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Award Number: W81XWH-06-1-0300

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

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REPORT DATE: February 2007

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE 01-02-2007		2. REPORT TYPE Annual		3. DATES COVERED 1 Feb 2006 – 31 Jan 2007	
4. TITLE AND SUBTITLE Novel and Efficient Synthesis of the Promising Drug Candidate Discodermolide				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-06-1-0300	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Kathlyn A. Parker, Ph.D. Email: kparker@notes.cc.sunysb.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) State University of New York Stony Brook, NY 11794-0002				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT During the first year of this grant, we have demonstrated proof of principle for both of the premises on which the project is built. We have shown that a macrolide that is available in large quantities can be degraded to provide a building block for a value-added polyketide, specifically discodermolide. Because of difficulties with the original scheme, we applied Corey's cis diene synthesis in this preparation; this proved to be a superior method. We have also shown that chiral, syn anti stereotriad building blocks may be efficiently accessed from a chiral allylic alcohol that was prepared by asymmetric catalysis. This is a practical new approach to these useful intermediates that should have many applications.					
15. SUBJECT TERMS Total synthesis, discodermolide, tubulin binder, natural product degradation					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	7	19b. TELEPHONE NUMBER (include area code)

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INTRODUCTION

(+)-Discodermolide is a marine natural product that has antitumor activity by virtue of its tubulin binding. Because this compound is available in only minute amounts from a deep sea sponge, a number of major research groups have attempted its chemical synthesis. Of those that have succeeded, all have used strategies based on chain extensions of the expensive small molecule, “Roche ester,” for the preparation of key building blocks. In an effort to introduce a new way of thinking about polyketide synthesis and also to determine whether a radical new approach might prove practical, we have designed a conceptually novel scheme for the total synthesis of (+)-discodermolide. Our building blocks will be derived from the chemical degradation of the macrolide fermentation product oleandomycin and from the chain extension of an allylic alcohol, prepared by asymmetric synthesis. Our novel approach and our new methods may find application in the synthesis of other polyketide antibiotics as well as in that of discodermolide and its analogs.

BODY

Major goals for year 1 of this project were (1) to complete Scheme 1 with the appropriate protecting groups and (2) to complete Scheme 2 with the appropriate protecting groups. Our experiments and those of others have recently refined our understanding of protecting groups that are useful in discodermolide synthesis. Therefore, we needed to modify these Schemes (from our preliminary results) so that they would employ the optimum protecting groups.

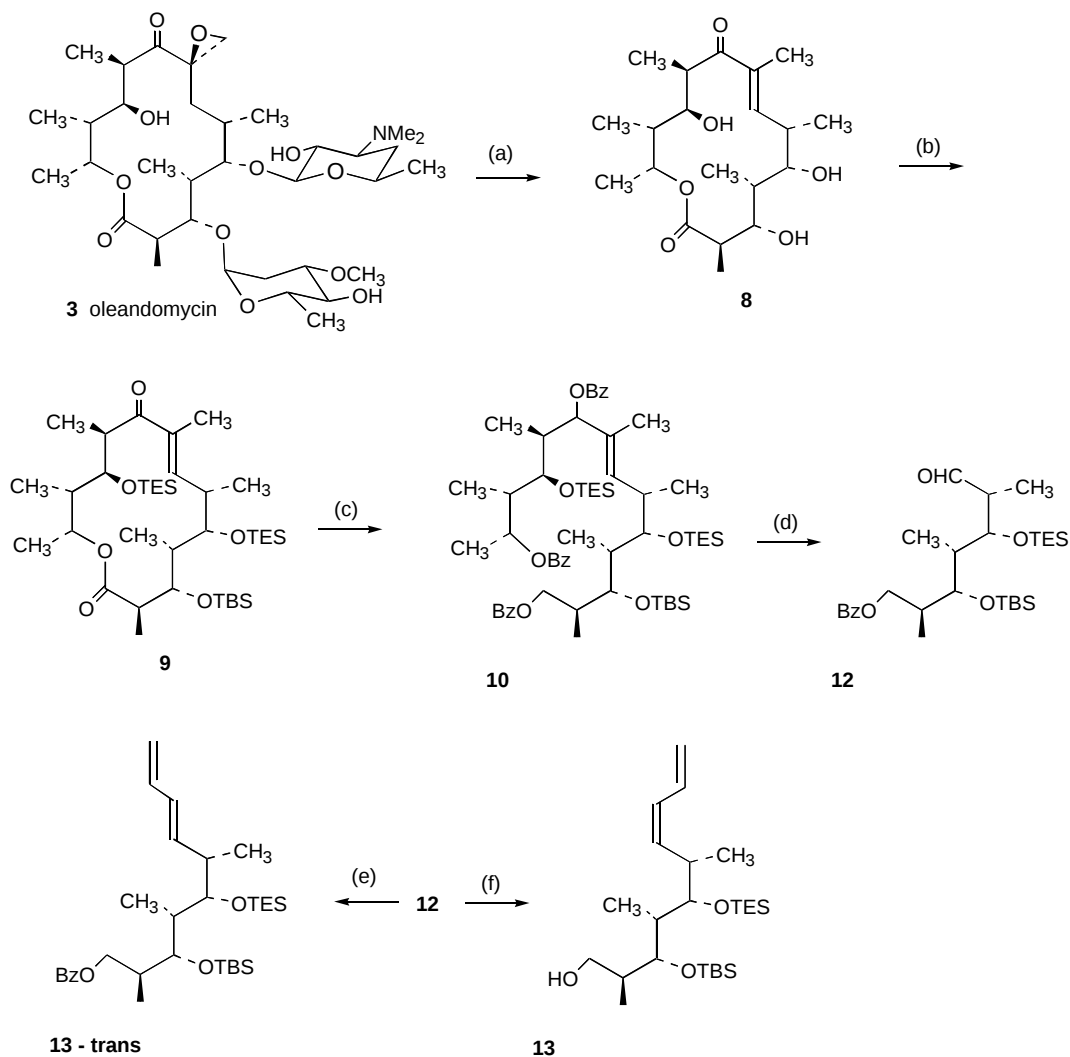
For a useful modification of Scheme 1, we needed to choose the two protecting groups, R and R', so that R would be the more easily removable. For the new Scheme 1, we chose R = TES and R' = TBS. A summary of the modified plan, an unexpected problem, and the resolution of this problem are shown below in “New Scheme 1.”

Only the penultimate step of “New Scheme 1” (introduction of the cis diene moiety, **12** → **13**, R = TES, R' = TBS) was problematic. Surprisingly, we found the Yamamoto protocol to be unsatisfactory in this context. Although it had been used by others in discodermolide syntheses¹ and also by us in the original Scheme 1 (**12** → **13**, 84% when R = TBS, R' = TES), reversing the positions of the two protecting groups in the substrate (New Scheme 1, **12**) for this step led to a low yield of diene product in which the trans diene **13-trans** predominated. Other methods for diene introduction that had been used in discodermolide syntheses were also unpromising. The Nozaki-Hiyama / Petersen method² gave a poor yield of material that appeared to be cis diene and an attempt to use Schreiber's two-step method³ was abandoned when the first step, a Stork-Zhao homologation, was low-yielding (24% of the cis vinyl iodide).

Following a clue from discodermolide studies by Masamune,⁴ we found the three-step, method of Corey⁵ for the preparation of cis dienes from hindered aldehydes. Thus we examined the condensation of aldehyde **12** with the dimethylaminopropyl Wittig reagent, then subjected the product to peracid oxidation, and thermolyzed the N-oxide which

underwent a Cope elimination. This procedure gave clean *cis* diene **13**. Because of the ease of applying this method, it is likely to be superior in other discodermolide systems as well as in ours.

New Scheme 1. Degradation of Oleandomycin to a Discodermolide Stereopentad Synthon - Accomplished

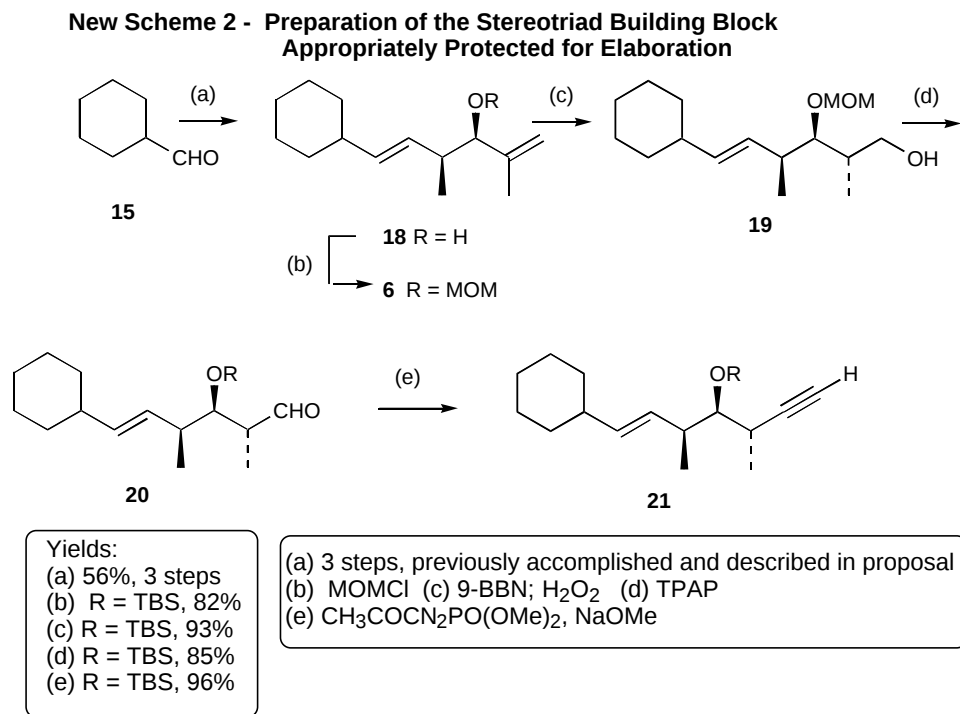


(a) 3 steps, described in proposal (b) 2 equiv TESOTf, lutidine, CH₂Cl₂, -78 °C; 6 equiv TBSOTf, lutidine, rt, 18 h, 96%
 (c) dibal, 81%, BzCl, 93% (d) O₃, DMS, chromatography (e) Ph₂PCH₂CH=CH₂, t-BuLi, Ti(OiPr)₄, MeI; then K₂CO₃
 (f) Ph₃P=CHCH₂CH₂NMe₂, m-CPBA, 50 °C; dibal

The work described above is the subject of a manuscript in preparation.⁶

From the reports of others,² we were aware that the TBS group was satisfactory for protecting the C-3 hydroxyl group but not for the hydroxyl group at the position that eventually becomes C-11. Therefore, we needed to prepare the key compound 5 or a synthetic equivalent in which the protecting group was something other than TBS, e.g. MOM. Furthermore, because of a lack of reproducibility in diimide reductions of propargyl alcohols that contain the vinyl iodide moiety, we opted to rearrange the steps for constructing the coupled product **26** (Scheme 3, proposal) or its equivalent. The

synthesis of a MOM-protected alkyne **21** for coupling with an equivalent of aldehyde **23** was accomplished as shown in New Scheme 2.



This preparation and related schemes are described in a published communication that is accompanied by a full experimental section in the Supporting Information.⁷

KEY RESEARCH ACCOMPLISHMENTS;

- Degradation of oleandomycin with introduction of protecting groups appropriate for elaboration to a known discodermolide intermediate.
- Application of the Corey cis diene protocol in discodermolide synthesis.
- Completion of the appropriately substituted building block **13** in 12 steps
- Proof of principle for the conversion of mass-produced macrolides to value-added polyketide structures.
- Demonstration that chiral syn, anti stereotriad building blocks may be efficiently accessed from inexpensive starting materials by elaborating a chiral allylic alcohol prepared by asymmetric catalysis.

REPORTABLE OUTCOMES:

Publication: “Scalable, Catalytic Asymmetric Synthesis of Syn, Anti Stereotriad Building Blocks for Polypropionate Antibiotics” Kathryn A. Parker and Huanyan Cao, *Organic Lett.* **2006**, 8, 3541-3544.

Manuscript: “A Deconstruction-Reconstruction Strategy for Accessing Valuable Polyketides. Preparation of the C15-C24 Stereopentad of Discodermolide by Semisynthesis” Kathlyn A. Parker and Peng Wang, in preparation:

Degrees obtained supported in part by this award:

Ph.D. SUNY Stony Brook: Huanyan Cao

Ph.D. SUNY Stony Brook: Peng Wang

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.

CONCLUSION: For the most part, the synthesis of discodermolide is proceeding by chemistry that was originally planned. The originally envisioned efficiency of this approach will be enhanced if we can perform the Corey cis diene protocol on a free alcohol and if we can discover a method to reduce propargyl alcohols to allylic alcohols in the presence of vinyl iodides.

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- ⁶ “A Deconstruction-Reconstruction Strategy for Accessing Valuable Polyketides. Preparation of the C15-C24 Stereopentad of Discodermolide by Semisynthesis” Kathlyn A. Parker and Peng Wang, in preparation.
- ⁷ “Scalable, Catalytic Asymmetric Synthesis of Syn, Anti Stereotriad Building Blocks for Polypropionate Antibiotics” Kathlyn A. Parker and Huanyan Cao, *Organic Lett.* **2006**, 8, 3541-3544.