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Application of RCM Reaction in the Construction of ABC Ring of Micrandilactone A

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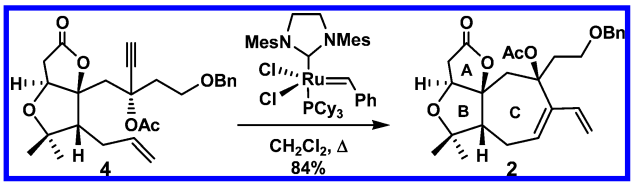
ABSTRACT



The functionalized ABC ring system of micrandilactone A was successfully constructed in 14 steps. The key reactions in this synthesis are the intermolecular Diels–Alder reaction (IMDA) and the eneyne ring-closing metathesis (RCM) reaction.

In our previous communication,[1] we discussed a convergent synthetic strategy for the total synthesis of micrandilactone A (**1**)[2] (Figure 1) and reported the synthesis of the FGH fragment **3**, using a Co-TMTU catalyzed PKR[3] and a Pd-thiourea catalyzed carbonylative annulation reaction.[4] Clearly, our next goals were to find efficient ways to construct the ABC fragment **2** and to assemble the polycyclic central unit of micrandilactone A.

We report herein our recent progress on the construction of the ABC ring system **2** by an intermolecular Diels−Alder reaction and an eneyne RCM process. The reported strategy has allowed the synthesis of this fragment (Scheme 1) with complete stereochemical control of the stereogenic centers and has demonstrated the feasibility of using the eneyne RCM reaction[5] for constructing the ABC ring system of micrandilactone A.

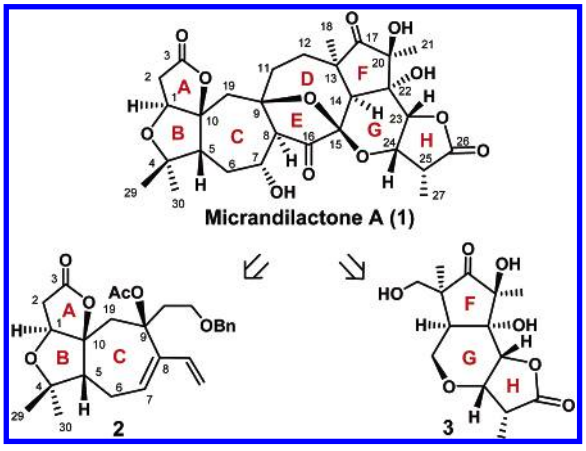


Figure 1. General retrosynthetic analysis.

Eneyne RCM has become one of the important methods for constructing cyclic molecules of various sizes in recent years.[6] Because ruthenium carbene complexes[7] not only exhibit high synthetic efficiency and activity but also tolerate

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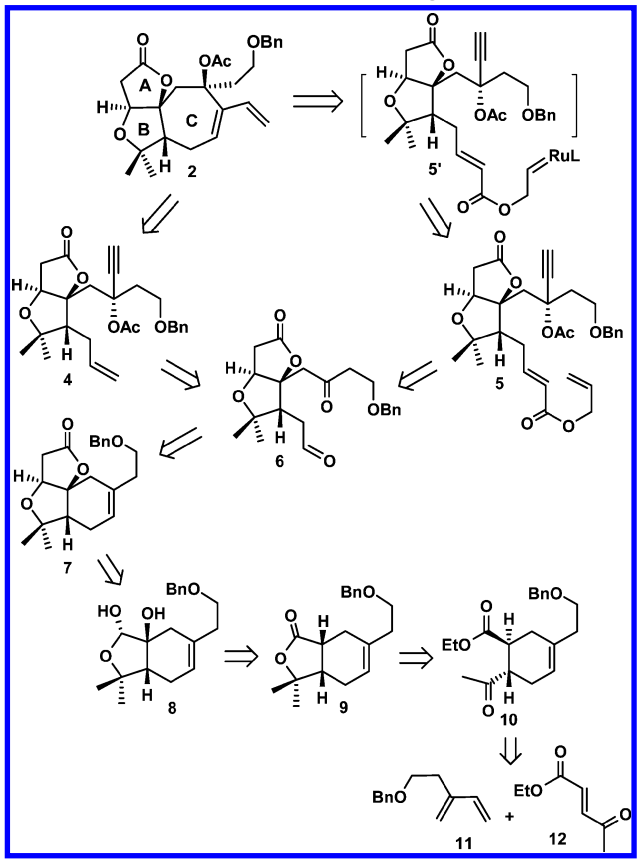
a range of functional groups, we therefore decided to synthesize the ABC fragment **2** via this approach. With regard to our target molecule **2**, we hoped that its seven-membered ring could be formed either by eneyne RCM[8] from substrate **4** or relay eneyne RCM[9] from substrate **5** (Scheme 1).

Scheme 1. General Strategy for the Construction of Functionalized ABC Ring **2**

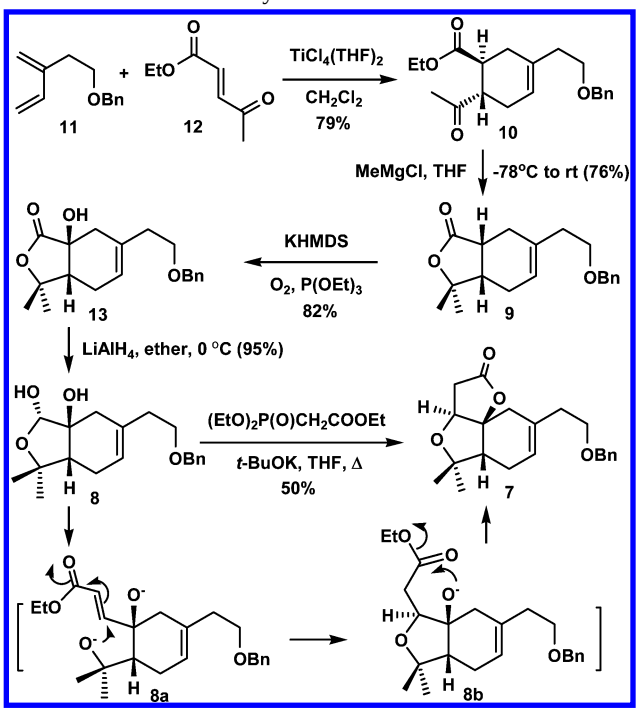


Retrosynthetically, we believed that substrates **4** and **5** could be generated from the same aldehyde **6** via olefinations; **6** in turn could potentially be derived from **7** via ozonolysis. Thus the stereoselective construction of tricyclic lactone **7** would be a crucial step. We expected that the reaction of lactol **8** with a Wittig−Horner reagent would potentially form the lactone **7** through a process that might involve sequential Wittig reaction, 1,4-addition, and lactonization[10] (see Scheme 2 for detail).

We also envisaged that lactol **8** could be derived from its precursor **9** by a two-step sequence involving stereoselective oxidative insertion of a tertiary hydroxyl group and selective reduction to the lactol. The conversion of **10** to **9** could easily be achieved by first treating ketoester **10** with MeMgCl and then effecting an intramolecular lactonization. Thus our proposed synthesis was reduced to the construction of ketoester **10**,[11] an important building block with *trans* dicarbonyl groups, which was expected to be available through the intermolecular Diels−Alder reaction of diene **11** with dienophile **12**.

Scheme 2 summarizes the synthesis of compound **7**. The intermolecular Diels−Alder reaction of diene **11** with dienophile **12** was carried out with $TiCl_4(THF)_2$ complex as a catalyst,[12] and product **10** was obtained regioselectively in 79% yield. Reaction of ketone **10** with MeMgCl in THF

Scheme 2. Synthesis of Intermediate **7**



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resulted in the formation of lactone **9** in 76% yield through an intramolecular lactonization process.

To introduce the tertiary hydroxyl group, lactone **9** was first treated with KHMDS and then reacted with O_2 in the presence of $P(OEt)_3$[13] to generate **13** in 82% yield. To obtain the tricyclic product **7**, compound **13** was first selectively reduced to lactol **8** with $LiAlH_4$ and then reacted with $(EtO)_2P(O)CH_2COOEt$ in the presence of *t*-BuOK to give the desired product **7** in 50% yield. The reaction course was believed to proceed through a tandem process involving intermediates **8a** and **8b** (Scheme 2).The stereochemistry of compound **7** was determined by ^1H NMR and NOE experiments (Figure 2).

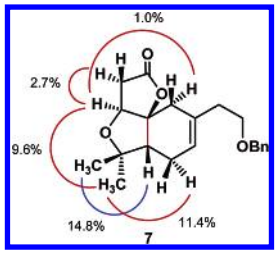
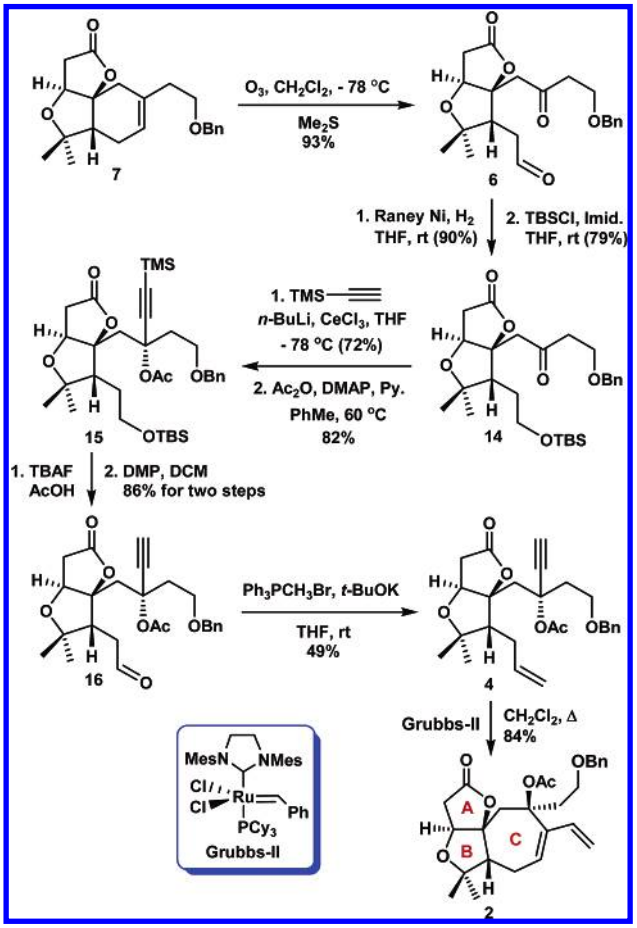


Figure 2. Diagnostic NOE Data for ABC ring **7**.

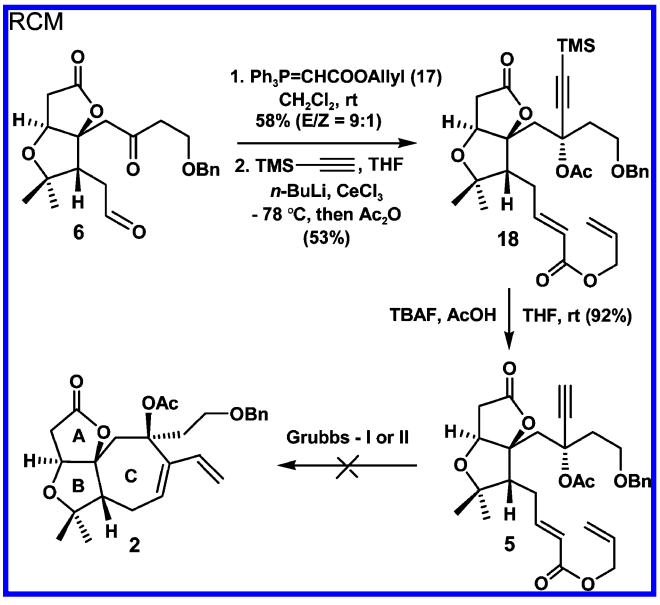
With compound **7** in hand, construction of the target substrate **2** proceeded expediently, as shown in Scheme 3. Ozonolysis of compound **7**, followed by reduction with Me_2S gave keto aldehyde **6** in 93% yield. Reduction of **6** in the presence of Raney Ni catalyst in THF furnished an alcohol (90% yield), which was converted to TBS ether **14** by the action of TBSCl-imidazole (imid) in 79% yield. Ketone **14** was then treated with lithium TMS acetylide in the presence of a catalytic amount of $CeCl_3$ at −78 °C to give a tertiary alcohol, and the latter compound was converted into its acetate **15** in 43% yield for the two steps. Desilylation of **15** with TBAF/AcOH resulted in the formation of a primary alcohol, which was converted into the aldehyde **16** by treatment with Dess−Martin periodinane (DMP) (86% yield for the two steps). Coupling of the ylide derived from phosphonium salt Ph_3PCH_3Br (*t*-BuOK, THF) with aldehyde **16** gave the desired olefin **4** in 49% yield. The low yield was presumably caused by enolization of the aldehyde moiety in compound **16** due to the basicity[14] of the Wittig reagent used.

Scheme 3. Synthesis of Compound **2**



We now started to investigate the proposed eneyne RCM and relay eneyne RCM reaction. Upon treatment of compound **4** with the first generation Grubbs catalyst, the starting

Scheme 4. Attempted Synthesis of **2** by the Relay Enyne RCM



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material was recovered. However, when the second generation Grubbs catalyst was employed, the desired product **2** was formed in 84% yield.

We then started to evaluate compound **5** as a substrate for obtaining **2** by the relay eneyne RCM reaction. To this end, compound **6** was treated with the Wittig reagent **17** (Scheme 4) and then reacted with lithium TMS-acetylide, followed by acetylation with Ac_2O. Then, after removal of TMS, the generated eneyne **5** was treated with the catalysts of Grubbs-1 and Grubbs-2, respectively. Unfortunately, the expected cyclized product **2** could not be identified under a variety of reaction conditions.

In summary, we have achieved a stereocontrolled synthesis of the ABC fragment of micrandilactone A (**1**). The key steps are the intermolecular Diels−Alder reaction and the eneyne RCM reaction. Model studies to assemble the polycyclic central unit of micrandilactone A (**1**) are currently underway in our lab and will be disclosed in due course.

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Supporting Information Available: Experimental procedure and ^1H 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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