## Abstract

After the discovery and elucidation of the naturally occurring compound from the altersolanol family, altersolanol P (AP) has become the focus in our laboratory. With biological activity against gram-positive bacterium, it proves to have a serious benefit in comprising an effective and efficient synthesis. With the completion of a Lewis Acid-mediated Diels Alder cycloaddition, a synthetic intermediate containing the complete carbon framework of AP was synthesized scale (in 80% yield and 8:1 regioselectivity). Following the work from my predecessors, I plan to syn-dihydroxilate and oxidize the cycloadduct intermediate to form an AP derivative.


## Studies en Route to Altersolanol Derivatives

Through the ages of antibiotics, bacteria have evolved antibiotic resistant qualities posing serious health risks to our society. The result of this has been the inevitable decrease in antibiotic effectiveness. In addition, the progression of improvements of currently employed classes of antibiotics has been relatively slow. With this, a need for new antibiotic active chemicals is pressing.

Organic molecules found in nature, *natural products,* are often known to exhibit pharmacological or biological activities that are beneficial in treating diseases, making them highly desirable components for both research and development. It is important to develop economical, pragmatic, and environmentally responsible routes leading to these natural products so that their biological activities can be further explored.

## Study Design

Having the target product in mind, we began developing a retrosynthetic plan. Following our plan, we began a Diels-Alder cycloaddition study of juglone and isoprene mediated with a lewis acid (**Figure 1**). This yielded a relatively pure, and regiospecific, cycloadduct product. We isomerized the cycloadduction to form a 1,4 diene and are currently working on di-hydroxilation and epoxidation studies to further our research.

I plan to introduce a syn-dihydroxylating agent such as a Prevost-Woodward reaction. If this produces the correct intermediate, with good regioselectivity and stereoselectivity, then derivatives of altersolanol P can be produced. Regioselectivity and stereoselectivity are explained as the specific position and direction of the added substituents, i.e. the methyl group away from the peri-OH and dihydroxilation being both in the same direction- dashed, shown in Figure 1. Additionally, an oxidation to form a napthoquinone-functionalized derivative can also be studied. Long-term goals are to test the antibacterial activity of our synthetic derivatives.

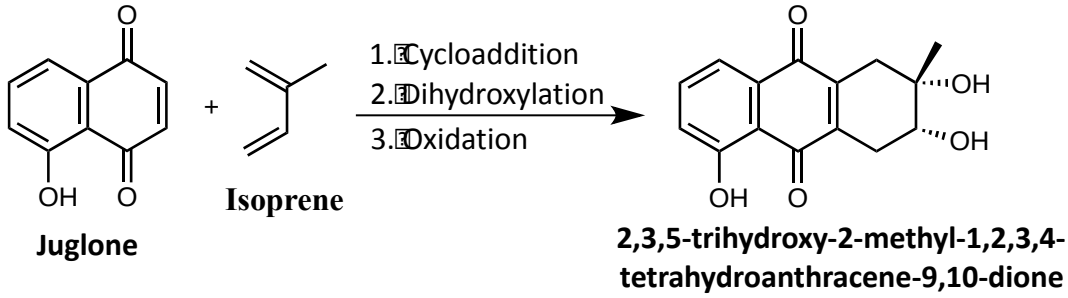
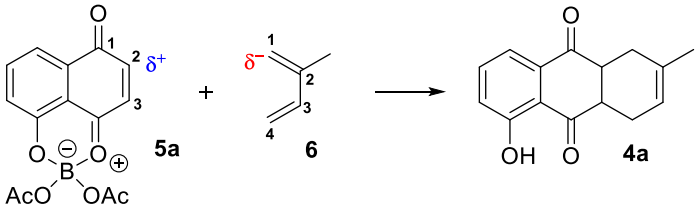



Figure 1: Synthetic plan from starting materials to altersolanol P derivative

## Results

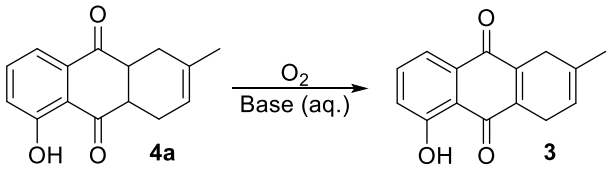
The purpose of this research project is to produce an efficient, user friendly, and environmentally conscientious synthetic route to derivatives of the naturally occurring chemical – Altersolanol P (AP), a chemical which has shown antibacterial activity against drug resistant strains of bacteria. This will allow for antibacterial testing previously unreported chemicals that are structurally similar to AP.

Examination of the Diels Alder study showed an optimization using boron triacetate, $B(OAc)_3$ which produced 78% yield and only the desired stereoisomer. Scheme 1 shows the Lewis acid-base complex that mediated the cycloaddition.




**Scheme 1.** Desired DA Reaction to give Product **4a**

After examining table 2, it is clear the most effective air oxidation form is mediated using 2M KOH. Based on the results of the study, the concentrations of the strong base did not significantly affect the yield. This observation can be seen in reactions 1, 3, and 5 where the difference in percent yield only ranged from 3-4 %. The type of strong base used also did not have a significant impact on the percent yield. Reactions 2 and 6, where the only difference is the type of base, only had a 6% difference in the percent yield. However, it was observed that the percent yield increased as the amount of the starting material was increased. For example, reactions 6 and 7, where the amount of starting material was increased from 0.5 mmol to 7 mmol, saw an increase of 20% isolated yield. This reaction was successfully scaled up to a multi-gram scale with 75% yield. It should be noted that the 1, 4-diene undergoes aromatization when open to air and should be stored under inert gas.



| Rxn | Base | Molarity | Volume (mL) | Time (min) | Amount SM (mmol) | Isolated Yield |
|---|---|---|---|---|---|---|
| 1 | NaOH | 1.25 | 3 | 15 | 0.2 | 57 % |
| 2 | NaOH | 2 | 5 | 15 | 0.5 | 48 % |
| 3 | NaOH | 3 | 3 | 15 | 0.2 | 56 % |
| 4 | NaOH | 5 | 3 | 15 | 0.2 | 60 % |
| 5 | NaOH | 2 | 80 | 15 | 7 | 72 % |
| 6 | KOH | 2 | 5 | 15 | 0.5 | 55 % |
| 7 | KOH | 2 | 20 | 15 | 7 | 75 % |
| 8 | $Na_2CO_3$ | 2 | 5 | 15 | 0.2 | - |

**Table 2.** Results from the Alkaline Air Oxidation Study

I expect this Prevost-Woodward reaction to stay true to its literature precedent. If this is the case, the project will move forward nicely. As research often tends to do, things don't go as planned. As backup plans, I have found significant research that the addition of an AD mix alpha reagent might cause syn-dihydroxilation or the use of potassium osmate(VI) dehydrate.

## Conclusion

We are currently two steps away from the target compound. We were able to produce the 1,4-diene from juglone and isoprene with an overall yield of 71%. We are still investigating the reaction conditions that would yield the 1,3-diene. Future work also includes a syn-dihydroxylation study and biological activity study.

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