Chemistry of bridged vitamin K model compounds

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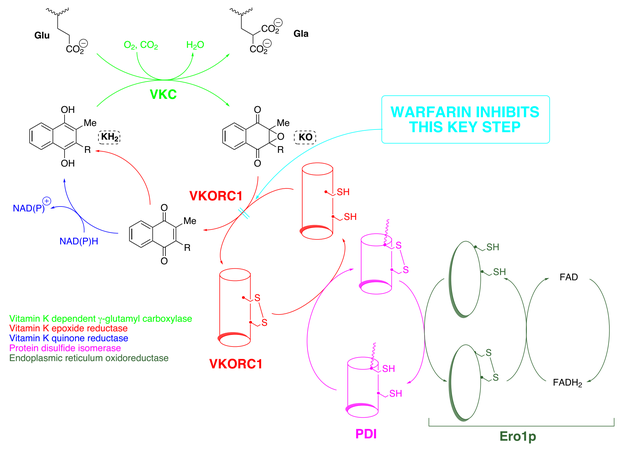
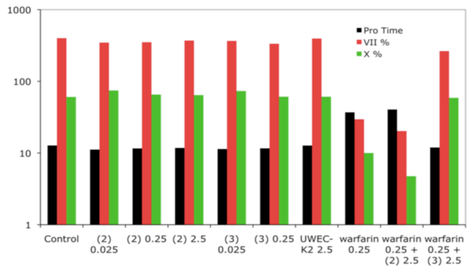
Background

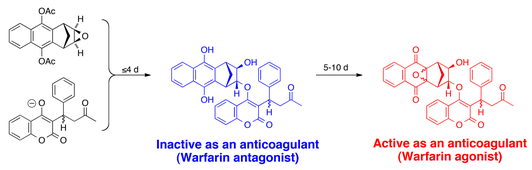
- Blood Clotting and the vitamin K Cycle
  - Two major enzymes involved
    - γ-glutamyl carboxylase (GGCX)
    - vitamin K oxide reductase (VKORC1)
  - Reduced vitamin K essential for making mature clotting factors
  - vitamin K 2,3-epoxide recycled through VKORC1
  - Warfarin inhibits VKORC1



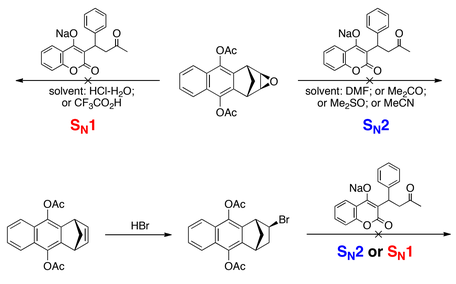
Anticoagulation: Studies in rats



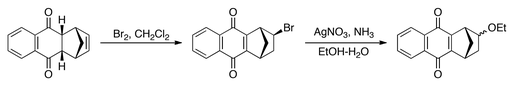
Rationalization of observed *in vivo* results



Attempts to conjugate UWEC-K2 with warfarin under S_N1 or S_N2 conditions

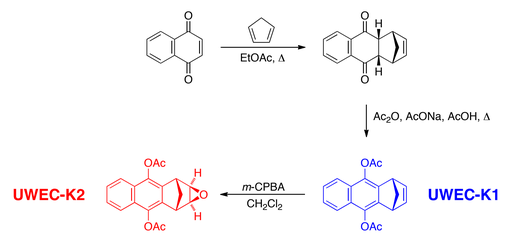


The first successful S_N1 coupling of a brominated vitamin K analogue



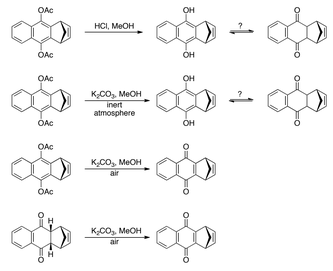
- addition of bromine to the diketone leads to quinone formation rather than simple addition.
- attempted S_N1 displacement of the bromide by ammonia in ethanol, with silver ion catalysis, led to formation of the ethyl ether.
  - this reaction is still under investigation to optimize the result
  - this reaction offers the best hope for synthesizing a warfarin conjugate

Synthesis of vitamin K analogs

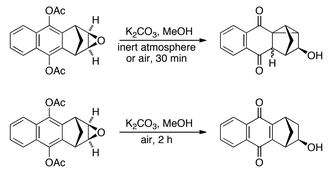


Hydrolysis and oxidation of UWEC-K1

- base hydrolysis is accompanied by oxidation to the quinone
- Diels-Alder diketone is also oxidized to the quinone under these conditions



Hydrolysis and oxidation of UWEC-K2



- base hydrolysis under an inert atmosphere gives the cyclopropyl carbinol
- extended base hydrolysis under air gives a mixture that includes the quinone

Acknowledgement:

- WiSys Technology Foundation
- University of Wisconsin-Eau Claire Office of Research and Sponsored Programs