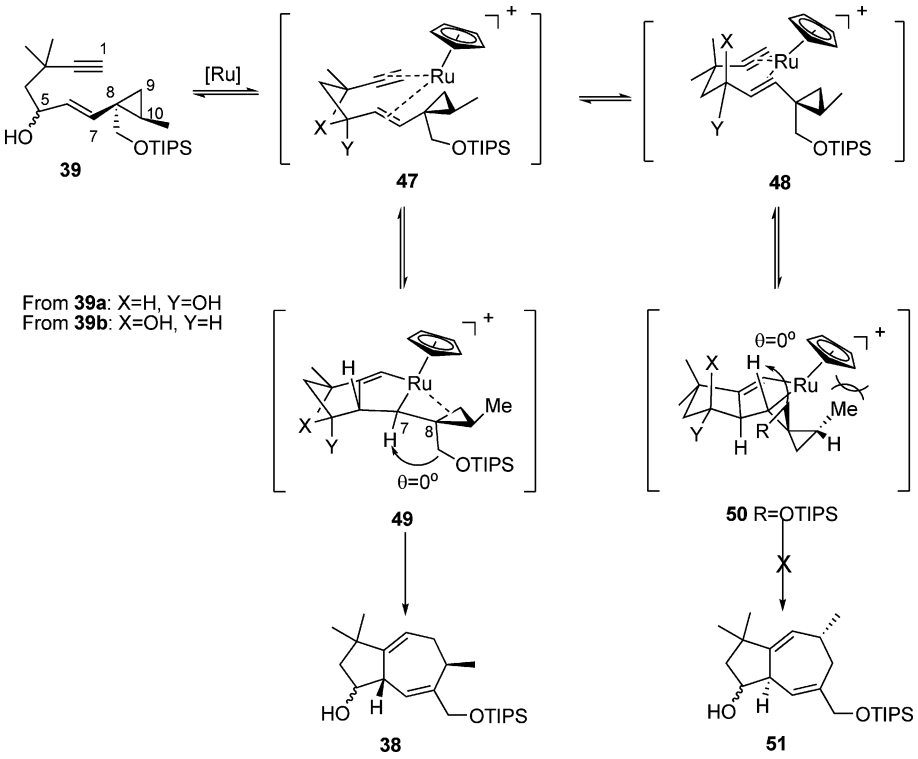
With strictly dried acetone as the solvent and carefully purified ruthenium catalyst and by stopping the reaction before completion by filtering off the catalyst through a silica gel pad, a small amount of the desired adduct **38** was obtained. Some recovered starting material **39**, with a diastereomeric ratio different from that of the original starting material, was also isolated. This demonstrated that one diastereoisomer of the mixture was consumed faster than the other one in the reaction, a result similar to that seen in the earlier model system (Scheme 6). Encouraged by this observation, the two diastereoisomers of **39** were separated by flash chromatography and subjected to the standard ruthenium-catalyzed [5+2] reaction conditions. Very different results were found (Scheme 10). A good yield (80%) of desired product **38a** was obtained with compound **39a**, and only a minor amount of the side product **44** was observed. However, with the other diastereoisomer (**39b**), the undesired side product **44** was obtained as the major product (42%). By changing the solvent to methylene chloride, which is much easier to dry completely, we were able to minimize the formation of the undesired elimination product **44**. Consistent results were obtained with both diastereoisomers, resulting in good yields of the desired cyclization products **38a** (88%) and **38b** (60%).

(12) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370.
(13) (a) Honda, M.; Mita, T.; Nishizawa, T.; Sano, T.; Segi, M.; Nakajima, T. *Tetrahedron Lett.* **2006**, *47*, 5751. (b) Honda, M.; Yamamoto, Y.; Tsuchida, H.; Segi, M.; Nakajima, T. *Tetrahedron Lett.* **2005**, *46*, 6465.

Scheme 11. Determination of the Absolute Configuration for **39a** and **39b**



Scheme 12. Proposed Mechanism of the Ru-Catalyzed [5+2] Cycloaddition



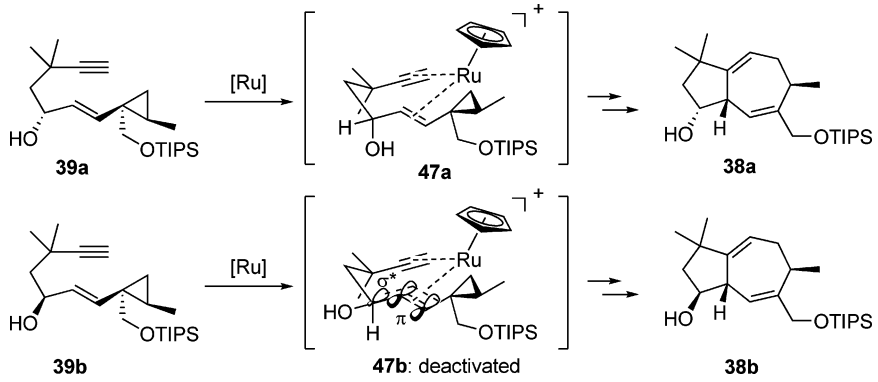
The absolute configuration of compounds **39a** and **39b** was determined by asymmetric reduction of ketone **46** (obtained from the Dess−Martin oxidation of compound **39**) with (*R*)- or (*S*)-CBS (Corey−Bakshi−Shibata) oxazaborolidine catalysts (Scheme 11).[14] This procedure afforded either diastereoisomer of **39** with a predictable stereochemical outcome. It was shown that diastereomer **39a** has the higher reactivity toward cycloaddition in the Ru-catalyzed [5+2] process.

The relative stereochemistry of compounds **38a** and **38b** was assigned on the basis of the coupling constants in ^{1}H NMR studies and COSY experiments. The relative stereochemistry of compound **38a** was further confirmed with NOE experiments, as shown in the Experimental Section. The proposed mechanism of the Ru-catalyzed [5+2] cycloaddition is anticipated to account for the observed diastereoselectivity and regioselectivity, as depicted in Scheme 12. Enyne **39** will react via an extended conformation, as shown in intermediates **47** or **48**, after complexation with the ruthenium catalyst to afford ruthenacyclopentanes **49** and **50**. To react with ruthenium, the cyclopropane has to adopt a conformation in which the H−C7−C8−CH_2OTIPS dihedral angle is close to 0°. The steric interaction between the methyl group at the C10 position and the Cp ligand on the ruthenium in intermediate **50** disfavors this pathway for the formation of compound **51**. Thus, compound **38** was isolated as a single diastereoisomer.

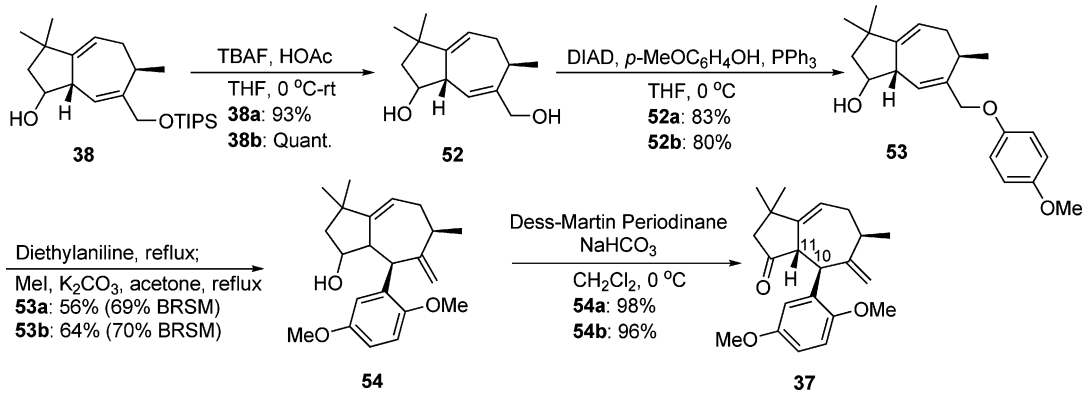
This mechanism also explains the different reactivities observed with diastereomers **39a** and **39b**. As shown in Scheme 13, the electron-withdrawing hydroxyl group at the pseudoequatorial position in intermediate **47b** will lower the reactivity of the double bond toward ruthenium and destabilize the transition state. This effect can be explained by the overlap of the σ^*_{CO} orbital with the alkene π orbital, which is absent in transition state **47a**. The observation is in agreement with the Stork/Houk-Jäger "inside alkoxy" model.[15]

(14) (a) Corey, E. J.; Helal, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

Scheme 13. Explanation for Different Reactivities of **39a** and **39b** in the Cycloaddition



Scheme 14. Preparation of Substrate **37** for the Ring Expansion Reaction



With cycloaddition products **38a** and **38b** in hand, further elaboration was necessary to obtain the bicyclo[5.4.0] core structure of frondosin A. For ease of reaction analysis and product characterization, compounds **38a** and **38b** were handled separately, but under similar reaction conditions. In principle, the diastereomers of **38** could be employed in the reaction sequence without prior separation.

Starting from compound **38**, removal of the triisopropylsilyl protecting group was achieved employing TBAF buffered with acetic acid (Scheme 14). The *p*-methoxyphenyl group was selectively installed on the more reactive allylic, and also primary, hydroxyl group under Mitsunobu conditions to yield compound **53**. Claisen rearrangement under thermal conditions (diethylaniline, 215 °C) proceeded, although it resulted in only a poor yield of the desired product. It was later found that the product is sensitive to acid, base, and an oxidative atmosphere. Thus, a protocol consisting of the Claisen rearrangement and methylation of the resulting phenol in one operation was employed to afford compound **54** as a single diastereomer in good yield. The stereochemistry of compound **51** was confirmed by NMR studies. The conformation of the bicyclic ring system contributes to the desired stereoselectivity observed in the reaction. Dess−Martin oxidation of compound **54** proceeded smoothly to afford ketone **37**.

To finish the bicyclo[5.4.0] core structure of frondosin A, a ring expansion was required. There were several strategies that were attempted for the ring expansion, cyclopropanation of the corresponding silyl enol ether of ketone **37** followed by fragmentation and Lewis acid-catalyzed ring expansion with diazoalkanes being the main strategies. However, due to the presence of two activated protons at the C10 and C11 positions, decomposition or formation of undesired products was observed in many of our ring expansion attempts. Finally, under carefully controlled conditions, with (TMS)CHN_2 and catalytic $BF_3{\cdot}OEt_2$, a mixture of compounds **55**, **56**, and **57** was obtained (Scheme 15). After desilylation with TBAF, the desired ketone **36** was isolated in 54% yield, along with its regioisomer ketone **58** and aldehyde **59**. Double bond migration was also achieved in the same transformation. Thus, the bicyclo[5.4.0] core structure of frondosin A was completed, and efforts to finish the synthesis were undertaken.

Finishing the synthesis of frondosin A entailed the reduction of the ketone to a methylene and deprotection of the methyl ethers. Direct reduction of a carbonyl functionality to the corresponding methylene group normally involves a Wolff−Kishner-type reduction. However, in our hands treating ketone **36** under standard Wolff−Kishner conditions[16] or Myers's modified conditions[17] resulted in either decomposition or formation of products lacking the exocyclic double bond. An alternative strategy involving the reduction of arylsulfonyl hydrazones with various boron hydrides resulted in complex mixtures.[18] The presence of the activated benzylic proton in ketone **36** may account for the above difficulties.

Another alternative for the deoxygenation of ketones involves making sulfur derivatives, which can then be reduced to give

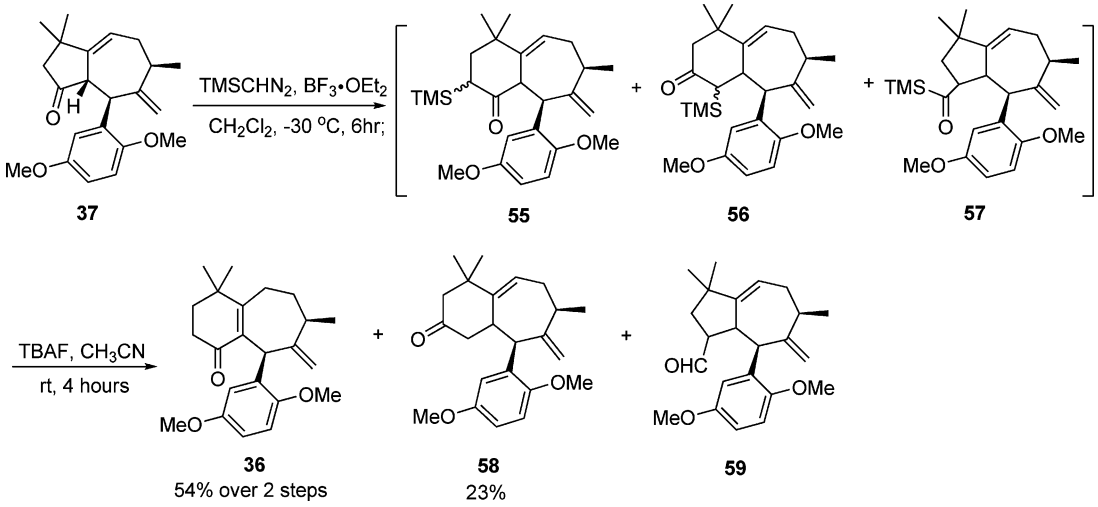
(15) (a) Haller, J.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 8031. (b) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

(16) (a) Kishner, N. *Zh. Russ. Fiz.-Khim. Ova., Chast Khim.* **1911**, *43*, 582. (b) Wolff, L. *Justus Liebigs Ann. Chem.* **1912**, *394*, 86. (c) Huang-Minlon. *J. Am. Chem. Soc.* **1946**, *68*, 2487 (d) Huang-Minlon *J. Am. Chem. Soc.* **1949**, *71*, 3301.

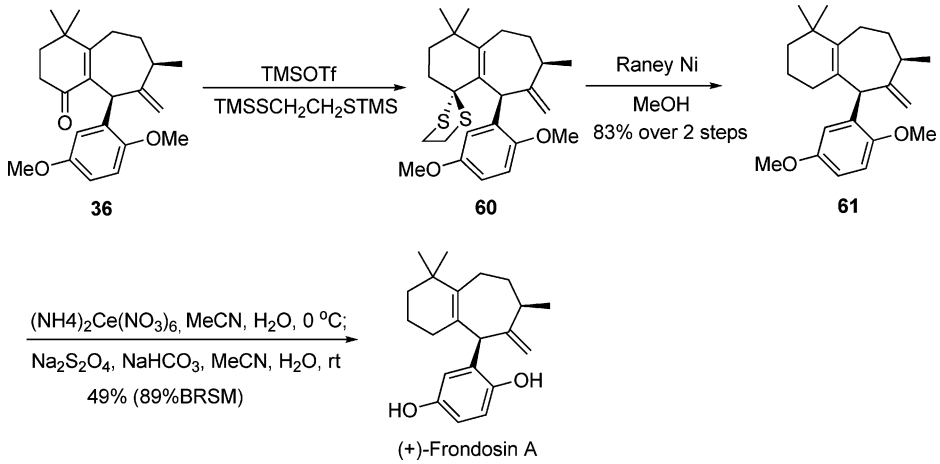
(17) Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436.

(18) (a) Caglioti, L.; Magi, M. *Tetrahedron* **1963**, *19*, 1127. (b) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662. (c) Kabalka, G. W.; Baker, J. D. *J. Org. Chem.* **1975**, *40*, 1834.

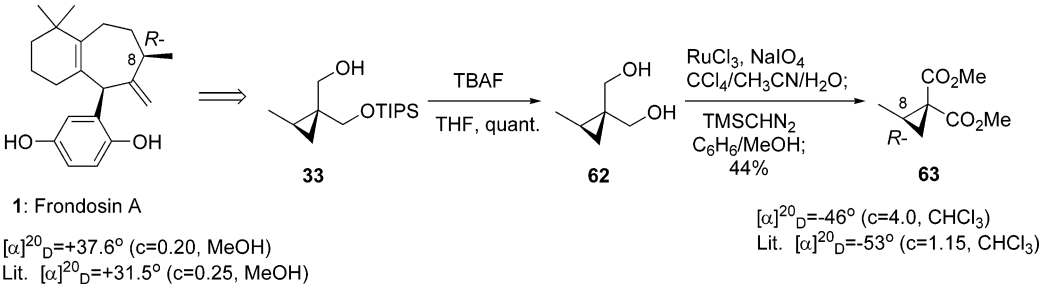
Scheme 15. Ring Expansion with Ketone **37**



Scheme 16. Completion of the Total Synthesis of Frondosin A



Scheme 17. Absolute Configuration of (+)-Frondosin A



the alkane. Attempts to make a thioketal (**60)** with 1,2-ethanedithiol, catalyzed by Lewis acids, afforded products lacking the exocyclic double bond. Evans reported 1,2-bis-[(trimethylsilyl)thio]ethane and catalytic zinc iodide as mild conditions for thioketal formation.[19] Applying these conditions with ketone **36** resulted in slow conversion to the thioketal along with an undesired isomerization of the exocyclic olefin. Realizing that zinc iodide might initiate certain radical processes facilitating the isomerization, different Lewis acids were screened. It was found subsequently that trimethylsilyl triflate could catalyze the reaction cleanly to give the desired thioketal **60** (Scheme 16). Upon treatment of the crude product **60** with Raney Ni, the desired deoxygenated product **61** could be isolated in over 80% yield.

Initial attempts for the final deprotection with BBr_3 resulted in decomposition. Treating compound **61** with sodium ethanethiolate in DMF at reflux only afforded monodeprotection products. The most effective method for the deprotection proved to be an oxidation−reduction sequence using ceric ammonium nitrate (CAN) followed by sodium dithionite. Because of the sensitivity of the system toward oxidation, it was necessary to perform the reaction only to partial conversion. Thus, an 89% yield was obtained when the reaction was stopped at 55% conversion.

The optical rotation of the synthetic (+)-frondosin A matches the reported value (Scheme 17).[1] Because the absolute stereo-

(19) Evans, D. A.; Truesdale, L. K.; Grimm, K. G.; Nesbitt, S. L. *J. Am. Chem. Soc.* **1977**, *99*, 5009.

chemistry of the final natural product is derived from alcohol **33**, its absolute configuration was verified by conversion to an ester (**63**) of known absolute configuration (Scheme 16).[20] Thus, frondosin A must have an *R*-stereogenic center at the C8 position. This is in agreement with the original assignment of (+)-frondosin B by Danishefsky.[3a] Trauner later questioned this assignment.[3d] Although (+)-frondosin A and (+)-frondosin B may not necessarily have the same configuration at the C8 position, our results with (+)-frondosin A suggest that Danishefsky's original assignment is very likely to be the correct one, which is also in agreement with recent work by MacMillan based upon his group's total synthesis of frondosin B.[21]

Conclusion

In summary, the first enantioselective total synthesis of (+)-frondosin A was accomplished in 7% overall yield, through 19 longest linear and 21 total steps. A Ru-catalyzed [5+2] cycloaddition of an enantioenriched cyclopropyl enyne was employed as the key step to construct the bicyclo[5.3.0] ring system with high regio- and diastereoselectivity. This first application of the Ru-catalyzed [5+2] cycloaddition in natural product synthesis highlights the efficiency of this methodology for generating complex fused ring systems. Subsequent Claisen rearrangement further elaborated the cycloadduct to give the frondosin core. This synthesis also serves to determine the absolute configuration of (+)-frondosin A and shed light on the configurational assignment of the frondosin family.

Experimental Section

Selected experimental procedures for the preparation of **42**, **33**, **38a**, **54a**, **36**, and **1** (frondosin A) appear below. Full experimental details for all compounds are given in the Supporting Information.

5-(Trimethylsilyl)-3,3-dimethyl-4-pentyn-1-ol (42). To a solution of 3-methylbutyne (**41**; 8.06 g, 118 mmol) in diethyl ether (100 mL) at −20 °C was added *n*-BuLi (110 mL, 2.19 M solution in hexanes, 237 mmol) followed by tetramethylethylenediamine (TMEDA; 17.7 mL, 118 mmol). The reaction was warmed to room temperature and heated to a gentle reflux for 10 h until a clear orange solution formed. The reaction was recooled to −78 °C, and a solution of ethylene oxide (6 mL, condensed from cylinder, 118 mmol) in THF (20 mL) was cannulated into the solution of the above dianion over 5 min. The reaction was stirred at −78 °C for 2 h, and then trimethylsilyl chloride (30 mL, 240 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 5 h. The solution was concentrated to about 200 mL under reduced pressure, 1 N HCl (200 mL) was added, and the mixture was stirred vigorously for 1 h. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and NaCl, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (20% Et_2O in petroleum ether) yielded product **42** (11.70 g, 63.6 mmol, 53% yield) as a colorless liquid. ^{1}H NMR and IR match the reported data.[11] R_f = 0.17 (20% Et_2O in petroleum ether). IR (thin film, cm^{-1}): 3345, 2967, 2162, 1451, 1409, 1364, 1251, 1062, 1029. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 (t, J = 6.2 Hz, 2H), 1.68 (t, J = 6.2 Hz, 2H), 1.21 (s, 6H), 0.59 (s, 9H) ppm.

(1,2-*trans*)-2-Methyl-1-(hydroxymethyl)-1-[(triisopropylsilanyl)oxy]cyclopropane [(±)-33]. To a solution of Et_2Zn (13.5 mL, 1.0 M in hexanes, 13.5.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added a solution of diiodomethane (7.2 g, 26.9 mmol) in CH_2Cl_2 (5 mL) over 5 min. The milky white solution was stirred for 10 min, and allylic alcohol **31** (1.75 g, 6.77 mmol) in CH_2Cl_2 (5 mL) was added over 5 min. The reaction was stirred for 10 min, then the ice bath was removed, and the reaction was warmed to room temperature and stirred for 1 h. The reaction was poured into saturated aqueous NH_4Cl (100 mL), diluted with CH_2Cl_2 (50 mL), and extracted. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (5% EtOAc in petroleum ether) yielded 1.40 g of (±)-**33** (76%) as a clear, colorless oil. R_f = 0.38 (20% Et_2O in petroleum ether). IR (thin film, cm^{-1}): 3452, 2944, 2867, 1464, 1108, 1063, 1014. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.90 (d, J = 11.5 Hz, 1H), 3.77 (d, J = 10.0 Hz, 1H), 3.62 (d, J = 11.5 Hz, 1H), 3.54 (d, J = 9.8 Hz, 1H), 3.11 (br s, 1H), 1.18 (d, J = 6.3 Hz, 3H), 1.07 (m, 21H), 0.87 (m, 1H), 0.55 (dd, J = 6.6, 4.9 Hz, 1H), 0.18 (t, J = 5.2 Hz, 1H) ppm. ^{13}CNMR (125 MHz, $CDCl_3$): δ 72.8, 66.2, 27.4, 17.9, 16.6, 15.8, 13.8, 11.7 ppm. HRMS (EI+): m/z calcd for $C_{15}H_{31}O_2Si$ $[M - H]^+$ 271.2093, found 271.2092.

(1*R*,2*R*)-2-Methyl-1-(hydroxymethyl)-1-[(triisopropylsilanyl)oxy]-cyclopropane (33). To a solution of Et_2Zn (43 mL, 1.0 M in hexanes, freshly prepared from neat Et_2Zn, 43 mmol) in DME (4.4 mL, 42.3 mmol) and CH_2Cl_2 (90 mL) at −30 °C was added dropwise a solution of diiodomethane (6.8 mL, 84.4 mmol) in CH_2Cl_2 (20 mL) over 10 min. The clear solution was stirred for 30 min, then butylboronic acid *N*,*N*,*N*′,*N*′-tetramethyl-L-tartaric acid diamide ester **32** (7.0 g, 25.9 mmol) in CH_2Cl_2 20 mL) was added over 10 min. After 15 min, allylic alcohol **31** (5.5 g, 21.3 mmol) in CH_2Cl_2 (20 mL) was added. The reaction was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched with 1 N HCl (100 mL) and saturated aqueous NH_4Cl (100 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with water, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (silica gel, 4% EtOAc in petroleum ether) yielded product **33** (6.0 g, quantitative yield) as a clear oil. The enantiomeric excess of the product was determined to be 94.6% ee by conversion into the trifluoroacetate ester and chiral GC, described below. R_f = 0.38 (5:1 petroleum ether/Et_2O). $[\alpha]_D^{24} = -27.4°$ (c = 1.10, CH_2Cl_2). The spectral data matched those of the racemic compound (±)-**33** described above.

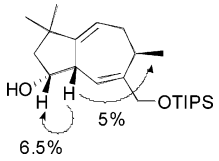
(1*R*,2*R*)-Trifluoroacetic Acid [2-Methyl-1-[[[(triisopropyl)silanyl]-oxy]methyl]cyclopropyl]methyl Ester. The enantiomeric excess of the above product was determined by conversion to the trifluoroacetate ester of alcohol (−)-**33**: To a solution of (−)-**33** (27 mg, 0.10 mmol) in CH_2Cl_2 (0.6 mL) under Ar at 0 °C was added pyridine (16 μL, 0.2 mmol) followed by trifluoroacetic anhydride (28 μL, 42 mg, 0.2 mmol), and the solution was stirred for 1 h. The reaction was quenched with H_2O (5 mL) and diluted with diethyl ether (5 mL) and the organic layer separated, washed with saturated aqueous $CuSO_4$, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (5% EtOAc in petroleum ether) yielded the trifluoroacetate ester of (−)-**33** (28.7 mg, 78%) as a clear, colorless, oil. The enantiomeric excess was determined to be 94.6% ee by chiral GC (Cyclosil B, 120 °C, 15 mL/min, minor product (1*S*,2*S*) t_R = 47.838 min and major product (1*R*,2*R*) t_R = 48.558 min).

(1*R*,3a*E*,6*R*,7*E*,8a*S*)-3,3,6-Trimethyl-7-[[(triisopropylsilanyl)oxy]-methyl]-1,2,3,5,6,8a-hexahydroazulen-1-ol (38a). To a solution of 1,6-enyne **39a** (2.95 g, 7.8 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added a solution of $[CpRu(CH_3CN)_3]PF_6$ (0.34 g, 0.78 mmol) in CH_2Cl_2 (50 mL). The reaction was stirred for 3 h as the solution warmed to room temperature, then the solution was filtered through a silica gel pad to remove the catalyst, and the filtrates were concentrated. Flash chromatography (5−10% Et_2O in petroleum ether) yielded product **38a** (2.59 g, 6.86 mmol, 88% yield) as a colorless oil. R_f = 0.17 (10% Et_2O in

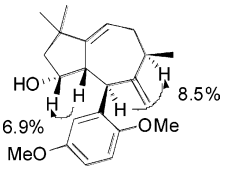
(20) di Lugano, F. R.; Monteiro, J.; Fliche, C.; Braun, J.; Le Goffic, F. *Synth. Commun.* **1992**, *22*, 1155.

(21) A recent asymmetric synthesis by MacMillan et al. also suggests that (+)-frondosin B has an *R*-chiral center at the C8 position: D. W. C. MacMillan, Princeton University, personal communication, 2007.

petroleum ether). IR (thin film, cm^{-1}): 3375, 2945, 2867, 1464, 1383, 1368, 1248, 1064. ^1H NMR (500 MHz, $CDCl_3$): δ 5.70 (d, J = 1.5 Hz, 1H), 5.50 (dt, J = 7.0, 3.4 Hz, 1H), 4.18 (s, 1H), 4.08 (m, 2H), 3.54 (s, 1H), 2.45 (m, 1H), 2.26 (m, 1H), 2.10 (m, 1H), 1.72 (d, J = 1.5 Hz, 1H) 1.70 (d, J = 4.0 Hz, 1H), 1.18 (s, 3H), 1.15 (d, J = 3.2 Hz, 3H), 1.08 (s, 3H), 1.04 (m, 21H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.2, 147.7, 120.1, 119.3, 75.7, 67.7, 66.0, 49.2, 48.3, 41.3, 31.1, 18.2, 17.5, 15.4, 12.1 ppm. HRMS (EI^+): m/z calcd for $C_{23}H_{42}O_2Si$ $[M]^+$ 378.2954, found 378.2954. $[\alpha]_D^{24}$ = 29.3° (c = 0.820, CH_2Cl_2). NOE:



(1*R*,6*R*,8*S*,8a*S*,*E*)-8-(2,5-Dimethoxyphenyl)-3,3,6-trimethyl-7-methylene-1,2,3,5,6,7,8,8a-octahydroazulen-1-ol (54a). A solution of **53a** (0.75 g, 2.28 mmol) in diethylaniline (8 mL) in a sealed tube was heated in a 220 °C oil bath. After 16 h, the reaction was cooled, and the solvent was removed under reduced pressure at 100 °C. The residue was dissolved in acetone (10 mL), and K_2CO_3 (0.69 g, 5.0 mmol) and CH_3I (0.62 mL, 10 mmol) were added. The reaction was heated at reflux for 3 h and then diluted with diethyl ether (50 mL). The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated. Flash chromatography (5−10% EtOAc in petroleum ether) yielded product **54a** (0.44 g, 1.28 mmol, 56% yield, 69% brsm) as a pale yellow liquid and the starting material **53a** (0.144 g, 0.44 mmol). R_f = 0.28 (10% EtOAc in petroleum ether). ^1H NMR (500 MHz, $CDCl_3$): δ 6.85 (d, J = 2.9 Hz, 1H), 6.82 (d, J = 8.9 Hz, 1H), 6.73 (dd, J = 3.1, 8.8 Hz, 1H), 5.61 (m, 1H) 4.82 (s, 1H), 4.43 (s, 1H), 4.04 (d, J = 11.5 Hz, 1H), 3.82 (t, J = 3.7 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 2.89 (d, J = 11.5 Hz, 1H) 2.51 (m, 2H), 1.95 (m, 1H), 1.70−1.56 (m, 4H), 1.22 (s, 2H) 1.17 (d, J = 5.5 Hz, 3H) 1.05 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.2, 153.6, 153.2, 150.9, 132.8, 128.4, 120.0, 116.6, 112.5, 111.2, 109.2, 74.9, 56.6, 55.7, 55.1, 47.1, 42.7, 41.2, 37.1, 33.1, 32.0, 21.8 ppm. IR (neat, cm^{-1}): 3564, 2954, 1495, 1464, 1281, 1227, 1049. HRMS (EI^+): m/z calcd for $C_{22}H_{30}O_3$ $[M]^+$ 342.2195, found 342.2210. $[\alpha]_D^{24}$ = −52.0° (c = 0.31, CH_2Cl_2). NOE:



(7*R*,9*S*)-9-(2,5-Dimethoxyphenyl)-4,4,7-trimethyl-8-methylene-2,3,4,5,6,7,8,9-octahydrobenzo-cyclohepten-1-one (36). To a solution of ketone **37** (0.33 g, 0.97 mmol) in CH_2Cl_2 (10 mL) at −25 °C was added $BF_3{\cdot}Et_2O$ (0.15 mL, 1.22 mmol) followed by $(TMS)CHN_2$ (0.61 mL, 2 M in ether, 1.22 mmol). The reaction was stirred at −25 °C for 8 h and then quenched with saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with diethyl ether (3 × 20 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give the crude product as a pale yellow liquid.

The crude product was then dissolved in acetonitrile (10 mL), and TBAF trihydrate (0.63 g, 2.0 mmol) was added at room temperature. The reaction was stirred for 4 h and then diluted with ethyl acetate (30 mL) and water (30 mL). The mixture was extracted with ethyl acetate (2 × 30 mL), washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography (5−10% ethyl acetate in petroleum ether) yielded the desired product **36** (185 mg, 0.52 mmol, 54% yield) along with ketone **58** (78 mg, 0.22 mmol, 23%) and aldehyde **59** (48 mg, 0.136 mmol, 14%). R_f = 0.25 (10% ethyl acetate in petroleum ether). IR (thin film, cm^{-1}): 2919, 2850, 1672, 1496, 1458, 1415, 1277, 1218, 1105, 1050. ^1H NMR (500 MHz, $CDCl_3$): δ 6.82 (d, J = 8.8 Hz, 1H), 6.67 (dd, J = 3.2, 8.8 Hz, 1H), 6.50 (d, J = 3.0 Hz, 1H), 5.24 (t, J = 2.7 Hz, 1H), 4.69 (d, J = 3.0 Hz, 1H), 4.23(m, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 2.83 (m, 1H), 2.32 (m, 3H), 2.19 (m, 1H), 2.01 (s, 1H), 1.91-(m, 1H), 1.78 (m, 1H), 1.41 (m, 1H), 1.24 (s, 3H), 1.20 (s, 3H), 1.08 (d, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.8, 163.5, 154.7, 153.7, 152.4, 134.5, 132.3, 114.4, 112.9, 111.3, 105.9, 57.2, 55.4, 45.0, 38.1, 37.4, 36.7, 34.9, 27.2, 26.8, 25.8, 19.3 ppm. HRMS (EI^+): m/z calcd for $C_{23}H_{30}O_3$ $[M]^+$ 354.2195, found 354.2190. $[\alpha]_D^{24}$ = 21.0° (c = 0.59, CH_2Cl_2).

Frondosin A (1). Compound **61** (4.4 mg, 0.013 mmol) in 1:1 H_2O/CH_3CN (0.13 mL, degassed by argon sparging for 30 min) at 0 °C was added dropwise to a solution of CAN (14 mg, 0.026 mmol) in 1:1 H_2O/CH_3CN (0.13 mL, also degassed). After 10 min, $NaHCO_3$ (43 mg, 0.52 mmol) was added, followed by $Na_2S_2O_4$ (23 mg, 0.13 mmol). The reaction was stirred vigorously at room temperature for 1 h. The mixture was filtered through a silica gel pad and concentrated under an argon atmosphere. Purification by achiral HPLC (2% isopropyl alcohol in heptane) yielded frondosin A (2.0 mg, 0.0064 mmol, 49% yield, 89% yield brsm), along with starting material **61** (2.0 mg, 0.0059 mmol, 45%). ^1H NMR, IR, and $[\alpha]_D^{20}$ match the reported data.[1] R_f = 0.33 (25% ethyl acetate in petroleum ether). IR (thin film, cm^{-1}): 3384, 2956, 2932, 2871, 1636, 1497, 1452, 1410, 1361, 1279, 1212, 1190, 1147. ^1H NMR (400 MHz, $CDCl_3$): δ 6.77 (d, J = 8.5 Hz, 1H), 6.67 (dd, J = 2.9, 8.5 Hz, 1H), 6.59 (d, J = 3.0 Hz, 1H), 4.85 (s, 1H), 4.52 (s, 1H), 3.95 (s, 1H), 2.49, (m, 2H), 2.04 (m, 1H), 1.87 (m, 3H), 1.56−1.51 (m, 4H), 1.29 (m, 1H), 1.10 (s, 3H), 1.09 (s, 3H), 1.06 (d, J = 7.0 Hz, 3H) ppm. HRMS (MALDI-TOF): m/z calcd for $C_{21}H_{28}O_2$, $[M + H]^+$ 313.2089, found $[M + H]^+$ 313.2081. $[\alpha]_D^{20}$ = 37.6° (c = 0.20, MeOH), lit.[1] $[\alpha]_D^{20}$ = 31.5° (c = 0.25, MeOH).

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences (Grant GM13598), for their generous support of our research. We also thank Johnson Matthey Co. for their kind donations of ruthenium chloride catalyst. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California−San Francisco supported by the NIH Division of Research Resources.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA073272B