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

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Abstract
Humulones and lupulones, the alpha and beta acids from hops, humulupus lupule, 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 assess the precise activity.

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

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 deamorization 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.

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.

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:

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