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Construction of the A ring of halichomycin via a RCM strategy

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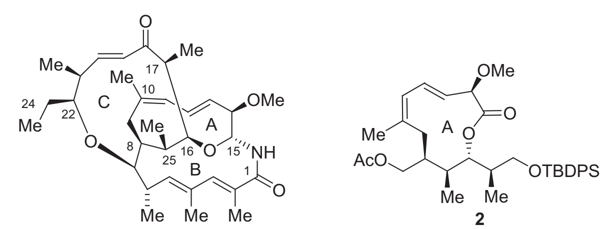
ABSTRACT

Attempts to the synthesis of the A ring of halichomycin via ring-closing metathesis (RCM) reaction were investigated. When triene **5** was used as the precursor of cyclization, only unexpected byproduct aldehyde **17** was obtained. When diene **6** was used as the precursor of cyclization, the desired product **20** was obtained in reasonable yield. This work demonstrated that both modification of the substrate and the RCM reaction conditions are important for obtaining the desired 11-membered macrocycle in reasonable yield.

Halichomycin is produced by a strain of *Streptomyces hygroscopicus*, which was isolated from the gastrointestinal tract of the marine fish *Halichoeres bleekeri* (Fig. 1).[1] It exhibits potent cytotoxicity (ED_{50} 0.13 μg/mL) against a murine P388 lymphocytic leukemia cell line, and has potential use as an anticancer drug. Halichomycin contains a structurally unique tricyclic macrolactam, which includes an 11/13-membered bicyclic hemimacrolactam (AB ring) and a fully functionalized 11-membered ether ring (C ring). It also has 10 stereocenters including six contiguous stereocenters, and five double bonds.

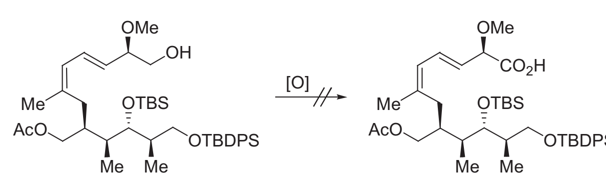
The total synthesis of halichomycin is highly challenging because of the overall complexity of the molecule. There are only a few groups that have reported its synthetic studies.[2] Our group has been actively studying the synthesis of halichomycin and reported an efficient and convergent synthesis of the C5–C18 fragment of halichomycin.[2c] However, our attempts to construct its A ring (**2**) via macrolactonization failed. The main problem was that the oxidation of alcohol **3** could not provide the desired macrocyclization precursor acid **4** (Scheme 1).[3] Considering no report on the construction of any single ring of this molecule has been published so far, we decided to explore an alternative strategy for the construction of the A ring of halichomycin.

Ring-closing metathesis (RCM) has become a ubiquitous tool for the synthesis of carbon- and heterocylic ring systems, and it is particularly well-suited for the efficient synthesis of macrocycles as an alternative to the classic macrolactonization approach.[4] However, applications of RCM to construct 11-membered macrocycles remain scarce and sometimes with rather low yield.[5] Moreover, the selectivity is dependent upon many factors, such as ring size and position of the olefin.[5a–c,e–g] Herein, we report the construction of the A ring of halichomycin via a RCM strategy.



halichomycin (**1**)   **2**

Figure 1. Structures of halichomycin and A ring of halichomycin.



3   **4**

Scheme 1. Our failed macrocyclization approach.

Retrosynthetic analysis of the A ring system (**2**) is shown in Scheme 2. In view of the existing conjugated dienes in compound **2**, we envisioned that the conjugated diene could be formed by 1,3-diene-ene RCM from compound **5** with simultaneous formation of the macrocycle. Although there are a few reports on the construction of macrocycles via 1,3-diene-ene RCM strategy, no such formation of 11-membered macrocycle is reported in the literature.[6] Given that RCM of the conjugated diene might lead to four differ-

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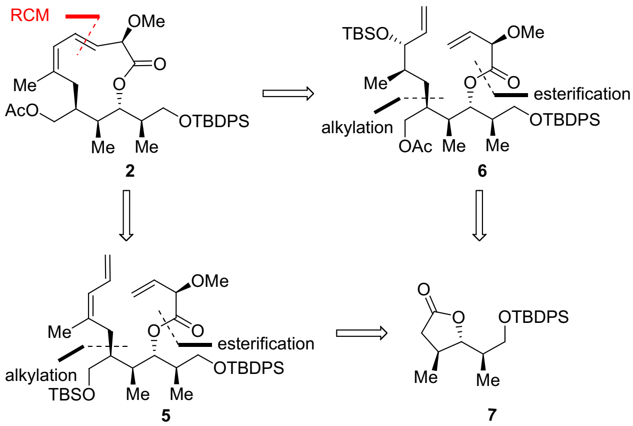


Scheme 2. Retrosynthetic analysis.

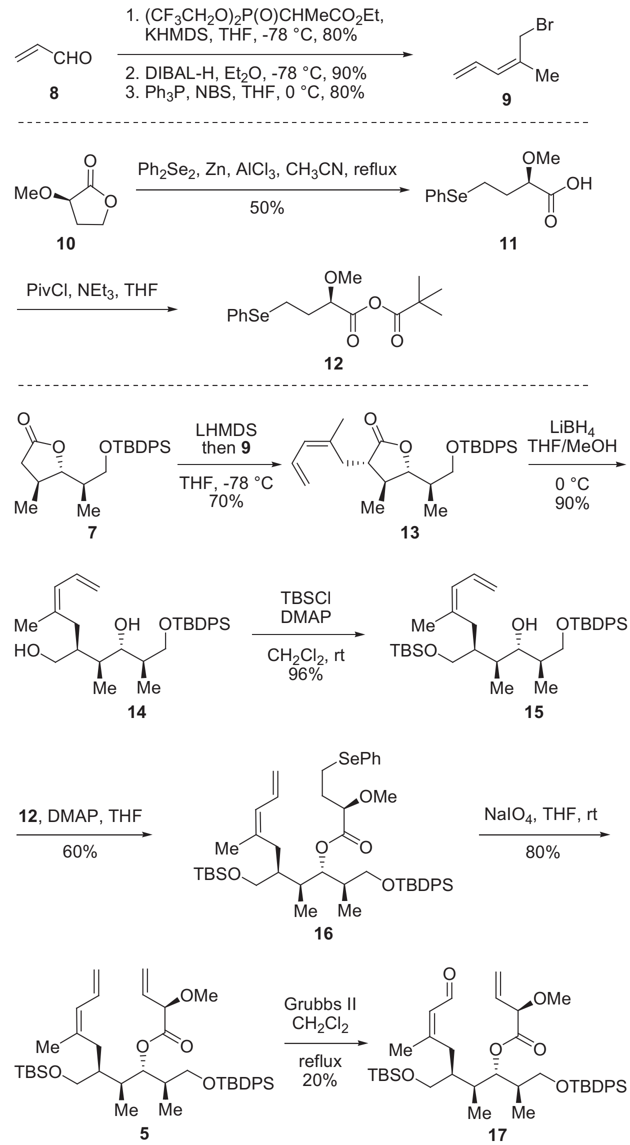
ent products (9- vs 11-membered ring and *cis*/*trans* isomers) and the conformation of the open-chain precursor could affect the RCM reaction, the masked conjugated diene **6** could be used as a cyclization precursor. Elimination of the hydroxyl group could generate a double bond after the RCM. Both compounds **5** and **6** could be prepared from the known compound **7**[2c] by sequential alkylation, reduction, selective mono-protection, and esterification.

Our first attempt to construct the A ring used triene **5** as the starting material since this route is short and can provide additional insights into the preparation of the 11-membered macrocycle containing conjugated diene. Our synthesis commenced with the preparation of dienylic bromide **9** and acid **11** as illustrated in Scheme 3. The dienylic bromide **9** was synthesized by a sequence of Still–Gennari's olefination,[7] reduction with DIBAL-H, and bromination. The acid **11** was prepared from the known lactone **10**, which is prepared from D-malic acid as reported in the literature.[8] Treatment of lactone **10** with $(PhSe)_2$ in the presence of $Zn/AlCl_3$ gave the corresponding acid **11** in 50% yield.[9]

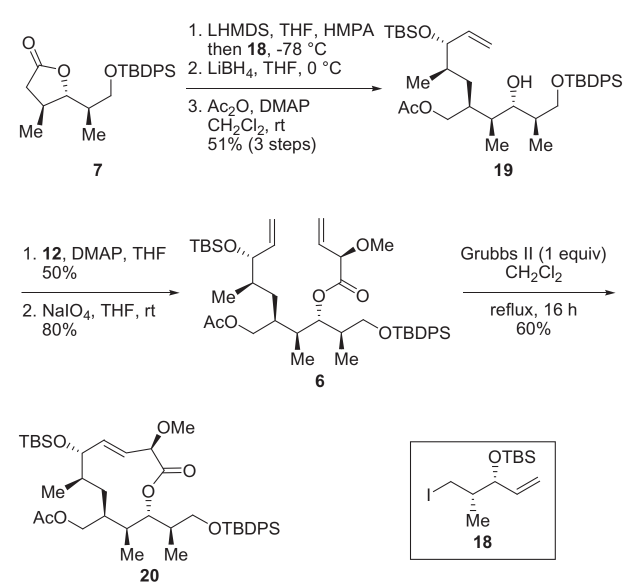
With three key fragments in hand, we investigated the synthesis of compound **5**. α-Alkylation of lactone **7** with dienylic bromide **9** smoothly afforded the desired coupling product **13**. Reduction of lactone **13** with lithium borohydride followed by selective protection of primary alcohol using TBSCl gave secondary alcohol **15**. Direct esterification of alcohol **15** and acid **11** under standard coupling conditions gave the desired ester **16** in low yield. To improve the yield, we investigated the DMAP-catalyzed method for mixed-anhydride acylation of alcohols recently developed by Ishihara.[10] Thus, acid **11** reacting with pivaloyl chloride in the presence of Et_3N provided the desired anhydride **12**, which was directly coupled with alcohol **15** under DMAP-catalyzed conditions to afford the desired ester **16** in 60% yield. The oxidative elimination of phenyl selenide in **16** with H_2O_2 provided the target triene **5** in only 30% yield.[11] Gratefully, when $NaIO_4$ was used as the oxidant, compound **5** could be obtained in 80% yield.[12]

Having succeeded in the synthesis of the cyclization precursor triene **5**, the stage was set for the RCM reaction. Compound **5** was treated with the second generation Grubbs catalyst (20% mol) in CH_2Cl_2 at reflux for 24 h. Interestingly, no desired cyclization product was observed; instead, the aldehyde **16** was isolated in 20% yield along with 20% of starting material. Literature search showed aldehyde as a byproduct of RCM reaction has already been reported.[13] A variety of RCM reaction conditions was further screened, including catalysts, solvents, and additives. However, no desired cyclization product was obtained.

We reasoned that the conformation of the backbone must have a profound influence on the outcomes of the RCM reaction. Therefore, we turned our attention to use compound **6** as the starting



Scheme 3. Synthesis of trienes **5** and failed RCM.



Scheme 4. Synthesis of A ring of halichomycin.

material of RCM, in which the (*Z*)-olefin was masked as a hydroxy group.

To prepare compound **6**, the iodide fragment **18** was needed, which was prepared following the protocol of Parthasarathi.[14] The chirally pure **18** was used as the starting material to decrease the number of diastereoisomers after α-alkylation, thus facilitating the synthesis. Compound **6** was quickly obtained following the same synthetic route as described for **5** (Scheme 4). However, two issues should be addressed: (1) the addition of HMPA was needed for the α-alkylation of lactone **7** with iodide **18**, which could dramatically increase the yield; (2) the primary alcohol was protected with the acetyl group in order to facilitate the later transformation of the hydroxy group.

Treatment of **6** with 20% mol of Grubbs' second-generation catalyst in CH_2Cl_2 at reflux successfully provided the expected (E)-20 as an exclusive isomer, but in 10% yield. In fact, it is a certain challenge to carry out RCM reaction with such a highly functionalized substrate. After several trials, we found that the addition of 25% mol Grubbs' second-generation catalyst to the reaction every 4 h (repeated 3 times) afforded the desired product **20** in 60% yield. It is of particular note that no (*Z*)-product and dimer product was detected.

In summary, synthesis of the A ring of halichomycin via ring-closing metathesis (RCM) reaction was investigated. When triene **5** was used as the precursor of cyclization, only unexpected byproduct aldehyde **17** was obtained. When diene **6** was used as the precursor of cyclization, the desired product **20** was obtained in reasonable yield. This work demonstrated that both modification of the substrate and the RCM reaction conditions are important for obtaining the desired 11-membered macrocycle in reasonable yield. Further efforts toward the total synthesis of halichomycin are currently underway in our laboratory and the result will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and data for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.027.

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