Formal Synthesis of CJ-12,954 and CJ-13,014

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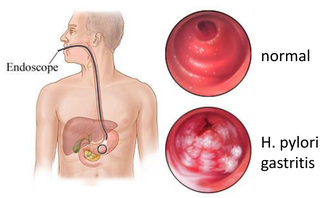
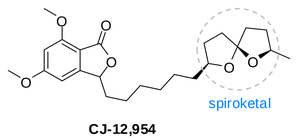
Introduction

CJ-12,954 and CJ-13,014 as anti-*Helicobacter pylori* agents

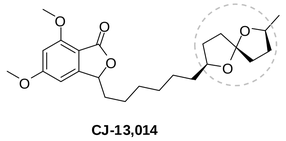
Helicobacter pylori are microaerophilic, Gram negative bacteria causing several diseases including gastric and duodenal ulcers. A variety of effective drugs for the treatment and eradication of *Helicobacter pylori* has been developed; however, none of the existing treatments are capable of complete eradication.



In 1997, Dekker and co-workers isolated the two most potent anti-*Helicobacter pylori* agents CJ-12,954 and CJ-13,014 from the basidiomycete *Phanerochaete velutina* CL6387.[1] The natural products CJ-12,954 and its epimer CJ-13,014 contains a 5,5-spiroketal backbone joined through a polymethylene chain to the phthalide unit. Dekker and co-workers were only able to assign the relative stereochemistry of the three stereogenic centres on the spiroketal backbone.

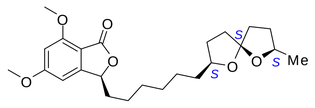


CJ-12,954



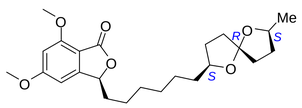
CJ-13,014

Brimble and co-workers attempted the first synthesis of these natural products via modified Julia olefination.[2] However, the synthesized isomers are inseparable and, in fact, enantiomeric to the natural products.



ent-CJ-12,954

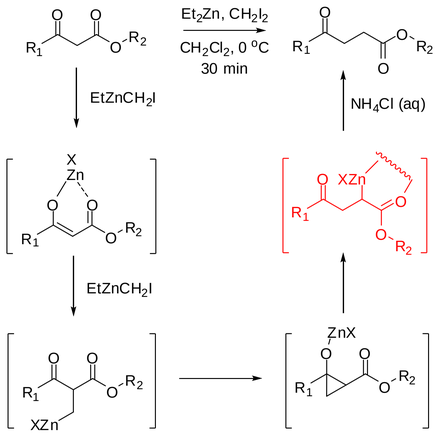
1:1 inseperable mixture



ent-CJ-13,014

Herein we propose the first formal synthesis of the natural products CJ-12,954 and CJ-13,014 employing the zinc-mediated tandem chain extension-aldol reaction developed in Zercher research group.

Zinc-mediated chain extension



One pot homologation reaction

Converts β-keto esters, amides, phosphonates, imides to their corresponding homologated products.[3]

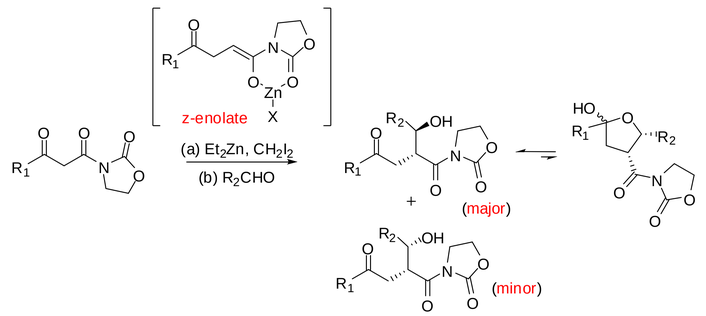
The proposed reaction mechanism was studied both experimentally and computationally.[4]

Tandem chain extension-aldol reaction

The opportunity to trap the zinc-organometallic intermediate generated in the chain extension reaction with various electrophiles such as aldehydes, ketones, iminium ions, imines, halogens led to the development of tandem chain extension protocols. Tandem chain extension aldol reaction was the first tandem protocol to be developed where the electrophile trapped was an aldehyde.

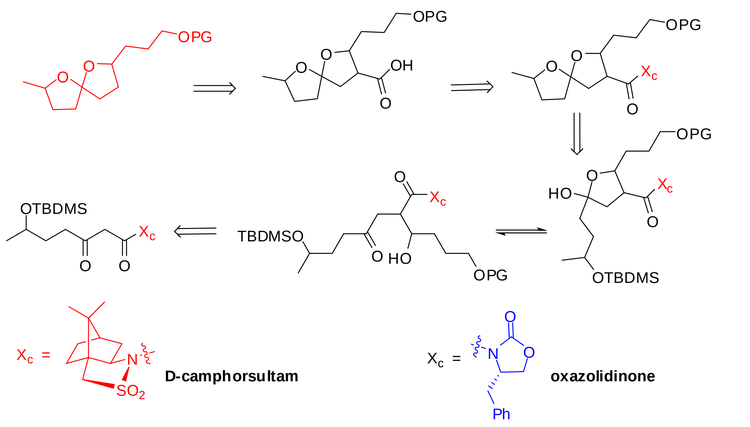
Tandem chain extension-aldol reaction

Tandem chain extension-aldol reaction of β-keto imides



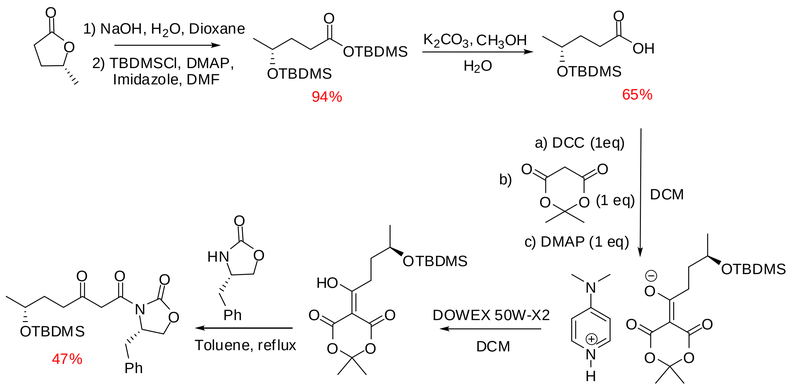
The diastereoselectivity of this reaction favors the anti isomer over the syn isomer as the reaction is believed to progress via an open transition state.[5]

Retrosynthetic Analysis



The formal synthesis of spiroketal back bone involving crucial tandem chain extension aldol reaction is designed. The stereochemistry could not be established when using D-camphorsultam as chiral auxiliary.[6]

DCC Coupling Route to β-keto imide



The key intermediate β-keto imide for the chain extension aldol reaction was synthesized using DCC coupling route.

References

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2) Brimble, M. A.; Bryant, C. *J. Chem.Commun*, **2006**, 4506-4508.
3) Brogan, J. B.; Zercher, C. K. *J. Org. Chem*. **1997**, *62*, 6444-6446.
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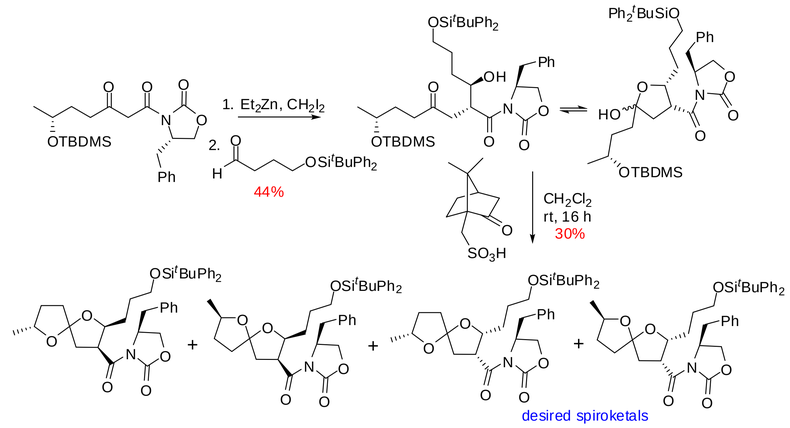
5) Lai, S.; Zercher, C. K.; Jasinski, J. P.; Reid, S. N.; Staples, R. J. *J. Org.Lett*. **2001**, 3, *26*, 4169-4171.
6) Aiken, K. Ph.D. Dissertation, University of New Hampshire, **2005**.

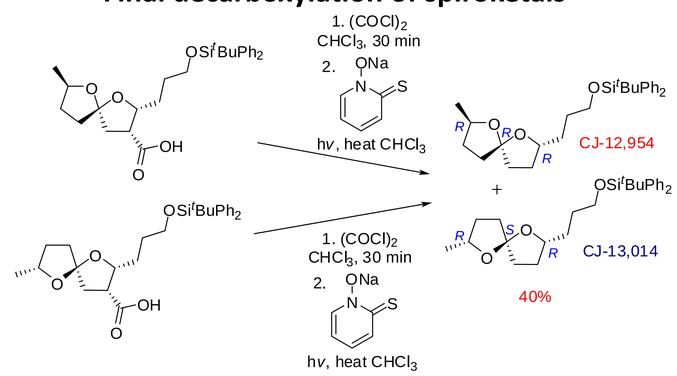
Synthesis of spiroketal backbone

Successful separation of spiroketals

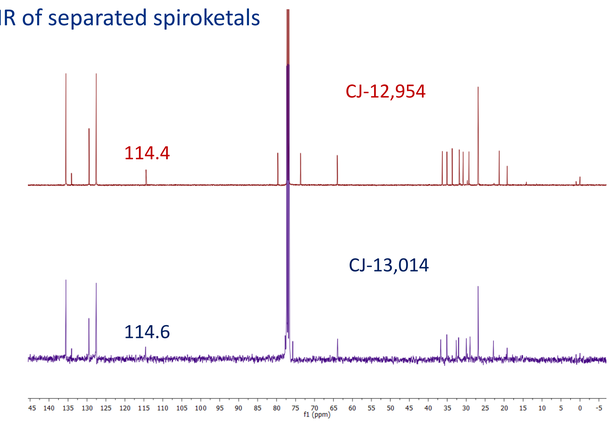


The tandem chain extension aldol reaction followed by spirocyclization facilitated the separation of advanced intermediates of the two natural products which Brimble and co-workers were unable to achieve.

Final decarboxylation of spiroketals



^{13}C NMR of separated spiroketals



Formal synthesis of CJ-12,954 and CJ-13,014 was successfully completed and characterized. Hence our zinc-mediated tandem chain extension aldol reaction proved to be an efficient methodology for the synthesis of spiroketal based natural products.

Acknowledgements

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