Proposal of a Novel Total Synthesis of a Natural Product

CHEM 6352

Due 5pm, Monday, Dec. 15, 2014.

Eligible molecular targets: See the attached list of compounds with references. If you have encountered a natural product target that you perceive to be of equivalent difficulty and wish to select it for this project because of your interest, you may do so but see me for first for approval.

Choosing a target: You should look over at least multiple targets if not all of them. Size is not a true indication of difficulty, and attempting a retrosynthetic analysis for several molecules will help see what structural elements are most difficult to create. Moreover, everyone sees synthesis somewhat differently, so what's difficult for someone else may be an obvious target for you. Remember it's best to keep trying new things until you truly feel comfortable with the target and approach. Revisions as new chemistry is discussed in class may also be helpful.

What to Include in Your Final Proposal

I) Background and Summary of Target: After choosing a target, you should read the paper(s) reporting the isolation, characterization and biological activity (if applicable) of your target. You may have to do more research to find all relevant papers. Provide a brief background for the molecule. Have there been any synthetic approaches or additional information for this target reported in the literature? A search using a chemical database (e.g. Scifinder Scholar or Reaxys) is recommended to identify this information. Be sure to include important and relevant references as footnotes.

Describe what you perceive to be the major synthetic challenges for your molecule. These could be the presence of medium rings, quaternary carbons, stereocenters, sensitive functional groups, odd atomic arrangements, etc. Are there any tough problems that you identified in your retrosynthesis?

II) Retrosynthesis (*First draft due Nov 11th, 2014. Second draft due Nov. 25th*). The first step in creating your synthesis should be a retrosynthetic analysis. As stated above, you should be doing this for several if not all of the molecules before choosing a target. Only through examining the chemical structure and how bond formation may occur can you find the target that best fits your knowledge and interest.

In order to provide feedback, I am asking for an initial retrosynthesis, created in a chemical drawing program (Chemdraw, Isisdraw, etc.), on the above dates at the beginning of class. I will provide comments on the strategy used, as well as feasibility and potential problems that may be encountered. I will NOT provide ideas, alternatives, or solutions to the problems that I see. However, pointing out these problems early should allow time to fix them. Thus, the retrosynthesis should be adequately detailed and explained that I may follow your logic. Include short descriptions of the transforms where necessary. A revised retrosynthesis will then be submitted to answer the feedback I give. ***A finalized version of your retrosynthesis will be incorporated in the final proposal.***

Note that a good and feasible retrosynthesis requires hard work and especially time. *Do not leave it to the last minute or you will not receive a good grade for the project*. Much thought is needed. A thorough retrosynthetic analysis will make planning a synthesis much easier. A lack of effort in a retrosynthesis will leave problems in a forward synthesis that cannot be easily overcome. Thus, thoughts of the forward synthesis should be kept in mind during these planning stages. I will be available if you want to ask if a transformation has a chance of succeeding.

III) Presentation of the Synthesis: All schemes should be created in a chemical drawing program and referenced *and described* in the written text. Reagents must be written over arrows rather than in a caption. For a model see a current synthesis in JACS or see the example on the website. Please single space. References should be included as footnotes (NOT endnotes).

Starting materials for your synthesis must be commercially available (i.e. found in a chemical catalog). Cheap (≤$5/gram) and plentiful starting materials are more attractive. The use of chiral, enantioenriched starting materials is an excellent strategy to begin an enantioselective synthesis. Use of chemical intermediates described by other synthetic chemists in the literature is appropriate, but their work should be properly referenced and the sequence described in your proposal. Use of Scifinder and Reaxys is encouraged to identify suitable starting points (and commercially available starting materials) for the synthesis and to find reaction conditions for proposed transformations. Any reference books, notes, etc. may be used as well. ***A draft of the synthesis is due Dec. 4***, which should include your retro. I will give feedback.

All necessary reaction conditions to describe the proposed transformation must be stated. Provide references to examples that set a precedent for the transformation you are proposing, *especially* if there are questions of chemoselectivity, regioselectivity, or stereoselectivity. The references in your class notes should help with this, but be sure to actually look at the reference you cite to be sure it is relevant. Any formation of new stereochemistry must be rationalized in an appropriate scheme. You must explain and defend why you think each step will work; mechanisms are encouraged. *I will be acting as a skeptic as I read these proposals, so it is your job to convince me it will work.*

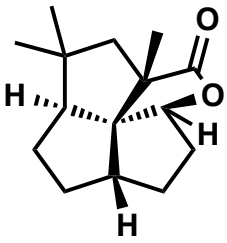
Grading: Grades will be on a percent scale. *Racemic syntheses will not receive full credit*. You may need to propose an enantioselective variant of an existing transformation for your synthesis. Grading will take into account the difficulty of the chosen target, reaction feasibility, synthetic efficiency, and innovation.

Difficulty: For the simple molecules, there must be fewer problems in the synthesis to achieve a higher grade. In more difficult molecules, greater risk is inherent and accepted in the proposal. That acceptance will not excuse any transformation that is physically impossible, however, so tread carefully.

Feasibility: Exact conditions for transformations should be carefully considered to avoid compatibility issues with other functional groups. Protecting groups should be used wisely to prevent detrimental side reactions. Stereochemical and steric biases should be considered to judge the likelihood of a transformation. Know the limits of your reaction conditions and do not exceed them. Key bond-forming events should be justified in the text, and evidence should be provided to support your claims.

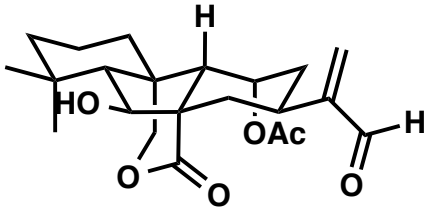
Efficiency: A better grade will be achieved by syntheses that demonstrate convergency, use fewer steps, minimize use of protecting groups, show atom economy, avoid unproductive functional group interconversions, and concentrate on productive bond formations.

Innovation: The art of synthesis advances chemical strategy and inspires new reaction development. Natural products are worthwhile targets that inspire the imagination. The ideal innovation in a proposal such as this is to use you background knowledge of chemistry to extrapolate to new bond-forming possibilities. Another manner of innovation is to use reactions in a previously unseen synthetic strategy to accomplish the formation of a complex functional group in a reliable manner. The synthetic chemist walks a fine line to propose new chemistry while providing evidence that the proposed transformation will work by showing examples of closely (or partially) related examples from the literature.



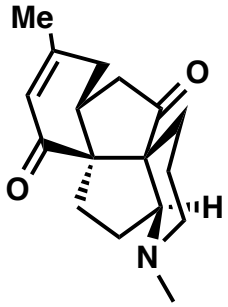
Penifulvin A

Org. Lett. **2006**, *8*, 1225–1228



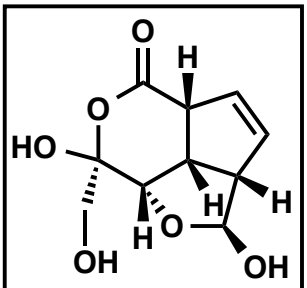
Maoecrystal Z

Org. Lett. **2006**, *8*, 4727-4730



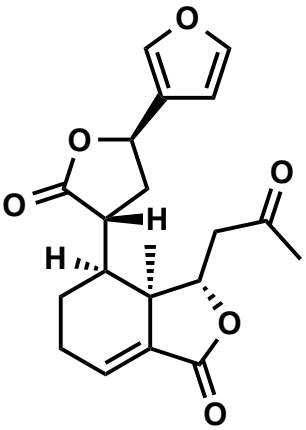
Lycojaponicmin C

Org Lett **2012**, *14*, 2614



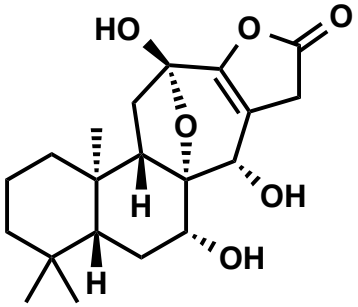
Lucknolide A

Org. Lett. **2010**, *12*, 3800-3803



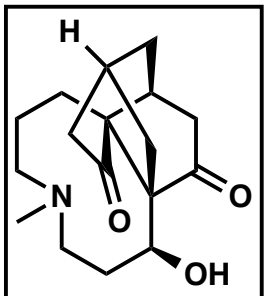
Cephaloziellin E

J. Nat. Prod. **2013**, *76*, 1700–1708



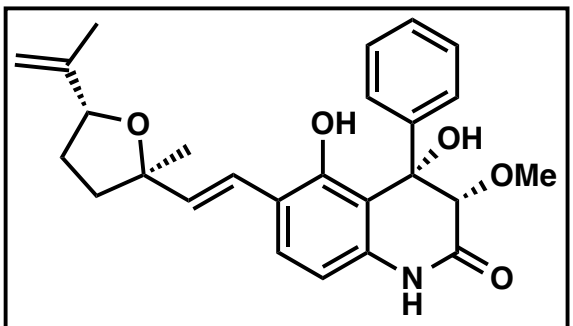
Bannaringaolide 4

J. Nat. Prod. **2004**, *67*, 1789-1795



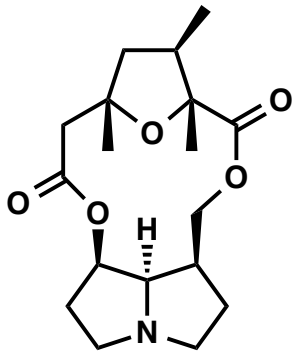
Palhinine A

Org. Lett. **2010**, *12*, 3922-3925



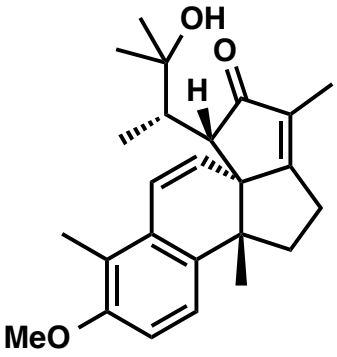
Aniduquinolone A

J. Nat. Prod. **2013**, *76*, 1896.



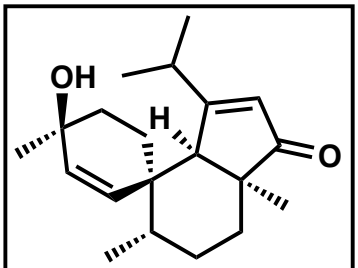
Nemorensine

Collect. Czech. Chem. Commun.
1973, *38*, 2504.
1976, *41*, 2952.
1980, *45*, 548.



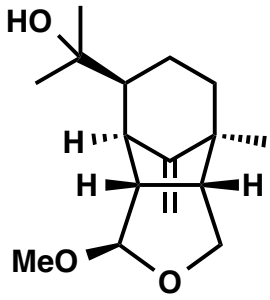
Agariblazeispirol C

Tetrahedron **2005**, *61*, 198



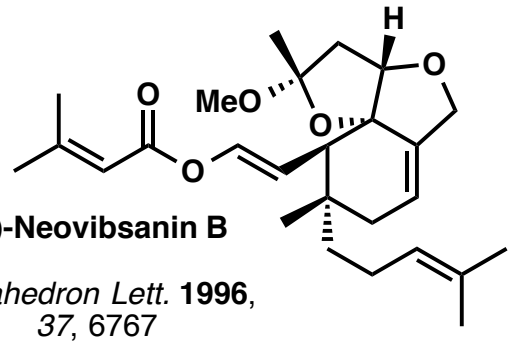
Cyanthiwigin AC

Org Lett **2003**, *5*, 4575



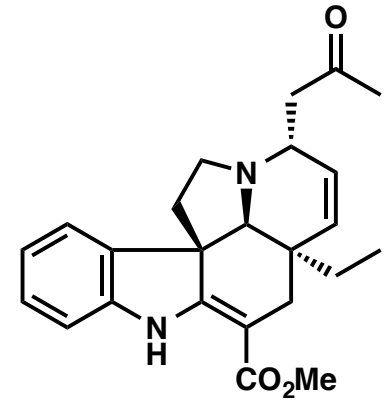
Drechslerine E

J. Nat. Prod. **2002**, *65*, 306-313



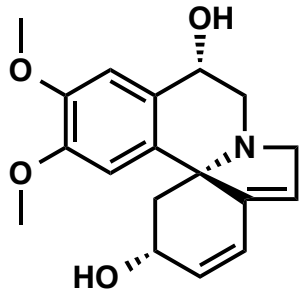
(+)-Neovibsanin B

Tetrahedron Lett. **1996**, *37*, 6767

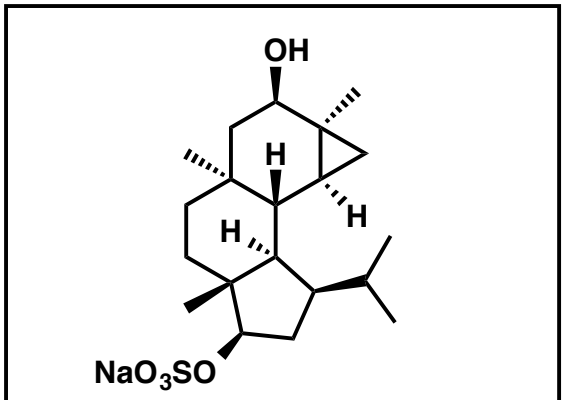


Melodinine R

J. Nat. Prod. **2012**, *75*, 220

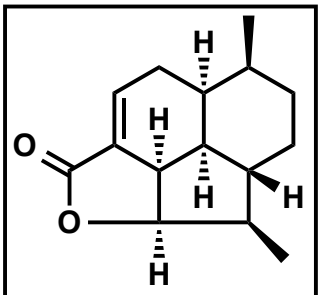


(+)-11a-hydroxyerythravine
J. Nat. Prod. **2007**, *70*, 48-53



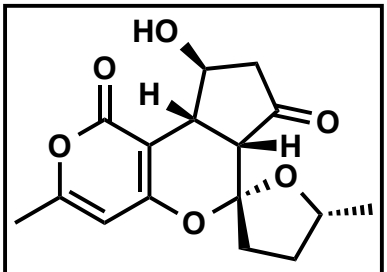
13-*epi*-neoverrucosane

Bull. Chem. Soc. Jpn. **2005**, *78*, 1345-1347



Mitchellene B

J. Nat. Prod. **2011**, *74*, 1888.



Tenuipyrone

Org. Lett. **2012**, *14*, 513