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During the third year of this grant, we optimized a new preparation of the “stereotriad building block” and studied the underlying chemistry for the new scheme. We also discovered and studied the one step, direct iododesilylation of dihydrooxasilines, a reaction that can be used to shorten our new scheme. In addition, we studied model conversions for a scheme that will convert a by-product from our degradation of oleandomycin to a useful “building block” for discodermolide. Thus, the oleandomycin degradation can supply two of the three synthons required for the total synthesis.

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## Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table of Contents</td>
<td>4</td>
</tr>
<tr>
<td>Introduction</td>
<td>5</td>
</tr>
<tr>
<td>Body</td>
<td>6</td>
</tr>
<tr>
<td>Key Research Accomplishments</td>
<td>9</td>
</tr>
<tr>
<td>Reportable Outcomes</td>
<td>9</td>
</tr>
<tr>
<td>Conclusion</td>
<td>10</td>
</tr>
<tr>
<td>References</td>
<td>10</td>
</tr>
<tr>
<td>Appendices</td>
<td>NA</td>
</tr>
</tbody>
</table>
INTRODUCTION

The goal of this project is to develop an efficient synthesis of the microtubule-binding antibiotic discodermolide (1). Discodermolide is considered an important lead structure for the development of drugs for the treatment of solid tumors. Because discodermolide is available only in minute quantities from the collection and extraction of a deep sea sponge, its development requires a supply from chemical synthesis.

Retrosynthetic analysis of the discodermolide molecule invariably leads to three building blocks, functionalized for linkage in the final steps of the synthesis. These building blocks correspond to stereopentad, stereotetrad, and stereotriad, stereochemical arrays (see 3, 4, and 5). An optimally convergent synthesis of discodermolide will contain a step that links the stereotetrad and the stereotriad and then couples the resulting C-1 to C-14 stretch with the stereopentad. Our approach to the discodermolide molecule is to obtain the stereopentad building block 3 (original proposal 13) from the chiral pool by degradation of the readily available macrolide antibiotic oleandomycin and to construct the C-1 to C-14 stretch (2, original proposal 26) by linking two building blocks derived from 2,3-Wittig rearrangement chemistry (Scheme 1, 4 and 5, original proposal 5 and 22 or 23).

The strategies underlying this novel synthesis and the new methods developed during the course of the project may find applications in the synthesis of polyketide antibiotics other than discodermolide and its analogs as well as these original targets.
In prior years of this project, we completed the syntheses of the stereopentad, stereotetrad and stereotriad building blocks. We also coupled the stereotetrad and a stereotriad equivalent and then modified the resulting advanced intermediate to the C-1 to C-14 stretch, a compound appropriate for coupling with the stereopentad. These accomplishments established the viability of our approach and the practicality of the reaction schemes that we have chosen for the construction of the three building blocks.

Before attempting to complete the total synthesis, we needed to optimize both the schemes and the conversions required for each. Because of technical problems in preparing the desired stereotriad building block by the chemistry originally proposed, we devised an alternative synthesis of the key intermediate. Part of this work has been reported. Also, in order to further demonstrate the fundamental concept of this project, that inexpensive polyketide antibiotics can be degraded to building blocks for highly valued polyketide drugs, we initiated a study of the semi-synthesis of the second generation version of Paterson’s ketone, a known discodermolide intermediate, from a side-product of the stereopentad synthesis.

Development of new methods for the preparation of vinyl iodides – improved synthesis of the stereotriad building block

The second annual report contained Scheme 2 (referred to there as “New Scheme 1”) in which a relay metathesis and an iododesilylation served as the key steps in a synthesis of a stereotriad-containing vinyl iodide. During the third year of this project, we generalized and optimized the iododesilylation step by testing the solvent dependence of this reaction in a model system and then applying it in the system of interest, . In addition to improving the retention of geometry in the iododesilylation step, we discovered that the use of DMSO as solvent or the placement of a participating substituent on the substrate effects inversion of the geometry during iododesilylation.

Scheme 2

Although the two-step conversion of dihydrooxasilines to vinyl iodides (alkyllithium and then N-iodosuccinimide) proceeds with generally good yields and solvent- or substituent-dependent selectivities, we imagined a one-step, direct iododesilylation of
these substrates to the desired targets. Therefore we tested the feasibility of this reaction and its stereochemical outcomes.

Model studies have now culminated in the one-step conversion of the stereotriad-containing dihydrooxasiline 11 to the Z-iodoolefin 12 (in which the secondary alcohol is protected as the silyl ether) when the solvent is hexafluoroisopropanol but to the (E)-iodoolefin 13 in DMSO.

Scheme 3

Extension of the solvent- and substituent-induced inversion of double bond geometry to more complex substrates is now under study. This could have additional applications in the synthesis of discodermolide i.e. (Z)-iodo olefin intermediates could be available from (E)-vinyl silane precursors. On the other hand, key intermediates for other complex antibiotics such as khafrefungin (14)9 or tyrandamycin A (15).10 could be available by simple modification of the (Z)-vinyl silane precursors.

Scale-up experiments on these preparations are also underway.

Preparation of a second discodermolide building block (the Weinreb amide of Paterson’s ketone) from the oleandomycin degradation
In conjunction with the original semisynthesis of the stereopentad synthon 3 by degradation of oleandomycin, we isolate ketone 16. Ketone 16 is clearly a syn, anti stereotriad-containing structure; it would be attractive to be able to convert this compound, available as a side-product from the primary degradation sequence, to a useful building block for discodermolide (or for another value-added polyketide antibiotic). Therefore we have outlined a conversion of ketone 16 to the second generation version of Paterson’s ketone, the Weinreb amide 21 (Scheme 4).

Scheme 4

We recognize the importance of testing the key steps of the proposed scheme in model systems before pursuing the planned transformation with the relatively valuable ketone 16. Therefore we devised a five-step preparation of the model hydroxyketone 22 and tested its periodate cleavage to aldehyde 23 (Scheme 5). In our hands, this proceeded nicely in 86% yield, promising good results when we work with valuable substrate. We also tested the proposed ring-opening step with delta decalactone (24), demonstrating the desired conversion to Weinreb amide 25 in 80% yield (Scheme 6).

Scheme 5

Scheme 6

We are therefore ready to implement Scheme 4.
KEY RESEARCH ACCOMPLISHMENTS

- Publication of the relay metathesis – iododesilylation approach to Z-vinyl iodides
- Discovery of a major improvement in control of geometry of iododesilylation products by choice of solvent or participating substituent
- Scale-up of oleandomycin degradation
- Model reactions for semi-synthesis of Paterson’s ketone as an alternative to the synthetic stereotetrad

REPORTABLE OUTCOMES

Publication year 1:

Publications year 2


Publication year 3

Manuscript in preparation:
Parker, Kathlyn A.; Denton, Richard W. “Trisubstituted Iodo Olefins from Vinyl Silanes or Dihydrooxasilines with Control of Geometry by Solvent or Substituent.” in preparation.
Degrees obtained supported in part by this award:

Ph.D. SUNY Stony Brook: Huanyan Cao
Ph.D. SUNY Stony Brook: Peng Wang
Ph.D. SUNY Stony Brook: Qiuzhe (Ben) Xie

Employment and research opportunities applied for and received based on experience/training supported by this award:

Huanyan Cao was a postdoctoral research associate in the Department of Chemical Engineering, Columbia University. He is now employed with Intelligent Biosystems (IBS) in Waltham, MA. Intelligent Biosystems is a biotech company that is focused on efficient gene sequencing.

Peng Wang is employed by Ren-Pharm International, Ltd. in Syosset, NY. Ren-pharm is a U.S. agent that represents bulk active pharmaceutical ingredient producers.

After obtaining his PhD degree, Qiuzhe (Ben) Xie moved to Cambridge Major in Germantown, Wisconsin, as a senior research scientist. Cambridge Major is a chemistry outsourcing partner that provides process R&D, scale up, and GMP manufacture of Active Pharmaceutical Ingredients. In November of 2008, Ben moved to Albany Molecular Research, Inc. (AMRI) in Albany, NY as senior research scientist. AMRI performs drug discovery, pharmaceutical development, and manufacturing of active ingredients and pharmaceutical intermediates.

CONCLUSION

We have demonstrated both underlying premises of the original plan of synthesis: that oleandomycin degradation would give one “building block” for discodermolide synthesis and that a short sequence based on the Wittig rearrangement would supply two others. Additional work has given us alternative, improved preparation of one of these “building blocks” and we envision a synthesis of another known intermediate from a by-product of the oleandomycin degradation. We hope to complete the total synthesis with the key intermediates from our schemes to date.

REFERENCES


5  A modification of the original approach afforded building blocks for polypropionates that contain anti, anti stereotriads; see Kathryn A. Parker and Qiuzhe Xie. “Asymmetric Catalysis Route to anti,anti Stereotriads, Illustrated by Applications.” *Organic Lett.* **2008**, *10*, 1349-1352.


