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Synthesis of a Model for C7–C13 of Lankamycin

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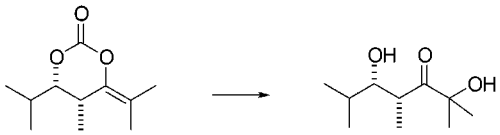
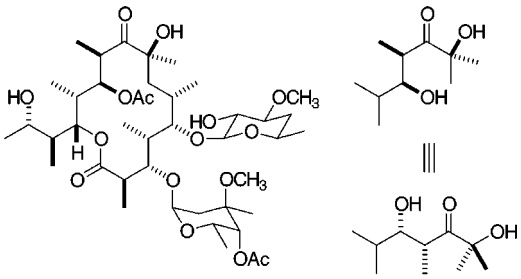
ABSTRACT



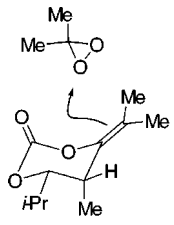
A convenient method is reported for construction of the C7–C13 segment of the macrolide antiobiotic lankamycin.

Lankamycin (**1**) was isolated in 1960 from *Streptomyces violaceoniger*[1] and in 1969 from *S. spinichromogenes* var. *Kujimyceticus*.[2] The compound is a member of the class of 14-membered macrolides[3] and exhibits moderate antibacterial activity against a number of Gram-positive microorganisms.[1,4] Of the 14-membered macrolides, lankamycin is unique in having a C8 tertiary alcohol function. In this Letter, we report a convenient method for elaboration of the C7−C13 segment of lankamycin, which contains this quaternary stereocenter as well as the C10 and C11 stereocenters.



1 **2**

As shown in Scheme 1, acyloxazolidinone **3** was converted into the corresponding dibutylboryl enolate, which was condensed with isobutryaldehyde to obtain the syn aldol.[5] Treatment of this substance with *N*,*O*-dimethylhydroxylamine afforded the *N*-methoxyamide **4**.[6] Reaction of **4** with 2-lithiopropene in ether gave aldol **5**, which was converted into phenyl carbonate **6** by reaction with phenyl chloroformate. Addition of Strykers' reagent, (triphenylphosphine)-copper(I) hydride,[7] provided the cyclic enol carbonate **7** in 90% yield. Compound **7** was also obtained, albeit in only 50% yield, by reaction of enone **6** with L-Selectride in THF at −78 °C. Treatment of enol carbonate **7** with dimethyldioxirane[8] gave a single diastereomeric epoxide in nearly quantitative yield. X-ray crystallographic analysis of this crystalline epoxide showed it to have structure **8**. The high facial selectivity of this oxidation is presumably a consequence of steric hindrance by the pseudoaxial methyl group:



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Hydrolysis of the carbonate with LiOH in aqueous THF provided keto diol **2** in quantitative yield.

(1) Gäumann, E.; Hütter, R.; Keller-Schierlein, W.; Neipp, L.; Prelog, V.; Zahner, H. *Helv. Chim. Acta* **1960**, *43*, 601.

(2) (a) Namiki, S.; Omura, S.; Nakayoshi, H.; Sawada, J. *J. Antibiot.* **1969**, *22*, 494. (b) Omura, S.; Namiki, S.; Shibata, M.; Muro, T.; Nakayoshi, H.; Sawada, J. *J. Antibiot.* **1969**, *22*, 500.

(3) Omura, S.; Tanaka, H. *Macrolide Antibiotics*; Academic Press: Orlando, 1984.

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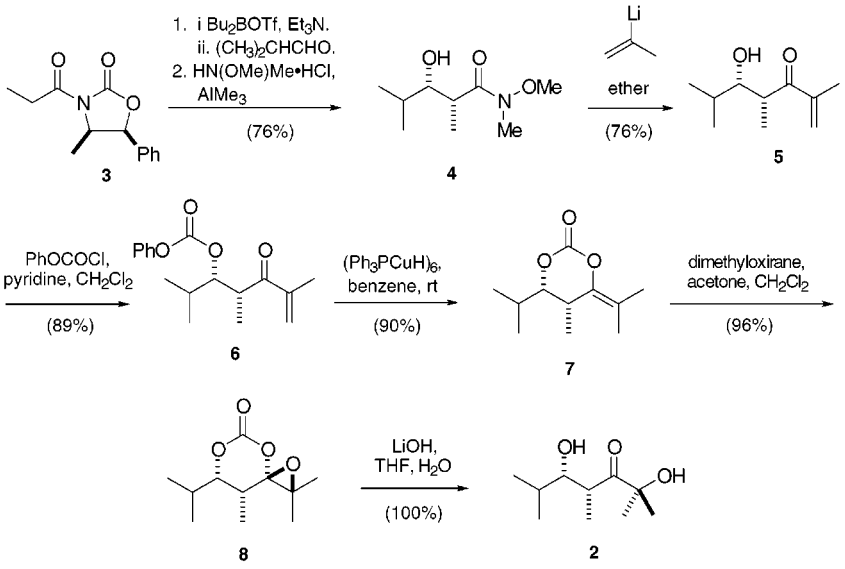
Scheme 1



In summary, the conversion of enone **5** into dihydroxy ketone **2** requires four steps, proceeds in good overall yield (ca. 80%), and represents a way of hydrating the double bond with highly stereoselective generation of the quaternary stereocenter corresponding to C8 in lankamycin.

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Supporting Information Available: Experimental procedures and characterization for all compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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