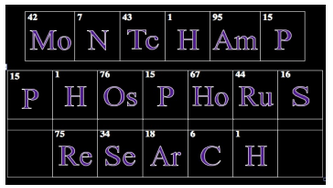
Streamlined Synthesis of a Potent Inhibitor of Dehydroquinate Synthase

Ella Fitterer and Jean-Luc Montchamp*

Department of Chemistry and Biochemistry, TCU Box 298860, Texas Christian University, Fort Worth, Texas, 76129, USA.

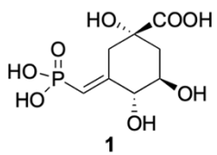
Email: j.montchamp@tcu.edu



Introduction:

This project is to synthesize a known sub-nanomolar inhibitor of dehydroquinate synthase for evaluation as an antimicrobial agent in collaboration with TCU's Biology Professor McGillivray. It is estimated that nearly 10 million individuals could die per year due to antimicrobial resistance by the year 2050.[1] The focus will be two-fold; first, the improved synthesis of alkenylphosphonate **1**, and then its elaboration into various prodrugs to improve its activity in vivo. The in vitro activity of **1** on dehydroquinate synthase is K_i = 0.29 nM, while the enzyme's substrate has K_m = 4 μM.[2] Dehydroquinate synthase is an enzyme that is part of the aromatic amino acid biosynthetic pathway, which is essential to bacteria and plants but does not exist in mammals — which is why we must eat vegetables and fruits. Thus, the toxicity to humans of antibacterial compounds targeting this pathway should be minimized.

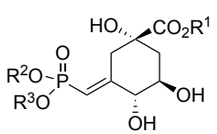
Compound **1** was synthesized previously,[2] but improvements to its synthesis must be made since it will be the starting material for the preparation of prodrugs. Prodrugs are compounds that are precursors of **1** but where the charge is masked. Because inhibitor **1** is highly hydrophilic, this prodrug strategy should be necessary to achieve biological activity in vivo. Initial work will aim at the large-scale preparation of **1** and particularly eliminate as much as possible the need for purification by chromatography.

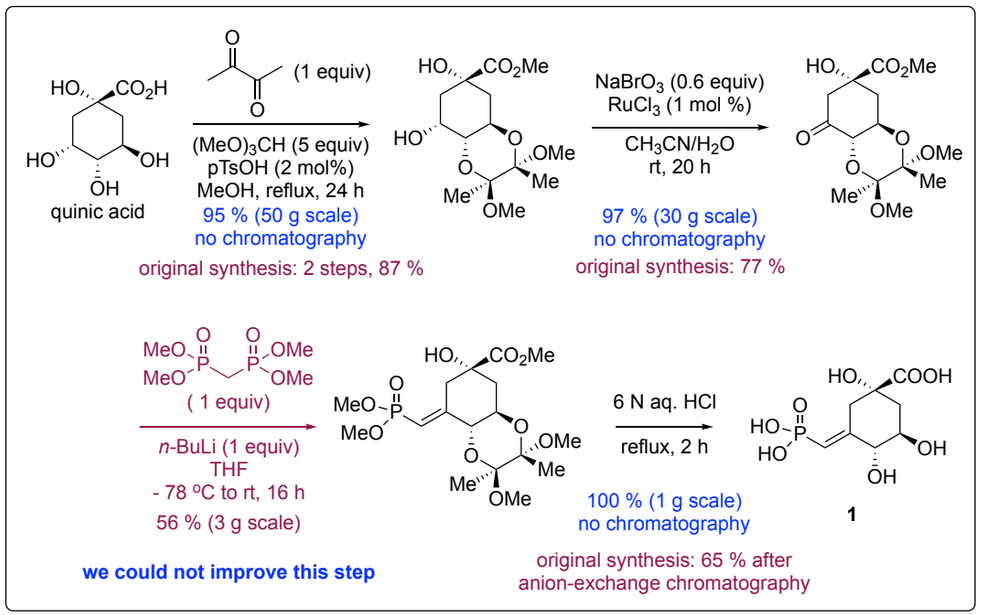


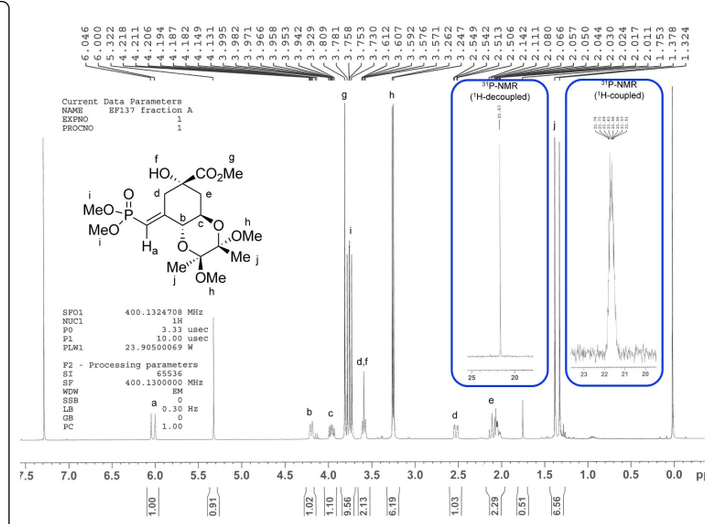
1

Future Work:

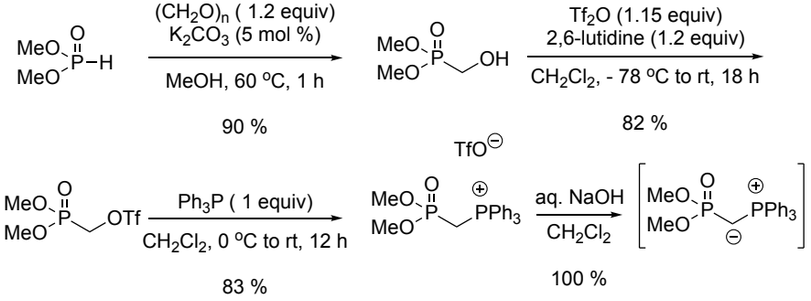
Synthesize prodrugs of Compound **1**



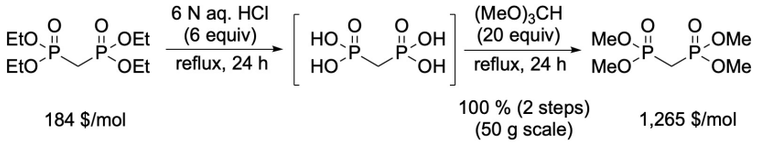




Synthesis of a Wittig reagent:



Synthesis of bisphosphonate reagent:



184 $/mol

100 % (2 steps)
(50 g scale)

1,265 $/mol

Conclusion:

The original synthesis had five steps with an overall yield of 25%. The new synthesis is four steps with an overall yield of 52%. Despite many attempts to improve the olefination, this original reaction is best.

References:

1. Centers for Disease Control. 2019. Antibiotic resistance threats in the United States, https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf (last accessed 09/23/2024).
2. Montchamp, J.-L., and J. W. Frost. 1997. Cyclohexenyl and Cyclohexylidene Inhibitors of 3-Dehydroquinate Synthase: Active Site Interactions Relevant to Enzyme Mechanism and Inhibitor Design. *Journal of the American Chemical Society* 119: 7645-7653.

Acknowledgements:

We gratefully acknowledge financial support from TCU Science and Engineering Research Center (SERC).