It is proposed to synthesize a number of gamma lactone analgesic antagonists which may prove useful as alternative treatments for narcotic addiction. More importantly, success of this project will produce a series of potent painkillers that will have virtually no addiction liability. These antagonists can be synthesized from commercially available starting materials and should not only provide valuable information on the exact shapes of the four sub-type receptors, which are unknown at this time, but would allow for the design and synthesis of analgesics with such specific action that they interact only with the sub-type receptor that interrupts pain, but not the one that causes euphoria and thus addiction.

I will be synthesizing several closely-related gamma lactones from the combination of commercially-available starting material with each of three acids and two esters. These five reagents, (t-butyl acetate, benzyl acetate and isobutyric, acetic, and phenylacetic acids), will be utilized to exchange the functional group of the parent molecule in attempts to control cell receptor affinity and antinociceptive properties of these analgesic blockers. I expect the complete reaction of each acid or ester to require two weeks, and the characterization and identification of each product to require a week per molecule, totaling fifteen weeks in all.

This is my senior year as an honors pre-med chemistry major. I've nearly completed the requirements for ACS certification as well as those for a concentration in biochemistry. These requirements include two semesters of advanced organic lab work and lecture, quantitative analysis, instrumental analysis, and additional coursework in a profuse number of biological courses. My qualifications concerning lactone synthesis itself include a year-and-a-half in Dr. Black's research lab, including this past summer, which was facilitated by my receiving a competitive CURSOR summer fellowship. In that time, a novel, streamlined synthesis of primary starting material was developed that is faster and higher-yielding than any method currently known and is being prepared for submission to the *Journal of Organic Chemistry*.

There are certain types of painkillers that are known to interact indiscriminately with each of the four known sub-type cell receptors. Unfortunately, this lack of specificity towards any one of these receptors leads to a compound that has very potent painkilling and addictive properties. Synthesis of the proposed gamma lactone antagonists will aid in the development of available chemical transformations in the analgesic molecule, such that specificity for only that receptor which is responsible for pain-relieving qualities is targeted. Such a molecule would be a powerful asset in the treatment of many diseases, not only due to its incredible antinociceptive properties, but also due to its potential as a non-addictive drug.

The gamma lactones and the obtained intermediates will be analyzed by nuclear magnetic resonance, infrared, and high resolution mass spectroscopy as well as thin layer chromatography to characterize and accurately identify these molecules. These are standard procedures with which I am familiar due to coursework I have undertaken or training I have received at Eastern. Pharmacological assays (both *in vitro* and *in vivo*) will be performed by Professor Kip McGilliard at EIU who, should the project succeed as hoped, will become a major collaborator.

The results of this synthesis and research will be submitted to the *Journal of Organic Chemistry*, *Synthetic Communications*, *Tetrahedron Letters*, *et al*. If truly promising biological assays are realized, the results will be submitted to the *Journal of Medicinal Chemistry*. However, if excellent *in vivo* results are found for compounds with no addiction liability, we will investigate patent protection, along with the University, prior to publication.

Jennifer Forsee (BS EIU; PhD Kansas (Georg), postdoc Stanford (Wender)