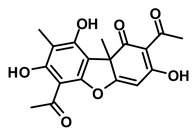
Progress Towards the Synthesis of Usnic Acid and its Analogs

University of New Haven

Justin Pantano and Dr. Pier F. Cirillo

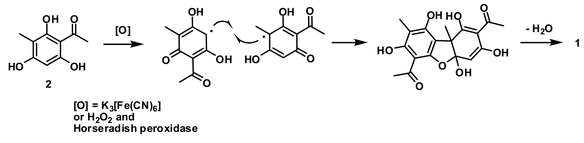
Introduction

Usnic acid (UA, **1**) is an abundant secondary metabolite of numerous species of lichen. UA exhibits antibiotic activity against *Streptococci*, *Staphylococci*, and *Mycobacteria*, along with antifungal and anti-inflammatory activities.[1] UA has also been used for weight loss, however this is discouraged due to hepatotoxicity.[2] We have been working towards a templated synthesis of UA, as well as the synthesis of its analogs as potential new antibiotics.

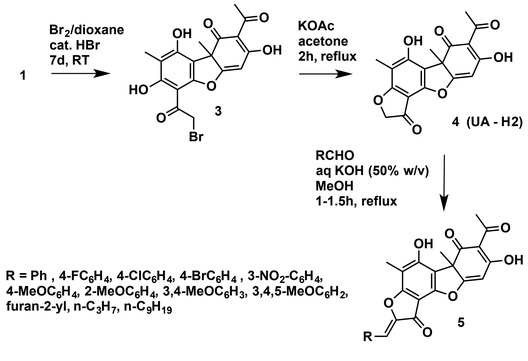


rac-UA **1**
Major tautomer

Background



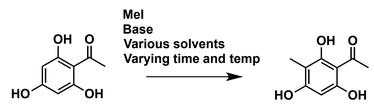
The first reported synthesis of UA was by Barton *et al* in 1956.[3] In this synthesis (scheme above), two different radicals of the same 3'-methyl-2',4',6'-trihydroxy-acetophenone **2** combine to give hydrated-UA, which after loss of water gave the final product in very low yield (<16%). Another published attempt does not report matching the original Barton group yield. However, using H_2O_2 with Horseradish Peroxidase as catalyst the yield is improved to 37%, though only on very small scale (5 mg).[4]



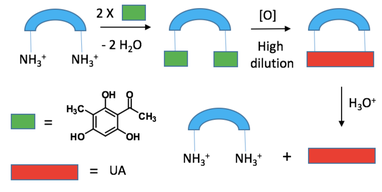
Luzina *et al* reported the selective bromination of UA and a series of reactions to create aurone derivatives **5** of UA[5] via the dehydrogenated UA **4** (UA-H_2, see scheme above). Higher yields of the final aurone product **5** were obtained using aromatic aldehydes, while lower yields were obtained with aliphatic aldehydes.

Objectives

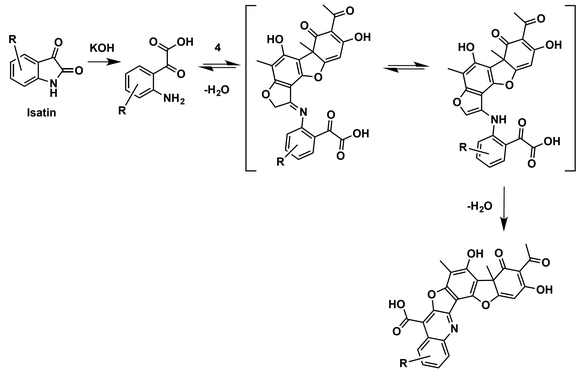
1) To synthesize gram quantities of 3'-methyl-2',4',6'-trihydroxyacetophenone **2** in order to explore the synthesis and chemistry of UA:



2) Build a diamine template upon which to attach the above acetophenone **2** for a potential templated synthesis of UA via the imines:



3) Explore the possibility to generate analogs of UA using isatins in a Pfitzinger reaction with UA-H_2 to generate the products shown below:



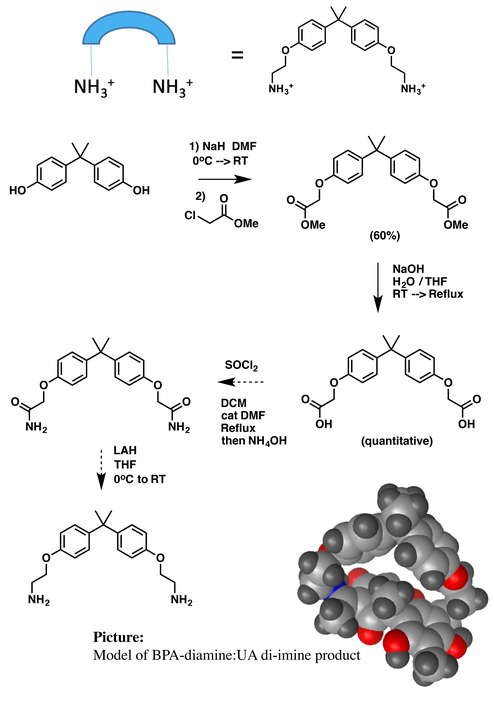
Results and Conclusions

1) The following results were obtained for the methylation of trihydroxyacetophenone:

Base	Solvent	Time	Temp	Results
K_2CO_3	Acetone	9h	0°C	17% yield in a 5:1 ratio of expected product vs. unreacted material
K_2CO_3	DMF	9h	0°C	O-methylated materials exclusively
Na_2CO_3	Acetone	Overnight	0°C to RT	Mixture of O- and C-methylated materials
Na_2CO_3	THF	Overnight	0°C to RT	No reaction

This published reaction was poorly reproducible, low yielding, and further work is needed to optimize the production of this intermediate.

2) Progress towards the synthesis of bis-phenol A – based template:



Picture:
Model of BPA-diamine:UA di-imine product

3) Using excess unsubstituted isatin and UA-H_2 with excess KOH, NaOEt, or DBU, the same result was obtained each time: UA-H2 was consumed and converted to a number of low Rf products that could not be separated, as well as a volatile high Rf fluorescent compound that has not yet been characterized. No reaction was observed without base, even at high temperature.
It was difficult to obtain enough material to characterize spectroscopically the products of the reaction. More work is needed to refine the reaction and purification process.

Acknowledgments

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References

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