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Olefinic-Lactone Cyclizations to Macrocycles

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Abstract

Olefinic-lactone cyclization reactions that result in the generation of macrocycles are described.

Macrocyclic motifs have drawn the attention of synthetic, biological, and medicinal chemists due to their presence in a number of biologically active small molecules that include both natural and non-natural products.^{1,2} For those scientists that target their synthesis, when the macrocycle of interest contains a lactone or lactam, a lactone or lactam-forming reaction has been a generally reliable method.^{3,4} However, when the target lacks these functionalities, synthetic chemists have been forced to turn to other, oftentimes less dependable methods to generate the macrocycle.⁵ From an awareness of the difficulties associated with the synthesis of non-lactone macrocycles, we became interested in using lactone formation to generate non-lactone macrocycles. As outlined in Scheme 1, central to the success of this idea would be a novel olefinic-lactone ring-closing metathesis reaction to give macrocyclic enol ethers (Scheme 1). To the best of our knowledge, similar cyclizations had not been demonstrated prior to this work.

To test the viability of the proposed strategy, we examined the olefinic-lactone cyclization of readily available 13-membered lactone **5** (eq 1). When **5** was subjected to our previously disclosed reduced Ti ethylidene conditions for olefinic-ester cyclizations we were pleased to isolate dihydropyran **6** in quantitative yield.⁶

Having demonstrated the cyclization of **5**, we decided to examine the scope of the reaction. The reaction to generate a dihydropyran was successful with several other substrates including 16- and 17-membered lactones **7** and **9**, respectively (Table 1, entries 2 and 3).⁷ We were also pleased to find that the cyclization was not limited to the generation of 6-membered enol ethers as 7-membered ring macrocycle **12** was also prepared from 17-membered lactone **11** (entry 4).

We next decided to demonstrate the utility of the products from the cyclization reactions. To this goal, we converted cyclic enol ether **8** into macrocyclic ketone **14**, macrocyclic ketal **13**, and macrocyclic pyran **15** as illustrated in Scheme 2. Exposure of **8** to *m*-CPBA in MeOH gave **13** in 68% yield.⁸ When **8** was sequentially hydrolyzed with SiO₂ and treated with benzoic anhydride we isolated ketoester **14** in 63% overall yield from lactone **7**. Finally, the reduction of **8** using Et₃SiH and TFA gave pyran **15** as a single diastereomer in 87% yield.

As a further illustration of its utility, we applied the lactone cyclization, ring expansion sequence to the synthesis of the natural products (*R*)-(-)-muscone and (*R*)-(+)-muscovopyridine (Scheme 3).^{9,10,11,12} Our synthesis of both substrates began with seco-acid **16**.¹³ Yamaguchi macrolactonization of **16** gave 13-membered cyclization precursor **17**. Olefinic-lactone cyclization resulted in the generation of macrocyclic dihydropyran **18**. Silica gel hydrolysis of the enol ether gave hydroxyketone **19**, which served as a precursor to both muscone and muscovopyridine. (*R*)-(+)-Muscovopyridine resulted from the oxidation of the 2° alcohol in **19** followed by pyridine formation.¹⁴ (*R*)-(-)-Muscone came from the deoxygenation of **19** using Barton-McCombie conditions.¹⁵

In summary, we have described a unique and efficient approach to macrocycles that utilizes an olefinic-lactone cyclization reaction in the key step. We continue in our study of the scope and utility of this reaction sequence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
The Use of Lactones to Generate non-Lactone Macrocycles.

Scheme 2.
The Ring-Expansion, Reduction, and Oxidation of **8**

Scheme 3.
Olefinic-Lactone Cyclizations to (-)-Muscone and (+)-Muscopyridine

Table 1

Olefinic lactone cyclizations

entry

lactone

1

entry

lactone

2

9

entry

lactone

11

3

entry

lactone