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AN APPROACH TO CHIRAL TRI-SUBSTITUTED OLEFINS: SYNTHESIS OF THE C(1)-C(7) SEGMENT OF HALICHOMYCIN

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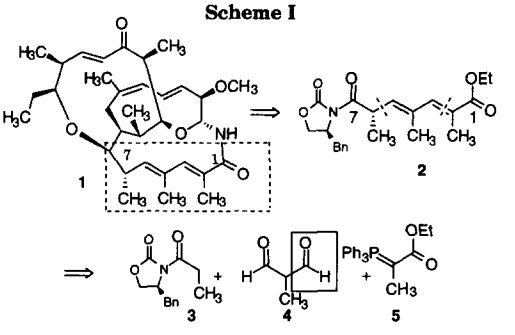
Abstract: A two step, stereocontrolled procedure has been developed for production of **2**, a precursor to the C(1)-C(7) segment of halichomycin (**1**). Copyright © 1996 Elsevier Science Ltd

As part of an ongoing program directed toward the synthesis of halichomycin (**1**),[1] we recently began investigating known methods for the stereocontrolled production of tri-substituted olefins possessing allylic stereogenic centers.[2] Although initially attracted to the commonly employed chiral starting material methyl-3-hydroxy-2-methylpropionate,[2a-c] the numerous oxidation state and protecting group changes required to manipulate this material led us to consider alternatives. Eventually, these efforts resulted in the development of an efficient two-step preparation of **2**,[3] a synthetic intermediate to the C(1)-C(7) segment of **1**, wherein a stereoselective aldol coupling between an acylated oxazolidinone (**3**) and a masked β-dicarbonyl (**4**) serves as the key step (Scheme I).

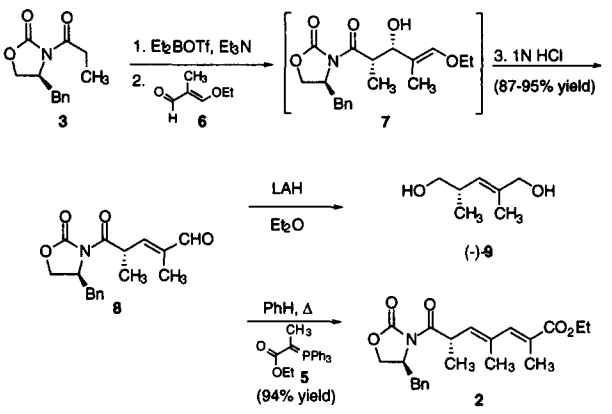
In considering possible masked β-dicarbonyl substrates we turned to 3-ethoxy-2-methylpropenal (**6**).[4] Although several precedents exist for this material serving as an electrophilic precursor to the needed tri-substituted olefin,[5] its reactivity in a stereoselective aldol reaction was hitherto unknown.[6] In the event, we found that under typical Evans' aldol conditions,[7] the coupling of **3** and **6** proceeds initially to a labile aldol product (**7**) which, upon warming to room temperature and *in situ* treatment with 1N HCl/MeOH (1:1), undergoes clean conversion to **8**[3] (Scheme II, 87% yield, >95% de as determined by ^{1}H NMR). Repeated experiments resulted in consistently high yields of the desired olefin; however, if the triflate was of poor quality or close attention was not given to the imide/triflate stoichiometry, a significant amount of a minor byproduct was observed (ca. 5-10%).[8] Given that the reaction could produce E or Z isomers of either syn- or anti-aldol products,[6] we evaluated the course of the reaction through chemical correlation. Comparison of the spectral and chiroptical data of the 1,5-diol [(-)-**9**], derived from reduction of **8**, with (+)-**9**, produced via known methods,[9] indicated that the coupling of **3** and **6** had proceeded as anticipated to furnish **8**. Having confirmed the structure of **8**, we turned to the completion of the C(1)-C(7) synthon and were delighted to find that homologation of **8** furnishes **2** in 94% yield. [10]

Scheme I



In summary, a highly diastereoselective one-pot procedure has been devised for the preparation of chiral tri-substituted olefin (**8**) in excellent yield. Standard homologation of **8** completes a two-step (82% yield) preparation of **2**, an intermediate poised for incorporation as the C(1)-C(7) segment in halichomycin (**1**). Efforts directed toward completing the total synthesis of **1** are currently underway in our laboratories.

Scheme II



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3. The structure assigned to each new compound is in accord with its infrared and high field ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry.

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5. (a) Zeller, P.; Bader, F.; Lindlar, H.; Montavon, M.; Muller, P.; Ruegg, R.; Ryser, G.; Saucy, G.; Schaeren, S. F.; Schwieter, U.; Stricker, K.; Tamm, R.; Zurcher, P.; Isler, O. *Helv. Chim. Acta* **1959**, *42*, 841. (b) Ruegg, R.; Lindlar, H.; Montavon, M.; Saucy, G.; Schaeren, S. F.; Schweiter, U.; Isler, O. *Helv. Chim. Acta* **1959**, *42*, 847. (c) Wang, C. J.; Salvino, J. M. *Tetrahedron Lett.* **1984**, *25*, 5243.

6. Heathcock has investigated 3-thiopropenals in stereoselective aldol reactions and reported that they can be selectively manipulated to produce either syn- or anti-aldol products, see: Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173.

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8. Given that the binary mixture is reduced to a single product upon reductive removal of the chiral auxiliary, this byproduct is likely derived from dehydration of the anti- or non-Evans syn aldol product.

9. For the synthesis of (+)-**9**, see: (a) Reference 2a. (b) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, *45*, 4347.

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