

Olefinic-Lactone Cyclizations to  
Macrocycles

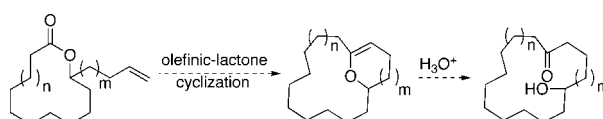
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Received November 26, 2008

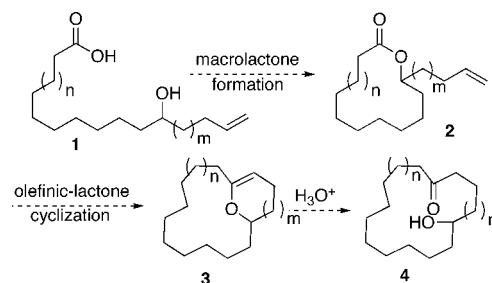
## ABSTRACT



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.<sup>1,2</sup> 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.<sup>3,4</sup> However, when the target lacks these functionalities, synthetic chemists have been forced to turn to other, oftentimes less dependable methods to generate the macrocycle.<sup>5</sup> From an awareness of the difficulties associated with the synthesis of nonlactone 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

Scheme 1. The Use of Lactones To Generate Non-Lactone  
Macrocycles

knowledge, similar cyclizations have 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.<sup>6</sup>

(1) For examples of natural products that contain macrocycles see refs 9 and 11 and: (a) Blunt, J. W.; Copp, B. R.; Hu, W.-P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2008**, 25, 35. (b) Ishibashi, M. In *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: New York, 2002; pp 57–98.

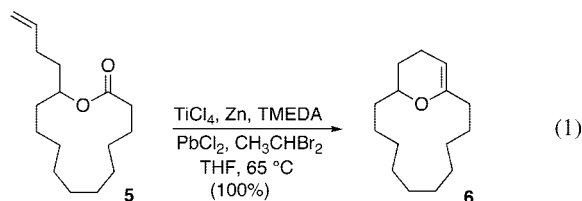
(2) For recent examples of bioactive non-natural products that contain macrocycles, see: (a) Shan, D.; Chen, S.; Njardarson, J. T.; Gaul, C.; Ma, X.; Danishefsky, S. J.; Huang, X.-Y. *Proc. Nat. Acad. Sci. U.S.A.* **2005**, 102, 3772. (b) Metaferia, B. B.; Chen, L.; Baker, H. L.; Huang, X.-Y.; Bewley, C. A. *J. Am. Chem. Soc.* **2007**, 129, 2434. (c) Anquetin, G.; Horgan, G.; Rawe, S.; Murray, D.; Madden, A.; MacMathuna, P.; Doran, P.; Murphy, P. V. *Eur. J. Org. Chem.* **2008**, 1953.

(3) For a review on macrolactonization, see: Parenty, A.; Moreau, X.; Capagne, M.-M. *Chem. Rev.* **2006**, 106, 911.

(4) For recent examples of macrolactamization, see: (a) Tan, L.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, 47, 3614. (b) Qin, H.-L.; Panek, J. S. *Org. Lett.* **2008**, 10, 2477. (c) Nicolaou, K. C.; Dethe, D. H.; Leung, G. Y. C.; Zou, B.; Chen, D. Y.-K. *Chem. Asian J.* **2008**, 3, 413. (d) Komano, K.; Shimamura, S.; Inoue, M.; Hiramata, M. *J. Am. Chem. Soc.* **2007**, 129, 14184.

(5) (a) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, 42, 2826. (b) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, 45, 6086.

(6) Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2007**, 129, 12604.



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 1 and 2).<sup>7</sup> We were also pleased to

**Table 1.** Olefinic Lactone Cyclizations

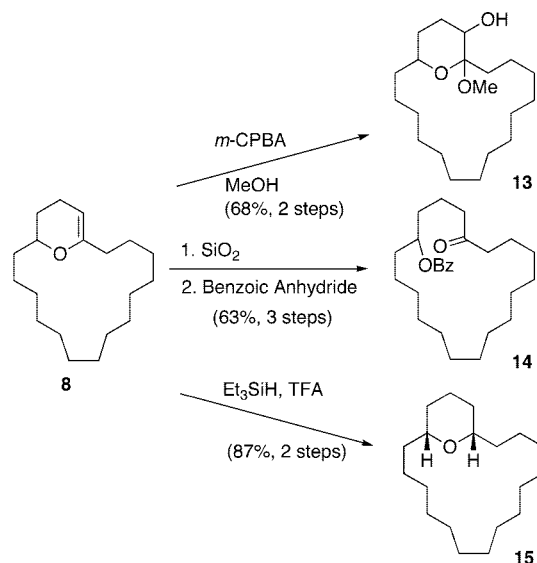
entry	lactone	cyclic enol ether	yield
1			87%
2			69%
3			78%

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 3).

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.

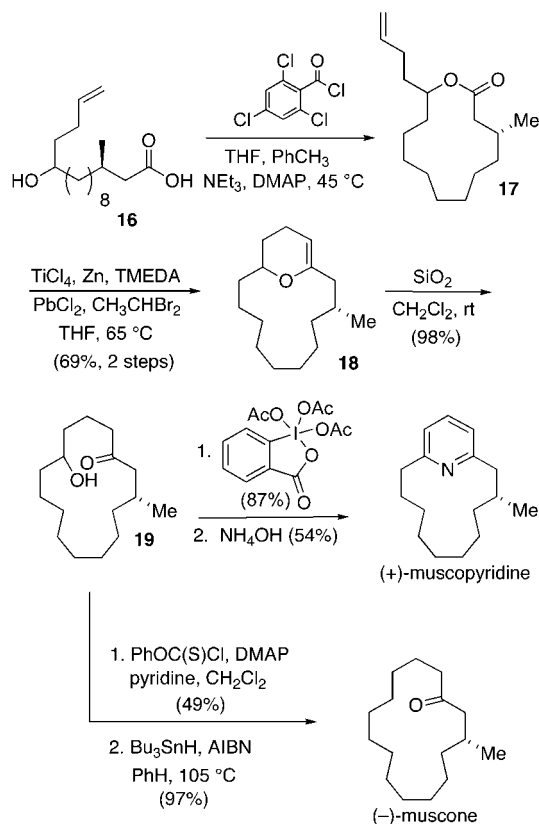
(7) In addition to the tertiary amine in **9**, acetals, ethers, and internal olefins are also amenable to the cyclization conditions. See ref 6 and: Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *J. Am. Chem. Soc.* **2005**, *127*, 848.

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



yield.<sup>8</sup> When **8** was sequentially hydrolyzed with SiO<sub>2</sub> and treated with benzoic anhydride, we isolated ketoester **14** in 63% overall yield from lactone **7**. Finally, the reduction of

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



**8** using Et<sub>3</sub>SiH 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).<sup>9–12</sup> Our synthesis of both substrates began with seco-acid **16**.<sup>13</sup> 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 secondary alcohol in **19** followed by pyridine formation.<sup>14</sup> (*R*)-(–)-Muscone came from the deoxygenation of **19** using Barton–McCombie conditions.<sup>15</sup>

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.

**Acknowledgment.** We are grateful to the National Institutes of Health, General Medical Sciences (GM56677) for support of this work. We would like to thank the support staff at the University of Utah and especially Dr. Charles Mayne (NMR) and Dr. Jim Muller (mass spectrometry) for help in obtaining data.

**Supporting Information Available:** Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) For synthetic work to muscovopyridine, see: (a) Suwa, K.; Morie, Y.; Suzuki, Y.; Ikeda, K.; Sato, M. *Tetrahedron Lett.* **2008**, *49*, 1510. (b) Furstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 308. (c) Hagiwara, H.; Katsumi, T.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Org. Chem.* **2000**, *65*, 7231. (d) Hadj-Abo, F.; Hesse, M. *Helv. Chim. Acta* **1992**, *75*, 1834. (e) Sakane, S.; Matsumura, Y.; Yamamura, Y.; Ishida, Y.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 672. (f) Utimoto, K.; Kato, S.; Tanaka, M.; Hoshino, Y.; Fujikura, S.; Nozaki, H. *Heterocycles* **1982**, *18*, 149. (g) Saimoto, H.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 3897. (h) Biemann, K.; Buchi, G.; Walker, B. H. *J. Am. Chem. Soc.* **1957**, *79*, 5558.

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