Exploring Hops Chemistry: Efficient Synthesis of Biologically Active Humulones and Lupulones

Lucas Sass and Prof. Kristopher V. Waynant, Dept. of Chemistry, University of Idaho, Moscow, ID 83843 kwaynant@uidaho.edu

Abstract

Humulones and lupulones, the alpha and beta acids from hops, humulus lupulus, have affirmed themselves as key ingredients in the multi-billion dollar brewing industry. Originally exploited for their bacteriostatic properties, these compounds also exhibit high levels of biological activity against a variety of diseases. Through an optimized synthetic route we have explored pathways to synthesize natural and enantiomeric humulones and lupulones. umulones and lupulones have affirmed themselves as key ingredients in the multi-billion dollar brewing industry. Originally exploited for their bacteriostatic properties, these compounds also exhibit high levels of biological activity against a variety of diseases.

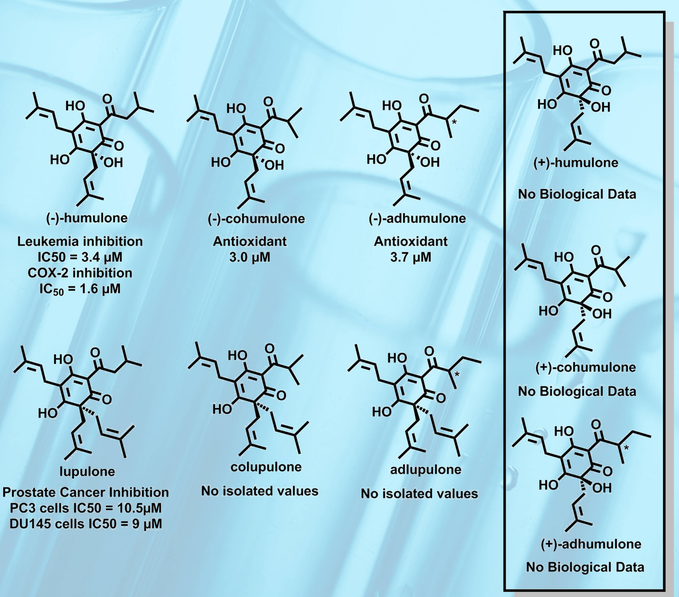
This project aims to:

1) Use these methodologies to effectively synthesize a library of humulones and lupulones to test for individual biological activity.

2) Build upon the humulone and lupulone scaffolds towards a variety of derivatives. Biological testing will be accomplished through collaborators and the NIH screen 60 program along with University of Idaho's agreement with Eli Lilly ®.

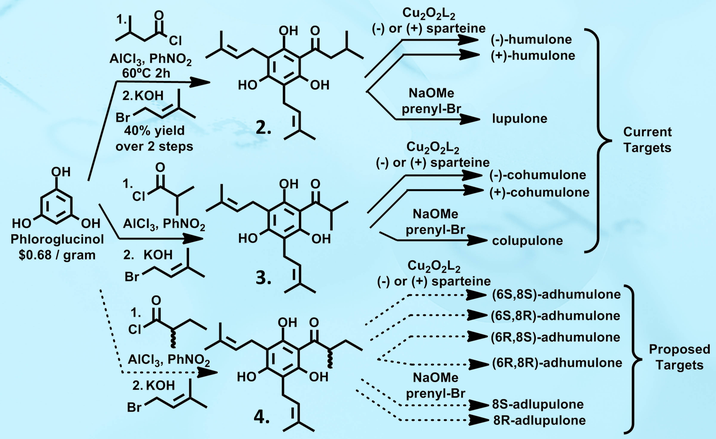
Biological Activity

Much of what is known about the biological activity of humulones and lupulones is based on pure hop extract (mixtures of congeners). Our goal is to synthetically create each pure asymmetric compound to asses the precise activity.



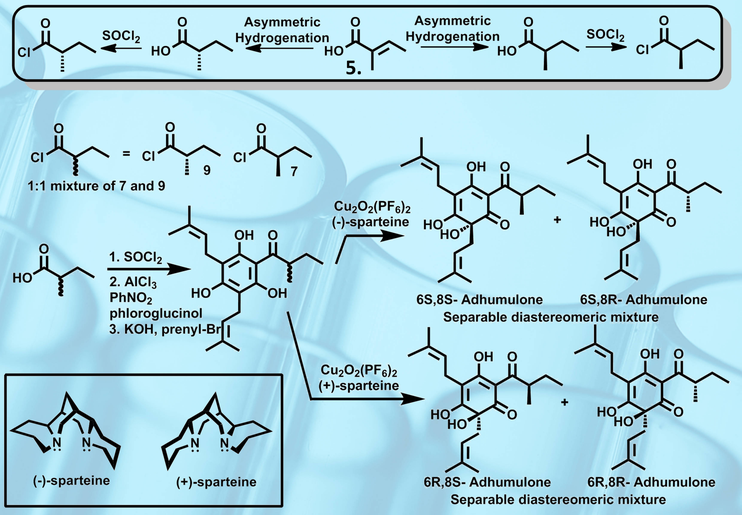
Synthetic Route

The common humulone/lupulone intermediate begins with phloroglucinol (1) at $0.68/g. Friedel-Crafts acylation followed by C-prenylation under basic conditions yields the common intermediates. Utilizing common intermediates 2-4, copper-mediated asymmetric dearomatization with sparteine ligands will successfully create the asymmetric center on the ring portion of the three humulones. Concurrently, access of the lupulones via reaction of 2-4 with a strong base to induce the third prenylation.



Adhumulone

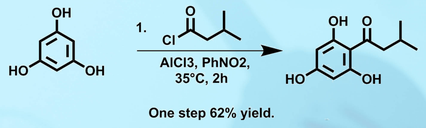
The exact stereochemistry at position 8 in adhumulone is currently unknown. We envision a synthetic route to all of the possible diastereomers through tiglic acid, 5, and our general procedures. This will allow for absolute confirmation of the natural compound.



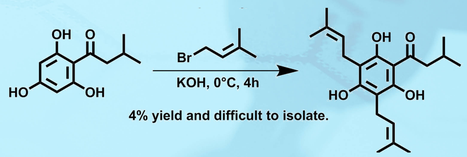
Optimization

Achieving a efficient route to the prenylated precursors to our target compounds has been the main focus of the project thus far. Several procedural variants have been explored towards reaching each of the intermediates.

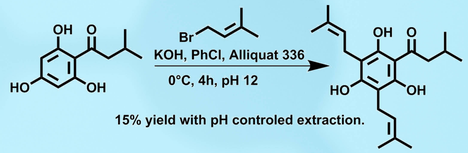
Our original route to the acylated intermediate utilized two reactions. This approach was problematic and time consuming to purify and also gave only poor yields.



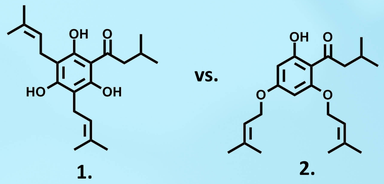
Our optimized route uses one reaction and with an improved aqueous extraction which negates the need for any further purification and greatly increas our yields



Our initial route to the prenylated intermediate gave a plethora of side products which made the product hard to isolate in large quantities.



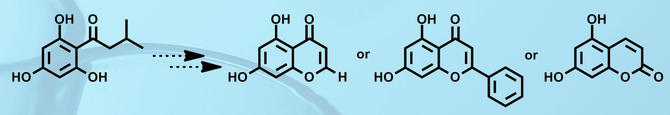
By using a phase transfer catalyst and pH controlled reaction and workup conditions we were able to improve this reaction however more work needs to be done to completely optimize these conditions.



We have determined that a large portion of our starting material ends up as an O-prenylated compound, 2. Our most current efforts are focused on determining how to avoid the formation of this side product.

Future Work

Towards the goal of creating a library of compounds derived from the common acyl-phloroglucinol intermediates, efforts to make several chromone, flavone, and coumarin moieties will be attempted.



References:

1. Van Cleemput, M.; Cattoor, K.; De Bosscher, K.; Haegeman, G.; De Keukeliere, D.; Heyerick, A. J. Nat. Prod. 2009, 72, 1220-1230.
2. Zhu, J.; Grigoriadis, N.P.; Lee, J.P.; Porco, J.A. Jr. J. Am. Chem. Soc. 2005, 127, 9342-3. (b) Qi, J.; Porco, J. A., Jr. J. Am. Chem. Soc. 2007, 129, 12682-12683.
3. Burckhardt, B.; Lucius Werthemann, R.; Troxler, R.J. US Patent No. 4101585, 1978.

ACKNOWLEDGEMENTS:

Lucas Sass has received both a MILES Undergraduate Research Internship and an INBRE Fellowship, NIH Grant No. P20 GM103408 (NIGMS) towards this project and we thank both funding agencies.`