APPLICATION CHECKLIST Presidential Faculty/Student Collaboration and Publication Grant

Deadline Feb. 15th (or following Monday if a weekend)

Please print and complete this checklist and attach it as the cover page of your grant application. For more information about Presidential Faculty/Student Collaboration and Publication grants, please see <www.gustavus.edu/oncampus/facdev/grants/presidential.cfm>.

FACULTY INFORMATION

Name: Scott Bur_____ Dept.: Chemistry _____
Email: Sbur@gustavus.edu_____ Rank: Assistant Professor_____

STUDENT INFORMATION

Name: David Guptill_____ Year: '09_____
Major: ACS Chemistry_____

CHECKLIST _____

Project Details

- ☑ Brief description of the proposed project including its collaborative nature
- ☑ Clear statement of anticipated outcomes
- ☑ Likely placement for publication or performance
- ☑ Anticipated research completion date

Participant Details

- ☑ Names and brief biographies of all participants
- ☑ Explanation of how this project fits into the career of the faculty
- ☑ Explanation of how this project fits into the educational trajectory of the student;
- ☐ (include year of graduation; student eligibility is limited to full-time returning students)

☑ **Presidential Budget Proposal Form attached as last page of application**

☑ **Eight copies of complete application (including this checklist) to be submitted to the**
☐ **Faculty Development Resource Center (SSC 119)**

☑ **If successful, my proposal can be used as an example to assist future faculty applicants.**
☐ **This decision will not in any way influence the evaluation of my application. Yes / No (please circle one)**

Presidential Faculty/Student Collaborative and Publication Grant Proposal

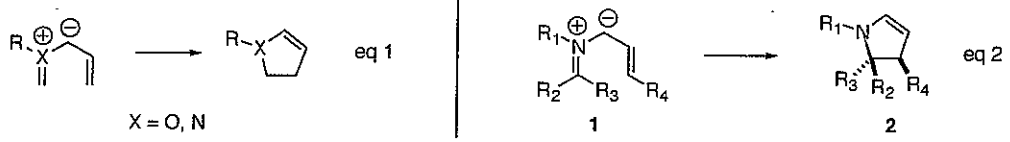
Scott K. Bur and David Guptill
Department of Chemistry
February 15, 2008

I. Proposal Description

Introduction

Heterocyclic compounds (cyclic molecules that contain elements such as nitrogen, oxygen, and sulfur) often display important biological activity. In fact, 67% of the compounds listed in the Comprehensive Medicinal Chemistry (CMC) database contain heterocyclic rings.[1,2] Consequently, the development of synthetic methods that form heterocyclic compounds can have a strong impact on the ease with which both natural products (compounds isolated from natural sources) and medicinally important compounds are constructed. While many methods have been developed for the synthesis of five-membered heterocycles, the frequency with which they appear in drug-like substances and natural products continues to drive research into their formation.

Pericyclic reactions (reactions that involve an internal reorganization of the electrons in certain bonds) constitute an important class of reactions for the formation of cyclic molecules. The 1,5-electrocyclization reaction (eq 1; an example of a pericyclic reaction) has been well-studied both in terms of mechanistic and kinetic details.[3-5] In particular, electrocyclization of compounds such as **1** are known to form five-membered nitrogen-containing rings such as **2** (eq 2).* Few applications of this approach to biologically relevant molecules have been reported, however.[6-9] One significant problem that impedes the broad application of this cyclization is that the generation of the reactive intermediate (*i.e.* **1**) from simple and readily available starting materials is not trivial.



Proposed Work and Progress to Date:

I proposed to use of vinylglycine[10] derivative **3** as a key building block to simplify the construction of electrocyclization precursors (Figure 1). My first year at Gustavus, Adam Langenfeld and I were awarded a Presidential Faculty/Student Collaborative grant to begin exploring this problem. I used the money budgeted for my stipend to hire a second student, and these students were able to learn how to make **3** in large enough quantities to begin building a reactive system such as **1**. We also

---

* The schemes and equations throughout this document include line-drawing representations of organic molecules. For those unfamiliar with this representation of molecular structure, the lines represent bonds between atoms. The vertices where these bonds intersect are carbon atoms. Other atoms are either specifically shown (O for oxygen, N for nitrogen, S for sulfur) or are represented by "generic" atoms with the designation "R." Multiple generic groups are given appropriate subscripts (*e.g.* R_1, R_2, etc.). Single lines between vertices denote single bonds, and double lines represent double bonds between atoms. For clarity, hydrogens that do not influence the reactivity of the molecule are omitted from the drawings.

received a grant from the Research Corporation for two years of continued work on this problem. During the duration of that grant, we approached the problem using chemistry that involved the reduction of **4** to **5**, a type of reaction that is well known (Scheme 1).[11] The fragment derived from the key methyl vinylglycine building block is highlighted at each step of this proposed scheme. Unfortunately, this reduction was unsuccessful, and computational analysis suggested to us that this simple reaction would not work on our system.

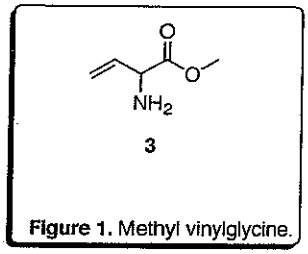
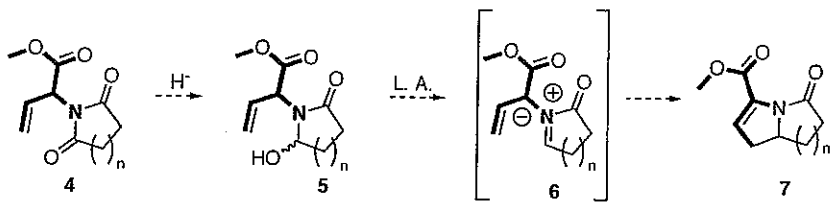
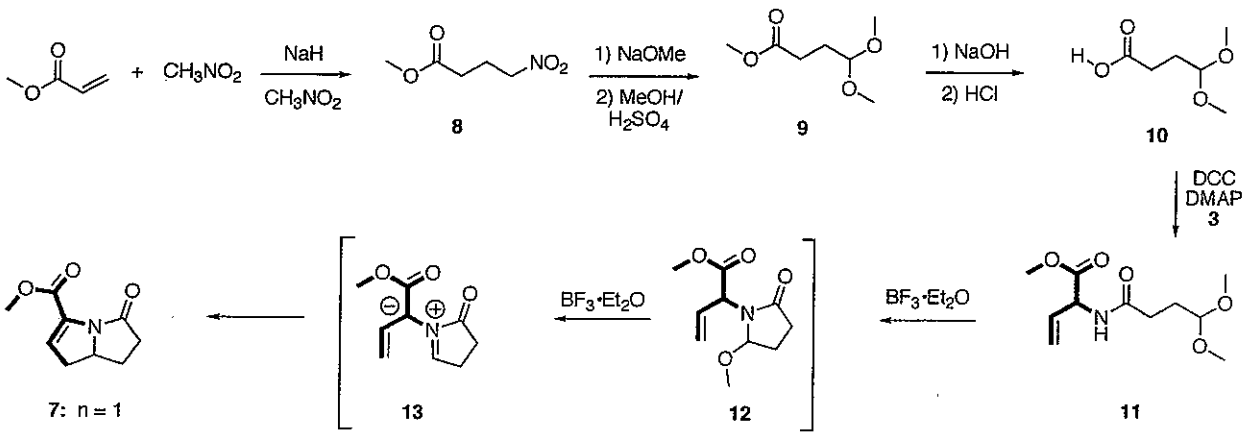


Figure 1. Methyl vinylglycine.



Scheme 1. Vinylglycine route to pyrrolizidine and indolizidine structures.

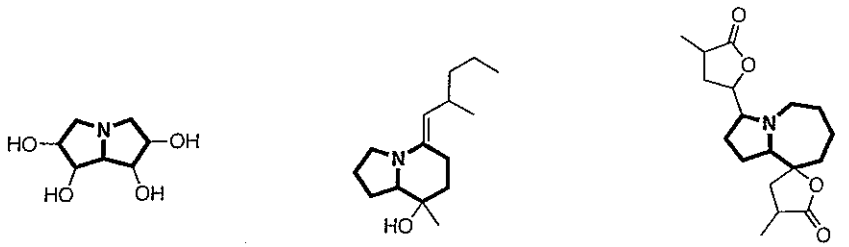
Last summer, David Guptill continued working on this project using a redesigned plan to arrive at the same reactive intermediate (Scheme 2). In particular, the reactivity of **5** was expected to be similar to that of **12**. The approach outlined in Scheme 2 also has the potential to be more flexible in that compound **8** can be made with a number of substituents ("R" groups) and with variable length in the chain. This latter feature can be leveraged to produce rings of various sizes (i.e. **7** with $n = 1, 2, 3$, *vide infra*). Much of David's efforts were directed toward the construction of compound **11**. Near the end of the summer, he ran one reaction demonstrating that mixing **11** with $BF_3 \cdot Et_2O$ effected the desired cyclization. This result is preliminary, and we have neither fully characterized **14** as the reaction product nor optimized the reaction conditions to achieve the highest yields. An additional summer of research will allow David to "clean up" these results so that they can be presented in both a national poster session and in a publication.



Scheme 2. Vinylglycine route to pyrrolizidine and indolizidine structures.

Molecules that are structurally similar to **7** have been isolated from natural sources, most notably the neurotoxins such as pumiliotoxin 251D produced by tropical rain forest frogs (Figure 2). The common skeleton of each natural product is highlighted for clarity. Notice that these molecules only differ in the size of the second ring (*i.e.* 7 n = 1, 2, 3) and the various functional groups that are attached to the bicyclic core. Further research will help establish what kind of functional groups can be

introduced into our reaction sequence. The most obvious place to change these two features is through making derivatives of compound **8**. Consequently, much of the summer will be spent examining how to make these derivatives.



Swainsonine
Glucosidase inhibitor
(anti-HIV candidate)

Pumiliotoxin 251D
Neurotoxin
Isolated from Ecuadoran
frogs *Epipedobates* tricolor

Croomine
anti-tussive
(cough supressent)
Isolated from the
Stemona plant genus

Figure 2. Biologically relevant natural products with 5-membered nitrogen heterocycle.

The highest priority for the summer is to optimize the reactions in Scheme 2, positioning us for publication this fall. The second priority is to explore ways in which the reactions can be modified to allow for the various substituents and ring sizes found in biologically interesting molecules like those in Figure 2. The last priority is to use the results from the beginning of the summer to craft an application for external funding from either the National Institutes of Health (NIH) or the National Science Foundation (NSF).

References

1. Xu, J.; Stevenson, J. "Drug-Like Index: A New Approach to Measure Drug-Like Compounds and Their Diversity." *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1177-1187.
2. Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. "A Knowledge-Based Approach in Designing Combinatorial or Medicinal Chemistry Libraries for Drug Discovery. 1. A Qualitative and Quantitative Characterization of Known Drug Databases." *J. Comb. Chem.* **1999**, *1*, 55-69.
3. Taylor, E. C.; Turchi, I. J. "1,5-Dipolar Cyclizations." *Chem. Rev.* **1979**, *79*, 181-231.
4. Huisgen, R. "1,5-Electrocyclizations - An Important Principle of Heterocyclic Chemistry." *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 947-1034.
5. Bakulev, V. A.; Kappe, C. O.; Padwa, A. In *Organic Synthesis: Theory and Application*; JAI Press: London, 1996; Vol. 3, pp 149-229.
6. Tiner-Harding, T.; Ullrich, J. W.; Chiu, F.-T.; Chen, S.-F.; Mariano, P. S. "Electron-Tranfer-Initiated Iminium Salt Photospirocyclization Methodologies. Model Studies for Harringtonine Alkaloid Synthesis." *J. Org. Chem.* **1982**, *47*, 3360-3362.
7. Chiu, F.-T.; Ullrich, J. W.; Mariano, P. S. "Model Studies Examining the Application of Allyliminium Salt Photospirocyclization Methodologies in Synthetic Approaches to the Harringtonine Alkaloids." *J. Org. Chem.* **1984**, *49*, 228-236.
8. Ullrich, J. W.; Chiu, F.-T.; Tiner-Harding, T.; Mariano, P. S. "Electron-Transfer-Initiated Photospirocyclization Reactions of β-Enaminone-Derived Allyliminium Salts." *J. Org. Chem.* **1984**, *49*, 220-228.
9. Speckamp, W. N. "Stereo- and Enantioselective Syntheses of 2,3-Dihydroindole Derivatives." *Heterocycles* **1984**, *21*, 211-234.

10. Afzali-Ardakani, A.; Rapoport, H. "L-Vinylglycine." *J. Org. Chem.* **1980**, *45*, 4817-4820.
11. Miller, S. A.; Chamberlin, A. R. "Enantiomerically Pure Polyhydroxylated Acyliminium Ions. Synthesis of Glycosidase Inhibitors (-)-Swainsonine and (+)-Castanospermine." *J. Am. Chem. Soc.* **1990**, *112*, 8100-8112.

II. Anticipated Outcomes

Although the 1,5-electrocyclization reaction has been known for some time, the problems associated with making the required starting materials has kept this reaction from being widely employed in the synthesis of pharmaceutically interesting molecules. If successful, this research will have a substantial impact on the field of organic synthesis and has the potential to spur new areas of research at Gustavus. The broader community of organic chemists has already taken interest in the idea as evidenced by the funding of the Research Corporation grant. David can expect to present his findings both at national meetings (*i.e.* American Chemical Society) and at the Sigma-Xi sponsored symposium at Gustavus Adolphus College. I can also present this work as a poster at a Gordon Research Conference (Heterocycles meeting) during my sabbatical. Success during the early part of the summer will also position us to submit competitive grant applications to other funding agencies such as the NSF and NIH. Involving David in the grant writing process will help prepare him for an independent research career.

In addition, David will become more familiar with most of the techniques of modern organic synthesis as well as some facets of natural products chemistry. He will learn about techniques for compound purification/isolation (column-, gas-, and high performance liquid chromatographic techniques) and structure identification using Nuclear Magnetic Resonance spectroscopic, Infra-red spectroscopic, and Mass spectrometric methods. This will make David an attractive applicant to graduate programs, and he will enter with considerable experience in a laboratory setting.

Funding of this project for the summer will also have beneficial effects on several other students. I have funding for 2 students (and a stipend for myself) this summer from the American Chemical Society's Petroleum Research Fund to work on an unrelated project. Consequently, David will be part of a larger research group. Each member of the group will have a richer experience for the interaction of different people on different projects. Organic chemistry is a collaborative venture, and professional interactions between people on different projects is common. In this respect, all of the research students will have a more authentic experience if this project is funded.

III. Biographies

Scott K. Bur (Advisor): Scott graduated from the University of Michigan in Ann Arbor with a BS in 1994. He worked for approximately one year at Parke-Davis Pharmaceuticals in Ann Arbor making drug analogues in support of an oncology project. He earned his PhD in organic chemistry from the University of Texas at Austin in 2000 after working with Stephen F. Martin in the field of synthetic methodology and natural products synthesis. From the fall of 2000 to the summer of 2003, he was a National Institutes of Health postdoctoral fellow at Emory University where he continued training under the direction of Albert Padwa. He joined the faculty at Gustavus Adolphus College in the fall of 2003. He has 13 research publications and two review articles from his work prior to joining Gustavus.

He has had four other review articles publication since he joined the faculty at Gustavus. (For curriculum vitae, see http://www.gac.edu/~sbur/CV.html)

David M. Guptill (Student): David attended and graduated from Centennial Senior High School as salutatorian in 2005. Throughout his years in high school he received letters in varying areas and groups, such as music, academics, and math league (in which he served as captain his senior year). He was involved in other non-academic activities including extensive study in the martial arts, receiving his black belt in the Korean art of Tang Soo Do in 2005. In the fall of 2005, he began his enrollment at Gustavus Adolphus College, receiving numerous scholarships related to both academic and the arts. David was involved in research at Gustavus during the summer of 2007, when he worked closely with professor Scott Bur. He was also one of four Gustavus students nominated for the prestigious Barry M. Goldwater scholarship in 2008. David intends to graduate from Gustavus with a degree in ACS chemistry and attend graduate school to further study organic chemistry.

IV. Career Statements

Scott K. Bur (Advisor): All of my research is planned around the involvement of undergraduate researchers. Although I have funding for 2 students already, the funded project is different than the one described here. Though a few key pieces of information are needed to seek external grants for this project, support for David's work will amplify our previous success in the form of both a brief publication and the submission of a National Institutes of Health grant application in the near future.

In general, summer research will allow me to focus my attention on teaching David (and others) the required skills needed to conduct research. This project requires multiple synthetic steps, and the products of each step must be purified and characterized before the next step is attempted. Projects of this nature often require large blocks of uninterrupted time for optimal results. Students may only finish one or two steps during an entire semester of independent research. In contrast, summer research will allow me to spend 8-10 hours per day with students. This offers me the best chance to advance a project to the point where outside funding can be secured and initial discoveries can be communicated.

During both CHE-141 and CHE-251, I often use molecules similar to those involved in my research as examples in lecture. We discuss both the organic chemistry and the biological pathways that make these molecules relevant. This helps students gain a broader context within which to view organic chemistry, and it assists in students' integration of chemistry and biochemistry lecture material. From this perspective, it is important that I continue to work with biologically relevant molecules such as those toward which the proposed chemistry could be applied.

David M. Guptill (Student): Since my first class in organic chemistry, the organic molecule has not yet ceased to fascinate me. What I find even more interesting is the construction of naturally occurring organic molecules for use in medicine. The implications of being able to provide medicinally useful compounds in an efficient and inexpensive way further my interest in this type of research. This research, I believe, does just that.

When it comes to the chemistry, I particularly enjoy learning and applying the chemistry necessary to solve the complex problems that arise. I believe continuing in this research will give me a deeper look into the world of research, expose me to complex situations in this research area, and further motivate me to find my own specific interest areas and seek them out. Ultimately, I intend my

career to involve this type of research, be it for a pharmaceutical company, or even with a college or university, helping aspiring chemists do just the same that I expect this research to do for me.

V. Budget

(See supplemental Budget Proposal Form)

VI. Placement for Publication

Initial communication of research discoveries can be published in *Organic Letters* or *Tetrahedron Letters*. In-depth studies can be published in *Journal of Organic Chemistry*, *Tetrahedron*, or *Journal of the American Chemical Society*. In addition to publication, the results can be communicated through both posters and seminar presentations at various national meetings (*i.e.* American Chemical Society, Council of Undergraduate Research, etc.) and at the Sigma Xi sponsored symposium here at Gustavus. Given previous success, the funds for this project should allow for submission of a publication this fall.

VII. Completion

Research will commence in early June, and critical results should be obtained by early August. Since this project can open up a broad area of research, it is impossible to predict a completion date for this overall project. The data required for a preliminary publication should be obtained by August, and this is when I plan to submit a report to the Dean of the Faculty.

BUDGET PROPOSAL FORM Presidential Faculty/Student Collaboration and Publication Grant

ITEM		AMOUNT
Equipment (not to include computer hardware)		$
1:	Cost:	
2:	Cost:	
3:	Cost:	
Materials		$
1:	Cost:	
2:	Cost:	
3:	Cost:	
Personnel		$ 3200
Student Stipend @ $400/week: 8 weeks = $3200		
Other Rate:		
Travel Costs		$
Airfare:		
Mileage: Number of miles _____ @ $0.445/mile		
Lodging		$
Number of days _____ @ $_____/day		
Other Expenses (check the faculty book white pages for excluded items)		$
1:	Cost:	
2:	Cost:	
3:	Cost:	
Faculty Stipend		$
TOTAL EXPENSES		$ 3200
AMOUNT REQUESTED		$ 3200

Have you applied for, or received funding from, another source to help support this project?

Funding Source:
Amount:

Please explain how the Presidential or RSC will be used in addition to the other funding.

Previous grants have provided all the the required materials. I just need a student to help with the work. Although not directly related to this project, an American Chemical Society PRF grant will provide my summer stipend.