ORGANIC LETTERS

2003
Vol. 5, No. 4
443−445

Synthesis of New 14-Membered Macrolide Antibiotics via a Novel Ring Contraction Metathesis

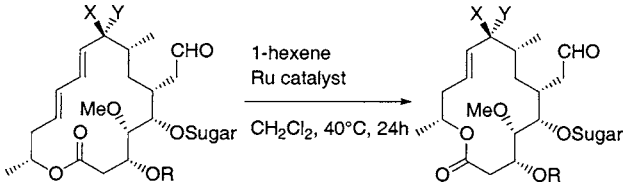
Tsvetelina I. Lazarova,* Sophie M. Binet, Nha H. Vo, Jason S. Chen, Ly T. Phan, and Yat Sun Or

Enanta Pharmaceuticals, 500 Arsenal Street, Watertown, Massachusetts 02472

tsvetelina.lazarova@sprlus.com

Received November 21, 2002

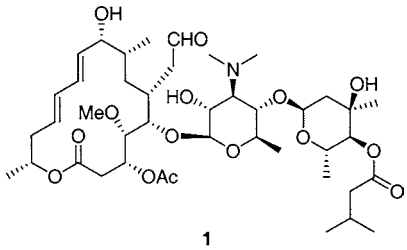
ABSTRACT



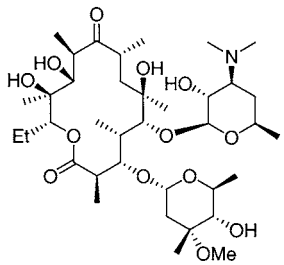
A novel ring opening ring closing metathesis (ROM-RCM) was demonstrated for cyclic conjugated dienes, effecting the excision of a C_2H_2 unit and a net ring contraction. Applying the ring contraction metathesis, new 14-membered ring macrolide antibiotics were synthesized in a single step from existing 16-membered ring macrolides. This new class of macrolide antibiotics will provide access to new therapeutics for the treatment of macrolide-resistant bacterial infections.

Macrolide antibiotics[1] have been the focus of widespread research due to increasing bacterial resistance.[2] There have been significant synthetic efforts to generate new core structures to address this challenge. The 16-membered ring macrolide antibiotics—for example, josamycin[3] (**1**)—are an important series within the macrolide class of antibiotics since they offer some advantages over 14-membered macrolides derived from erythromycin[4] (**2**) (Figure 1). These advantages include better gastrointestinal tolerance, lack of drug−drug interactions, and activity against resistance-expressing strains.[5] However, 14-membered macrolides demonstrate better pharmacokinetics and efficacy.

In our laboratory, we focused on the transformation of existing 16-membered macrolides into novel macrolide core structures that retain the beneficial properties of the parent compounds while offering the improved pharmacokinetics



1



2

Figure 1. Structures of josamycin (**1**) and erythromycin (**2**).

(1) (a) Zhanel, G. G.; Dueck, M.; Hoba, D. J.; Vercaigne, L. M.; Embil, J. M.; Gin, A. S.; Karlowsky, J. A. *Drugs* **2001**, *61* (4), 443−498. (b) Bryskier, A. *Expert Opin. Invest. Drugs* **1999**, *8* (8), 1171−1194. (c) Kirst, H. A. *Expert Opin. Ther. Pat.* **1998**, *8* (2), 111−120.

(2) (a) Zuckerman, J. M.; Kaye, K. M. *Infec. Dis. Clin. North Am.* **1995**, *9* (3), 731−745. (b) Bahal, N.; Nahata, M. C. *Ann. Pharmacother.* **1992**, *26* (1), 48−55.

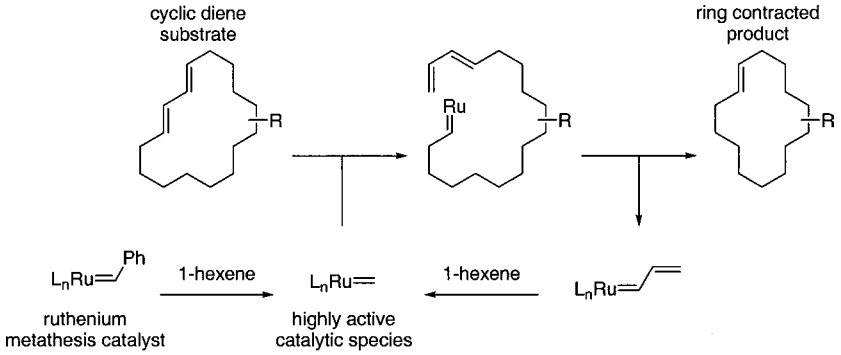
(3) (a) Kirst, H. A. *Prog. Med. Chem.* **1994**, *31*, 265−295. (b) Kirst, H. A.; Sides, G. D. *Antimicrob. Agents Chemother.* **1989**, *33*, 1413−1418.

(4) (a) Kirst, H. A.; Sides, G. D. *Antimicrob. Agents Chemother.* **1989**, *33*, 1413−1418. (b) Cachet, T.; Van den Mooter, G.; Hauchecorne, R.; Vinckier, C.; Hoogmartens, J. *Int. J. Pharma.* In press.

(5) Delaforge, M.; Sartori, E. *Biochem. Pharmacol.* **1989**, *38*, 2061−2068.

10.1021/ol027322n CCC: $25.00
Published on Web 01/25/2003

Scheme 1. Ring Contraction Metathesis



and efficacy of 14-membered macrolides. We focused on the conjugated diene found in 16-membered macrolides such as josamycin, reasoning that a ring opening ring closing metathesis (ROM-RCM)[6] could excise a C_2H_2 unit from the conjugated diene, resulting in a net ring contraction (Scheme 1). We decided to explore such a ring-contraction metathesis as a potential means of transforming 16-membered macrolides into novel 14-membered macrolides, thereby generating a new series of macrolide core structures from which new macrolide antibiotics could be developed. An initial ROM on an unstrained ring would be necessary, but there was sufficient literature precedence suggesting that this barrier could be overcome.[7]

Using josamycin as a model 16-membered macrolide, we developed a single-step ring-contraction metathesis reaction, transforming josamycin into 14-membered macrolide **3**. We tried using the commonly used catalyst $(PCy_3)_2(Cl)_2Ru{=}CHPh$[8] with no success. However, we found that the use of highly active catalyst **4**[9] gave satisfactory results. Exposing josamycin (**1**) to 1-hexene and a catalytic amount of catalyst **4** yielded macrolide **3** in 78% isolated yield (Scheme 2). The structure of **3** was confirmed by 2D NMR experiments.

The scope of the ring-contraction metathesis appears quite broad, and it can be applied to other 16-membered macrolides. Ring contraction of kitasamycin (**5**) and 9-*epi*-josamycin (**6**) under the same reaction conditions affords 14-membered macrolides **7** and **8**, respectively, in 65% and 42% yield. The lower yields reflect difficult chromatographic purification, not incomplete conversion.

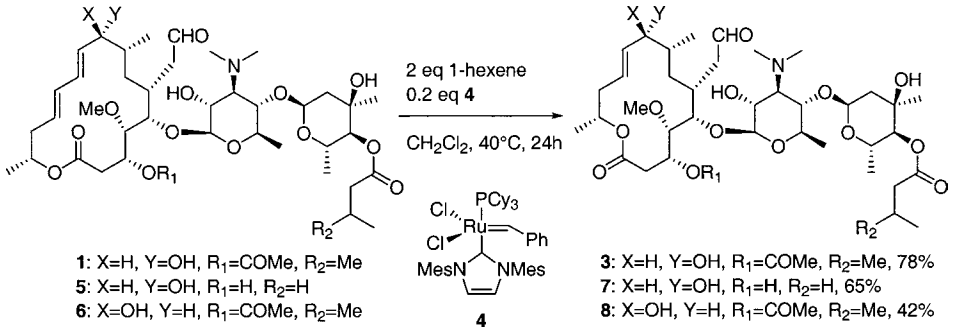
An investigation of the reaction conditions revealed that without additives—such as 1-hexene—the reaction is stoichiometric in ruthenium catalyst, and the percentage conversion is proportional to the amount of catalyst used. Ethylene is often used as an additive in metathesis reactions to help initiate and propagate the catalytic cycle by generating a highly active $L_nRu{=}CH_2$ species.[10] Reaction of a ruthenium-based metathesis catalyst with 1-hexene can generate the same $L_nRu{=}CH_2$ species (Scheme 1). We believe that under our reaction conditions, 1-hexene served as a convenient, nongaseous alternative to ethylene.

Further investigation of reaction conditions revealed that the Lewis acid titanium isopropoxide could replace 1-hexene, yielding comparable results. Titanium isopropoxide has been reported to destabilize chelates between the ruthenium catalyst and various hydrogen bond acceptors present in the reaction mixture.[11] Such chelates may result in the ruthenium catalyst being sequestered in an inactive form. Though the use of titanium isopropoxide proved to be unnecessary for our macrolide ring contraction reaction, the presence of viable alternative reaction conditions may make the ring-contraction metathesis reaction applicable to a broader range of substrates.

The new 14-membered macrolide antibiotics were tested against erythromycin-resistant strains *S. pneumoniae* 7701 and *S. pyogenes* 1323, and they showed antibacterial activity similar to that of their parent 16-membered macrolides.[12]

In conclusion, we synthesized new 14-membered macrolide antibiotic core structures in a single step transformation

Scheme 2. Synthesis of New Macrolide Cores via Ring Contraction



from existing 16-membered macrolides via a novel ring contraction metathesis. Efforts to develop these new 14-membered macrolide cores into macrolide antibiotics with improved activity against a broad panel of macrolide-resistant bacterial strains are in progress. Further efforts will also be directed toward widening the scope of the reaction to other macrolide natural products.

Acknowledgment. We thank Greg Heffron and Gerhard Wagner of Harvard Medical School for help with the structural elucidation of the new 14-membered macrolides. We thank Theresa Haley and Andrew Napper of Enanta Pharmaceuticals for determining MIC values for the new macrolides.

Supporting Information Available: Detailed experimental procedures for synthesis. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027322N

(6) (a) Grubbs, R. H.; Chang, S. *Tetrahedron*, **1998**, *54* (18), 4413−4450. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39* (17), 3012−3043.

(7) (a) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3* (3), 449−451. (b) Smith, A. B.; Adams, C. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2001**, *123* (5), 990−991. (c) Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2* (14), 2145−2147.

(8) Schwab, P.; Gruibbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(9) Laleh, J.; Hillier, A. C.; Nolan, S. P. *Organometallics* **2002**, *21* (2), 442−444.

(10) (a) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119* (6), 1488−1489. (b) Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120* (10), 2343−2351.

(11) (a) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron Lett.* **1999**, *40* (22), 4187−4188. (b) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651−4654. (c) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136.

(12) The MIC assays were performed in accordance with the National Committee of Clinical Laboratory Standards (NCCLS) guidelines: (a) NCCLS Document M7-A5 (Vol. 20: No. 2). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, 5th ed., Jan 2000. (b) NCCLS Document M100-S11 (Vol. 21: No. 1). Performance Standards for Antimicrobial Susceptibility Testing: Eleventh Informational Supplement, Jan. 2001. (c) Amsterdam, D. Susceptibility Testing of Antimicrobials in Liquid Media. In Lorain, V. *Antibiotics in Laboratory Medicine*, 4th ed.; Williams & Wilkins: Baltimore, MD, 1996; pp 52−111.