Second generation approach:

- Our original synthesis of 12-epi-pleuromutilin failed to deliver a library of fully synthetic compounds for several reasons.
- The new sequence improves efficiency, incorporates C14 and C12 extensions and is modular to novel hydridenones.

Revised core synthesis:

- Formation of the C9 quaternary center is challenging and fails on other hydridenones.
- Serendipitous discovery of a novel Wolff rearrangement delivers the desired C9 stereochemistry with perfect dr.
- Novel oral bioavailability and Gram-negative activity within the last five years.
- Despite their activity, pleuromutilins suffer from poor pharmacokinetics, partly due to the hydrophobic tricyclic core. Additionally, they are metabolized rapidly by cytochrome P450. Most pleuromutilins cannot be taken orally.

Macrocyclization strategy:

- In order to prepare fully synthetic analogs, we designed our macrocyclization strategy with several ideas in mind:
  - Improve yield, efficiency, and diastereoselectivity when forming secondary alcohols.
  - Install thiol side chains late-stage for potency against Gram-positive bacteria.
  - Explore equatorial modifications for potency against Gram-negative bacteria.
- A diastereoselective propargylation reaction and reductive coupling were used to form the eight-membered ring.
- The macrocycle can be elaborated to derivatives including the functionalized glycolic ester in 4-5 synthetic steps.
- Our macrocyclization strategy is tolerant to other bicyclic cores.
- Novel cores can be used to probe effects of substituents on metabolic stability and provide new SAR information.

References: