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Cyclopropene Cycloadditions with Annulated Furans: Total Synthesis of (+)- and (–)-Frondosin B and (+)-Frondosin A

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1. Introduction

1-1. Frondosins

- Frondosins are family of marine-derived meroterpenoid natural products. (*Figure 1*)
- The family possesses a bicyclo[5.4.0] undecene core.
- They are expected to act as anti-cancer drug.

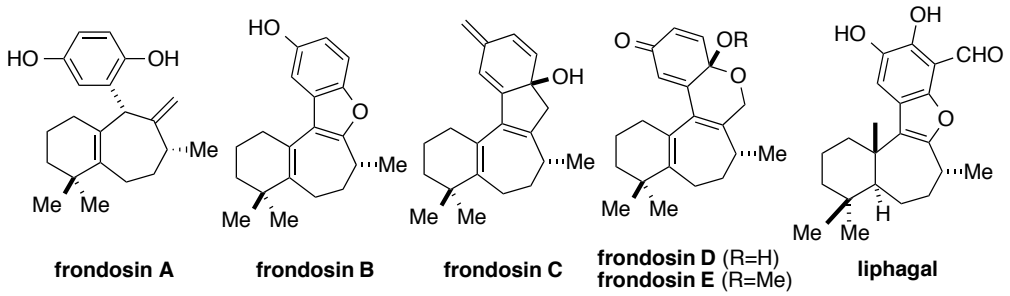


Figure 1. frondosins and liphagal

1-2. This Work

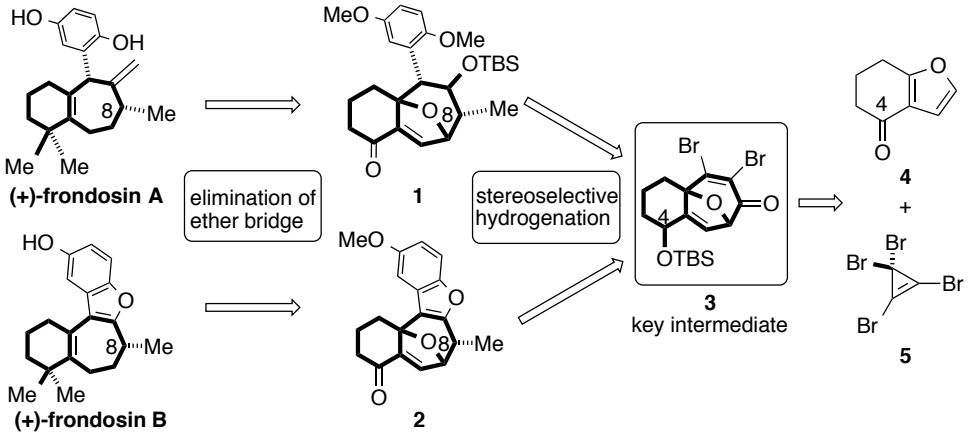
- Some total syntheses of (+)-frondosin B[1] and (+)-frondosin A[2] were reported separately. Although frondosins possess the similar structure, their precursors were different.

  ⇒ The authors focused on a bicyclo undecene core, the common structure to frondosins.

  ⇒ Bromoenone **3** was synthesized as the common precursor to frondosin A and frondosin B (*Scheme 1*).

  ⇒ Is this method applicable to the synthesis of other frondosins?

Scheme 1. Retrosynthesis of (+)-frondosin A and (+)-frondosin B



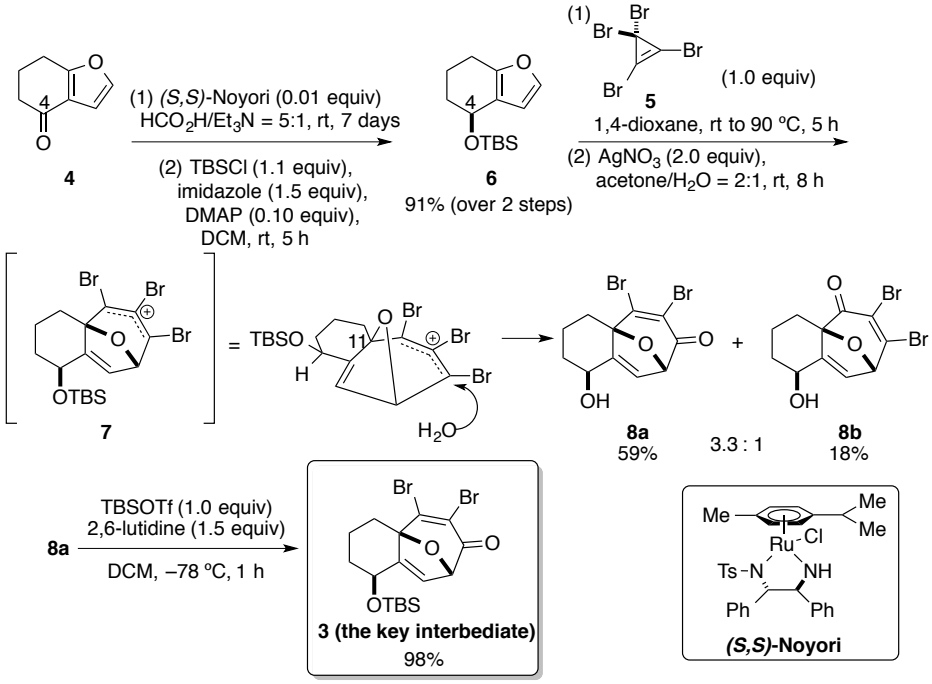
- Frondosin B and frondosin A have one stereogenic center, therefore controlling of the stereoselectivity of C8 is important.
- The introduction of the ether bridge controls the stereoselective hydrogenation at C8.
- The stereoselectivity of the ether bridge depends on C4 stereogenic center.
- The different reactivity of bromine on compound **3** makes the following selective functionalization possible.

  ⇒ Compound **3** is well-designed precursor to control the stereoselectivity.

2. Results and Discussion

2-1. [4+3] cycloaddition (compound **4** + **5** to compound **3**) (Key step 1)

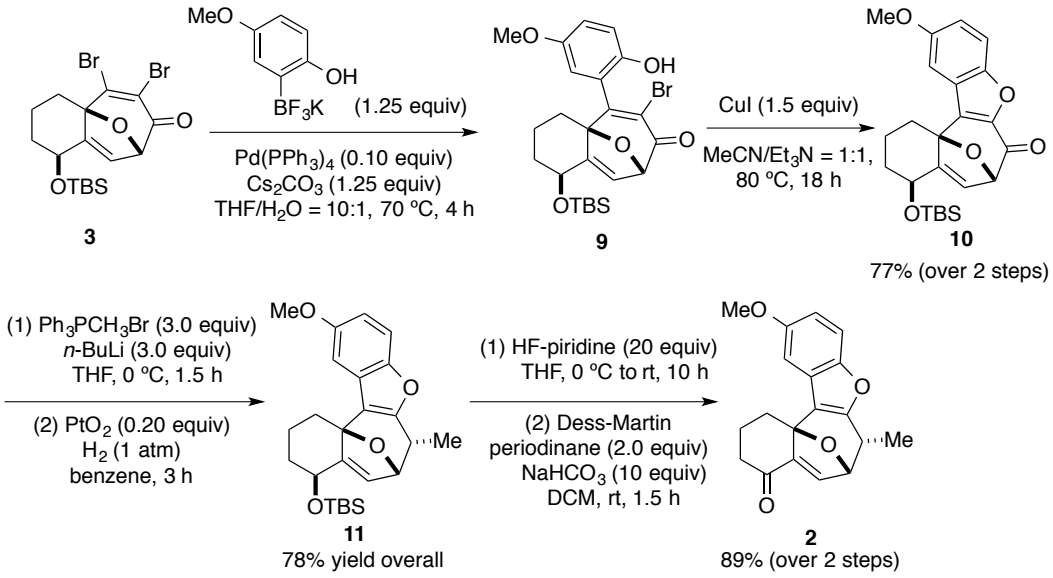
Scheme 2. Synthesis of bromoenone **3**



- The key intermediate **3**, was obtained by Diels-Alder reaction between furan **6** and tetrabromocyclopentene (TBCP) **5** and the following step.
- The stereoselectivity of the ether bridge is controlled by the configuration of C4.
- Bromoenone **8a** was obtained as the major regioisomer (**8a**:**8b** = 3.3:1) because of steric hindrance at C11 of cation **7**.

2-2. Functionalization of bromoenone 3 (compound 3 to compound 2)

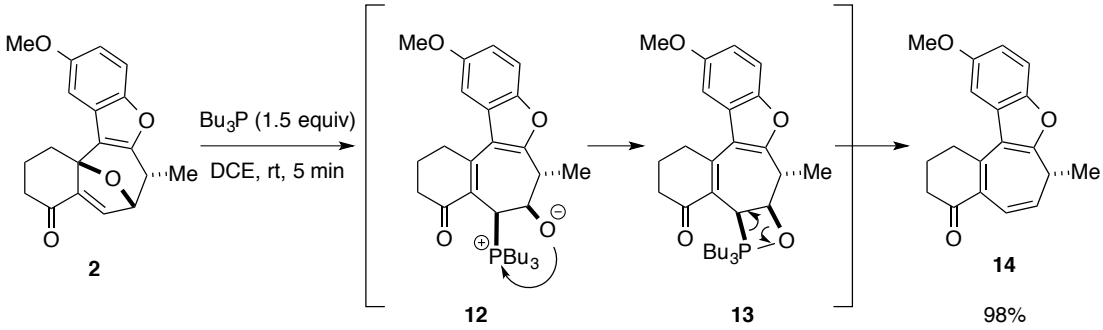
Scheme 3. Synthesis of ether bridged furan **2**



- Stereoselective hydrogenation controlled by ether bridged bending 7-membered ring gave compound **11**.
- Compound **11** had *R*-configuration at C8 center, confirmed by the single crystal XRD analysis.

2-3. Opening of the ether bridge (compound **2** to compound **15**) **(Key step 2)**

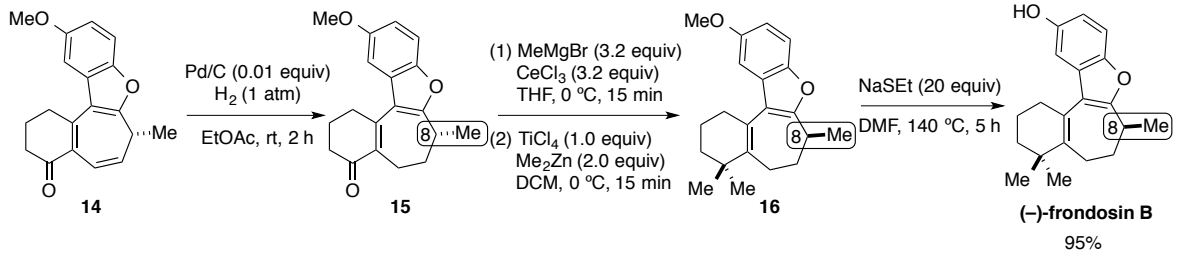
Scheme 4. Phosphine-induced elimination of ether bridge



- Bu_3P attacked on β-carbon from *exo*-face then gave cation **12**.
- Cation **12** immediately formed a 4-membered ring then the phosphine oxide was eliminated.
- The process similar to Wittig reaction afforded the desired olefin **14**.

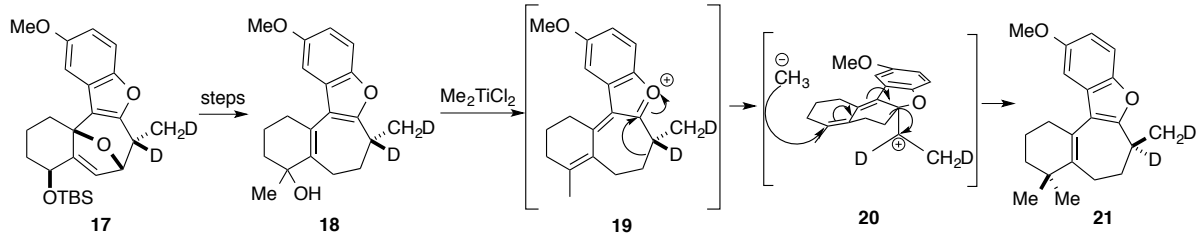
2-4. Unusual inversion of C8 center (compound **15** to (–)-frondosin B)

Scheme 5. Synthesis from compound **15** to (–)-frondosin B



- The stereochemical inversion of C8 was observed.
- The same inversion was reported in the previous work[3], but the mechanism was not revealed.
- Due to the inversion, not **(+)**-frondosin B but **(–)**-frondosin B was obtained (15 steps from compound **4**, 19 %).
- Deuterium labeling experiments revealed that the inversion ocurred in the last methylation step.

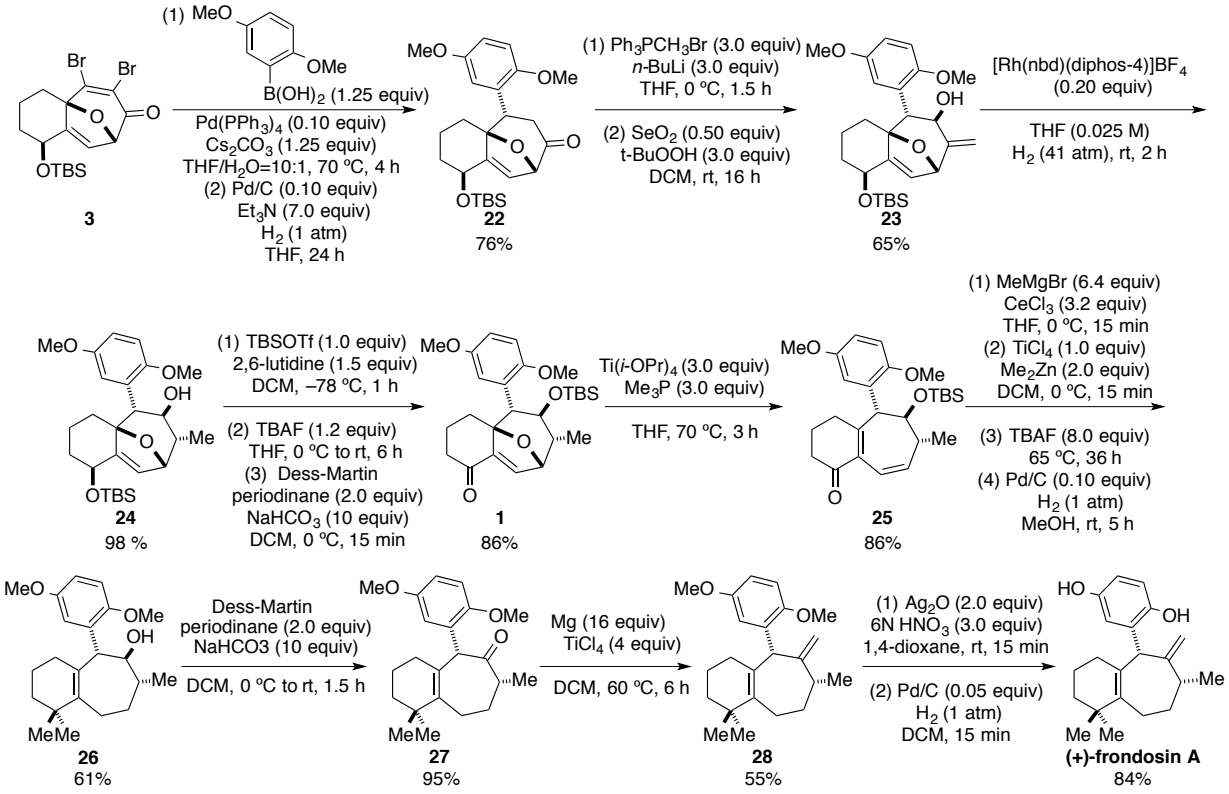
Scheme 6. Deuterium labeling experiments



- CH_2D-group on the cation **21** turned toward the *exo*-direction, then the following S_N2-like reaction on cation **20** caused the inversion.
- The hypothesis said that the inversion is caused by the extended conjugation system of compound **16**.
- (+)-frondosin was obtained by introducing *R*-configuration to compound **4** by using (*R*,*R*)-Noyori catalyst in advance.

2-5. Total Synthesis of (+)-frondosin A

Scheme 7. Synthesis of (+)-frondosin A from bromoenone **3**



- (+)-frondosin A was also synthesized from compound **3** (21 steps from compound **4**, 5 %).
- Opening the ether bridge was conducted by using $Ti(O^iPr)_4$ as a Lewis acid and using Me_3P as a more nucleophile phosphine.
- No inversion at C8 was observed in the synthesis process of frondosin A.

  ⇒This fact supports the hypothesis that the inversion of C8 was due to the extended conjugated system of frondosin B.

3. Conclusion

- The authors obtained (+)-frondosin A and (+)-frondosin B from bromoenone **3**, the same precursor.
- The authors confirmed the mechanism of the unusual inversion of configuration, and established the enantioselective synthesis of frondosin A and frondosin B.

4. Reference

(1) M. Inoue, A. J. Frontier and S. J. Danishefsky, *Angew. Chem., Int. Ed.* **2000**, *39*, 761.
(2) B. M. Trost, Y. Hu and D. B. Horne, *J. Am. Chem. Soc.* **2007**, *129*, 11781.
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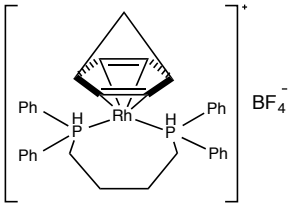
5. Appendix



[Rh(nbd)(diphos-4)]BF_4