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TITLE: Synthesis of Acetogenin analogs as Potential Therapeutics
for Treating Prostate Cancer

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13. ABSTRACT (Maximum 200 Words) New, flexible, economical, and practical syntheses of the natural products swuamotacin and bullatacin have been completed. The compounds have been submitted for biological testing, and preparation of analogs is underway. This work will provide much needed information on the structure activity relationships of this class of annonaceous acetogenins. The Promising and sometimes contradictory reports on the biological activity of the acetogenins will be solidly addressed in this work, and these findings will be essential tools in the exploitation of these compounds for their therapeutic potential in the flight against prostate cancer.				
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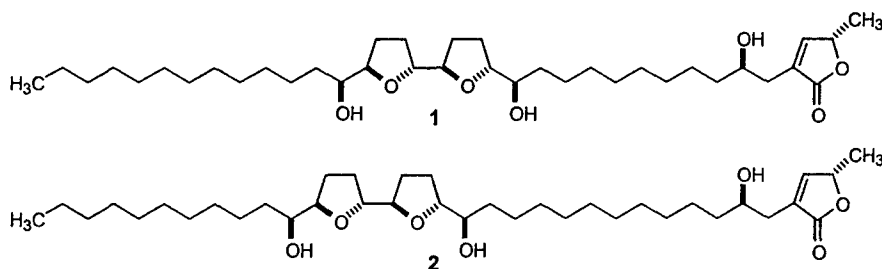
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Introduction

The objective for this project as described under the statement of work is to prepare synthetic analogs based on the natural acetogenins squamotacin **1** and bullatacin **2** so that structure-activity relationships concerning the location of the bis-THF part of the molecule relative to the rest of the structure can be investigated (Scheme 1).¹ During the second year we encountered several serious synthetic challenges concerning reaction efficiency and scalability that required a reworking of the synthetic plan in several places. This year all of previous synthetic hurdles that prevented scale-up have been overcome. Squamotacin and bullatacin have been prepared and submitted for biological testing, and we are currently preparing analogs. We have not yet, however, received the biological activity data from our collaborator.

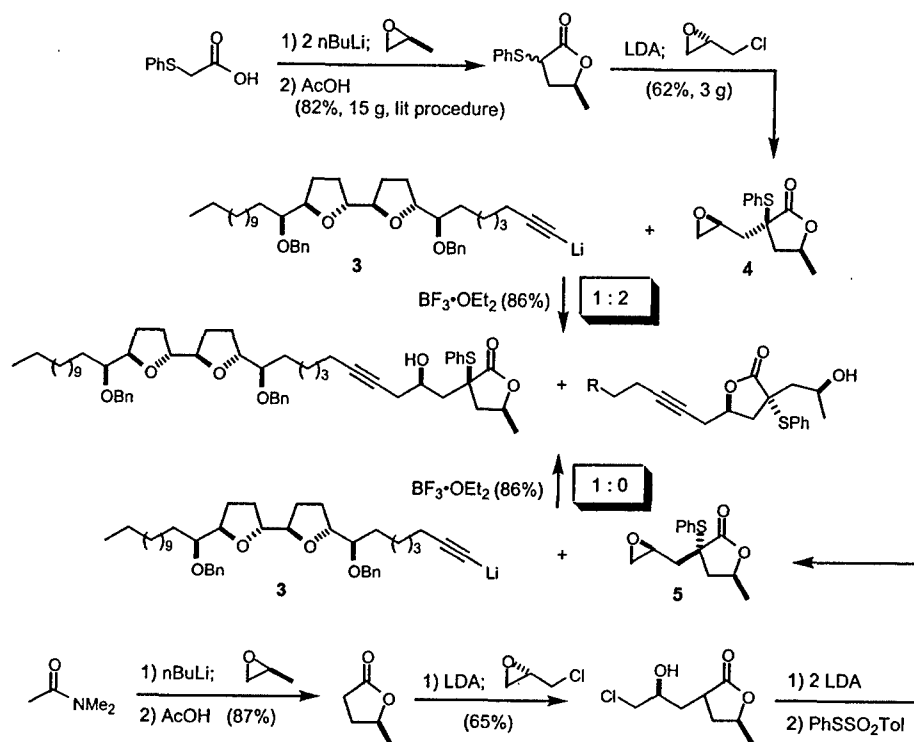
Scheme 1



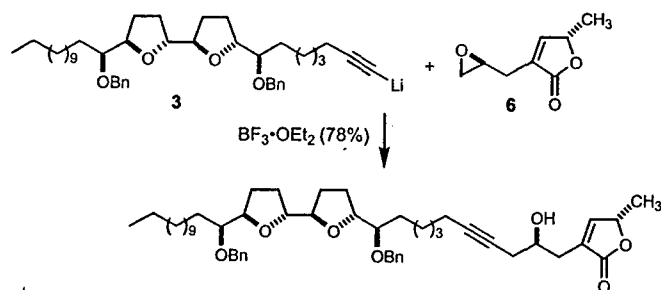
Body

In the last few steps of the synthesis we encountered a problematic trans-lactonization in the addition of alkyne **3** to epoxide **4** (Scheme 2). Switching to the epimeric epoxide solved this problem, and we first completed the synthesis with this route. Discoveries made investigating these epoxide additions turned out to be general and unusual, and we published those findings.² In the current version of the synthesis we have settled on the somewhat surprising solution of employing a butenolide-epoxide electrophile *in a non-protected form* (Scheme 3). Given the reported susceptibility of these and related butenolides to undergo stereochemical scrambling at C(4) when first attempting this reaction were dubious of a successful outcome. None-the-less, we carried on and were delighted to observe that the stereochemical integrity in this reaction was complete (NMR, HPLC, and confirmed by independent synthesis of each diastereomer). In the past, three strategies have primarily been employed to prepare this butenolide portion: a) alkylation of White's lactone with an iodide or triflate (Scheme 4, **A**);^{3,4} b) ring opening of propylene oxide by the dilithiated free acid (**B**);⁵ and c) condensation of a propargylic alcohol and an epoxide (**C**).⁶ In a comparison to the known procedures for installation of the butenolide, ours appears to be the most efficient. The preparation of butenolide **6** is shown in Scheme 5.

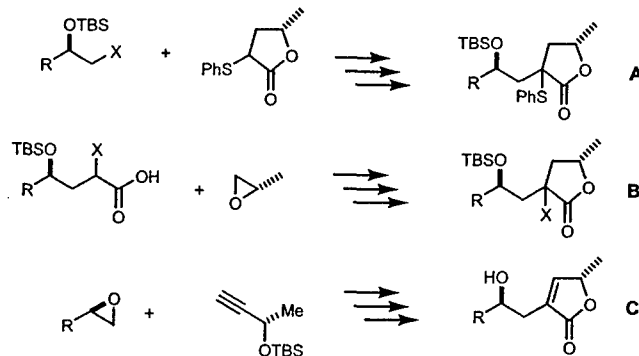
Scheme 2



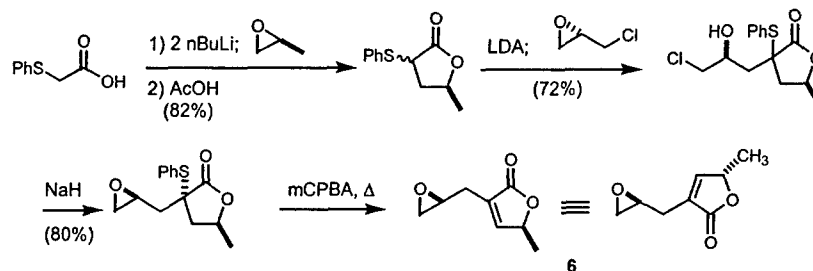
Scheme 3



Scheme 4

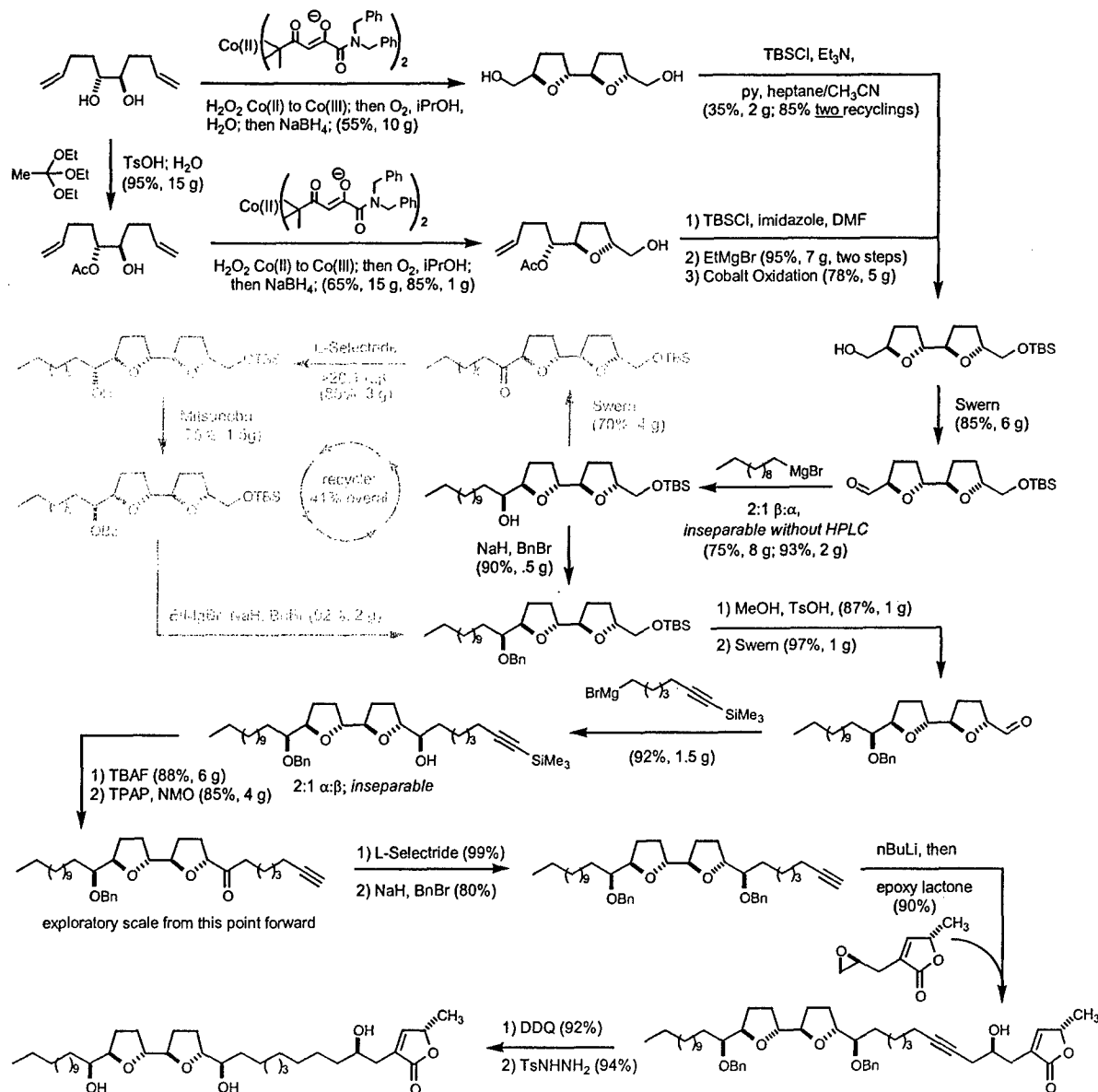


Scheme 5



The complete synthetic route is shown in (Scheme 6). We are currently engaged in preparing analogs using this sequence.

Scheme 6



We are in the process of writing a full paper describing the synthesis and we plan to hold-off on publishing until the biological activity data becomes available for inclusion (which shouldn't be long).

Key Research Accomplishments

- Designed, developed and implemented a new efficient synthesis of the annonaceous acetogenins suitable for analog preparation.
- The natural products squamotacin and bullatacin have been prepared and submitted for biological testing.

Reportable Outcomes

Manuscripts (The funds from this Army medical research project have unquestionably had a very positive effect on the overall well being of the PI's research group. We felt it was appropriate to acknowledge the Army in several of our synthetic chemistry papers, even though these publications were unrelated to the project.)

Julie Cong-Dung Le and Brian L. Pagenkopf. Asymmetric Hydrogenation of *Ortho*-alkoxy Substituted Arylenamides. *J. Org. Chem.* 69, 4177 – 4180; (2004).

Ming Yu, G. Dan Pantos, Jonathan L. Sessler and Brian L. Pagenkopf. Synthesis of 2,2'-Bipyrroles and 2,2'-Thienylpyrroles from Donor-acceptor Cyclopropanes and 2-Cyanoheteroles. *Org. Lett.* 6, 1057 – 1059; (2004). (This paper will likely be listed in Professor Sessler's annual report, but it should be credited to this grant.)

Darren W. Engers, Martin J. Bassindale and Brian L. Pagenkopf. Synthesis of the C(1) – C(12) Segment of Peloruside A by an α -Benzyloxymethyl Ketone Aldol Strategy. *Org. Lett.* 6, 663 – 666; (2004).

Jeffrey S. T. Gorman, Scott T. Iacono and Brian L. Pagenkopf. Selective Oxidation of Zirconocyclopentenones via Organoboranes. *Org. Lett.* 6, 67 – 70; (2004).

Ming Yu and Brian L. Pagenkopf. A Powerful New Strategy for Diversity-oriented Synthesis of Pyrroles from Donor-acceptor Cyclopropanes and Nitriles. *Org. Lett.* 5, 5099 – 5101; (2003).

Ming Yu and Brian L. Pagenkopf. Allylation of Donor-Acceptor Cyclopropanes. *Org. Lett.* 5, 4639 – 4640; (2003).

Hongda Zhao and Brian L. Pagenkopf. Stereospecific and Efficient Alkynylation at the More Hindered Carbon of Trisubstituted Epoxides. *Chem. Commun.* 2592 – 2593; (2003).

Presentations

1. April 19, 2004. Synthesis of squamotacin and synthesis and electronic properties of pi-conjugated siloles; University of Pennsylvania, Department of Chemistry; Philadelphia, Pennsylvania.
2. April 20, 2004. Synthesis of squamotacin and synthesis and electronic properties of pi-conjugated siloles; Temple University, Department of Chemistry; Philadelphia, Pennsylvania.
3. April 21, 2004. Synthesis of squamotacin and recent advances in the chemistry of donor-acceptor cyclopropanes; Princeton University, Department of Chemistry; Princeton, New Jersey.
4. April 22, 2004. Synthesis of squamotacin and synthesis and electronic properties of pi-conjugated siloles; University of Delaware, Department of Chemistry; Newark, Delaware.
5. April 29, 2004. Synthesis of squamotacin and studies toward the synthesis of peloruside A; Oregon State University, Department of Chemistry; Corvallis, Oregon.
6. April 30, 2004. Synthesis of squamotacin and electronic properties of pi-conjugated siloles; University of Oregon, Department of Chemistry; Eugene, Oregon.
7. May 21, 2004. Synthesis of squamotacin and electronic properties of pi-conjugated siloles; University of California at Santa Barbara, Department of Chemistry; Santa Barbara, California.

Funding Applied For

A revised version of a previously reviewed NIH will be submitted.

Funding Received

A grant from the Petroleum Research Fund has been awarded to explore the oxidative cyclization that was discovered while working on this project. "Stereoselective THF Synthesis by Cobalt Catalyzed Air Oxidation of Hydroxy Olefins" \$80,000 total over two years starting September, 2003.

Employment

The graduate students involved on this project have not yet graduated. Three postdoctoral fellows were engaged at various times on this project. Two have gained employment, and the third is in the interview process.

Dr. Brandon Young (2002); Texas Biotechnology Corporation

Dr. John F. Reichwein (2003); Encysive Pharmaceuticals

Conclusions

We have met the greatest challenge of the project: developing and implementing a practical synthesis of the acetogenins.

So what? Steady progress is being made toward the primary goal of generating a library of acetogenin analogs for biological testing. The synthetic routes that we have developed for both the bis-THF and butenolide portions of the acetogenins are superior to previously reported methods in terms of scalability, reproducibility and economy. These protocols will have a positive effect on acetogenin cancer research.

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- ⁶ Hoye, T. R.; Humpal, P. E.; Jimenez, J. I.; Mayer, M. J.; Tan, L.; Ye, Z. *Tetrahedron Lett.* **1994** *35*, 7517-7520; Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989-5995.

Appendices

none