Total Synthesis of Fully Synthetic (+)-Pleuromutilin Analogs

Mikaela DiBello[1], Olivia Goethe[1], and Seth Herzon[1,2]

1.Department of Chemistry, Yale University, New Haven, CT.

2. Department of Pharmacology, Yale University, New Haven, CT.

(+)-Pleuromutilin class background

- First isolated in 1951.[1]
- Binds to the peptidyl transferase center of the bacterial ribosome and inhibits protein synthesis. (**Fig. 1**)

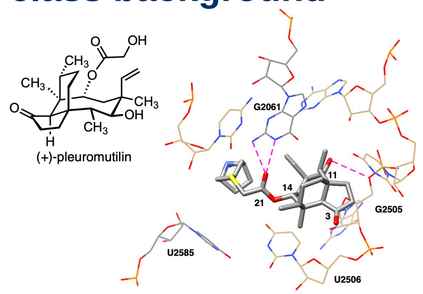
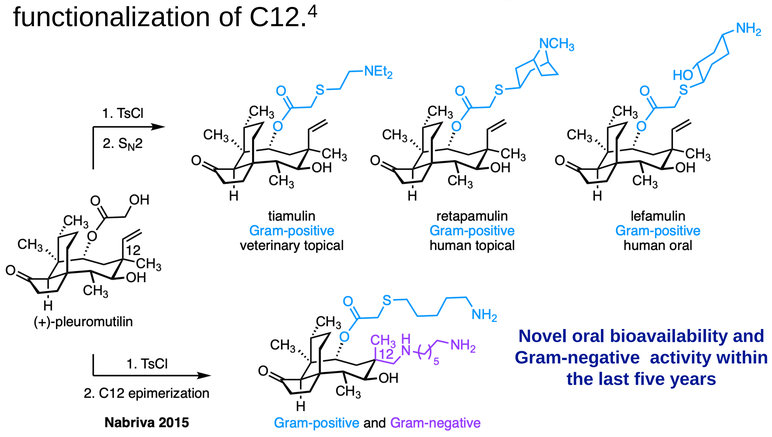


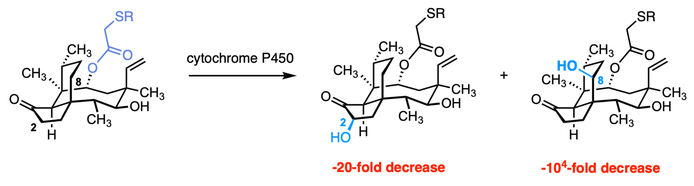
Figure 1. Retapamulin bound to the ribosome

- Three enantioselective syntheses of (+)-pleuromutilin have been completed. The Herzon lab completed the first convergent synthesis in 2017.[2]
- Thousands of analogs have been prepared at the C14 position and exhibit activity against Gram-positive bacteria.[3]
- Nabriva demonstrated that activity against Gram-negative bacteria can be achieved following epimerization and functionalization of C12.[4]



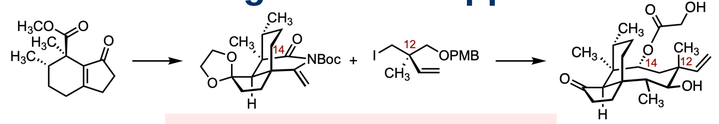
Novel oral bioavailability and Gram-negative activity within the last five years

- 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.[3]



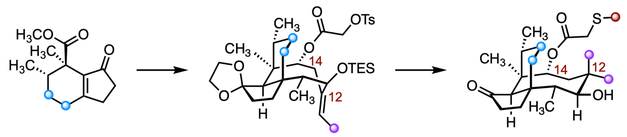
- New fully synthetic analogs will help add to the knowledge base of pleuromutilin's bioactivity and realize the potential of this exciting class.

Second generation approach:



14 steps to natural product, 0.05 % yield

- Our original synthesis of 12-*epi*-pleuromutilin failed to deliver a library of fully synthetic compounds for several reasons.

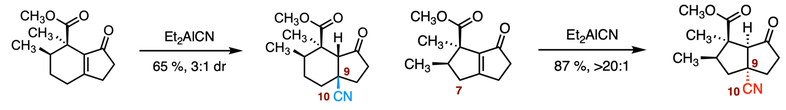


10 steps to diversifiable intermediate, 16.7 % yield

- The new sequence improves efficiency, incorporates C14 and C12 extensions and is modular to novel hydrindenones

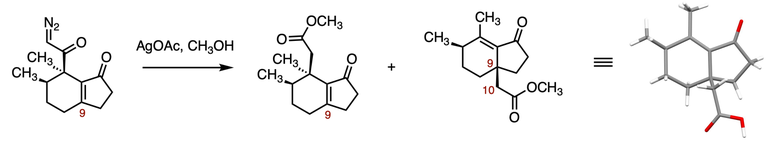
Revised core synthesis

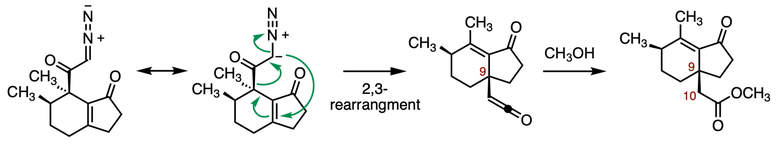
- Formation of the C9 quaternary center is challenging and fails on other hydrindenones.



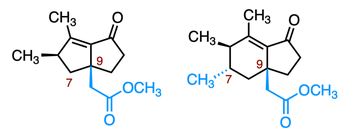
Moderate diastereoselectivity at C9 **Wrong facial selectivity**

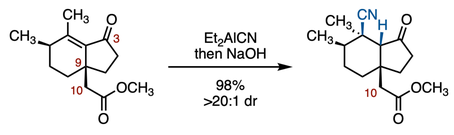
- Serendipitous discovery of a novel Wolff rearrangement delivers the desired C9 stereochemistry with perfect dr.





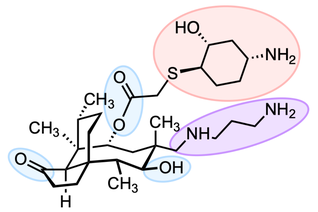
- Other hydrindenone cores are tolerated, and 1,4- addition to the rearranged enone is facile.





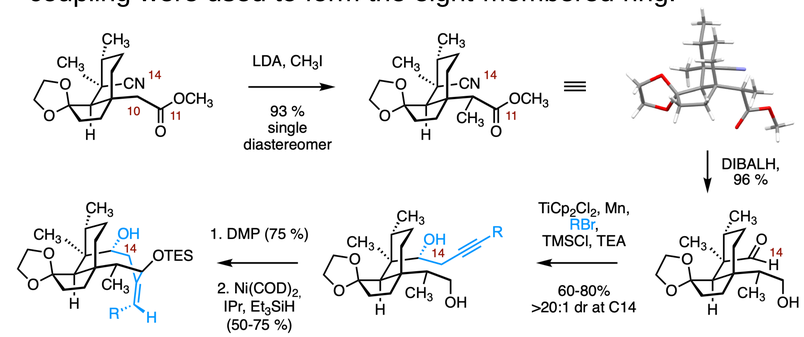
Macrocyclization strategy

- In order to prepare fully synthetic analogs, we designed our macrocyclization strategy with several ideas in mind

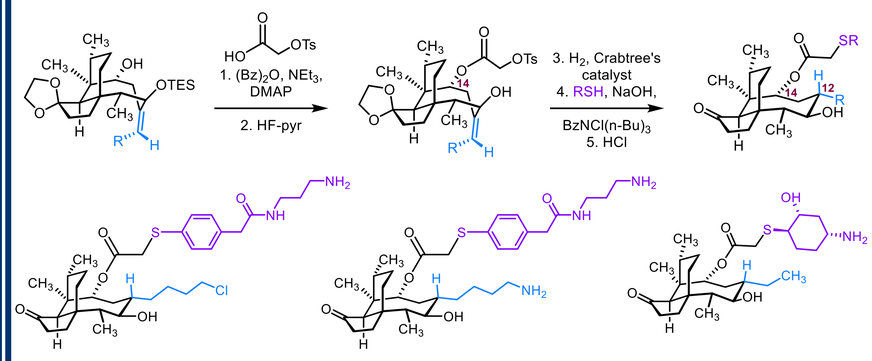


- Improve yield, efficiency, and diastereoselectivity when forming secondary alcohols.
- Install thiol side chains late-stage for potency against Gram-positive bacteria.
- Explore equatorial modifications for potency against Gram-negative bacteria.

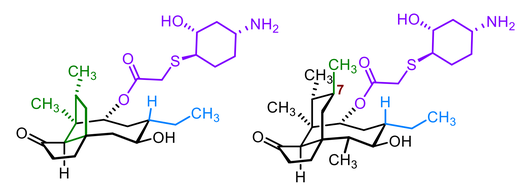
- A diastereoselective propargylation reaction and reductive coupling were used to form the eight-membered ring.



- 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

1. Kavanagh, F.; Hervey, A.; Robbins, W. J. *Proc. Natl. Acad. Sci. U. S. A.* **1951,** *37* (9), 570-574.
2. Murphy, S. K.; Zeng, M.; Herzon, S. B. *Science* **2017**, *356*, 956.
3. Goethe, O.; Heuer., A; Ma, X.; Wang, Z.; Herzon, S. B. *Nat. Prod. Rep.*, **2018**, Advance Article
4. Paukner, S.; Strickmann, D. B.; Ivezic-Schoenfeld, Z. ECCMID, Barcelona, Spain, 2014.