Total Synthesis and Structural Elucidation of Cryptolatifolione

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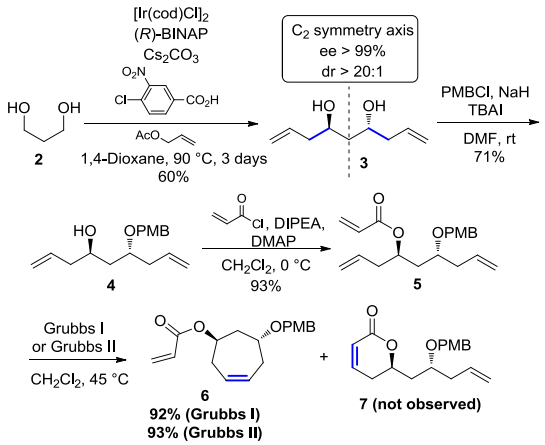
Introduction

Cryptolatifolione (**1**) was first isolated from the bark of *Cryptocarya latifolia* by Wijewardene and coworkers.[1] The authors assigned the stereogenic center at C-6 as *R*, but the absolute configuration at C-8 remains unknown. This work aims the total synthesis of **1** and its epimer at C-8, and the elucidation of the absolute configuration of cryptolatifolione (**1**).

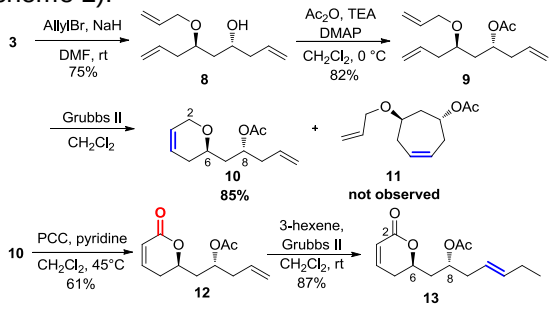
Results and Discussion

Synthesis of acrylate **5** began with the enantioselective iridium catalyzed allylation[2] of **2** to provide diol **3** in 60% yield, dr > 20:1 and ee > 99% (Scheme 1). Diol **3** was monoprotected as the PMB ether in 71% yield, followed by esterification with acryloyl chloride in 93% yield. In the next step, we were surprised to observe that the ring closing metathesis furnished exclusively the seven-membered ring **6**, instead of the desired dihydropyranone **7**.



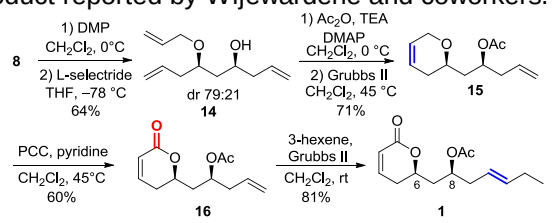
Scheme 1. First approach to Cryptolatifolione (**1**)

We then decided to replace the acrylate by an allyl group, and install the carbonyl group in a later stage *via* C-H oxidation. For that, diol **3** was treated with allyl bromide to produce ether **8** in 75% yield, followed by esterification with Ac_2O in 82% yield (Scheme 2). In the next step, we were pleased to observe that dihydropyran **10** could be obtained in high selectivity (>95:5) in 85% yield using only 1 mol% of Grubbs' catalyst II (Scheme 2). After several experiments, we found that use of PCC and pyridine selectively oxidized the C-2 position to furnish the dihydropyranone **12** in 61% yield. The last C-C bond was constructed by a cross-metathesis reaction between **12** and 3-hexene. Dihydropyranone **13** was isolated exclusively as the *E*-isomer at the newly created double bond (Scheme 2).



Scheme 2. Synthesis of epimer **13**

The *syn* C-6/C-8 stereochemistry was secured after Dess-Martin periodinane oxidation of alcohol **8** and reduction under chelation control, affording diol **14** in 64% yield (*dr*=79:21). The remaining steps were carried out as described for **13**. Dihydropyranone **1**, obtained after cross metathesis reaction, proved to be identical to the natural product reported by Wijewardene and coworkers.[1]



Scheme 3. Synthesis of Cryptolatifolione (**1**)

Conclusions

In summary, we developed the first total synthesis of Cryptolatifolione (**1**) in 8 steps and 10% overall yield, and its epimer at C-8 in 6 steps and 17% overall yield. The syntheses feature construction of four C-C bonds by catalytic methods and the use of a C-H oxidation to install the carbonyl group in a protecting group-free fashion.

Acknowlegments

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[1] Drewes, S. E.; Horn, M. M.; Wijewardene, C. S. *Phytochemistry* **1996**, *41*, 333.
[2] Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018.