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TITLE: Novel and Efficient Synthesis of the Promising Drug Candidate Discodermolide

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14. ABSTRACT During the second year of this grant, we have exploited our new "stereotriad building blocks" and prepared a major structural component of the target. Thus we prepared two key intermediates and linked them to obtain the C-1 to C-13 stretch of discodermolide. One-carbon homologation with the Stork –Zhao reaction gave the C-1 to C-14 stretch, appropriate for connection with our stereopentad piece. We also modified the “building block” synthesis in order to prepare “anti, anti” stereotriads and we initiated a new and improved scheme to the polypropionate building blocks that bear a Z-vinyl iodide.

15. SUBJECT TERMS Total synthesis, discodermolide, tubulin binder, natural product degradation

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INTRODUCTION

The goal of this project is to develop an efficient synthesis of the microtubule-binding antibiotic discodermolide. 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 which would be linked in the final steps of the synthesis. Most often, these building blocks contain a stereotetrad, a stereotriad, and a stereopentad stereochemical array.

BODY

The synthesis of the stereopentad building block from the degradation – reconstruction approach originally described (Scheme 1 as shown with optimal protecting groups in our proposal) was published.\(^1\)

The stereotriad building blocks, prepared as described in our 2006 publication,\(^2\) were elaborated to key intermediates equivalent to the a stereotriad and stereotetrad moieties in the target. These were joined to provide a major structural entity, the C-1 to C-13 stretch of discodermolide, protected appropriately for further elaboration. Chain extension by a Stork Zhao reaction afforded a milestone compound (24 in our proposal) in which the C-1 to C-14 stretch was present and protected appropriately for coupling with our stereopentad-containing diene.\(^3\)

The completion of the synthesis of 24 by this approach is less efficient than our originally proposed route because we needed an efficient method for the reduction of a propargyl alcohol in the presence of a vinyl iodide. In the original proposal, we described this transformation with diimide in a model system (Scheme 4). However, diimide reduction did not prove to be a reproducible method. In work supported by another grant, we discovered a solution to this problem. Although attempts to reduce 31 (Scheme 4) with Pd/BaSO\(_4\) in methanol indeed afforded deiodinated diene, conditions involving Pd/CaCO\(_3\) gave the desired iodo diene 32. Application of this methodology in our original Scheme 3 should improve the efficiency with which we obtain the key intermediate 25.

In a demonstration of the generality of the 2,3-Wittig approach to stereotriads, we exploited the stereoselective rearrangement of (E)-allylic propargylic ethers coupled with an optimized protocol for the carbometallation of the resulting propargyl alcohols. Protection and hydroboration afforded anti, anti stereotriad building blocks that were converted to known intermediates for the synthesis of the cytotoxic polyketide natural products scytophycin C and aplyronine A.\(^4\)

Thinking that we might by-pass entirely the yield-limiting Stork Zhao olefination in our discodermolide synthesis, we considered the iodination of a dihydrosiloxine. An appropriate dihydrosiloxine intermediate might be obtained by ring closing metathesis of a vinyl silyl ether derived from our conveniently prepared stereodiad intermediate. The concept and its successful implementation are shown in New Scheme 1 below. These results are described in a manuscript that is currently in preparation.\(^5\)
KEY RESEARCH ACCOMPLISHMENTS:

- Publication of the degradation – reconstruction approach to the stereopentad of discodermolide.
- Completion of the synthesis of the C-1 to C-14 stretch of discodermolide, appropriately protected for further transformations, and publication of this milestone.
- Discovery of conditions for the selective reduction of a propargyl alcohol in the presence of a vinyl iodide (support from another grant)
- Development of a new approach to the preparation of the key vinyl iodide intermediate 5
- Elaboration of our key stereodiad intermediates to anti, anti stereotriad equivalents and publication of this achievement

REPORTABLE OUTCOMES:

Publications year 1:


Publications year 2


Manuscript 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 is currently a postdoctoral research associate in the Department of Chemical Engineering, Columbia University.

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.

Qiuzhe (Ben) Xie is a senior research scientist at Cambridge Major in Germantown, Wisconsin. Cambridge Major is a chemistry outsourcing partner that provides process R&D, scale up, and GMP manufacture of Active Pharmaceutical Ingredients

CONCLUSION: The two major, key intermediates for the synthesis of discodermolide have been obtained by chemistry as originally proposed. We have also invented alternative and potentially superior methods for the preparation of key building blocks. We are now well-positioned to complete the synthesis. Furthermore, our new methodology should be of use in the practical synthesis of related polyketide, antitumor compounds by us and by others.


