Synthesizing a Cell-Specific DNA-Damaging Molecule

Heather Noelle Lewis

Department of Chemistry and Biochemistry, University of North Carolina at Wilmington, 601 South College Road, Wilmington, NC 28403

Abstract

A key intermediate to the overall synthesis of methyl-lexitropsin is being modified to reduce the expense of the development of the molecule. Several methods were tested, until the optimal synthesis was reached. Four primary steps are involved in this synthesis. The first is a nitration of a trichloro pyrrole ring. The next step was the addition of an amine methyl ester pyrrole ring to the trichloro pyrrole ring developed in the first step. The third step involved adding an alkene to the nitro end of the intermediate, which required an initial reduction of the nitro. The final step is the hydrolysis of the methyl ester into an alcohol. The overall successful reaction scheme, and the results obtained are summarized in this paper.

Introduction

The drugs used to treat cancer today are effective, though there are some drawbacks. Many existing drugs target all rapidly dividing cells, and so individuals who undergo chemotherapy suffer from hair loss and nausea, since hair and stomach cells are some of the most rapidly dividing cells in the human body. Another drawback of these drugs is that some of them result in secondary cancers. This is because the drugs used today cause extensive and random damage to DNA. Some kinds of damage lead to cell death (which is the desired outcome of a cancer drug), while other kinds of damage lead to mutations, which may result in secondary cancers, in other words, the drugs used to *treat* cancer could also *cause* cancer. These problems can be minimized if drugs are developed that target only cancer cells, and cause only the kind of damage that leads to the death of the cell, and not cause mutations.

Compounds are being developed in our lab that could potentially alleviate these side effects. The overall design of the molecule is shown in Fig. 1 and consists of two main components, a DNA damaging section and a cell targeting section, which are connected by a linker. The DNA damaging portion of the entire molecule is a molecule known to only attack DNA in portions that are known to specifically result in the death of the cell, namely A-T rich regions located in the minor groove of the DNA. The cell-targeting portion is known to attach to particular receptors located on specific types of cells. The DNA damaging and cell targeting portions of the molecule will be connected by a linker that will be modified to optimize the properties of both portions of the molecule.

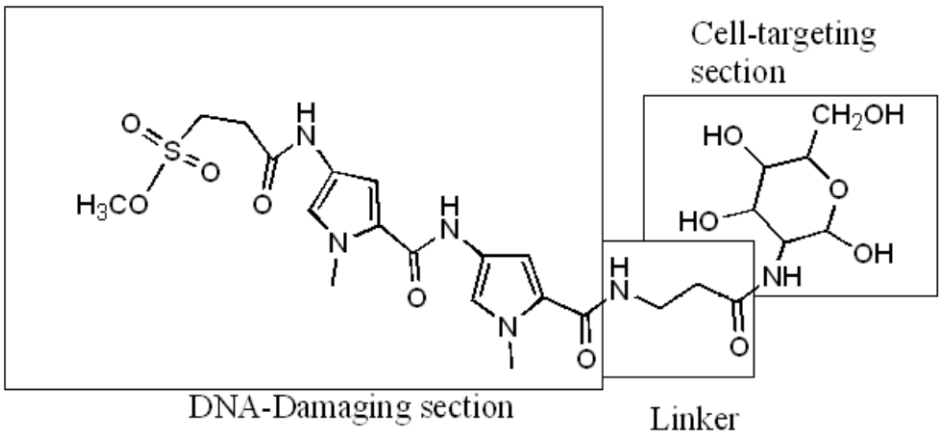


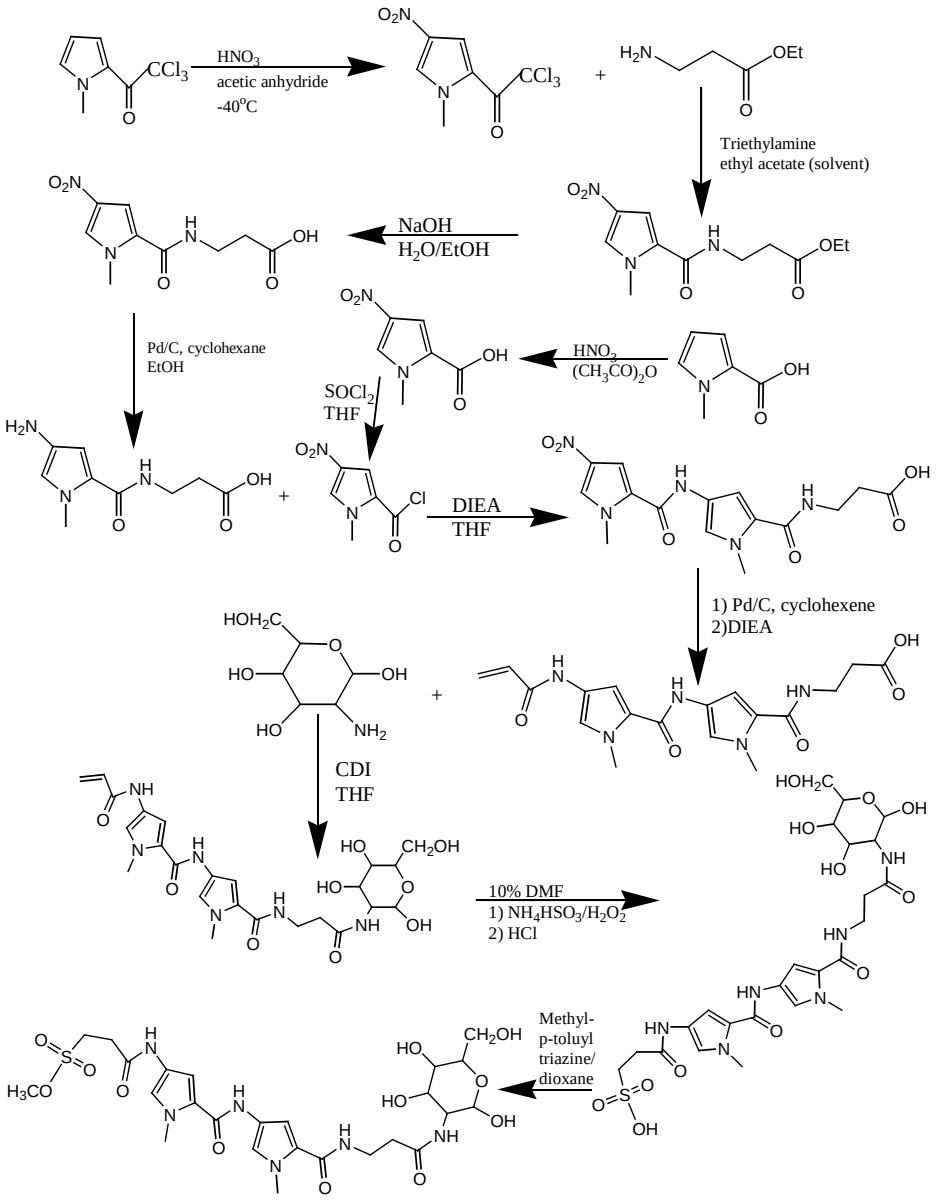
Figure 1. Illustration of the general design of the molecule

The current synthetic route used to make the desired molecule requires 11 steps, and the linker is added in step 2 of the whole synthesis, as seen in scheme I. This means that every time a new compound with a different linker is required, one has to start the synthesis all over, almost from the beginning.

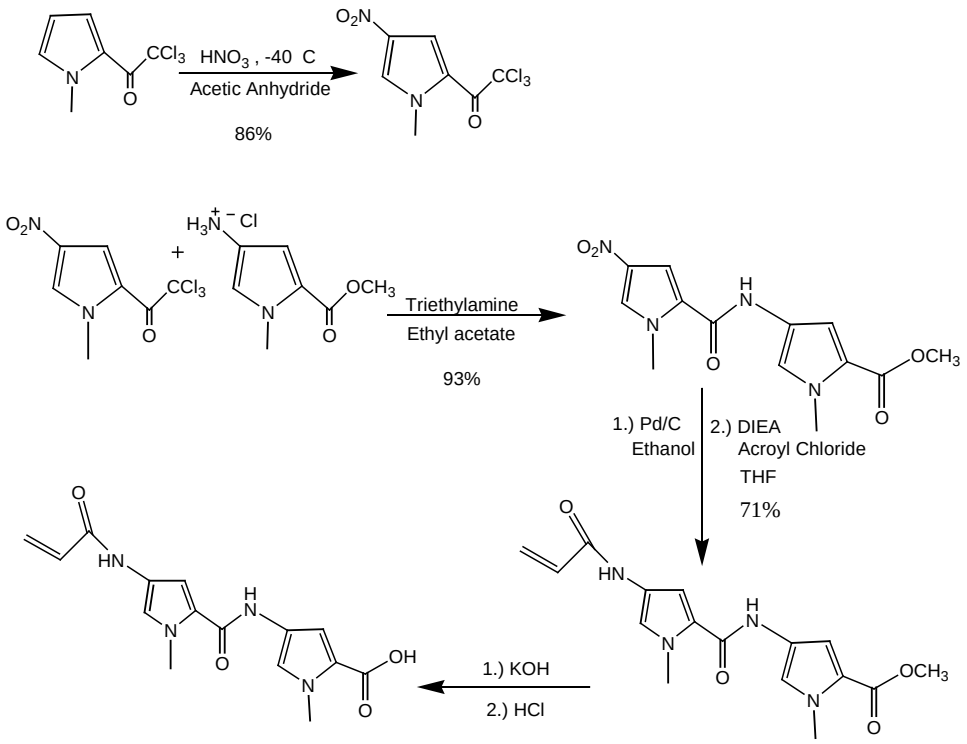
It was the goal of my research in this project to develop a new synthetic route so that the linker can be added at a much later stage in the overall synthetic route. This would enable us to prepare on a large scale the intermediate compound required, in the step before the addition of the linker (scheme II). Every time a new linker is to be tested, we can now start from this intermediate, thus reducing the number of reaction steps that have to be repeated (scheme III).

Results and Future Work

The current synthesis used to make the desired compounds is long and involving, scheme I. In an attempt to modify this, several different syntheses were attempted before arriving at the most effective one, scheme II. This modified synthesis involves developing a key intermediate of the DNA damaging portion of the molecule.



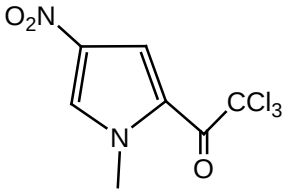
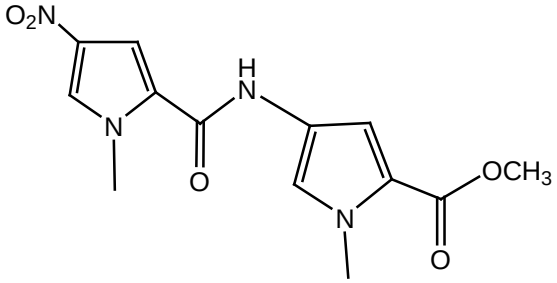
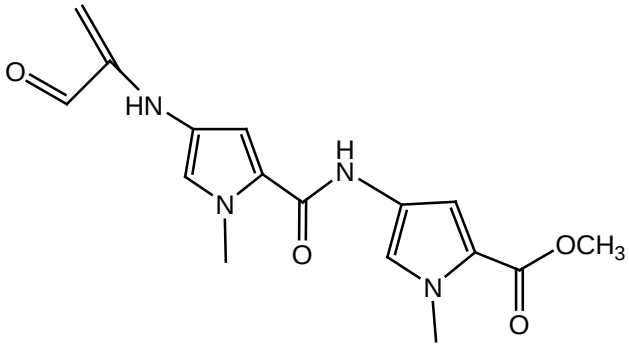
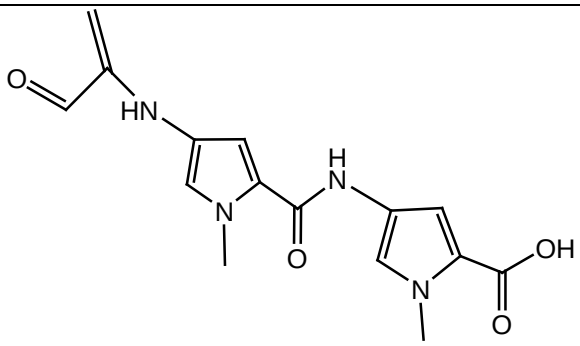
Scheme I. Current synthesis of methyl-lexatropsin to be modified.

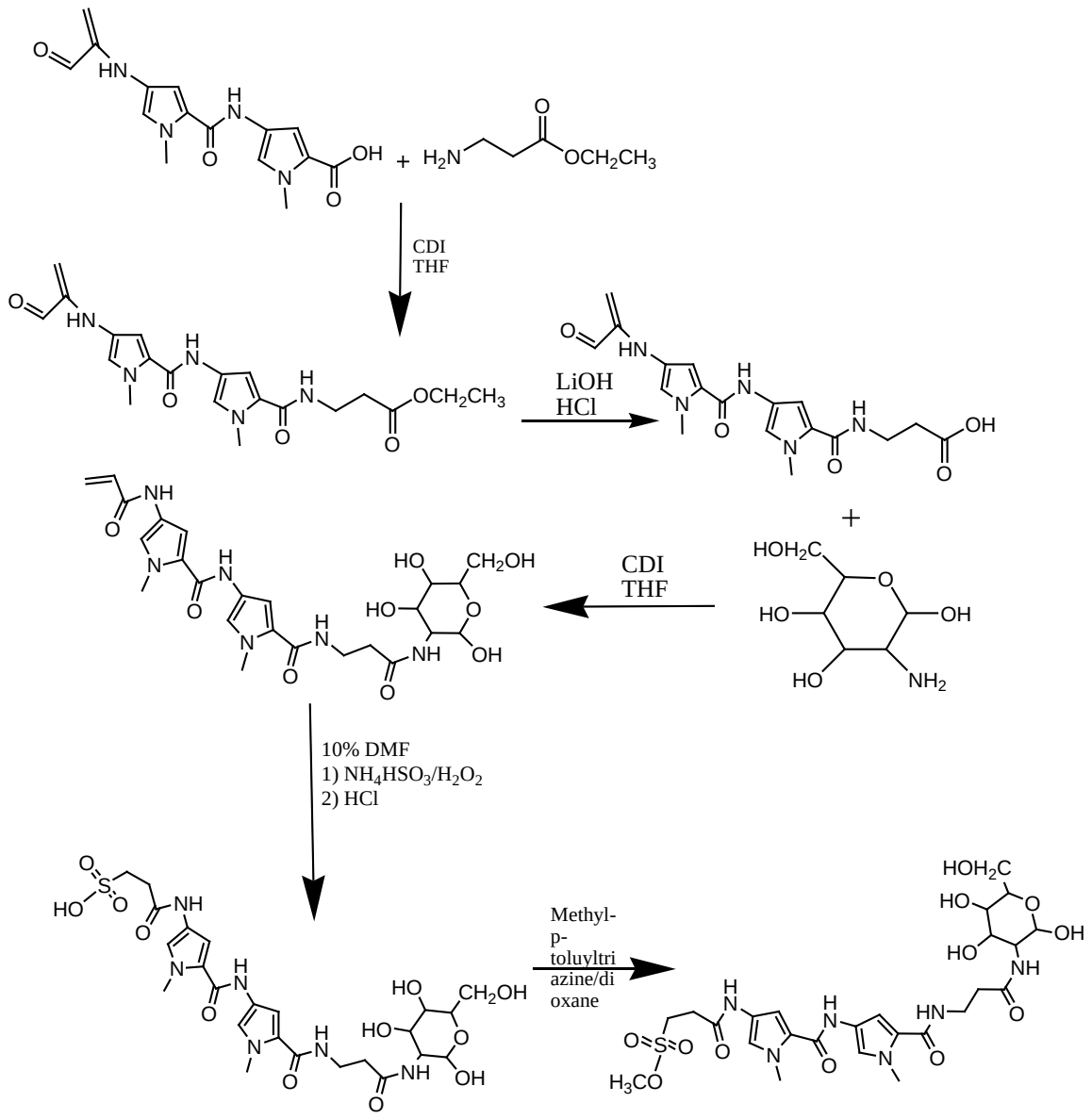


Scheme II. New synthesis of key intermediate.

All of the results obtained are summarized in the table below. Once the key intermediate is made in a large amount it will be possible to condense the overall synthesis from 11 steps down to 5 steps. To do this, one would start the synthesis with the key intermediate followed by the addition of the linker and the targeting segment of the molecule, seen in scheme III. The linker is added further on in the synthesis rather than in step 2. Since the linker is the most critical part of the molecule, one would want to ensure its success with higher percent yields rather than risking loosing it in the process of more difficult steps. By eliminating the reactions that produces lower percent yields before the linker is added, the overall synthesis is more effective. This modification also allows for the experimenter to test the efficacy of the desired linker more quickly.

Table 1. Percent yield results for compounds used to develop the key intermediate

Compound	Percent Yield
	86%
	93%
	71%
	In progress



Scheme III. Future synthesis of methyl-lexitropsin, using the key intermediate

Conclusions

It was necessary to modify the current synthesis used to develop this cell-specific DNA-damaging molecule. Due to the extensiveness of the synthesis, in addition to the expense, it had become difficult for one to develop an entire molecule each time a new linker were to be tested. This modification allows for large amounts of the intermediate to be synthesized potentially reducing the overall synthesis of the molecule down to a few, more simple steps. By eliminating the more complicated syntheses early on in development, experimenters could arrive at the desired molecules more quickly with a higher yield of more expensive and important components.

This research was just recently completed at the end of April 2005, and was presented at the South Eastern Regional Conference of the American Chemical Society held in Raleigh in November 2004. The research was also recently presented at the Department of Chemistry and Biochemistry as well as the seminar, Research in the Capital in April 2005. Because of this experience I will be attending the graduate program in the Department of Chemistry and Biochemistry in the fall of 2005 to continue the exciting research in this particular lab. This project was the most valuable educational experience I have ever had, and I am extremely grateful to the UNCW Undergraduate Research Committee for awarding me this fellowship.