Natural Product Synthesis Through (4+3) Cycloaddition: (+/-)-Frondosin B and (+/-)-Liphagal

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Introduction

Previous work in our laboratory revealed a new type of (4+3) cycloaddition that proceeds via an oxallyl-type cation producing hard to synthesize 7-membered rings. This synthetic method is very useful in the field of natural product (NP) synthesis since many of these small molecules contain furan fused cycloheptenes or straightforward synthetic derivatives thereof. The scope of this conversion has already been demonstrated using simple furfuryl alcohols and 1,3-dienes. A more recent study aimed at synthesizing more elaborate polycycles containing cyclohept[furan] substructures, those one often finds in NPs. We envisaged a total synthesis for frondosin B and liphagal as obvious targets for our method. Also the latter NP was identified as inhibitor for one isozyme of the phosphatidylinositol 3-kinase (PI3K) enzyme and had already been the subject of research. Herein, we present a full account of our investigations towards a new and short synthesis of (+/-)-frondosin B and (+/-)-5-epi-liphagal.

I. Discovery

During investigations towards a total synthesis of rumusoxeal, an intriguing conversion was noticed. Interestingly, the predicted hydrolysis induced cascade reaction follows a different pathway, in such a way, a useful furan[furan] motif is formed.

II. Preparation Precursors

Longer route is more practical

Shorter route, however purification needs to be improved.

III. Frondosin B

(+/-)-5-epi-liphagal

(+/-)-frondosin B

IV. Liphagal

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V. Determination of Absolute Configuration

Conclusion

Herein, we present a new and efficient route towards (+/-)-frondosin B and two analogs of (+/-)-liphagal, displaying all successes and missteps. This approach has value in terms of shortness and selectivity. Although only sub-mg amounts of (+/-)-O2CO2-dimethyl-liphagal were obtained, proper amounts of 5-epi-liphagal (30 mg) and (+/-)-5-epi-(SR)-hydroxy-liphagal (6.5 mg) were isolated and characterized. Including, determination of the absolute stereochemistry supported by XRD-measurements on a key intermediate (7).