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# A Highly Efficient Synthesis of the FGH Ring of Micrandilactone A. Application of Thioureas as Ligands in the Co-catalyzed Pauson–Khand Reaction and Pd-Catalyzed Carbonylative Annulation

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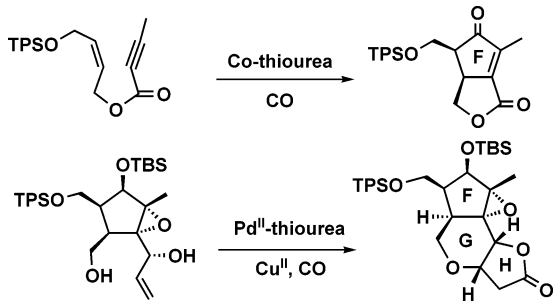
## ABSTRACT




**The functionalized FGH ring system of micrandilactone A was successfully constructed in high selectivity and good yields. The key reactions in our strategy are the Co–thiourea-catalyzed stereoselective, intramolecular Pauson–Khand reaction and Pd–thiourea-catalyzed stereoselective, intramolecular annulation.**

Micrandilactone A (**1**) (Figure 1) was isolated from *Scutellaria micrantha*, a medicinal plant native to Yunnan province of China, which was traditionally used for the treatment of rheumatic lumbago and traumatic injury and related diseases. The structure of micrandilactone A (**1**) has been confirmed by spectroscopic data in conjunction with a single-crystal X-ray analysis.[1]

Micrandilactone A (**1**) is distinguished by its novel triterpene framework, and a dense pattern of oxygenated functionality. The molecule is bounded by 27 atoms of carbon and oxygen. Thirteen carbons are stereogenic, and 14 carbons bear some forms of oxygenation. The biosynthetically modified eight-membered D ring linked by a ketal presents the potential problem for its synthesis with regard to its unfavorable entropy, bond angle deformations, and

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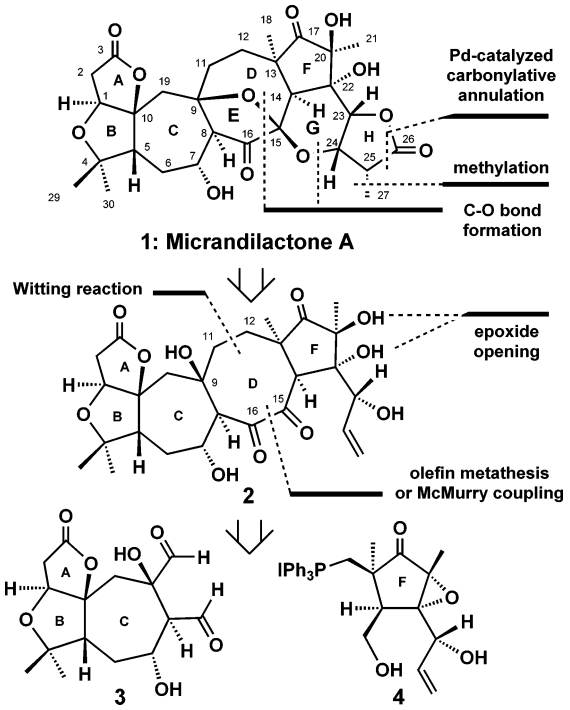



**Figure 1.** Retrosynthetic analysis of micrandilactone A.

destabilizing transannular interactions created by this medium sized ring.[2] Therefore, micrandilactone A (**1**) is a challenging and attractive target for total synthesis.

Figure 1 shows the bond disconnections that lead to a convergent strategy employed in our synthetic program. Retrosynthetic disassembly of micrandilactone A (**1**) leads to **2** by cleavage of three C−O bands and two C−C bonds. Synthetically, these bonds could be assembled by a tandem ketalization and the Pd-catalyzed carbonylative annulation, followed by methylation to install the methyl group at C-25. Compound **2** in turn could be retrosynthetically traced back to **3** and **4**, which have the necessary functionalities to affect the subsequent union of **3** and **4** through the Wittig reaction to form the top C11−C12 bond, and the olefin metathesis[3] or McMurry[4] coupling to form the bottom C15−C16 bond of the eight-membered D ring. Thus, the resulting D ring could be utilized to construct diketone **2**.

We report herein an efficient synthetic approach to stereoselectively construct the framework of FGH ring (Figure 2), featuring the Co−thiourea-catalyzed intramolecular Pauson−Khand reaction (PKR),[5] and the Pd−thiourea-catalyzed tandem alkoxycarbonylation.[6] The demonstrated chemistries illustrate the feasibility of our proposed synthetic strategy toward the total synthesis of micrandilactone A.

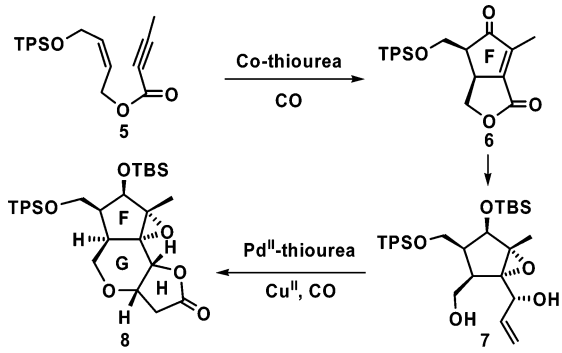
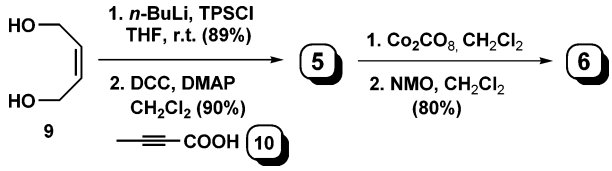



**Figure 2.** Synthesis of FGH ring **8**.

Scheme 1 summarized the synthesis of **6** by the Co-mediated PKR. The synthesis of enyne **5** commenced with

**Scheme 1.** $Co_2CO_8$-Mediated PKR To Synthesize **6**




diol **9**, which was first protected as its mono-TPS ether, and then reacted with acid **10**. Thus, **6** was obtained in 80% yield by treatment of **5** with $Co_2CO_8$ (1.2 equiv).[7]

However, there were two major issues associated with this PKR. First, although the above Co-mediated intramolecular PKR works well, an excess amount of $Co_2CO_8$ had to be used to ensure high yield, which is too expensive for total synthesis. Second, the quality of commercially available $Co_2CO_8$ is sometimes unreliable, making it difficult to use for a large-scale synthesis.

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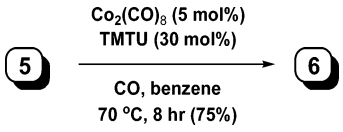
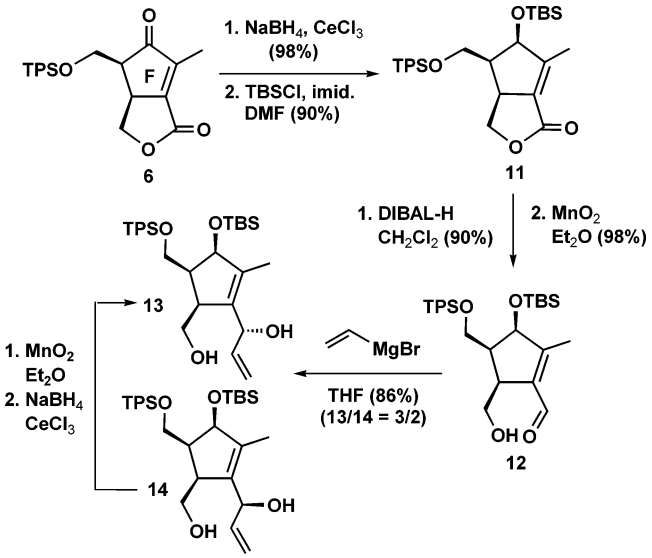
We recently reported that thiourea is an effective ligand in the Pd-catalyzed carbonylation reactions.[8] The observed beneficial effect of thiourea as a ligand to incorporate CO into scaffolds prompted us to apply it in the catalytic PKR. To this end, we identified TMTU (tetramethyl thiourea) as an effective ligand in the co-catalyzed PKR,[9] and under the optimal conditions **6** was obtained in 75% yield (Scheme 2).

**Scheme 2.** Pd−Thiourea-Catalyzed PKR To Synthesize **6**



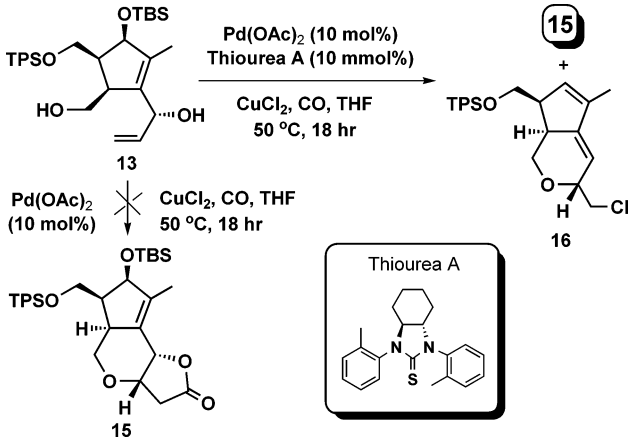

Realizing an effective way to synthesize **6**, we started to work on the construction of FGH ring **8** (Figure 2). To this end, **6** was first converted to its corresponding alcohol by Luche reduction and then silylated with TBSCl and imidazole to give **11** in 89% overall yield. Compound **11** was further reduced with DIBAL-H, and the resulting alcohol was oxidized with $MnO_2$ in $Et_2O$ to give aldehyde **12**. Vinylation of **12** with vinylmagnesium bromide afforded **13** and **14** in 86% yield as diastereoisomers. The stereochemistry of **13** was established by a NMR study of its derivative (see the Supporting Information for details), and its counterpart **14** was converted to **13** by an oxidation−reduction process (Scheme 3).

**Scheme 3.** Synthesis of Compound **13**




With **13** in hand, we then tested its Pd-catalyzed carbonylative cyclization. However, our attempts to obtain **15** from **13** (Scheme 4) under the previously reported catalytic system[10] in THF under atmospheric pressure of CO at 50 °C were unsuccessful due to complete decomposition of **13**.

**Scheme 4.** Carbonylative Annulation of **13**

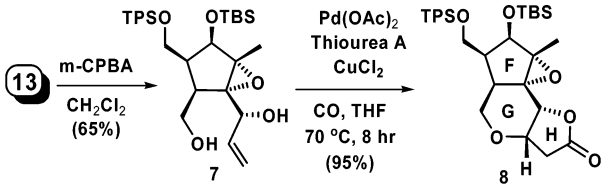



This failure led us to explore thioureas A[11] (Scheme 4) as a ligand in this Pd-catalyzed carbonylative annulation due to its successful employment in our carbonylative reactions.[8c,8d]

The reaction proceeded as indicated in Scheme 4. As expected, the desired product **15** was formed in 25% yield, together with 30% of **16**. Though a variety of conditions were screened, no improvement was observed. Interestingly, when we used **14** as a substrate, **16** was formed exclusively under identical conditions.

Based on our proposed mechanistic interpretation,[12] the double bond in cyclopentene **13** seems to be detrimental to the desired reaction, and its removal would be beneficial. Thus, we transformed **13** into its corresponding epoxide **7** by regioselective epoxidation with *m*-CPBA in $CH_2Cl_2$. To our delight, compound **8** was obtained in 95% yield (Scheme 5) when **7** was reacted under the optimized carbonylative conditions (see the Supporting Information).

**Scheme 5.** Synthesis of Compound **8**




The stereochemistryof the synthesized compound **8** was confirmed by spectroscopic data in conjunction with single-crystal X-ray analysis (Figure 3).

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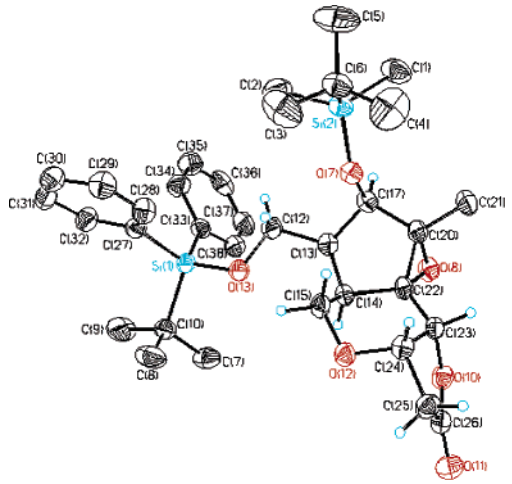
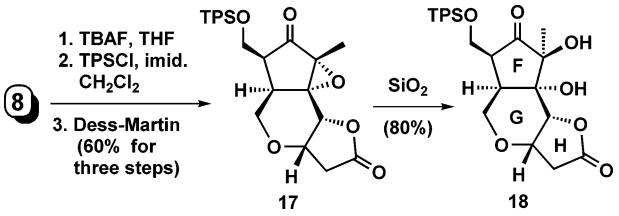


**Figure 3.** X-ray structure of compound **8**.

We then moved to the stage to construct **18** with the essential functionalities presented in FGH ring of micrandilactone A. To achieve a mild condition to generate diol **18** from its epoxide precursor **8**, we first carried out desilylation, and the resulting primary alcohol was then selectively protected as its silyl ether. Thus, the remained secondary alcohol could be selectively oxidized to ketone **17** by Dess−Martin periodide. As a result, this activated epoxide ring opened fairly easily, and the reaction was expected to occur through the $S_N2$-type *trans*-opening to give the diol **18** by treatment of **17** with silica gel (Scheme 6).[13]

**Scheme 6.** Synthesis of Compound **8b**




In summary, a convergent approach for the construction of the FGH ring system of micrandilactone A (3 rings, 6 stereogeneic carbons including 2 quartery carbons) was successfully accomplished in 15 steps. We demonstrated the unique role of thioureas in the co-catalyzed stereoselective, intramolecular PKR and the Pd-catalyzed stereoselective, intramolecular alkoxycarbonylation. The illustrated chemistries show the feasibility of our proposed strategy toward the total synthesis of micrandilactone A, which is currently underway in our laboratories.

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**Supporting Information Available:** Experimental procedure and NMR and $^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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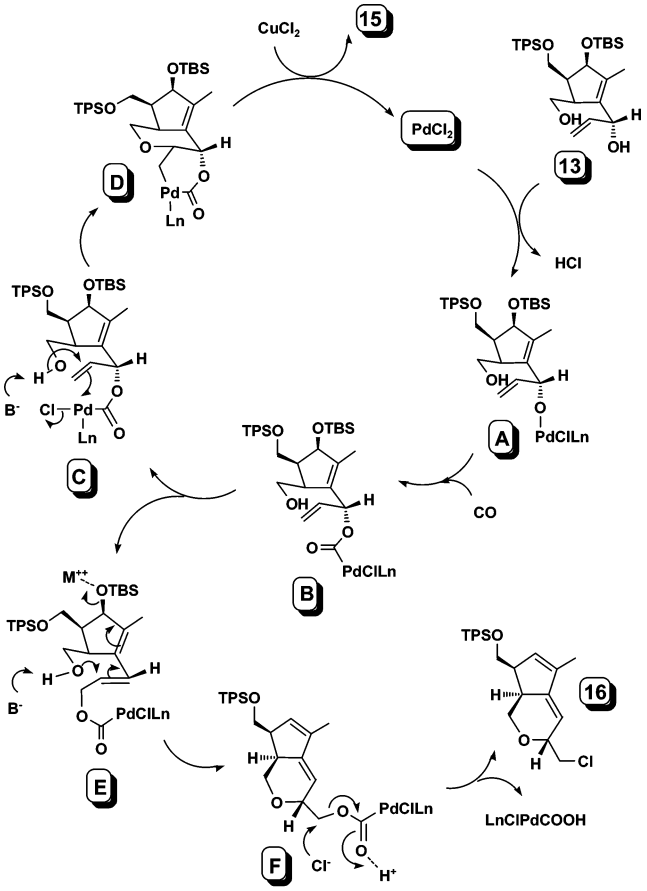
(12) To understand the formation of compounds **15** and **16**, we proposed the following catalytic cycle. Although less evident. we speculated that the overall process for the formation of **15** may involve the attack of **13** on the $PdCl_2$ to generate complex **A**, followed by insertion of CO to give intermediate **B**. Intramolecular nucleophilic addition of the primary alcohol to the resulting acylpalladium complex **B** leads to formation of intermediate **D** through **C**, which might undergo reductive elimination to produce the five-membered lactone **15** and palladium(0). The palladium(0) is then oxidized with $CuCl_2$ to palladium(II), completing the catalytic cycle. On the other hand, the resulting intermediate **B** in the above catalytic cycle might also competitively undergo the allylic rearrangement to afford **E**, which could lead to formation of **16** through the downstream addition−elimination process, followed by chloride displacement of the activated homoallylic alcohol **F**. The proposed catalytic cycle is shown below:




The proposed catalytic cycle

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