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| <b>13. SUPPLEMENTARY NOTES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                         |                                         |                                   |                                                              |                                                  |
| <b>14. ABSTRACT</b><br>The goal of this project is to develop an efficient route to the synthesis of Eleutherobin and its analogues utilizing tandem Diels-Alder and Grob fragmentation strategy. During the first year of the grant, a highly improved synthesis of the key compound for Grob fragmentation study has been accomplished. In addition, two key fragments for an asymmetricsynthesis of Eleutherobin by intramolecular Diels-Alder reaction were prepared in a very concise manner.                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                         |                                         |                                   |                                                              |                                                  |
| <b>15. SUBJECT TERMS</b><br>Eleutherobin, tandem Diels-Alder                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                         |                                         |                                   |                                                              |                                                  |
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| <b>a. REPORT</b><br>U                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <b>b. ABSTRACT</b><br>U | <b>c. THIS PAGE</b><br>U                |                                   |                                                              | <b>USAMRMC</b>                                   |
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## Table of Contents

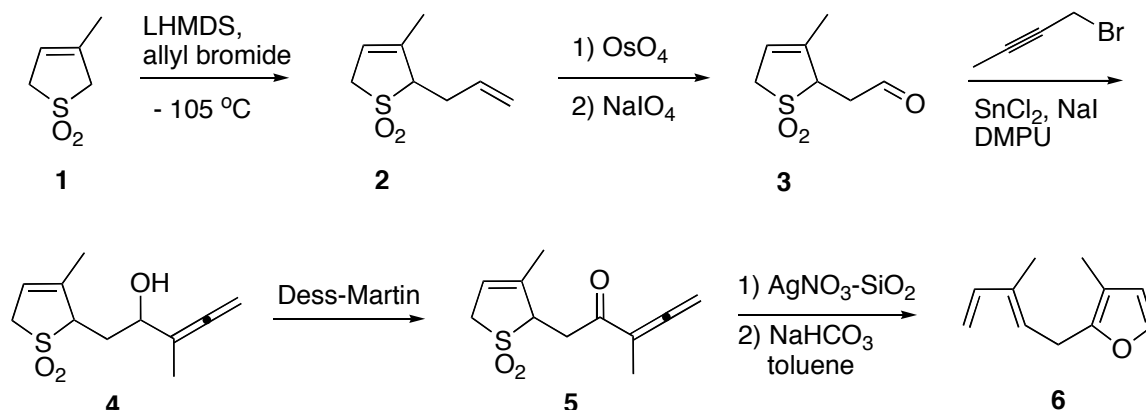
|                                   |   |
|-----------------------------------|---|
| Introduction.....                 | 4 |
| Body.....                         | 4 |
| Key Research Accomplishments..... | 7 |
| Reportable Outcomes.....          | 7 |
| Conclusions.....                  | 7 |
| References.....                   | 8 |
| Appendices.....                   | 8 |

## 1. Introduction

Eleutherobin, a highly potent tubulin-acting agent, has been an interesting target molecule in the treatment of prostate cancer whose current chemotherapeutics may pose a problem of cross-resistance. In addition, development of Eleutherobin analogues based on comparison of the Docetaxel structure could provide prostate cancer specific agent. However, limited availability of this highly active molecule has been a huge problem in the clinical research field and subsequently a highly efficient approach to the synthesis of members of this unique natural product class using the tandem Diels-Alder cycloaddition methodology has been developed in our laboratory. Our aims are as follows: 1) development of efficient synthetic route to Eleutherobin 2) preparation of synthetic analogues of Eleutherobin and their biological activity assay. During the first year of the grant, we have successfully established a route to the advanced intermediate **9**, which is very crucial to the accomplishment of the first aim. Furthermore, an asymmetric approach utilizing intramolecular Diels-Alder reaction was also pursued, which will fortify our current research.

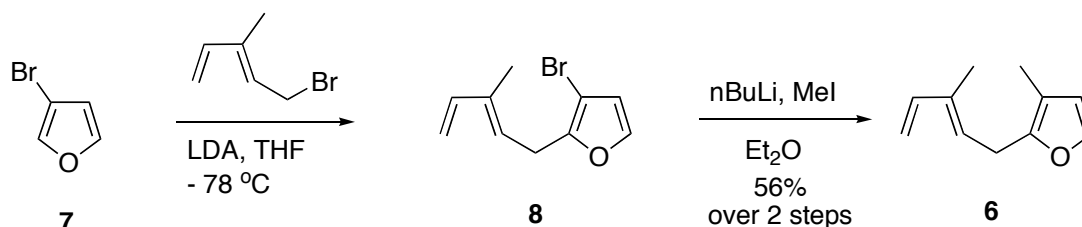
## 2. Body

Previous synthesis of diene **6** as shown in Scheme 1 exhibited a number of problems in its large-scale preparation.<sup>1)</sup> For instance, monoalkylation of the sulfolene **1** was successful only at an extremely low temperature (-105 °C) to prevent dialkylation. Oxidative cleavage of the terminal olefin of allyl sulfolene **2** and the following allenylation step to obtain the allenic alcohol **4** required tedious work-ups to obtain a decent yield. These issues must be resolved to establish a method useful for the large-scale preparation.



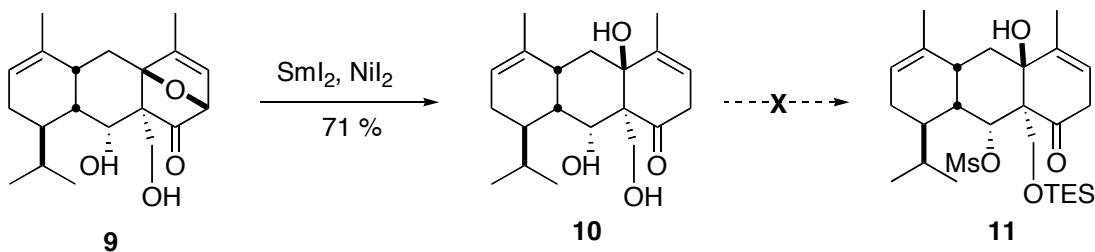
Scheme 1. Previous Synthesis of Diene **6**

Thus, a highly straightforward and facile method to make the desired diene **6** has been developed. As shown in Scheme 2, this improved synthesis utilized the simple alkylation of 3-bromofuran, which was easily obtained in large scale by retro Diels-Alder reaction.<sup>2)</sup> The corresponding dienyl bromide was also obtained without any difficulty from the prenyl alcohol by a series of conventional transformations with SeO<sub>2</sub> oxidation as a key step.<sup>3)</sup> Thus, halogen-directed regioselective alkylation and the following methylation provided the desired diene **6** in 56% yield over only two steps.<sup>4)</sup> With this improved synthesis, diene **6** was prepared in multigrams without the issues encountered previously.



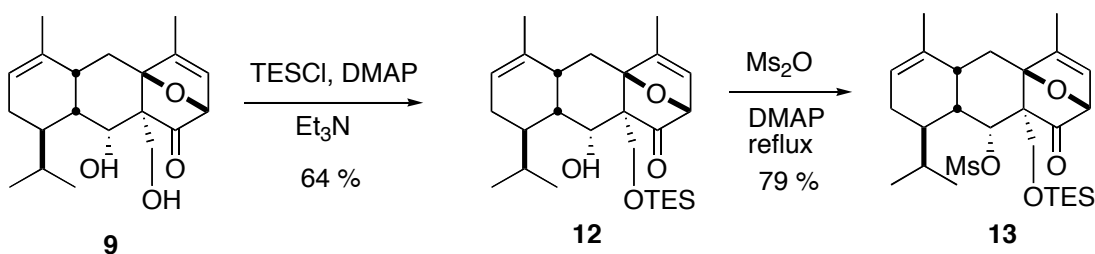
Scheme 2. Improved synthesis of Diene 6

Now that the route towards diol **9** is well secured by the improved synthesis of diene **6**, we first turned our attention to the activation of the secondary hydroxyl group in the triol **10** shown in Scheme 3. Previous attempts to introduce activating group on the secondary alcohol of the triol **10** have failed.



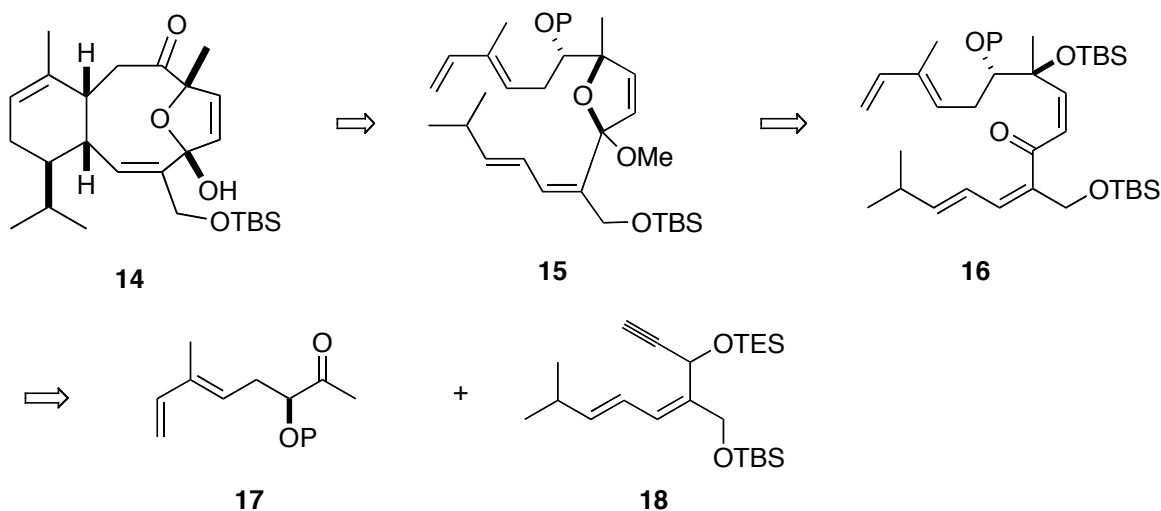
Scheme 3. Previous failure to synthesize the Grob substrate **11**

Thus, we felt that it would be prudent to investigate this issue. Introduction of either a tosyl or a halide group also failed probably due to its sterically congested environment. Fortunately, attachment of mesyl group on the same hydroxyl unit was carried out successfully to provide the key compound **13** needed for the C-O bond cleavage. This success allowed us to approach the desired compound **11** in a very straightforward manner after C-O cleavage reaction of the compound **13**. We hoped that the C-O bond would be cleaved under the SmI<sub>2</sub>-NiI<sub>2</sub> reaction condition considering our previous result as shown in scheme 3. However, we were not able to obtain the desired compound **11** from C-O bond cleavage of the compound **13** under various SmI<sub>2</sub> cleavage conditions. This finding suggested that the C-O bond cleavage reaction was quite sensitive to the substrate structure since the triol **10** was easily obtained from the diol **9** with the naked hydroxyl groups as shown in Scheme 3.



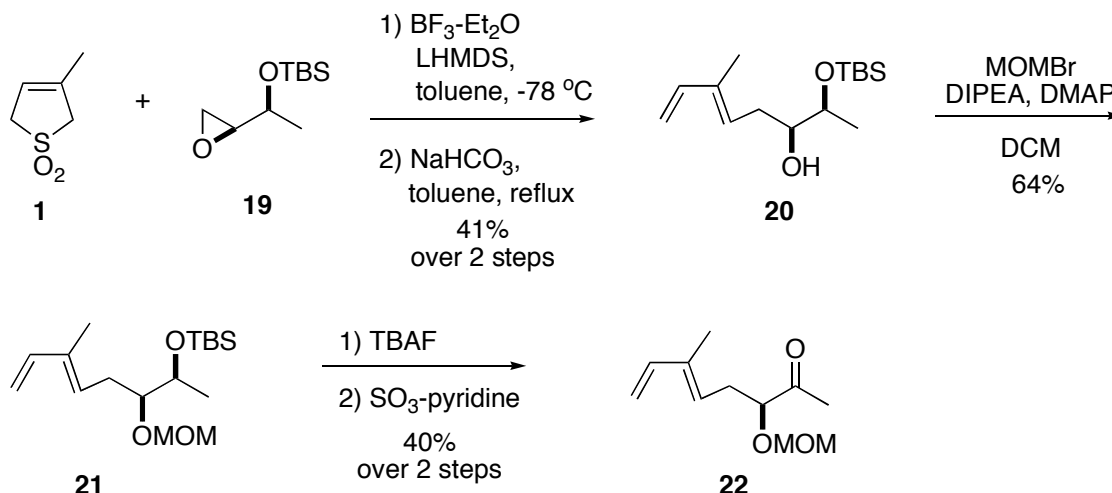
Scheme 4. Successful construction of C-O cleavage reaction substrate **13**

On the other hand, it was conceived that the same Diels-Alder reaction could be applied in asymmetric synthesis of Eleutherobin and this approach has been examined as well. Retrosynthetic pathway of this approach is shown in Scheme 5. Here the same Diels-Alder reaction could be utilized in formation of the desired core structure **14** in a very straightforward manner. In addition, the asymmetric nature of this synthesis will add another great value on our current study for future bioassay.



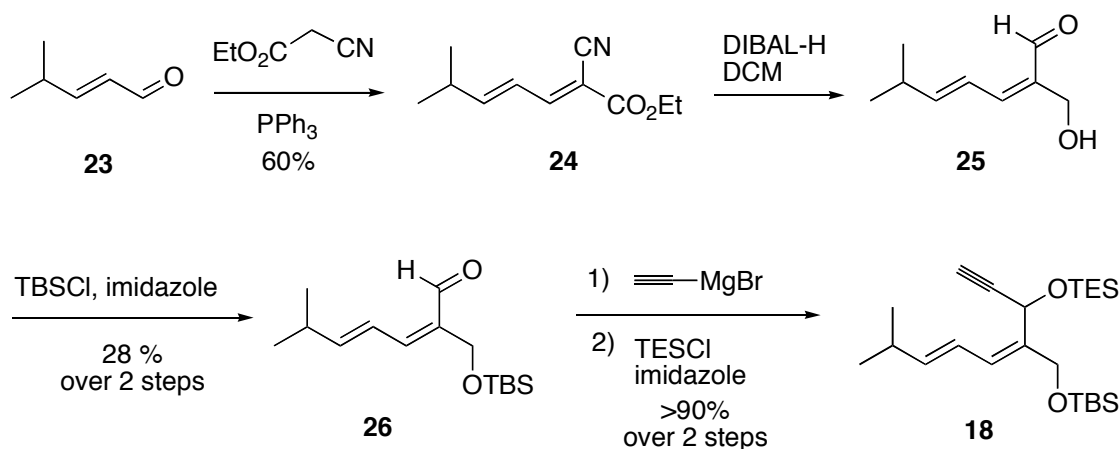
Scheme 5. Retrosynthesis of Eleutherobin core **14** based on asymmetric approach

As shown in Scheme 6, the synthesis of MOM protected diene **22** commenced with the novel epoxide opening reaction of sulfone **1** where the corresponding chiral epoxide **19** was readily available from L-tartaric acid.<sup>5)</sup> The resulting secondary alcohol **20** was converted to the ketone **22** through MOM protection, desilylation and oxidation.

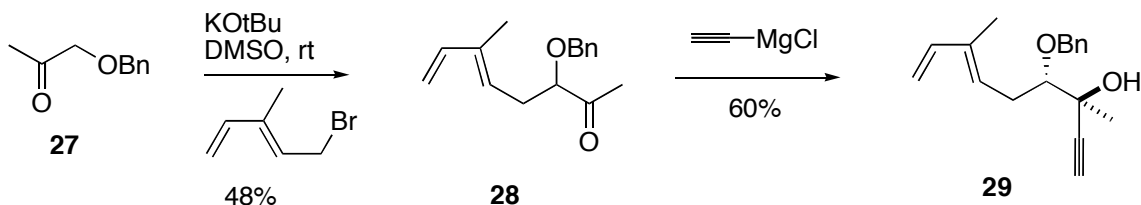


Scheme 6. Synthesis of the top fragment **22**

On the other hand, the commercially available aldehyde **23** was converted into conjugated cyanoester **24** in a highly stereoselective manner as shown in Scheme 7. DIBAL-H reduction yielded the desired aldehyde **26** after TBS protection of the primary alcohol in compound **25** in a fairly low yield.<sup>6)</sup> This reaction condition could be optimized but more importantly, this route was pursued for its brevity and simplicity. Then, the required fragment **18** was synthesized from Grignard addition and TES protection.



Now, the remaining task is the coupling of two fragments **18** and **22** to explore the intramolecular Diels-Alder reaction. As a preliminary result, Grignard addition on the racemic ketone **28** yielded a single stereoisomer. This finding further support our idea that coupling between the compound **18** and **22** would occur in a chelation-controlled fashion to furnish the desired compound **16**. It is also worth mentioning that the benzyl protected diene **28** could be prepared in a racemic form by a simple alkylation reaction as shown in Scheme 8.



### 3. Key Research Accomplishment

- Significantly improved synthesis of one of the key fragments
- Establishment of the synthetic route towards the target molecule **9** for the activation study
- Finding on structure dependence of the  $\text{SmI}_2$  mediated C-O bond cleavage
- Discovery of novel epoxide opening reaction by sulfolene
- Preparation of two key fragments for asymmetric synthesis.

### 4. Reportable outcomes

N/A

### 5. Conclusion

During the first year of the grant, we have established a synthetic route towards the advanced intermediate for studying the Grob fragmentation and large scale preparation of diene **6** is now feasible, which sets the stage of study on the alternate activation as described in the proposal (Task 1). Finding on the structure dependence of C-O bond cleavage reaction gave further insight on this reaction. With the established route to target compound **9**, we will now attempt to do an intensive research on the selective activation for the Grob fragmentation. The asymmetric synthetic route toward Eleutherobin has been also examined, where we are able to prepare two key fragments in a very concise manner.

“So What?”

As a result of the work done over the past 1 year, a highly improved synthetic route to the advanced intermediate was developed. This will provide a well secured way of supplying enough material for further study including synthesis of biologically potent analogues of Eleutherobin. Development of epoxide opening reaction by sulfolene can be utilized in the synthesis of diene-containing natural product precursor synthesis.

## 6. References

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## 7. Appendices

N/A