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14. ABSTRACT

In a novel approach to the potential antitumor drug discodermolide, we have prepared new ''stereotriad building blocks'' and used them to build one of two key intermediates. We prepared the other critical intermediate, the so called ''stereopentad,'' by degradation of oleandomycin. We also modified the ''building block'' synthesis in order to prepare ''anti, anti'' stereotriads and we developed a new route to polypropionate building blocks that bear a Z-vinyl iodide or an *E*-vinyl iodide. We showed that proper choice of catalyst allows the reduction of a propargyl alcohol to a *Z*allylic alcohol in the presence of a vinyl iodide. Thus we have shown the viability of all high-risk steps in the total synthesis.

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

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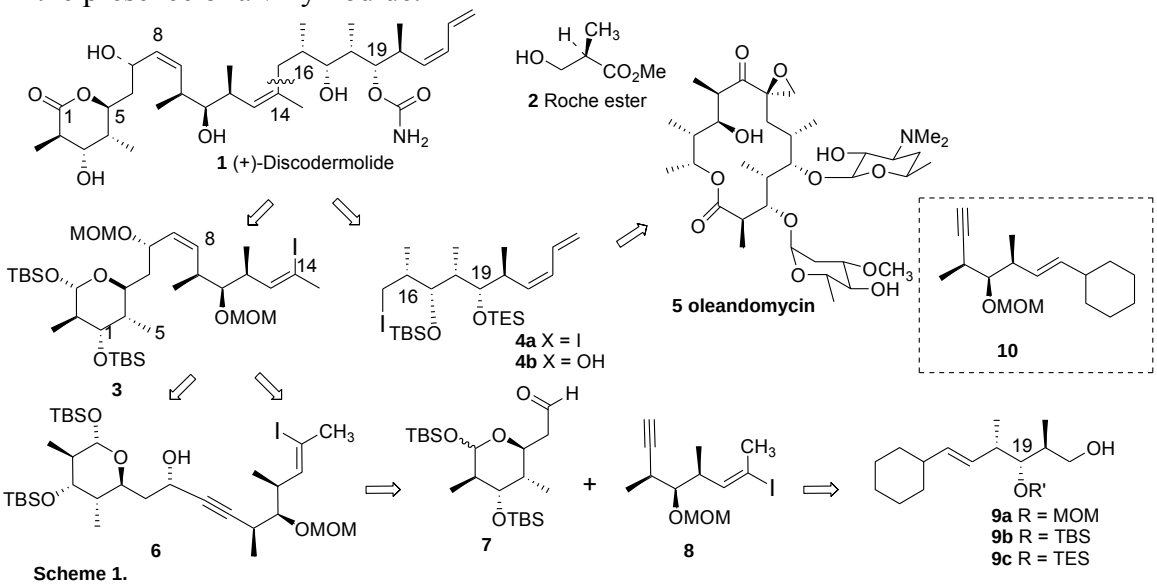
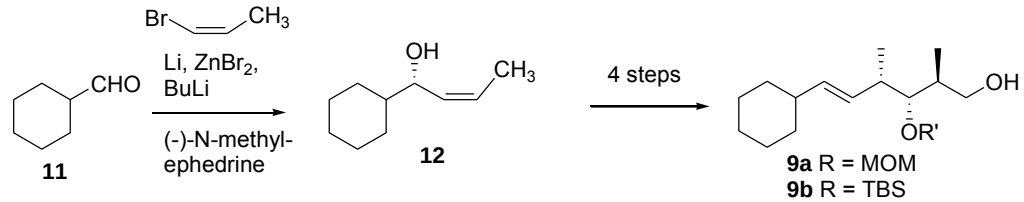
INTRODUCTION: Discodermolide (**1**) is a tubulin-binding drug that shows outstanding antitumor properties in cells.[1] Despite the difficulties associated with obtaining it from the natural source (*Discodermia dissoluta*, a deep-sea sponge that is harvested by a manned submersible) and the length of pioneering total syntheses based on Roche ester (**2**), discodermolide generated great interest as a potential pharmaceutical because it was active at submicromolar levels, stimulated minimal multi-drug resistance (mdr), and exhibited synergism with taxol.[2] Consequently, Novartis undertook the heroic task of preparing 60 g of discodermolide by a hybrid scheme that combined the most efficient components of the later Smith and Paterson syntheses.[3] Access to this material enabled Novartis to begin clinical trials in 2002.

BODY: Recognizing that the future of discodermolide in the treatment of cancer would require improved efficiency in the chemical synthesis, we analyzed its structure and proposed a total synthesis (Scheme 1) that featured novel and relatively short approaches to the compounds that we perceived to be the optimum key intermediates. Our proposed preparation of the known stereopentad intermediate **4b** was by semi-synthesis from the inexpensive agricultural antibiotic oleandomycin **5**. The C-1 to C-14 equivalent **3** was to be derived, by way of alkyne **6**, from aldehyde **7** and alkyne **8**. Each of these would be available from the stereotriad building blocks **9**, viewed as available by catalytic asymmetric synthesis. In addition to transformations that had good precedent, our highly convergent plan required less obvious chemistry: the development of an efficient degradation of oleandomycin and the semi-reduction of a propargyl alcohol or ether in the presence of a vinyl iodide.



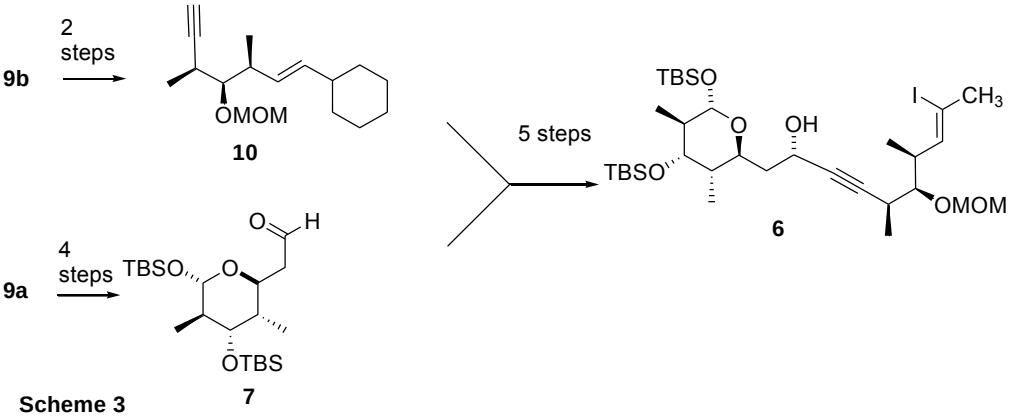
Scheme 1.

The first major achievement of this project was the demonstration that appropriately protected syn, anti stereotriad building blocks for discodermolide and related polyketide antibiotics could be obtained from variations on a short, scalable scheme that did not rely on Roche ester as a starting material. This practical advance is summarized in Scheme 2 (reported with full experimental details in reference 4,[4] see Appendix). A "spin-off" of this work was the preparation of anti, anti stereotriad building blocks (reported with full experimental details in reference 5,[5] see Appendix).



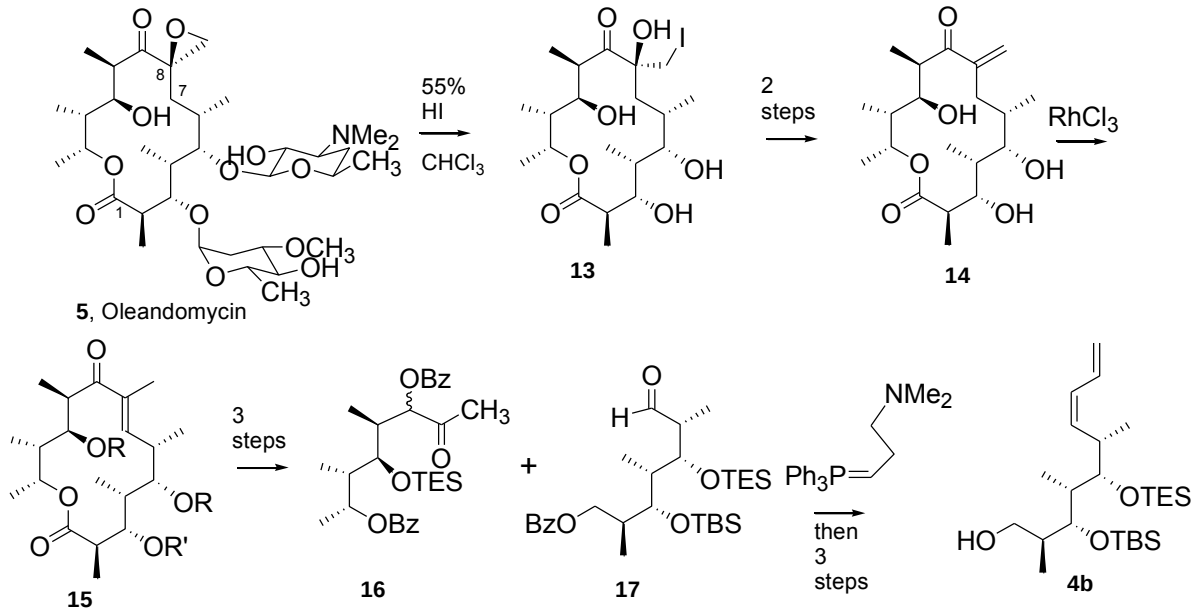
Scheme 2

The utility of the new building blocks was then showcased by the preparation of the C-1 to C-14 stretch of discodermolide. This demonstration of the practicality of the catalytic asymmetric approach to the stereotriad is shown in Scheme 3 (reported with full experimental details in reference 6,[6] see Appendix).



Scheme 3

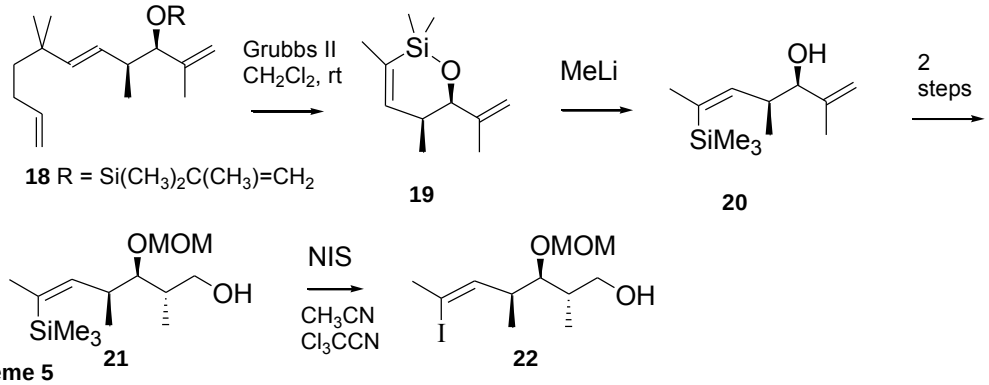
The original, unorthodox approach to the stereopentad building block of discodermolide by semi-synthesis from oleandomycin was demonstrated as shown in Scheme 4 (reported with full experimental details in reference 7,[7] see Appendix). This scheme represents the culmination of a series of modifications of oleandomycin and its degradation products and offers some unprecedented chemistry: direct cleavage of the aminoglycoside substituent in one step, isomerization of the exocyclic double bond in deoxyoleandomycin to an endocyclic position, and the selective protection of two of three hydroxyl groups in a modified oleandolide.



Scheme 4

Focusing on the improvement of the synthesis of the C-1 to C-14 stretch, we recognized that the preparation could be made optimally convergent only if it were possible to utilize an iodoolefin substituted alkyne (**8**) in the convergent step. Furthermore, the efficient synthesis of a (Z)-iodoolefinic building block by methodology not relying on the low-yielding Stork Zhao reaction would facilitate this goal. Therefore we proceeded to examine two transformations essential for the optimization of the preparation of major building block **3**.

As an alternative to the Stork Zhao introduction of a vinyl iodide, we considered the iododesilylation of dihydrooxasiline precursors to alkyne **8**. We were able to prepare the required dihydrooxasilines in an unprecedented and very convenient procedure by relay metathesis with the Grubbs II catalyst. We were able to carry out the iododesilylation of these substrates with retention of geometry on the double bond (as is appropriate for elaboration to discodermolide) in nonpolar solvents. This chemistry, in the context of discodermolide synthesis is shown in Scheme 5 (reported with full experimental details in reference 8,[8] see Appendix).



Scheme 5

In addition, we found that the iododesilylation reaction proceeded with inversion of the geometry of the double bond (as is appropriate for some other polypropionate antibiotics) in polar, aprotic

solvents. The potential of this conversion is described with full experimental details in a manuscript that is currently in revision[9] (see Appendix).

In a final demonstration of the feasibility of conversions proposed in the original scheme (i.e. **6** -> **3)**, we showed that vinyl iodides are stable to hydrogenation conditions that reduce a propargyl alcohol to a cis allylic alcohol. This result is reported with full experimental details in reference 10,[10] see Appendix.

The ability to effect this conversion in an advanced discodermolide intermediate will allow us to reduce the number of steps in the synthesis by one and to improve the overall yield by eliminating the inherently low-yielding Stork-Zhao step (used in the sequence from **10** to **6**).

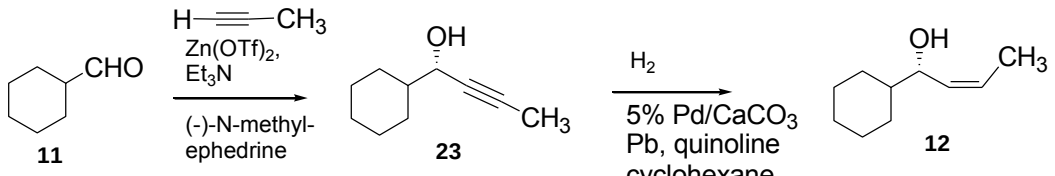
A completed synthesis of discodermolide based on this progress would be competitive with the most recent syntheses from Smith and Paterson and with the recently reported Ardisson synthesis.[11] Nonetheless, continuing work in the synthetic arena, market forces, and a reevaluation of the status of discodermolide as a drug candidate prompt us to modify our plans for the completion of the synthesis.

Our recent attempts to scale up the oleandomycin degradation have been unrewarding. Both the rhodium chloride isomerization/ deglycosylation and the HI-induced hydrolysis of the aminoglycoside are poorly behaved in the hands of a new co-worker. Although we could probably overcome these difficulties, another problem has appeared. Furthermore, we now think that our overall goal should be modified.

Over the past two years; we have found it increasingly expensive to purchase oleandomycin. Although there is precedent for its manufacture on a large scale, the economics of its production may require its wide use as a livestock antibiotic, a market that seems to have disappeared. Therefore, as a purely practical matter, it behooves us to modify our approach to the stereopentad.

Recently the status of discodermolide as a drug candidate has changed. Novartis has revealed the halting of its clinical trial. This decision has been attributed, in review articles, to toxicity at higher doses. At this time, it appears that this drug, which has the potential for many positive therapeutic features and in which so much time, money, and effort have been invested, will not be developed – at least not in the absence of tumor targeting mechanisms. Consequently, we are now considering the modification of our original plan in order to obtain a discodermolide that is functionalized for conjugation to a targeting moiety.

In moving forward toward completion of the synthesis of discodermolide (or a derivative functionalized for conjugation with a targeting moiety), we plan use the most efficient methods available to us; these include reactions from other syntheses as well as from our own sequence. We believe that our stereotriad synthesis is the most practical of those available but that it can still be improved. Therefore we have begun to optimize its synthesis by developing a modified preparation of the chiral allylic alcohol starting material **12.** In the new two-step preparation of **12** (Scheme 6), we avoid the need to prepare a vinyllithium reagent and the need to use butyllithium (compare Scheme 2).



Scheme 6

Rather, a chiral propynylzinc reagent is prepared under neutral conditions. Then, a subsequent hydrogenation supplies the required allylic alcohol. Our experience with this two-step approach suggests that it will be easily scaled up. This is important as the transmetalation of cis-1-bromopropene and the use of butyllithium in the first step of the overall sequence to the stereotriad (our common precursor to the three major building blocks) is scale-limiting.

A plan to complete the synthesis of discodermolide, functionalized appropriately for incorporation in a conjugate that will deliver it to tumor tissue, is the topic of proposal for an Idea Expansion Award, recently submitted to the Department of Defense Breast Cancer Research Program.

KEY RESEARCH ACCOMPLISHMENTS

- One-step hydrolysis of desosamine glycoside (of general interest in the field of organic synthesis and medicinal chemistry).
- Application of the Corey cis diene protocol in discodermolide synthesis (of general interest in the field of organic synthesis).
- Degradation of oleandomycin with introduction of protecting groups appropriate for elaboration to a known discodermolide intermediate.
- Completion of the appropriately substituted building block **4b** (C-15 to C-24 stretch of discodermolide) 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. synthesis (of general interest in the field of organic synthesis).
- Demonstration that chiral anti, anti stereotriad building blocks can be obtained by a modification of the above method synthesis (of general interest in the field of organic synthesis).
- Preparation of the C-1 to C-14 stretch of discodermolide (**6**) from the syn, anti stereotriad building block in 10 steps.
- Discovery that dihydrooxasilines can be prepared by relay metathesis with the commercially available, air-stable Grubbs II catalyst (of general interest in the field of organic synthesis).
- Elaboration of the dihydrooxasiline to both (*E*)- and (*Z*)- vinyl iodide-containing polypropionate building blocks (of general interest in the field of organic synthesis).
- Discovery of conditions that allow the semi-hydrogenation of a propargyl alcohol in the presence of a trisubstituted (*Z*)-vinyl iodide (of general interest in the field of organic synthesis).

REPORTABLE OUTCOMES:

Publications and manuscript under revision: references 4-10 below and reprints in Appendix.

Presentations

Award Address: Francis P. Garvan-John M. Olin Medal to Parker, Kathlyn A.. **Key steps.** Abstracts of Papers, 237th ACS National Meeting, Salt Lake City, UT, United States, March 22-26, 2009 (2009), ORGN-009.

Xie, Quizhe; Parker, Kathlyn A.. **Scalable, catalytic asymmetric synthesis of anti-,anti-stereotriad building blocks for polypropionate natural products.** Abstracts of Papers, 234th ACS National Meeting, Boston, MA, United States, August 19-23, 2007 (2007), ORGN-485.

Degrees obtained supported in part by this award:

Ph.D. SUNY Stony Brook: Zhou Zhou
Ph.D. SUNY Stony Brook: Peng Wang
Ph.D. SUNY Stony Brook: Qiu-zhe Xie
Ph.D. SUNY Stony Brook: Hong Zhao
B.S. *cum laude*, SUNY Stony Brook, Vicky Chen

Degrees to be awarded in May, 2010

Ph.D. SUNY Stony Brook: Erik Stolarzewicz
Ph.D. SUNY Stony Brook: Pei Wang

Continuing in the PhD program at SUNY Stony Brook

Junyong Lee
Hee Nam Lim
Daniel C. Elliot
Matthew E. Calder
Keon Soo Kim

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

Huanyan Cao's laboratory contributions to this project preceeded the date of funding. After his graduation in December, 2005, he accepted a position as 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.

After graduation, Hong Zhao accepted a postdoctoral position in the Organic Synthesis Core Facility at the Memorial Sloan Kettering Cancer Center.

Zhou Zhou is currently a postdoctoral research associate in the Department of Physiology and Biophysics at the Weill Cornell Medical Center.

Vicky Chen graduated with a BS *cum laude* and is working as a translator/interpreter while contemplating graduate school options.

Proposal submitted: **"**Salvaging Discodermolide as an Antitumor Drug. Selective Delivery" for an Idea Expansion Award, Department of Defense Breast Cancer Research Program.

Personnel
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Erik Stolarzewicz (graduate research assistant)
Peter Wambua Mulundi (graduate research assistant)
Zhou Zhou (graduate research assistant)
Pei Wang (graduate research assistant)
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Daniel C. Elliot (graduate research assistant)
Matthew E. Calder (graduate research assistant)
Keon Soo Kim (graduate research assistant)
Vicky Chen (undergraduate research assistant, summer)

CONCLUSIONS

Pursuit of a synthesis of discodermolide, designed to be optimally convergent has provided methodology that allows direct access to intermediates with essential functional group patterns. Although discodermolide itself now has an uncertain future as a drug, slight modification of our original scheme, most features of which have now been demonstrated, should provide access to a selectively protected discodermolide, appropriate for incorporation in a targeting conjugate drug.

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optimization of the effective synthetic route**."** Chemistry--A European Journal (2008), 14(35), 11092-11112.

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Scalable, Catalytic Asymmetric Synthesis of Syn, Anti Stereotriad Building Blocks for Polypropionate Antibiotics

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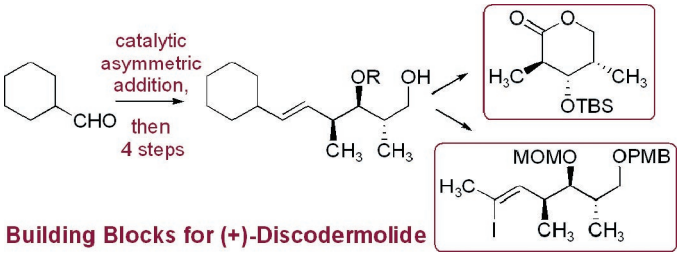
ABSTRACT



Asymmetric catalysis and chirality transfer by the 2,3-Wittig rearrangement were combined to provide a syn, anti stereotriad-containing olefinic alcohol in five steps from inexpensive starting materials. Development of this compound, a versatile intermediate for polypropionate synthesis, gave known building blocks for discodermolide.

The biosynthetic cascades controlled by the type I polyketide synthases produce a large and diverse family of natural products, in which the key structural feature is a long, methyl- and oxygen-substituted carbon chain.[1] Many of these metabolites are important medicinals, and many more have promising activity.

The construction of the long, multiply substituted chains required for the chemical synthesis of the nonaromatic polyketides is usually based on the iterative lengthening of an acyclic substituted chain and/or the coupling of several appropriately substituted chains. In this context, stereotriad-containing building blocks[2,3] have found widespread use. The anti, syn stereotriad that appears in antibacterial (e.g., erythromycin, streptovaricin) and antifungal (amphotericin) macrolides has been the subject of the most attention. It appears three times in the structure of the important non-macrolide (+)-discodermolide (**1**, Figure 1).

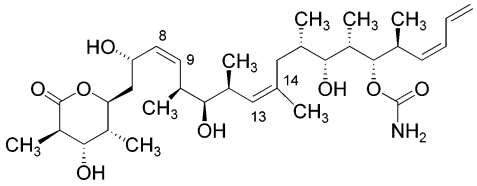


Figure 1. (+)-Discodermolide (**1**).

(+)-Discodermolide is a marine natural product, isolated in truly meager amounts from the Caribbean sponge *Discoderma dissolute*.[4] Originally identified in an immunosup-

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pressant screen, discodermolide was later shown to have antimitotic activity that results from its binding to microtubules.[5] Discodermolide is a particularly attractive drug candidate because it maintains activity against multidrug resistant organisms[6] and because it demonstrates synergism with taxol.[7,8] Because of the difficulty in obtaining this valuable compound from its deep-sea source, drug development has necessitated its preparation by total synthesis. Among the impressive total syntheses that have been reported,[9,10] Schreiber's original synthesis,[11] the "gram-scale" preparation by Smith,[12] and the subsequent "practical" synthesis of Paterson[13] are noteworthy for having supplied materials for biological testing. Proceeding on the premise that discodermolide will indeed become available in substantial amounts, the Novartis group has scaled up a "hybrid" synthesis and, with synthetic material, advanced discodermolide to phase I clinical trials.[14]

Retrosynthesis of discodermolide quickly reveals probable disconnects through or adjacent to the 8,9- and 13,14-olefinic bonds. Consequently, the total syntheses of this target have generally relied on strategies in which an anti, syn stereotriad-containing building block, functionalized on both ends (Figure 2), is parlayed into three more advanced intermediates, appropriately extended and/or activated for sequential coupling.

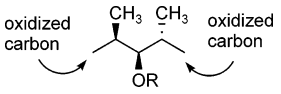

Figure 2. Functionalized syn, anti stereotriad building blocks for polypropionate construction.

In general, the stereotriad-containing building blocks for discodermolide synthesis have been prepared by variations on the chiral aldol strategy for the chain extension of an aldehyde derived from the Roche ester **3** (Figure 3). For example, Smith's "common precursor" or "CP" **2** was prepared in eight steps from the Roche ester **3**.[15] There are two notable exceptions to this rule. In almost simultaneous disclosures, Dias[16] and Day[17] and later the Novartis group[18] have described the use of recoverable auxiliaries (see **6**, Figure 3) as the sources of chiral induction in Evans aldol condensations with methacrolein. The resulting stereodiads were then converted to the stereotriad-containing lactone **5**. Lactone **5** has been converted to the more advanced discodermolide intermediate **4** (see **6** → **5** → **4**), a precursor to both the C-1−C-6 and C-9−C-14 synthons in the Smith[19] and Novartis[20] syntheses. It has also been employed in a total synthesis of sanglifehrin A[21] and converted to a useful Horner−Wadsworth−Emmons reagent.[22] Recently, Myles

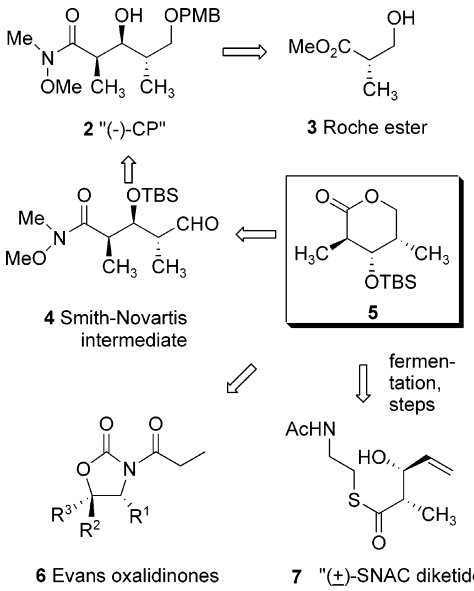

Figure 3. Origins of key building blocks in the chiral pool.

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(10) For contributions that describe improvements on the reports cited in ref 9, see: (a) Smith, A. B., III; Freeze, B. S.; Xian, M.; Hirose, T. *Org. Lett.* **2005**, *7*, 1825−1828. (b) Smith, A. B.; Freeze, B. S.; Brouard, I.; Hirose, T. *Org. Lett.* **2003**, *5*, 4405. (c) Paterson, I.; Lyothier, I. *J. Org. Chem.* **2005**, *70*, 5494. (d) Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; O'Brien, M.; Scott, J. P.; Sereinig, N. *J. Org. Chem.* **2005**, *70*, 150. (e) Paterson, I.; Lyothier, I. *Org. Lett.* **2004**, *6*, 4933.

(11) (a) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054. (b) Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621.

(12) Smith, A. B., III; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823.

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(14) Mickel, S. J.; Niederer, D.; Daeffler, R.; Osmani, A.; Kuesters, E.; Schmid, E.; Schaer, K.; Gamboni, R.; Chen, W.; Loeser, E.; Kinder, F. R., Jr.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Repic, O.; Wang, R.-M.; Florence, G.; Lyothier, I.; Paterson, I. *Org. Process Res. Dev.* **2004**, *8*, 122.

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(18) Loiseleur, O.; Koch, G.; Wagner, T. *Org. Process Res. Dev.* **2004**, *8*, 597.

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and co-workers at Kosan prepared this key lactone by chemical modification of a fermentation product (see **7** → **5**, Figure 3) from a genetically engineered *Streptomyces*.[23]

In this paper, we describe the preparation of key discodermolide intermediates **5** and **9** from the stereotriad-containing alcohols **8** (Figure 4). Each of these chiral alcohols

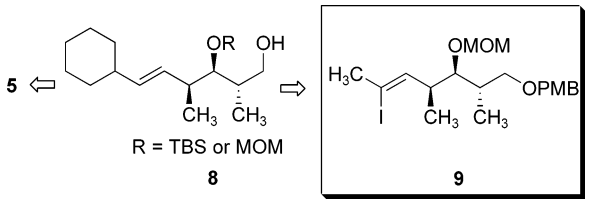


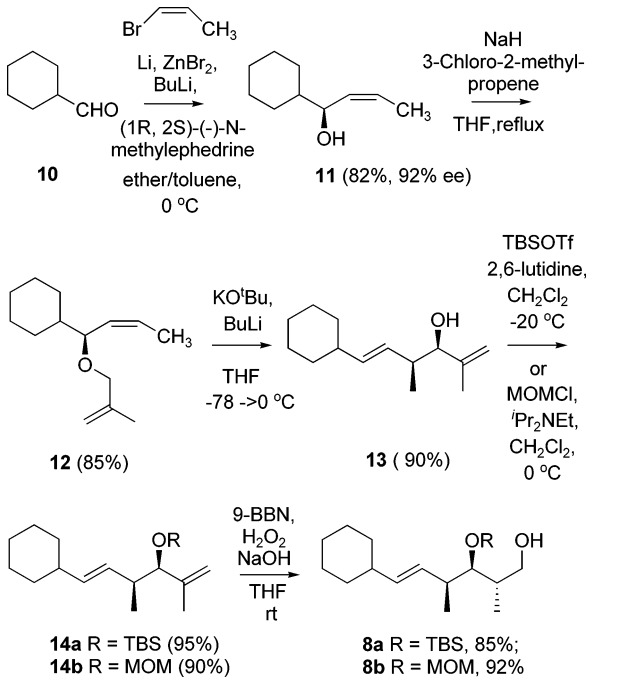
Figure 4. Examples of polypropionate building blocks available from alcohols **8**.

8 is readily available by the catalytic asymmetric synthesis of a chiral cis allylic alcohol and then elaboration by the remarkably efficient and totally overlooked "Midland sequence" (methallylation, 2,3-Wittig rearrangement, protection, and hydroboration).[24]

In 1984, when this efficient chemistry was demonstrated, chiral cis allylic alcohols could be obtained only indirectly.[25,26] More recently introduced methodology for the catalytic asymmetric synthesis of allylic alcohols in combination with the Midland sequence allows the preparation of stereotriad building blocks **8** in only five steps from inexpensive, commercially available starting materials (Scheme 1). In this work, we used cyclohexanecarboxaldehyde-derived intermediates for convenience in handling.

Thus, treatment of cyclohexanecarboxyaldehyde (**10**) with the complex prepared from *Z*-propenylzinc bromide and lithiated (+)-*N*-methylephedrine, according to Oppolzer's asymmetric addition protocol,[27] afforded the cis allylic alcohol **11** in 82% yield (92% ee).[28] Alkylation of the alcohol **11** gave the doubly allylic ether **12** which, on treatment with the KO^{t}Bu/^{n}BuLi reagent, underwent the 2,3-Wittig rearrangement to provide alcohol **13** with two chiral centers established. The ratio of the syn/anti diastereomers of this rearrangement product was, as judged by analysis of the ^{1}H NMR spectrum, 97:3.[29] Silylation and hydroboration provided the key intermediate **8a**. Alternatively, MOM alkylation followed by hydroboration gave alcohol **8b**. This strategy allows the preparation of these versatile intermediates in high overall yield and high enantiomeric excess without the sacrifice of a chiral starting material or the need to recycle a chiral auxiliary.

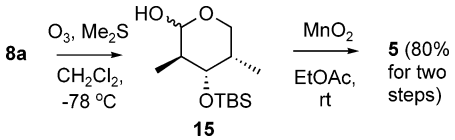
Scheme 1. Asymmetric Catalysis Route to Chiral Stereotriad Building Blocks



Alcohols **8** are versatile stereotriad-containing building blocks. To illustrate the potential of this approach for the practical synthesis of complex polyketides, we have applied it in the synthesis of lactone **5** and of vinyl iodide **9**, which are both intermediates in established syntheses of discodermolide.

The TBS monoprotected diol **8a** was easily converted to lactone **5** in two steps (Scheme 2). Ozonolysis with dimethyl sulfide workup followed by MnO_2 oxidation of the crude

Scheme 2. Preparation of Lactone **5**



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(25) First, a propargyl alcohol was oxidized to an ynone that was then reduced with a chiral reagent (Midland used *R*-alpine-borane); then semihydrogenation provided the allylic alcohol. See: (a) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (b) Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2814.

(26) Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339.

(27) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777.

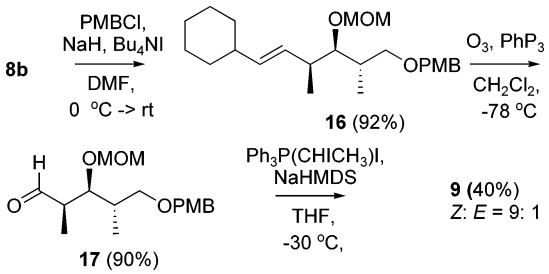
(28) The ee was obtained by Mosher ester analysis; see Supporting Information.

(29) Careful integration of the 3−4 ppm region of the 1H NMR spectrum (300 Hz) revealed the ratio of syn diastereomer (d, J = 6.0 Hz centered at 3.87 ppm) to anti diastereomer (d, J = 8.4 Hz, centered at 3.66 ppm) to be 97:3. For the assignment, see ref 24a.

lactol **15** gave lactone **5** directly (recrystallized product, 80% for two steps).

The MOM-protected diol **8b** has been converted to vinyl iodide **9**, an intermediate in Smith's later generation discodermolide syntheses in which it serves as the precursor to the C-9−C-14 moiety.[10a,b] Preparation of vinyl iodide **9** from alcohol **8b** was achieved in three steps (Scheme 3). Introduction of the PMB group was followed by ozonolysis to give the aldehyde **17**. Then, the Stork−Zhao procedure gave the known building block **9**.

Scheme 3. Preparation of Vinyl Iodide **9**



Thus, chiral syn, anti stereotriad building blocks, useful for the preparation of polypropionate antibiotics, may be efficiently accessed by short schemes from inexpensive starting materials. Asymmetric catalysis replaces the need for the stoichiometric consumption of a chiral starting material or a chiral reagent or the recycling of a chiral auxiliary. Extension of this strategy to the preparation of advanced intermediates for antibiotic synthesis will be described in due course.

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Note Added after ASAP Publication. Figure 2 was referenced in error twice in the version posted July 11, 2006; this error was corrected July 13, 2006. Subsequently, an error was discovered in the abstract graphic. A corrected version was posted July 17, 2006.

Supporting Information Available: Detailed descriptions of the experimental procedures and complete analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Asymmetric Catalysis Route to *anti*,*anti* Stereotriads, Illustrated by Applications

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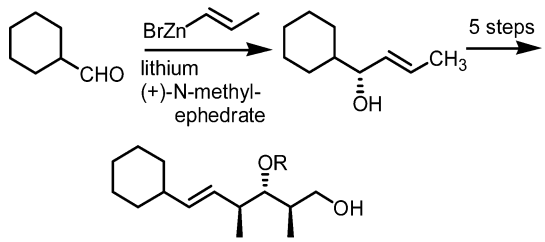
Received December 12, 2007

ABSTRACT



versatile *anti, anti* stereotriad building block

A short sequence based on asymmetric catalysis, chirality transfer, and an optimized carbometallation protocol gave an *anti*,*anti* stereotriad building block in six steps. Both enantiomers of the chirality source, *N*-methyl ephedrine, are inexpensive, and the auxiliary is recoverable. In one chiral series, the building block was converted to the "B-2" intermediate in Miyashita's synthesis of scytophycin C; in the enantiomeric series, it was converted to a key intermediate for aplyronine A and to the polyketide "cap" for the callipeltins.

As new and promising polypropionate antibiotics are discovered in nature, interest in these compounds as biological probes and as potential therapeutics continues to expand. The preparation of polypropionates is a challenge that has been met by the development of a variety of new methodologies. Nonetheless, the complexity of many target structures is such that more efficient syntheses from inexpensive materials are needed.

The *anti*,*anti* stereotriad is a noticeable feature of the structures of numerous polyketide antibiotics. Among these are macrolides isolated from aquatic organisms, primarily from marine sponges (e.g., swinholides) but also from sea snails (aplyronines, e.g., aplyronine A, **1a**) and fresh water cyanobacteria (scytophycins, e.g., scytophycin C, **1b**),[1] that bear a stereochemically rich, *N*-vinyl formamide-terminated side chain. There is speculation that the compounds isolated from the higher marine organisms are, in fact, the metabolites of cyanobacteria that are symbiotic with the hosts.[2] These marine macrolides alter the dynamics of the actin polymerization/depolymerization process by binding globular (monomeric) actin (G-actin) and by severing filamentous actin (F-actin). Perhaps, at least in part, because their action interferes with cell division,[3] these compounds are highly cytotoxic.

The *anti*,*anti* stereotriad is also found in a second class of marine natural products, the callipeltins. These cyclic and acyclic peptides are notable for their unusual amino acid residues as well as for their impressive biological activities.

(1) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237.

(2) (a) Andrianasolo, E. H.; Gross, H.; Goeger, D.; Musafija-Girt, M.; McPhail, K.; Leal, R. M.; Mooberry, S. L.; Gerwick, W. H. *Org. Lett.* **2005**, 7, 1375 and references therein. (b) Luesch, H.; Harrigan, G. G.; Goetz, G.; Horgen, F. D. *Curr. Med. Chem.* **2002**, *9*, 1791.

(3) Recent data suggest, however, that toxicity is not directly correlated with depolymerizing activity; see: (a) Suenaga, K.; Kimura, T.; Kuroda, T.; Matsui, K.; Miya, S.; Kuribayashi, S.; Sakakura, A.; Kigoshi, H. *Tetrahedron* **2006**, 62, 8278 and references therein. (b) Ojika, M.; Kigoshi, H.; Yoshida, Y.; Ishigaki, T.; Nisiwaki, M.; Tsukada, I.; Arakawa, M.; Ekimoto, H.; Yamada, K. *Tetrahedron* **2007**, *63*, 3138. (c) Also of interest in this context: Fuerstner, A.; Nagano, T.; Mueller, C.; Seidel, G.; Mueller, O. *Chem. Eur. J.* **2007**, *13*, 1452.

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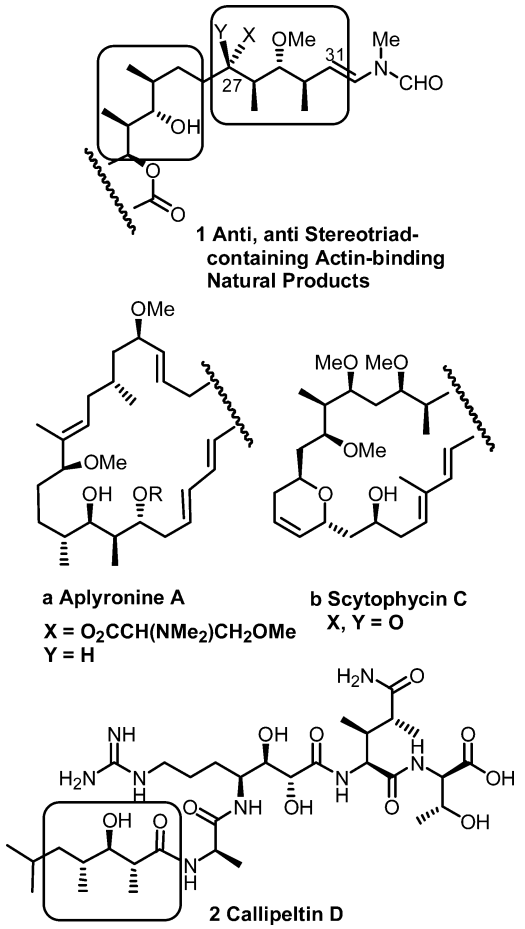
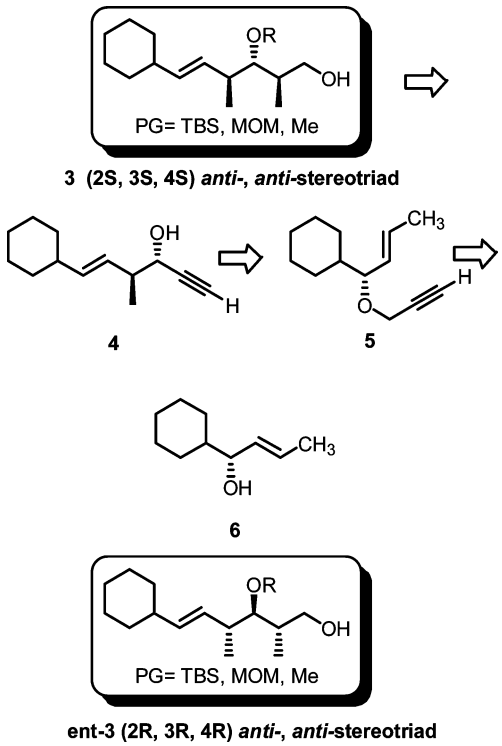


Figure 1. *anti*,*anti* Stereotriads in selected natural products.

In callipeltins A, C, D (**2**), and F-L from *Callipelta* sp. and *Latrunculia* sp.,[4] and in the closely related neamphamide A from *Neamphius huxleyi*,[5] a (2*R*,3*R*,4*R*)-3-hydroxy-2,4,6-trimethylheptanoic acid moiety acts as an N-terminal "cap" of the peptide chain.

In order to gain easy access to polypropionate-derived natural products, we have focused on the exploitation of the 2,3-Wittig rearrangement. In 2006, we described the stereoselective rearrangement of a methallyl ether of a chiral *cis* allylic alcohol to produce a *syn* stereodiad that was subsequently elaborated to *syn*,*anti* stereotriad intermediates for a discodermolide synthesis.[6] The corresponding *anti* stereodiad is not cleanly available by variations of this direct approach; however, an *anti* stereodiad is available by the Wittig rearrangement of a *propargyl* ether of a *trans* allylic alcohol.[7] Therefore we considered the possibility that the *anti*,*anti* stereotriad equivalent **3** might be elaborated from propargyl ether **5** by way of the rearrangement product **4**.

Scheme 1. Enantiomeric Stereotriad Building Block Targets and Retrosynthetic Postulate



This approach to the *anti*,*anti* stereotriad **3** offered two desirable features. First, the precursor of the Wittig rearrangement substrate, chiral alcohol **6**, should be available by an asymmetric addition reaction in which the chiral ligand can be easily recovered. Second, the enantiomeric stereotriad **ent-3** should be equally available by applying the same approach in the enantiomeric series.

The practicality of our overall strategy and its utility have now been demonstrated by the facile preparation of Miyashita's "B-2" (**7**), a building block in the synthesis of scytophycin C (**1b**);[8,9] aldehyde **8**, an intermediate in Paterson's approach to aplyronine A (**1a**); and the TBS-protected (for use in total synthesis) 3-hydroxy-2,4,6-trimethylheptanoic acid **9** (TBS-Htmha), the "cap" for callipeltins (e.g., **2**).[10]

(4) D'Auria, M. V.; Sepe, V.; D'Orsi, R.; Bellotta, F.; Debitus, C.; Zampella, A. *Tetrahedron* **2007**, *63*, 131 and references therein. For the total synthesis of Callipeltin D, see Cranfill, D. C.; Morales-Ramos, A. I.; Lipton, M. A. *Org. Lett.* **2005**, *7*, 5881.

(5) Oku, N.; Gustafson, K. R.; Cartner, L. K.; Wilson, J. A.; Shigematsu, N.; Hess, S.; Pannell, L. K.; Boyd, M. R.; McMahon, J. B. *J. Nat. Prod.* **2004**, *67*, 1407.

(6) Parker, K. A.; Cao, H. *Org. Lett.* **2006**, *8*, 3541.

(7) Tsai, D. J. S.; Midland, M. M. *J. Org. Chem.* **1984**, *49*, 1842.

(8) For the structure determination and biological activities of scytophycin C, see: Smith, C. D.; Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *Cancer Res.* **1993**, *53*, 1343.

(9) (a) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3579. (b) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3583. (c) A total synthesis of scytophycin C was also reported by Paterson, I.; Watson, C.; Yeung, K.-S.; Ward, R. A.; Wallace, P. A. *Tetrahedron* **1998**, *54*, 11955.

(10) (a) For an elegant and efficient synthesis of TBS-Htmha in which the source of chirality is pseudoephedrine was reported by Lipton, see: Turk, J. A.; Visbal, G. S.; Lipton, M. A. *J. Org. Chem.* **2003**, *68*, 7841. (b) For an earlier synthesis of the *O*-benzyl-protected acid, see: Zampella, A.; D'Auria, M. V. *Tetrahedron: Asymm*etry **2002**, *13*, 1237. (c) For preparations of the (2*R*,3*R*,4*S*)-diastereomer, see: Zampella, A.; Sorgente, M.; D'Auria, M. V. *Tetrahedron: Asymmetry* **2002**, *13*, 681. Guerlavais, V.; Carroll, P. J.; Joullie, M. M. *Tetrahedron: Asymmetry* **2002**, *13*, 675.

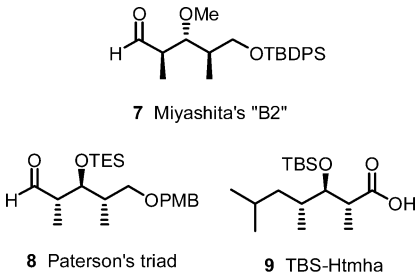
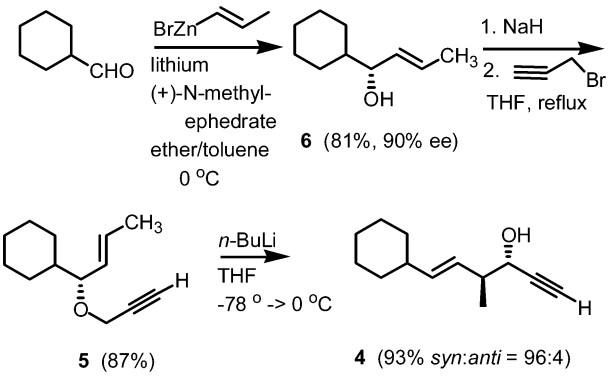


Figure 2. Illustrative targets.

Preparation of stereotriad building block **3** was to be based on elaboration of the 2,3-Wittig rearrangement product **4**. Synthesis of this key intermediate began (Scheme 2) with the addition of (*E*)-1-propenylzinc bromide to cyclohexanecarboxaldehyde in the presence of (+)-*N*-methylephedrine according to the method of Oppolzer.[11] Allylic alcohol **6** was obtained in 81% yield and 90% ee.[12] Alkylation with propargyl bromide afforded ether **5** in 87% yield. Application of standard [2,3]-Wittig rearrangement conditions afforded (*E*)-propargylic alcohol **4** (93% yield). The ratio of the *anti*/*syn* diastereomers in this rearrangement product was, as judged by integration of the ^{1}H NMR spectrum, 96:4.

Scheme 2. Three-Step Preparation of the Chiral *anti* Stereodiad



At this point, our plan was to convert alcohol **4** to the key intermediate **3** (R = Me) by a sequence consisting of carbometallation with a proton quench, O-methylation, and hydroboration (see Scheme 3). Efforts to obtain useful results by applying the Duboudin carbometallation protocol[13] to substrate **4** afforded a low yield of the desired α-adduct **10** along with the *β*-adduct and recovered starting material. In order to develop an efficient conversion of terminal propargyl alcohols to methallyl alcohols, we studied the product distribution of the carbometallation of 1-cyclohexyl-2-propyn-1-ol (Table 1).[14,15]

Scheme 3. Conversion of *anti* Stereodiad **4** to *anti*,*anti* Stereotriad **3** and Elaboration to Miyashita's "B-2" **7**

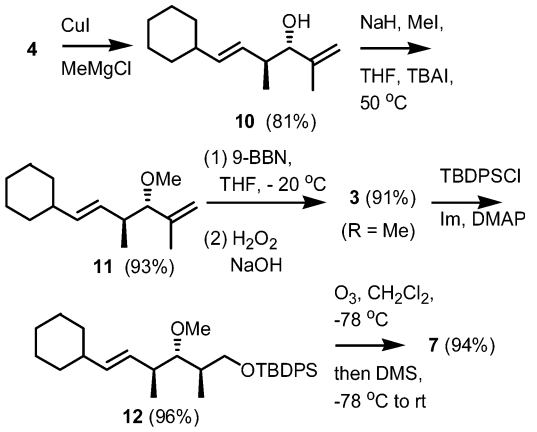


Table 1. Distribution of Starting Material (SM) and Products: CuI-Catalyzed Addition of Methylmagnesium Halide to 1-Cyclohexyl-2-propyn-1-ol

MeMgX X, equiv	CuI (equiv)	solvent	SM, α-adduct, *β*-adduct (%)
Br, 2.5	0.95	THF	54, 24, 22
Br, 4.0	2.0	THF	28, 58, 14
Br, 4.0	3.0	THF	62, 22, 16
Br, 4.0	2.0	Et_2O	65, 4, 31
Br, 4.0	2.0	dioxane	100, 0, 0
Cl, 4.0	2.0	THF	21, 79, trace
I, 4.0	2.0	THF	87, 13, trace

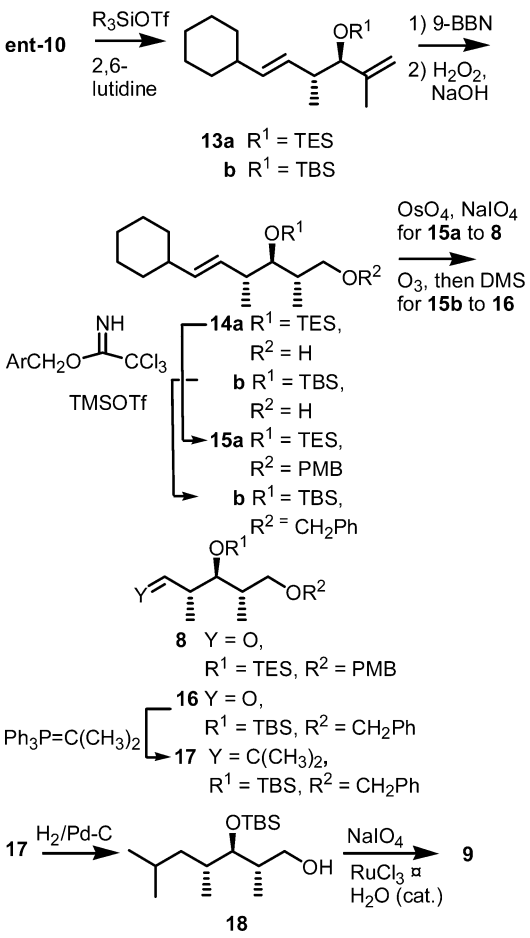
Application of the most favorable protocol to substrate **4** resulted in the isolation of an 81% yield of the desired alcohol **10** along with the recovery of some starting material. Methylation and hydroboration gave the desired synthon **3** (R = Me). Silylation and ozonolysis demonstrated its utility by conversion to the desired "B-2," aldehyde **7**.

An advantage of the asymmetric addition−rearrangement approach to stereotriad-containing intermediates is that both enantiomers of key compound **3** are readily available. For the preparation of Paterson's triad **8** or TBS-Htmha (**9**), it is more efficient to use a synthon derived from **ent-10** than one derived from the previously prepared **10**. Therefore the five-step asymmetric synthesis was applied in the enantiomeric series (**ent-6** → **ent-4** → **ent-10**, as in Schemes 2 and 3).

Both targets **8** and **9** were then prepared (Scheme 4). Conversion of **ent-10** to Paterson's triad **8** was accomplished

(11) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777.
(12) The ee was determined by Mosher ester analysis; see Supporting Information. The chiral ligand was recovered quantitatively in purity that was appropriate for use in further reactions.
(13) (a) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 1−11. (b) Duboudin, J. G.; Jousseaume, B. J.; Bonakdar, A. *J. Organomet. Chem.* **1979**, *168*, 227−232.
(14) Details will be reported in a full paper.
(15) During the course of our work, a similar study was reported for the carbometallation of terminal, secondary propargyl alcohols in which the substituent was a straight-chain alkyl group. See: Lu, Z.; Ma, S. *J. Org. Chem.* **2006**, *71*, 2655.

Scheme 4. Preparation of Paterson's Triad **8** and TBS-Htmha **9**



by silylation with TES triflate, hydroboration with 9-BBN (→ **14a**), and protection with *p*-methoxybenzyl trichloroacetamidate. Under standard ozonolysis conditions, olefin **15a** suffered oxidative removal of the PMB group as indicated by the appearance of *p*-methoxybenzaldehyde. However, a two-step procedure with OsO_4 and buffered $NaIO_4$ provided the aldehyde target **8**.[16] For elaboration of **ent-10** to the protected hydroxy trimethylheptanoic acid **9**, silylation with TBSOTf (→ **13b**) was followed by benzylation with benzyl trichloroacetimidate to give the fully protected olefin **15b**. Ozonolysis provided aldehyde **16** which was subjected to the Wittig reaction. Treatment of the trisubstituted olefin **17** with hydrogen in the presence of palladium on carbon effected both debenzylation and saturation of the double bond. Oxidation of primary alcohol **18**[17] gave TBS-Htmha (**9**).

The advantages of this approach to *anti,anti* stereotriad building blocks are (1) the use of asymmetric catalysis as a source of chirality, (2) the ready availability of catalysts for both chiral series, (3) the functional group pattern in the synthon (**3** or **ent-3**) itself, which allows generation of an aldehyde in one step in high yield, and (4) the relatively robust protocols required for the short scheme that provides synthon **3** or **ent-3**. More sophisticated applications are being pursued.

Acknowledgment. This work was supported by the Department of Defense Army Breast Cancer Initiative (BC051816), and the National Science Foundation (CHE-0131146, NMR instrumentation).

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Short Synthesis of the C1–C14 Stretch of Discodermolide from Building Blocks Prepared by Asymmetric Catalysis

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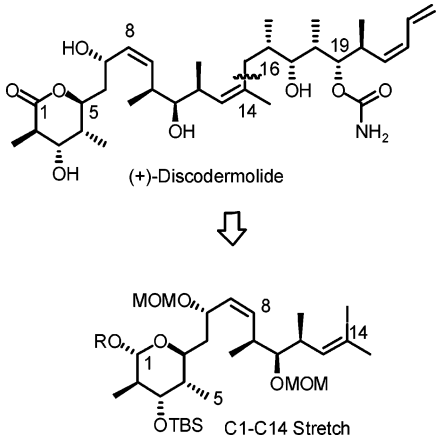
ABSTRACT



A convergent and stereoselective synthesis of the C1–C14 stretch of (+)-discodermolide demonstrates the utility of the "asymmetric catalysis approach" to complex polypropionates. The preparation of this complex synthon requires 15 steps in the longest linear sequence and 19 steps total from inexpensive materials.

The real need[1] for an efficient preparation of discodermolide (**1**), a polyketide marine natural product considered a candidate for use as a drug for the treatment of solid tumors, has sustained interest in its total synthesis. Indeed, research and development accomplishments targeted toward this goal[2] exemplify the remarkable power of the science of organic synthesis at the turn of the 21st century.

Of the likely convergent steps for the completion of the C1−C24 carbon backbone, the joining of protected intermediates that contain the C1−C14 stretch and the C15−C24 stretch appears to be optimally convergent. An approach based on this retrosynthetic analysis served as the basis of the Marshall total synthesis.[3] This dissection has also been employed in Panek's total synthesis,[4] in Smith's fourth generation synthesis,[5] and in the very recent Ardisson synthesis.[6] Also, both Cossy[7] and Kiyooka[8] have prepared advanced C1−C13 intermediates in anticipation of similar endgames.

Our own focus for the completion of a fully functionalized carbon chain has also been on the connection between C14

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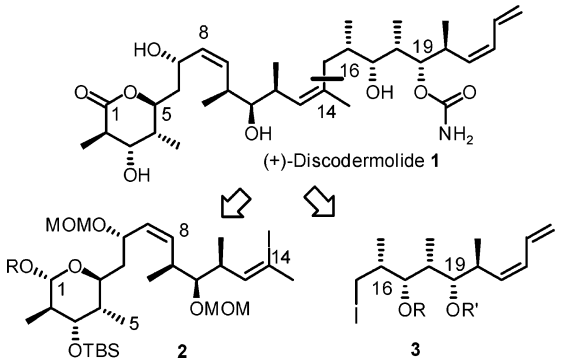


Figure 1. First disconnect for the retrosynthesis of (+)-discodermolide.

and C15. Our goals therefore have been the efficient syntheses of the two large synthons (**2** and **3**,[9] Figure 1) for use in a late-stage linkage. We have recently reported a synthesis of the alcohol corresponding to iodide **3** (R = TBS, R′= TES) from the fermentation product oleandomycin.[10] We now address the synthesis of vinyl iodide **2** (R = TBS).

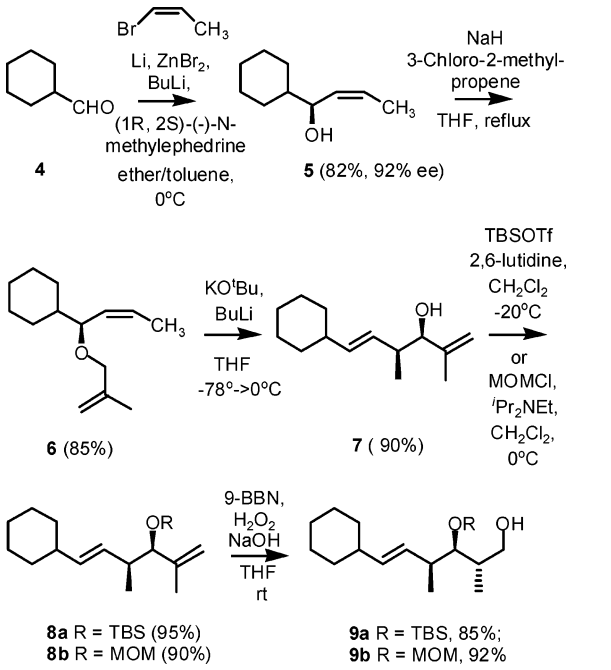
For the preparation of key intermediate **2**, we initially examined an approach based on the pseudosymmetry of the C1−C13 stretch.[11] Although this early model study has not yet been extended to total synthesis, the further pursuit of the pseudosymmetry strategy[12] highlighted the need for inexpensive and scalable preparations of stereotriad-containing precursors.

A solution to this perceived problem was found in a short scheme based on a catalytic asymmetric addition (**4** → **5**)[13] and highly stereoselective [2,3]-Wittig rearrangement (**6** → **7**) and hydroboration reactions (**8** → **9**).[14] Thus, the building blocks **9a** and **9b**, protected for incorporation in different regions of the target **2**, were prepared as summarized in Scheme 1.[15]

With an inexpensive source of stereotriad-containing building blocks available to us, we reanalyzed our original approach and adapted it to minimize not only the number of steps but the conversion of material. We now describe the rapid preparation of the C1−C14 piece of (+)-discodermolide, appropriately protected for incorporation in a total synthesis, by a convergent scheme based on the readily available **9a** and **9b**.

As our sequence for the preparation of key intermediate **2** would rely on the highly stereoselective but low-yielding Stork-Zhao reaction, we initially considered approaches in

Scheme 1. Synthesis of Stereotriad Building Blocks by Asymmetric Catalysis



which the iodoolefination transformation was employed prior to the convergent acetylide-addition step (see Figure 2). However, we noted the reported incompatibility of the C13−14 trisubstituted iodo olefin moiety with introduction of a cis C8−9 olefin by way of reduction of the corresponding acetylene.[4]

Therefore, in this, our first attempt to prepare the C1−C14 stretch of discodermolide, we chose to elaborate the iodo olefin late in the preparation of **2** and settled on aldehyde **10** as its immediate precursor. We imagined this compound to be derived from the acetylide-addition product **11**, which would be derived from the two stereotriad-containing building blocks **12** and **13**. Each of these would be obtained from one of the monoprotected diols **9**.

Synthesis of the protected lactal aldehyde **12** is outlined in Scheme 2. Oxidation of the TBS-protected stereotriad-containing alcohol **9a** with TPAP/NMO[16] gave aldehyde **14** in 96% yield. Brown asymmetric allylation[17] with the reagent prepared from (−)-*B*-methoxydiisopinocampheylborane under the "salt-free" conditions afforded a mixture of alcohols in which one stereoisomer was clearly predominate. Simple silica gel flash chromatography separated the major isomer **15** (71% yield) from the minor isomer (17% yield).

On the basis of extensive precedent, we had predicted that the major stereoisomer from this addition would be the *syn*, *anti*, *anti* stereoisomer **15**.[18] This assignment was confirmed by applying the acetonide method of Rychnovsky[19] to diols derived from the separated epimeric alcohols (see the Supporting Information).

(8) (a) Kiyooka, S.-i.; Shahid, K. A.; Goto, F.; Okazaki, M.; Shuto, Y. *J. Org. Chem.* **2003**, *68*, 7967. (b) Shahid, K. A.; Mursheda, J.; Okazaki, M.; Shuto, Y.; Goto, F.; Kiyooka, S.-i. *Tetrahedron Lett.* **2002**, *43*, 6377. Corrigendum: *Tetrahedron Lett.* **2003**, *44*, 1519.

(9) Several examples of iodides **3** are known discodermolide intermediates; see references 3−5 and 7 and Loiseleur, O.; Koch, G.; Cercus, J.; Schuerch, F. *Org. Process Res. Dev.* **2005**, *9*, 259.

(10) Parker, K. A.; Wang, P. *Org. Lett.* **2007**, *9*, 4793.

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(13) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777.

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(17) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

(18) For a particularly relevant precedent, see Chattopadhyay, S. K.; Pattenden, G. *Tetrahedron Lett.* **1995**, *36*, 5271.

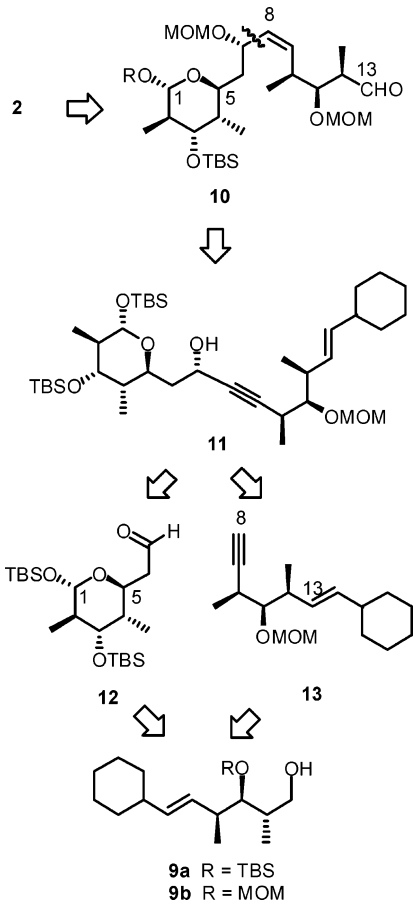
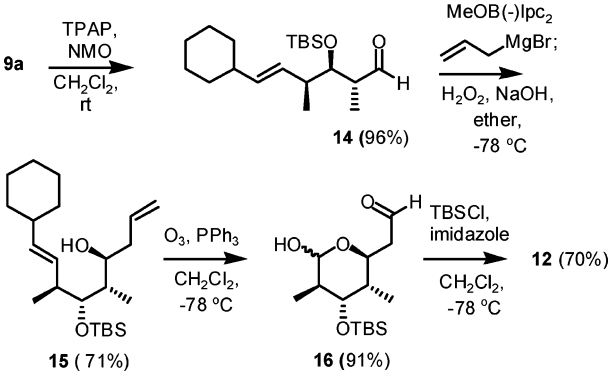


Figure 2. Retrosynthesis of key intermediate **2** to building blocks **9a** and **9b**.

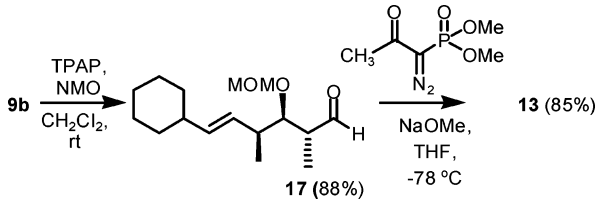
Cleavage of the two double bonds in diene **15** by ozonolysis accompanied by cyclization gave lactol **16** (a 1:1 mixture of β and α anomers as indicated by NMR analysis). This mixture was subjected to silylation to afford the protected hemiacetal **12** as the α anomer in 70% yield after silica gel flash chromatography.

Synthesis of the other coupling partner, acetylene **13**, was straightforward (Scheme 3). Subjection of MOM-protected

Scheme 2. Elaboration of Building Block **9a** to Intermediate **12**



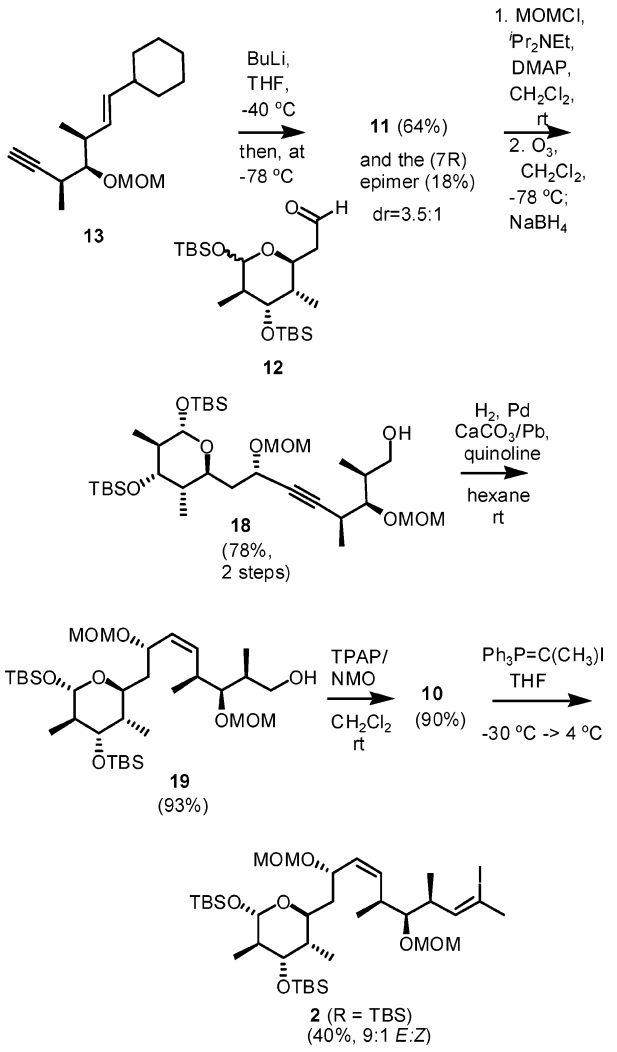
Scheme 3. Elaboration of Building Block **9b** to Intermediate **13**



stereotriad-containing alcohol **9b** to TPAP/NMO gave aldehyde **17** in 88% yield. Aldehyde **17** was converted to acetylene **13** in one step by the Ohira-Bestmann reagent in 85% yield.[20]

With easy access to both intermediates **12** and **13**, we carried out the convergent step (Scheme 4). Treatment of acetylene **13** with BuLi at −40 °C, followed by addition of aldehyde **12**, afforded a separable 3.5:1 mixture of alcohols. The configuration at C7 of the major epimer was assigned

Scheme 4. Convergent Preparation of Vinyl Iodide **2** from Intermediates **12** and **13**



as (S) by the "broadened" version[21] of the modified (or advanced) Mosher method;[22] see the Supporting Information for details. The isolated yield of alcohol **11** (R = TBS) was 64%.

Propargyl alcohol **11** (R = TBS) was elaborated to the target **2** (R = TBS) in five steps (Scheme 4). First, the C7 hydroxyl was protected as the MOM ether. Then cleavage of the double bond by O_3 followed by $NaBH_4$ reductive workup afforded alcohol **18** (78% for two steps). Reduction of the C8−C9 triple bond to the *cis* olefin by hydrogenation under Lindlar conditions provided (*Z*)-olefin **19** in excellent yield. TPAP-NMO oxidation gave aldehyde **10** (90% yield) and the Stork-Zhao olefination gave the target C1−C14 equivalent, vinyl iodide **2** (R = TBS) in 40% yield (*Z:E* = 9:1).

The synthesis of the fully functionalized C1−C14 fragment of (+)-discodermolide (compound **2**) required 10 steps from the key building blocks **9a** and **9b**, each of which was prepared by a five-step sequence (Scheme 1) based on asymmetric catalysis and inexpensive, commercially available starting materials. Building blocks **9** are attractive alternatives to stereotriads derived from (*R*)-(−)-3-hydroxy-2-methylpropionic acid methyl ester (Roche ester). A particularly advantageous example of their use is in the context of the preparation of the C1−C7 equivalent **16** in which both aldehyde and protected aldehyde groups are generated in a single ozonolysis step. Access to the C1−C14 stretch (key intermediate **2**) and to the C15−C24 stretch (alcohol corresponding to iodide **3**, R = TBS, R′ = TES) of discodermolide has now set the stage for us to complete a total synthesis.

Acknowledgment. This work was supported by the National Institutes of Health (CA-87503), the Army Breast Cancer Initiative (BC 051816), and the National Science Foundation (CHE-0131146, NMR instrumentation).

Supporting Information Available: Detailed descriptions of the experimental procedures and complete analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Deconstruction–Reconstruction Strategy for Accessing Valuable Polyketides. Preparation of the C15–C24 Stereopentad of Discodermolide

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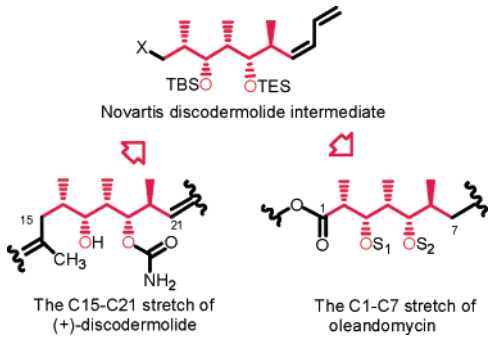
ABSTRACT



An advanced, known intermediate for discodermolide synthesis was prepared by an efficient sequence from the readily available fermentation product oleandomycin. The scheme makes use of a new method for the direct cleavage of aminoglycosides, a critical double-bond isomerization, and a selective protection of two of three hydroxyl groups in a modified oleandolide. This synthesis illustrates a new strategy, "deconstruction–reconstruction", for accessing stereochemically complex polyketide building blocks.

The polyketide antibiotics continue to offer a variety of interesting activities, both as potential medicinals and as biochemical tools. For some of these compounds, particularly some of the stereochemically complex marine natural products, study and development have been limited by a lack of material.[1] For example, the interesting antitumor compound discodermolide (**1**, Figure 1), originally obtained by the harvesting of a deep sea sponge, became available in quantities sufficient for clinical testing only after considerable effort by synthetic chemists.[2]

The synthesis of complex polyketides by linking linear, functionalized carbon chains requires access to smaller building blocks, many of which contain alternating methyl and oxygen substituents. These are almost universally prepared by one or more of the many stereo- and enantioselective variations on the chiral aldol condensation, accompanied by protection steps and adjustment of oxidation state.[3] Analysis of the total number of operations required for the preparation of longer polyketide synthons by repeated application of this procedure prompted us to seek alternative approaches.

We noted the richness of the chiral pool and, in particular, the macrolide antibiotics that are used in human and veterinary medicine. In this paper, we illustrate the potential of a deconstruction-reconstruction strategy for the preparation of difficult to obtain, stereochemically complex synthetic intermediates from these large-scale fermentation products.

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(2) (a) Mickel, S. J. *Pure Appl. Chem.* **2007**, *79*, 685 and references therein. (b) de Lemos, E.; Poree, F.-H.; Commercon, A.; Betzer, J.-F.; Pancrazi, A.; Ardisson, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1917.
(3) For examples and exceptions to the rule, see: Parker, K. A.; Cao, H. *Org. Lett.* **2006**, *8*, 3541 and references therein.

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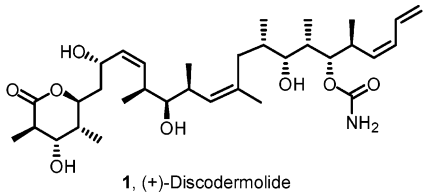
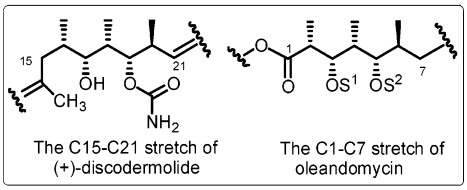
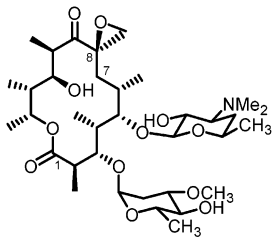


1, (+)-Discodermolide

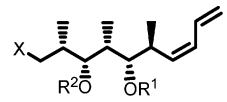




2, Oleandomycin

Figure 1. Analysis of the stereopentad substructures of discodermolide and oleandomycin.

Recognizing the C15−C21 stretch of discodermolide in the C1−C7 stretch of oleandomycin[4] (**2,** Figure 1), we imagined excising a stereopentad-containing fragment and then elaborating it to one of the C15−C24 iodides **3b**−**d** (Figure 2). Each of these iodides, prepared from the corresponding alcohol, has served as a key intermediate in a successful total synthesis.[5]



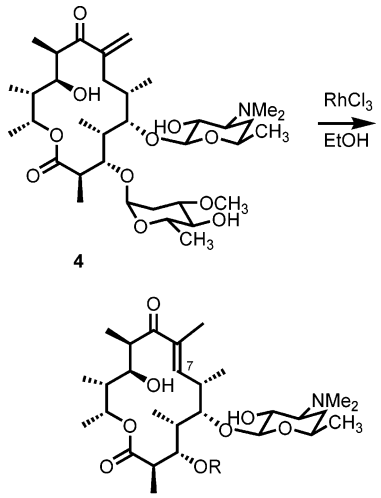
3a X = I, R^1 = TBS, R^2 = PMB
3b X = I, R^1 = TES, R^2 = PMB
3c X = I, R^1 = PMB, R^2 = TBS
3d X = I, R^1 = TES, R^2 = TBS
3e X = OH, R^1 = TES, R^2 = TBS

Figure 2. Some known discodermolide stereopentad equivalents.

Focusing on alcohol **3e** as our target, we realized that we needed to discover methods for two crucial transformations. First, because we considered C7 of oleandomycin as the progenitor of C21 in discodermolide, we viewed the C7−C8 bond of the oleandomycin macrolide as a target for cleavage. Thus, we needed a method for the functionalization of C7. Second, although the C3 and C5 oxygens are differentially protected in the natural product, the carbohydrate ligands are not attractive protecting groups. We wanted to replace each of them individually or to remove them both and protect the exposed hydroxyl groups selectively and appropriately.

A method for functionalizing C7 of the oleandomycin macrocycle was identified during experiments with deoxy oleandomycin (**4**) (Scheme 1).[6] Treatment with $RhCl_3-H_2O$ in ethanol[7] gave the novel oleandomycins **5a** and **5b**, the latter the result of cleavage of the more labile glycoside bond. Each of these derivatives was isolated as a clean compound.

Scheme 1. Isomerization of C8,C8a Olefin to C7,C8 Olefin



4

5a R = oleandrose, 30%
5b R = H, 31%

Given the ability to effect the desired olefin isomerization and to remove the more labile oleandrose substituent,[8] we investigated methods of removing the desosamine ligand. After examination of literature methods[9] and lengthy experimentation, we discovered that treatment of oleandomycin with 55% HI in a two-phase system for 4 h not only opened

(4) Oleandomycin can be purchased in gram quantities most readily as its phosphate salt. Larger quantities may be obtained from Biovet JSC.

(5) (a) In their early and elegant total synthesis of discodermolide, Marshall and co-workers coupled iodides **3a** and **3b**, derived from the corresponding alcohols, with a complex iodo olefin that represented the C1−C14 stretch of discodermolide. They reported an inability to selectively deprotect the C19 hydroxyl group in advanced intermediates derived from the TBS ether **3a** and completed the synthesis with intermediates derived from the TES ether **3b**. See: Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885. (b) Panek also used ether **3b**; see: Arefolov, A.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 5596. (c) In their fourth-generation synthesis, Smith and co-workers used iodide **3c**; see: Smith, A. B., III; Freeze, B. S.; Xian, M.; Hirose, T. *Org. Lett.* **2005**, *7*, 1825. (d) Recently, the Novartis group reported the preparation of iodide **3d** and its use in a formal total synthesis; see: Loiseleur, O.; Koch, G.; Cercus, J.; Schuerch, F. *Org. Process Res. Dev.* **2005**, *9*, 259. (e) The CNRS/Sanofi-Aventis group also used iodide **3d**; see ref 2b.

(6) Sciavolino, F. C. U. S. Patent 4069379, 1978.

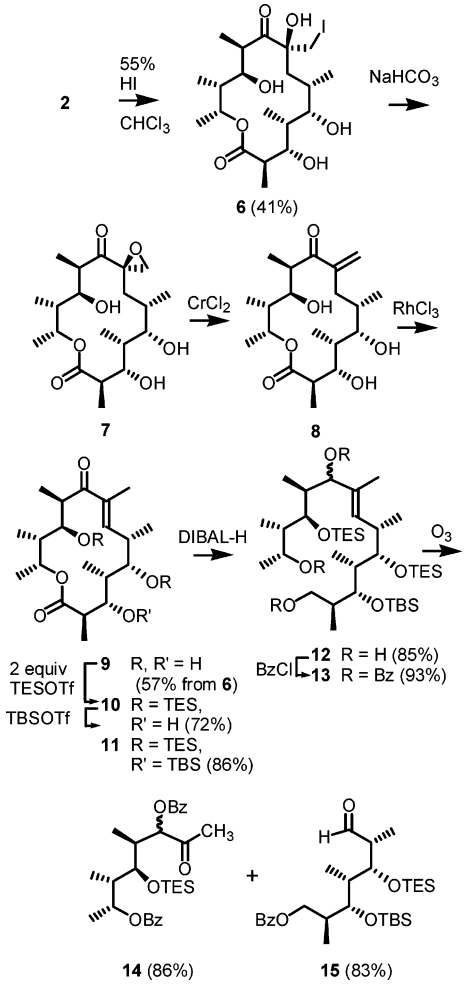
(7) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359.

(8) Els, I. H.; Celmer, W. D.; Murai, K. *J. Am. Chem. Soc.* **1958**, *80*, 3777.

(9) Paterson, I.; Arya, P. *Tetrahedron* **1988**, *44*, 253 and references therein.

the epoxide ring and cleaved the sensitive oleandroside but also cleaved the more robust desosamine linkage, affording the known iodohydrin **6**[9] (Scheme 2).

Scheme 2. Deconstruction of Oleandomycin: Excision of the Stereopentad Synthon



This one-step procedure for cleaving desosamine from a macrolide conjugate is a considerable improvement over other protocols. The resulting rapid access to the globally deprotected macrolide committed us to a strategy based on selective protection of the hydroxyl groups of a fully deglycosylated intermediate.

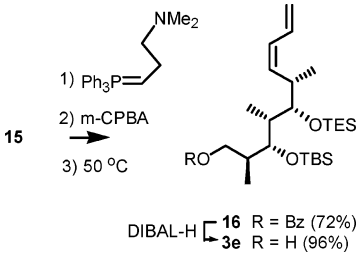
Conversion of iodohydrin **6** to the desirable enone **9** was accomplished by adapting known and newly established chemistry to the aglycon system. Thus, treatment with $NaHCO_3$ afforded the known oleandolide **7**[10] and deoxygenation of the epoxide by the method of Sciavolino[6] provided enone **8**.[11] Application of the $RhCl_3$ isomerization procedure then afforded the key intermediate enone **9**.

At this point, we sought a method for the selective protection of the C3 and C5 hydroxyl groups. Treatment of triol **9** with 2 equiv of TESOTf proved to be an efficient solution to this problem, providing di-TES ether **10**.[12] Silylation of this material with TBDMSOTf gave the tris silyl ether **11**. The protecting group pattern in this compound corresponds to that required for elaboration to the known target **3e**.

Dissection of the macrocycle was accomplished by a three step sequence. DIBAL-H reduction of both the ketone and lactone groups gave triol **12** which was converted to the corresponding tribenzoate **13**. Ozonolytic cleavage of the olefinic bond then gave two products, ketone **14** and aldehyde **15,** which were readily separated by chromatography.

Completion of the synthesis of the C15−C24 synthon then required only the elaboration of the terminal cis diene. Efforts to introduce this moiety by direct methods, previously employed for this purpose in what appeared to be similar systems, were disappointing.[13,14] Success was achieved by employing the dimethylaminopropyl Wittig reagent and subjecting the product to Cope elimination (**15** → **16**). This procedure is touted by Corey[15] for the preparation of cis dienes from hindered aldehydes. Cleavage of benzoate **16** with DIBAL-H afforded alcohol **3e** (Scheme 3).

Scheme 3. Reconstruction: The Discodermolide Stereopentad Synthon by the Amino Wittig/Cope Elimination Procedure



The preparation of alcohol **3e** in 12 steps and approximately 7% overall yield from oleandomycin demon-

(10) Oleandolide (**7**) was first prepared by a nine-step degradation of oleandomycin; see: Tatsuta, K.; Kobayashi, Y.; Gunji, H.; Masuda, H. *Tetrahedron Lett.* **1988**, *29*, 3975.

(11) Like iodohydrin **6**, enone **8**, on standing, converted to material that exhibited two spots on TLC. Therefore, it was used in the next step immediately after isolation.

(12) The regioselectivity of this reaction was established by analysis of the COSY spectrum of the benzoate of the product; see the Supporting Information.

(13) The Nozaki−Hiyama/Petersen method employed in the Marshall and Paterson work gave only a low yield of what appeared to be cis diene products; see ref 5a and: Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Seger, M.; Schreiner, K.; Daeffler, R.; Osmani, A.; Bixel, D.; Loiseleur, O.; Cercus, J.; Stettler, H.; Schaer, K.; Gamboni, R.; Bach, A.; Chen, G.-P.; Chen, W.; Geng, P.; Lee, G. T.; Loeser, E.; McKenna, J.; Kinder, F. R., Jr.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Reel, N.; Repic, O.; Rogers, L.; Shieh, W.-C.; Wang, R.-M.; Waykole, L.; Xue, S.; Florence, G.; Paterson, I. *Org. Process Res. Dev.* **2004**, *8*, 113. The Yamamoto method used by Smith (ref 5c) in his fourth-generation synthesis afforded only a 19% yield of diene in our system; this product was identified as the trans isomer of the desired **16**. Schreiber's method for diene synthesis was limited by an unexpectedly low yield of vinyl iodide (24%) in the Stork−Zhao step; see: Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054.

(14) (a) Masamune obtained good yields with the phenylselenylpropyl Wittig reagent in a condensation with a stereopentad-containing aldehyde; see: Filla, S. A.; Song, J. J.; Chen, L.; Masamune, S. *Tetrahedron Lett.* **1999**, *40*, 5449. We did not investigate this reagent. (b) See also ref 2b.

(15) Corey, E. J.; Desai, M. C. *Tetrahedron Lett.* **1985**, *26*, 5747.

strates proof-of-principle for the conversion of mass-produced macrolides to value-added polyketide structures. The possibility that ketone **14** might serve as a precursor of a stereotriad or stereotetrad building block for discodermolide or another precious antibiotic has not escaped our attention.

Acknowledgment. This work was supported by the National Institutes of Health (CA87503), the Department of Defense Army Breast Cancer Initiative (BC051816), and the National Science Foundation (CHE-0131146, NMR instrumentation). We are grateful to Dr. Roland Lau of Apex Scientific, Stony Brook, NY, for a gift of oleandomycin phosphate.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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A Relay Ring-Closing Metathesis Synthesis of Dihydrooxasilines, Precursors of (*Z*)-Iodo Olefins

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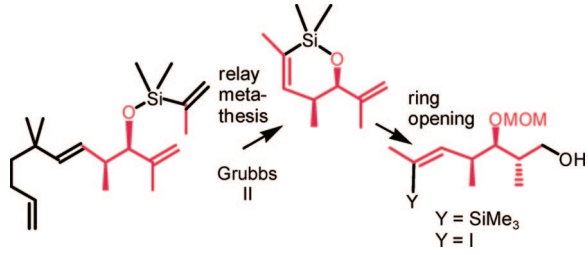
ABSTRACT



A convenient Grubbs II metathesis provides dihydrooxasilines by relay RCM (RRCM). Dihydrooxasilines undergo ring opening to give *Z*-vinyl silanes. These can then be converted to *Z*-vinyl iodides. This sequence provides a short, high yield, and convenient route to trisubstituted *Z*-vinyl iodides, useful intermediates for the preparation of polypropionate antibiotics.

Iodo olefins are important intermediates in organic synthesis. As key reactants in the convergent steps of many total syntheses, they are often the reagents of choice in Heck, Stille and Suzuki, Sonogashira, and Negishi coupling methods[1] as well as in the popular Nozaki−Hiyama−Kishi (NHK) addition reaction.[2] Stereochemical homogeneity in the products of these transformations depends on the availability of geometrically clean iodo olefins as starting materials.

We have been interested in the preparation of a 2-iodo (*Z*)-olefin of general structure **1** (Figure 1) and, in particular, the iodoolefinic alkyne **2**,[3] which we projected as a key intermediate in the synthesis of discodermolide (**3**).[4]

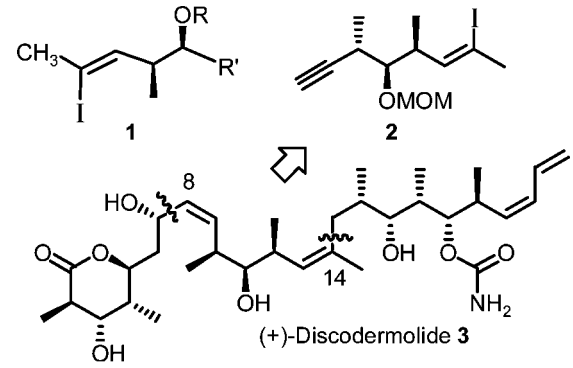


Figure 1. Functional group pattern in target intermediates and relationship to the structure of discodermolide.

Given the small number of approaches to vinyl iodides of this substitution pattern,[5] we considered the design of a new method that might be high yielding and that would be easy to implement.

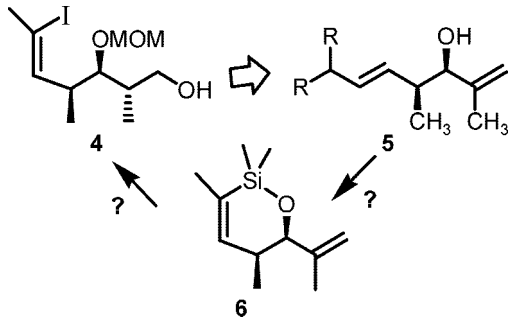
(1) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.

(2) For a review, see: (a) Fuerstner, A. *Chem. Rev.* **1999**, *99*, 991. For the asymmetric NHK reaction, see: (b) Choi, H.-w.; Nakajima, K.; Demeke, D.; Kang, F.-A.; Jun, H.-S.; Wan, Z.-K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435. See also: (c) Berkessel, A.; Menche, D.; Sklorz, C. A.; Schroder, M.l.; Paterson, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 1032.

(3) Parker, K. A.; Cao, H. US Patent Applications, Serial No. 11/421,290 and Serial No. 11/697,340. We had prepared alkyne **2** by a scheme that employed the Stork−Zhao conversion, a transformation that is low-yielding for the preparation of trisubstituted olefins. See: Arimoto, H.; Kaufman, M. D.; Kobayashi, K.; Qiu, Y.; Smith, A. B., III. *Synlett* **1998**, *7*, 765.

10.1021/ol802063h CCC: $40.75
Published on Web 11/12/2008

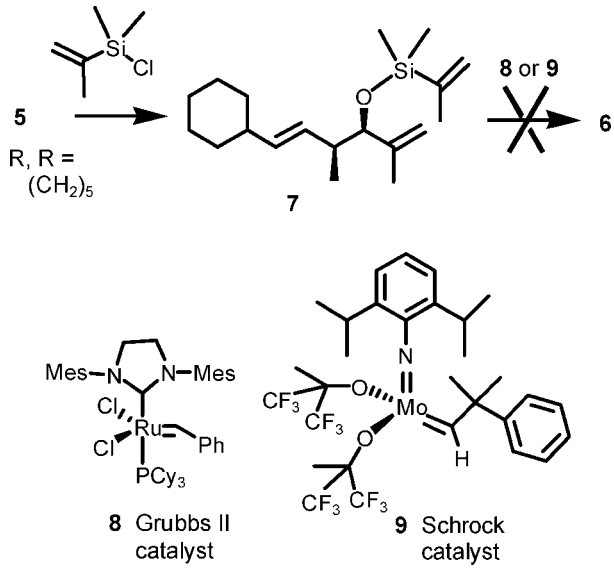
Scheme 1. Desired Iodo Olefin-Containing Polyketide Building Block, Readily Available Potential Precursor, and Possible Intermediate



We were especially motivated to prepare alcohol **4**, an obvious precursor to alkyne **2** and a generally useful intermediate, from a precursor of general structure **5**. Alcohols **5** are readily available from a short scheme based on asymmetric catalysis.[6] Thus, we considered the possibility that the dihydrooxasiline **6** might serve as an intermediate in the desired conversion.

Imagining the silyl ether **6** to be the product of a ring-closing metathesis (RCM) reaction, we set out to attempt this cyclization.[7] Silylation of the known alcohol **5** (R, R = $(CH_2)_5$, Scheme 2) with isopropenyldimethylsilyl chloride

Scheme 2. Initial Plan for the Ring-Closing/Ring-Opening Strategy for the Preparation of Alcohol **6**

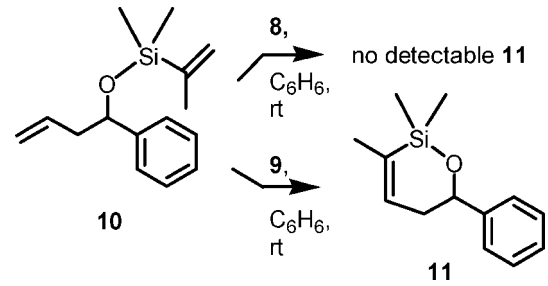


provided the desired **7**. In this metathesis substrate, the functional group pattern should allow RCM to favor the formation of a 6-membered ring containing a trisubstituted olefin (not a cyclobutane and not a 5-membered ring containing a tetrasubstituted olefin).[8]

Attempted RCM with Grubbs's second-generation catalyst (**8**) or with Schrock's catalyst **9** resulted in the recovery of starting material. We repeated both the Grubbs II and Schrock experiments under an atmosphere of ethylene,[9] recovering silyl ether **7** in both cases.

In order to find conditions that would effect the desired closure, we prepared the model substrate **10** and subjected it to metathesis conditions (Scheme 3). Material recovered

Scheme 3. Test of Metathesis Conditions with Model Silyl Ether



from the Grubbs II reaction showed two spots on tlc, one of which represented the starting material **10** and the other a new compound(s), which was clearly not the cyclized **11**.[10] This result was not particularly surprising. The literature sports no examples of ruthenium catalyst-promoted ring closing olefin metathesis to 1,2-dihydrooxasilines; both Grubbs generation I catalyst[11] and Grubbs generation II catalyst (**8**)[11c] are reported to fail with the relevant substrates.[12] On the other hand, the Schrock catalyst converted silyl ether **10** to the RCM product in 97% yield.

(4) (a) Florence, G. J.; Gardner, N. M.; Paterson, I. *Nat. Prod. Rep.* **2008**, *25*, 342. (b) Smith, A. B.; Freeze, B. S. *Tetrahedron* **2008**, *64*, 261. (c) Mickel, S. J. *Pure Appl. Chem.* **2007**, *79*, 685, and references therein.

(5) Those that are generally appropriate for introduction of the vinyl iodide moiety into advanced intermediates include: (a) The Stork−Zhao reaction: Chen, J.; Wang, T.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827. (b) Iododemetalation: de Lemos, E.; Poree, F.-H.; Commercon, A.; Betzer, J.-F.; Pancrazi, A.; Ardisson, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1917. Arefolov, A.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 5596. (c) The Tanino−Miyashita olefination: Tanino, K.; Arakawa, K.; Satoh, M.; Iwata, Y.; Miyashita, M. *Tetrahedron Lett.* **2006**, *47*, 861.

(6) (a) Parker, K. A.; Cao, H. *Org. Lett.* **2006**, *8*, 3541. See also: (b) Tsai, D. J. S.; Midland, M. M. *J. Org. Chem.* **1984**, *49*, 1842.

(7) All exploratory reactions were carried out with racemic materials. Structures **14**−**20**, **6**, and **4** in Schemes 4 and 5 represent chiral compounds.

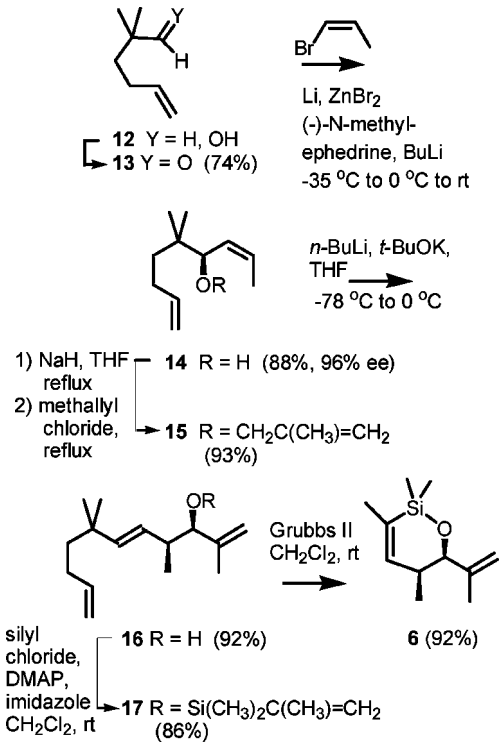
(8) Denmark and Yang have shown that, in simple systems, dihydrooxasilines with di- and trisubstituted olefins were formed with the Schrock catalyst. However, an attempt to effect closure to a tetrasubstituted olefin was not successful. See: Denmark, S. E.; Yang, S.-M. *Tetrahedron* **2004**, *60*, 9695.

(9) Chen, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Org. Lett.* **2004**, *6*, 4077.

(10) The NMR spectrum of the compound represented by the second spot (approximately 10% of the recovered material) contained absorptions in the silylmethyl, vinylmethyl, allyl, vinyl, and aromatic regions (as does silyl ether **10**); however, the integral of the aromatic region was enhanced. Metathesis of the catalyst with the substrate is the likely origin of this minor product.

(11) (a) Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Salter, M. M. *J. Org. Chem.* **2000**, *65*, 6508. (b) Ahmed, M.; Barrett, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Procopiou, P. A.; Salter, M. M. *Tetrahedron* **1999**, *55*, 3219. (c) Denmark, S. E.;Yang, S.-M.;*Org. Lett.* **2001**, *3*, 1749, and ref 8. See also entry 2 in Table I in: (d) Kroell, R. M.; Schuler, N.; Lubbad, S.; Buchmeiser, M. R. *Chem. Commun.* **2003**, 2742.

Scheme 4. Relay Metathesis-Based Synthesis of Dihydooxasiline **6**



All of the above suggested that the Grubbs II catalyst would not effect RCM to dihydrooxasilines (as is believed), that the Schrock catalyst would effect such a closure, but that the Schrock catalyst was not generating the critical metal carbene by metathesis with our substrate **7**, even when the reaction was run under ethylene.

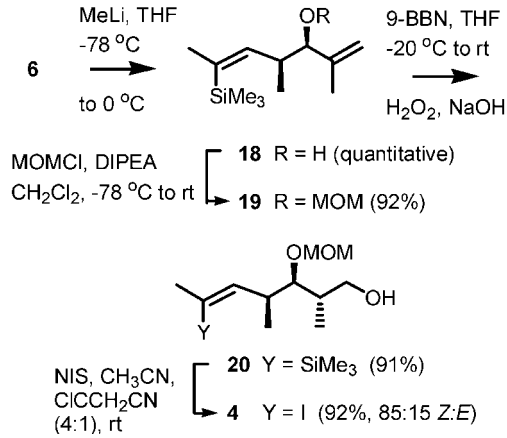
In an effort to drive the initiation of the metathesis reaction, we resolved to prepare substrate **17**, designed so that it would participate in a Hoye-type "relay."[13] In our design, the tether between the initiating terminal olefin and the site of desired reactivity was to be three carbons long, setting up a cascade in which the first ring formed would be a cyclopentene. Also, the tether would contain, adjacent to the internal olefin, two methyl substituents. This design would promote ring closure in the first step of the metathesis reaction by the famous "gem dimethyl effect."[14] Furthermore, substitution at this position would be advantageous in the synthesis of the substrate precursor **16**, the product of a 2,3-Wittig rearrangement,[6] by favoring the syn relationship of the adjacent methyl and hydroxyl substituents.

Synthesis of the "relay substrate" **17** relied on methods already established. Preparation of aldehyde **13**, which would supply the excisable tether, followed the strategy of Ashby[15] (see the Supporting Information for details). Addition of the chiral zinc reagent[16] from *cis*-1-bromopropene[17] and (−)-*N*-methylephedrate afforded the (*S*)-alcohol **14**, which was converted to the methallyl ether **15**. Treatment with the *n*-BuLi/KO-*t*-Bu reagent effected the expected stereoselective 2,3-Wittig rearrangement. Silylation of the resulting (3*S*,4*S*)-undecatrienol **16** afforded the relay metathesis susbstrate **17**.

When exposed to the Grubbs II catalyst **8**, silyl ether **17** underwent the relay RCM (RRCM) reaction to provide the desired cyclic silyl ether **6** in high yield. The surprising but welcome success of this reaction provides another example[18] of the power of the relay metathesis strategy.

With **6** in hand, we studied methods for effecting the desired conversion to a linear vinyl iodide such as our target **4** (Scheme 5). Ring cleavage of silyl ether **6** with methyl-

Scheme 5. Ring Cleavage, Modification, and Iododesilylation



lithium[19] proved to be a high yield transformation, giving vinyl silane **18**. Then protection of the alcohol (**18** → **19**) and hydroboration with 9-BBN gave silane **20**.[20] Iododesilylation of silane **20** with recrystallized NIS in CH_3CN/CCl_3CN[21] gave a high yield of the known alcohol **4** as an 85:15 *Z*/*E* mixture.[22]

A small amount of a byproduct was also isolated. The NMR spectrum of this compound showed the MOM and

(12) A related enyne RCM proceeds with catalyst **8**. See Miller, R. L.; Maifeld, S. V.; Lee, D. *Org. Lett.* **2004**, *6*, 2773.

(13) (a) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210. (b) For a review, see: Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912.

(14) (a) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735. (b) For a discussion of this effect in ring-closing enyne metathesis, see: Kim, Y. J.; Grimm, J. B.; Lee, D. *Tetrahedron Lett.* **2007**, *48*, 7961.

(15) Ashby, E. C.; Park, B.; Patil, G. S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* **1993**, *58*, 424.

(16) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777.

(17) *cis*-1-Bromopropene is conveniently prepared in multigram quantities by the method of: Fuller, C. E.; Walker, D. G. *J. Org. Chem.* **1991**, *56*, 4066.

(18) Hoye's original paper (ref 13a) describes several different cases in which the relay strategy proved advantageous. For others, see: (a) Zakarian, J. E.; El-Azizi, Y.; Collins, S. K. *Org. Lett.* **2008**, 2027. (b) Cho, E. J.; Lee, D. *Org. Lett.* **2008**, *10*, 257. (c) Dudley, G. B.; Engel, D. A.; Ghiviriga, I.; Lam, H.; Poon, K. W. C.; Singletary, J. A. *Org. Lett.* **2007**, *9*, 2839. (d) Roethle, P. A.; Chen, I. T.; Trauner, D. *J. Am. Chem. Soc.* **2007**, *129*, 8960. (e) Collins, S. K. *J. Organomet. Chem.* **2006**, *691*, 5122. (f) Crimmins, M. T.; Zhang, Y.; Diaz, F. A. *Org. Lett.* **2006**, *8*, 2369. (g) For an example of the use of relay strategy in macrocyclic enyne metathesis, see: Collins, S. K.; El-Azizi, Y.; Schmitzer, A. R. *J. Org. Chem.* **2007**, *72*, 6397.

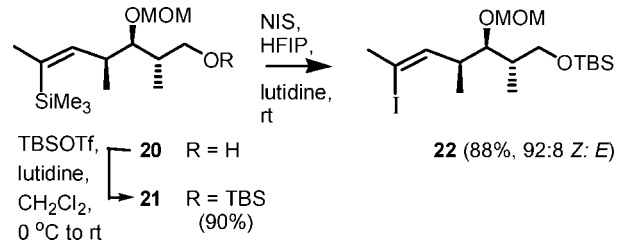
(19) For a cleavage of a related cyclic silyl ether with phenyllithium, see Barrett's synthesis of glycosphingolipids; see reference 11a.

TMS groups but no vinyl proton and its infrared spectrum showed no absorption for a hydroxyl group.

We attempted to improve the ratio of isomers in the iododesilylation product of alcohol **20** by adopting hexafluoro isopropanol (HFIP) as solvent.[23] This experiment afforded a crude product, which contained many compounds (as indicated by tlc). Only minor amounts of the desired vinyl iodide **4** (both E and Z, as judged by analysis of the NMR spectrum) could be seen; furthermore, the aforementioned byproduct appeared to be the major component of the product mixture. We suspect that this byproduct results from an iodoetherification reaction and that the use of HFIP in iododesilylations may be limited to substrates that cannot take part in this type of pathway.[24]

Improved results were obtained when TBS ether **21** was subjected to the iododesilylation conditions in HFIP. This reaction afforded an 88% yield of the known vinyl iodide **22** (a key intermediate in Smith's fourth-generation discodermolide synthesis)[22] as a 92:8 mixture of (*Z*)- and (*E*)-isomers.

Scheme 6. Protection and Stereoselective Iododesilylation



Overall, the preparation depicted in Schemes 4−6 provides the original target, iodo olefin **4**, in 29% yield (corrected for the presence of the *E*-isomer) and the vinyl iodide building block **22** in 27% yield (likewise corrected for the presence of *E*-isomer) from alcohol **12**. Thus, the relay RCM preparation of dihydrooxasilines followed by ring opening and iododesilylation provides efficient access to (*Z*)-vinyl iodides. As it is generally accepted that the Schrock catalyst is required for the closure of vinyl silane metathesis substrates, the effectiveness of the Grubbs II catalyst in the relay RCM reaction (**17** → **6**) is noteworthy and will be the subject of further examination.

Acknowledgment. This work was supported by the Army Breast Cancer Initiative (BC 051816), the National Institutes of Health (GM 74776), and the National Science Foundation (CHE-0131146, NMR instrumentation). We thank Professor Richard Franck of Hunter College for valuable discussions.

Supporting Information Available: Detailed descriptions of the experimental procedures and complete analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802063H

(20) The corresponding TBS ether is a known compound, prepared in 11 steps including a chiral resolution; see: (a) Arefolov, A.; Panek, J. S. *Org. Lett.* **2002**, *4*, 2397. (b) Arefolov, A.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 5596. (c) Beresis, R. T.; Solomon, J. S.; Yang, M. G.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1998**, *75*, 78.

(21) (a) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647. A detailed protocol for NIS iododesilylation in acetonitrile/chloroacetonitrile can be found in the Supporting Information of reference 20a.

(22) Smith, A. B., III.; Freeze, B. S.; Xian, M.; Hirose, T. *Org. Lett.* **2005**, *7*, 1825.

(23) (a) Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822. (b) lardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727.

(24) Iodoetherification by addition to vinyl silanes to form tetrahydropyrans has not been reported. However, iodolactonization in vinyl silane substrates is known; see: (a) Kira, K.; Hamajima, A.; Isobe, M. *Tetrahedron* **2002**, *58*, 1875. (b) Kobayashi, Y.; Yoshida, S.; Nakayama, Y. *Eur. J. Org. Chem.* **2001**, 1873. (c) Kira, K.; Isobe, M. *Tetrahedron Lett.* **2001**, *42*, 2821. (d) Kitano, Y.; Okamoto, S.; Sato, F. *Chem. Lett.* **1989**, 2163. Also, Zakarian (ref 23b) noted the isolation of products derived from addition to a vinylsilane of iodonium and the carbonyl of a benzoate by way of a 5-membered ring.

Iodoolefinic Polypropionate Building Blocks fromVinyl Silanes or Directly from Dihydrooxasilines with Control of Geometry by Solvent

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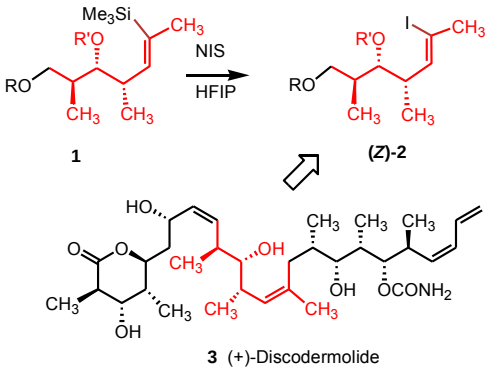
ABSTRACT

Iododesilylation of trisubstituted (*Z*)-silyl olefins proceeds with retention of geometry in hexafluoroisopropanol (HFIP) but, for unhindered cases, with inversion of geometry in DMSO. Iododesilylation of dihydrooxasilines shows a similar solvent effect, affording (*Z*)-vinyl iodides in HFIP and (*E*)-vinyl iodides in DMSO. When an acyloxy substituent is positioned to participate in the reaction, all protocols afford inversion of geometry. Proper choice of method delivers geometrically clean, stereotriad-containing (*Z*)- or (*E*)-vinyl iodide building blocks.

Vinyl iodides with defined geometry are important chemical intermediates.[1] Their preparation from vinyl silanes with retention of geometry is an attractive method that has been optimized by the use of acetonitrile/ trichloroacetonitrile[2] or hexafluoroisopropanol (HFIP)[3] as solvent. We recently took advantage of this transformation in order to convert a representative (*Z*)-vinyl silane **1a** (**1** R = TBS, R' = MOM) to the corresponding vinyl iodide **(Z)-2a** (**(Z)-2**, R = TBS, R' = MOM, Scheme 1), which we viewed as a useful intermediate for the synthesis of discodermolide (**3**).[4]

(*E*)-Vinyl iodides geometrically isomeric to protected diol **2** and related stereoisomers are attractive synthons

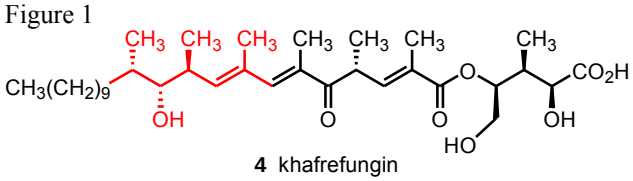
Scheme 1



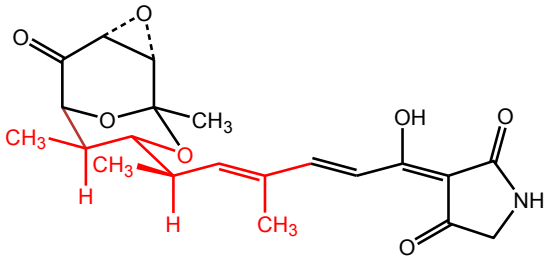
(1) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.
(2) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647.
(3) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727-1730.
(4) Xie, Q.; Denton, R. W.; Parker, K. A. *Org. Lett.* **2008**, *10*, 5345-5348.

for polypropionate antibiotics that contain trisubstituted (*E*)-olefins. For example, a syn, anti (*E*)-isomer of iodide **2** is considered a building block for khafrefungin (**4**)[5] and the anti, anti (*E*)-isomer is a potential building block for tyrandamycin A (**5**,[6] see Figure 1). Complex intermediates that contain trisubstituted (*E*)-olefins adjacent to a series of asymmetric centers are most often prepared from methyl acetylenes by hydrozirconation / iodination[7] or hydrostannylation / iodination.[8] They have also been prepared from (*E*)-vinyl silanes by iododesilyation with retention of geometry.[2-4]

Figure 1



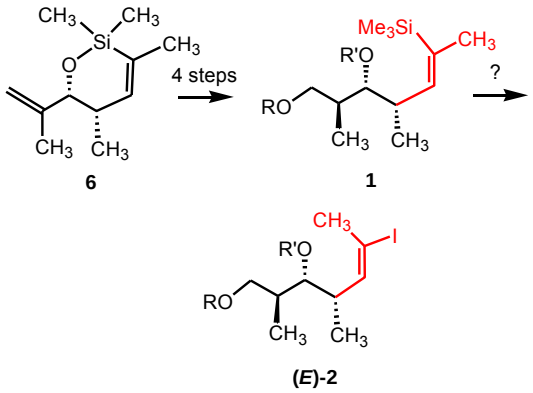
4 khafrefungin



5 tyrandamycin A

We noted that iododesilylation in some solvent systems gives appreciable amounts of vinyl iodides in which the geometry of the double bond has not been retained.[2,3,9] We imagined that we might find conditions that would lead from the protected homoallylic alcohol substrates **1**, which are readily accessible from dihydrooxasilines **6**,[4] to the desired vinyl iodides **(*E*)-2** with complete inversion of the geometry of the double bond (Scheme 2).[10] We now describe the results of this venture and, also, the extension of the iododesilylation methodology directly to dihydrooxasiline substrates. We first examined the chemistry of interest in the model homoallylic system **10**.

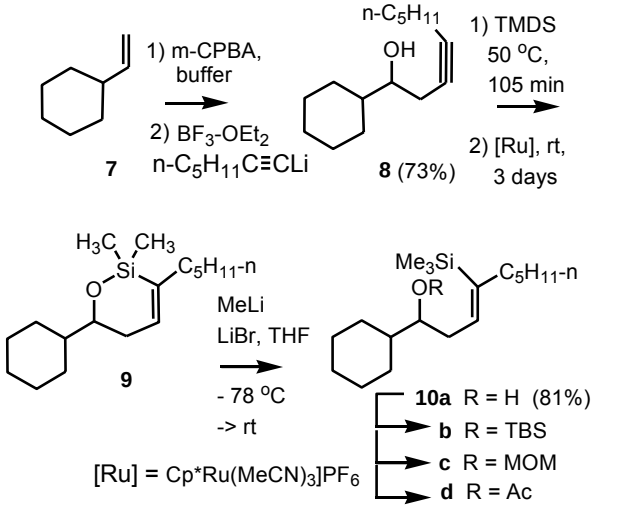
Scheme 2



6 **1** **(*E*)-2**

Vinyl silanes **10** were easily prepared in 5-6 steps (Scheme 3). Epoxidation of vinylcyclohexane (**7**) followed by ring opening with lithiated *n*-heptyne gave homopropargyl alcohol **8**.[11] Functionalization of alcohol **8** with tetramethyldisilazane (TMDS) and intramolecular hydrosilyation catalyzed by the cationic ruthenium complex, $[Cp^*Ru(MeCN)_3]PF_6$[12] provided the dihydrooxasiline **9**. Ring cleavage with methyllithium yielded the desired hydroxy vinyl silane **10a**. Derivatization gave additional substrates **10b**, **10c**, and **10d** for our studies.

Scheme 3



(5) For total syntheses and biological activities of khafrefungin and its isomers, see Shirokawa, S.; Shinoyama, M.; Ooi, I.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 849 and references therein.

(6) For leading references on tyrandamycins A and B, see Shiratani, T.; Kimura, K.; Yoshihara, K.; Hatakeyama, S.; Irie, H.; Miyashita, M. *Chemical Commun.* **1996**, 21.

7) (a) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.

(8) Benechie, M.; Skrydstrup, T.; Khuong-Huu, F. *Tetrahedron Lett.* **1991,** *32*, 7535.

(9) As part of an extensive study of solvent effects on the stereoselectivity of the halodesilylation of (E)-1-silyloctenes, Tamao had shown that NBS in DMF gave 1-bromooctenes with a high inversion: retention (Z:E) ratio; see Tamao, K.; Akita, M.; Maeda, K.; Kumada, M. *J. Org. Chem.* **1987**, *52*, 1100.

(10) During the course of our work, Oguri, Oikawa et al. reported complete inversion of geometry in the iododesilylation of a (Z)-trisubstituted olefin, unsubstituted on the carbon chain, in DMF; see Migita, A.; Shichijo, Y.; Oguri, H.i; Watanabe, M.; Tokiwano, T.; Oikawa, H. *Tetrahedron Lett.* **2008**, *49*, 1021.

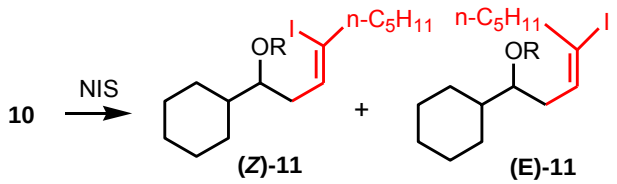
11) This compound was first prepared by Qiuzhe Xie, PhD thesis, Stony Brook University, 2008.

(12) (a) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2003**, *125*, 30. (b) The ruthenium complex, $[Cp^*Ru(MeCN)_3]PF_6$ was prepared according to Mbaye, M. D.; Demerseman, B.; Renaud, J. –L.; Toupet, L.; Bruneau, C. *Adv. Synth. Catal.* **2004**, *346*, 835.

Iododesilylation of **10a-d** with **NIS** was studied in three solvent media (Table 1). In HFIP containing lutidine, alcohol **10a** gave a mixture of products that contained only a small amount of the expected (*Z*)-vinyl iodide.[4] On the other hand, iododesilylation of substrates **10b** and **10c** in HFIP with lutidine gave good yields of vinyl iodides **(Z)-11b** and **(Z)-11c**, respectively, as the almost exclusive products. These results are consistent with the known propensity of HFIP to favor iododesilylation with high levels of retention of geometry. However, reaction of acetate **10d** gave a 5:95 mixture of (*Z*)- and (*E*)-vinyl iodides **(Z)-11d** and **(E)-11d.** This example suggests that the homoallylic ester substituent participates in the reaction, adding to the iodonium ion and then eliminating anti to the TMS group to provide the (*E*)-geometry.[13] This pathway is not entirely surprising;[2, 3] however the high level of inverted geometry is impressive and clearly useful.

In a 4:1 mixture of MeCN/$ClCH_2CN$, iododesilylation of **10a-c** gave product mixtures in which the (*Z*)-olefins predominated. However, an increase in the amount of the (*E*)-isomer was apparent for the reactions of **10b** and **10c**. Homoallylic acetate **10d**, under these conditions, again gave almost exclusively the (*E*)-olefin.

Table 1: Yields and Stereoselectivity in Iododesilylation of Vinyl Silane **10** as a Function of Solvent



	Yield (ratio of (Z)-11 to (E)-11) *Rxn time (hr)*		
Substrate 10	HFIP	MeCN/$ClCH_2CN$ (1:4)	DMSO
a (R = H)	- [a] 1.5	82% (86:14)[b] 18	*85% (15:85)* *67*
b (R = TBS	72% (97:3) 0.5	53% (72:28) 2	*94% (4:96)* *117*
c (R = MOM)	75% (97:3) 0.5	87% (82:18) 19	*86% (3:97)* *6*
d (R = Ac)	*94% (5:95)* *0.5*	*48% (7:93)* *17*	*43%* ***(E)-11*** *only* *18*

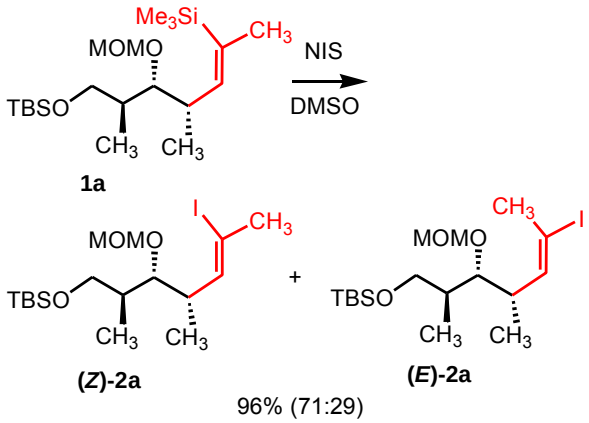
a. See reference 4.
b. Solvent was neat MeCN

(13) No iodohydrin by-products were observed in this reaction mixture. See references 2 and 3.

Remarkably, reaction of silanes **10a-c** in DMSO supplied also almost entirely the inverted *E*-iodoolefinic products. These results are consistent with a high level of participation by solvent.

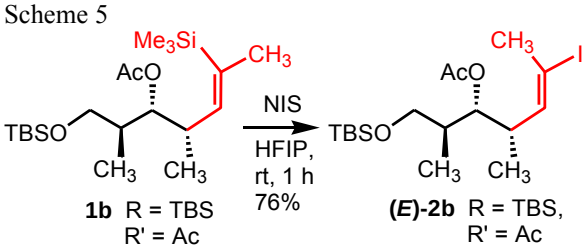
Extension of the solvent-induced inversion of double bond geometry to more complex substrates was partially successful. Application of the DMSO protocol to substrate **1a** afforded a disappointing 71:29 ratio of the known **(Z)-2a** and the desired **(E)-2a** (Scheme 4). The appearance of a significant amount of the retention product is consistent with the increased bulk at the allylic position[2] in substrate **1a** relative to the model system.

Scheme 4



On the other hand, treatment of the acetate **1b** with NIS (in HFIP with 2,6-lutidine) gave only vinyl iodide **(E)-2b** in 76% yield (Scheme 5; for the synthesis of substrate **1b**, see the Supporting Information).

Scheme 5



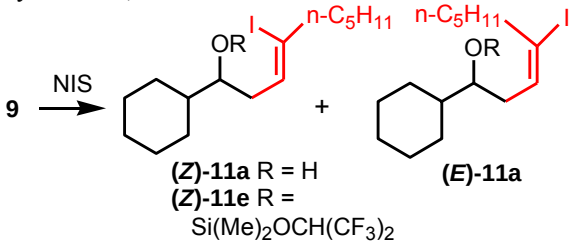
Although the two-step conversion of dihydrooxasilines to vinyl iodides proceeds with generally good yields and solvent- or substituent-dependent selectivities (see **9** -> **10** -> **(Z)-11** or **(E)-11**), we imagined that a one-step, direct iododesilylation of these substrates might provide the desired targets. Therefore we tested the feasibility of the proposed reaction and its stereochemical outcomes with the model substrate **9** under different conditions as above.

Treatment of **9** with NIS in HFIP afforded compound **(Z)-11e**, which contained the (Z)-iodo olefin and a dimethyl(hexafluoroisopropoxy)silyl ether in 62% yield.

This interesting product, which results from interception of the dimethylsiloxy species by the trifluoroisopropanol solvent, is viewed as a prototype for building blocks in which the homoallylic alcohol is protected as a consequence of the geometry-retaining iododesilylation procedure.

Iododesilylation of substrate **9** in the acetonitrile and DMSO media gave homoallylic alcohols **11a**. In the former case, the ratio of (*Z*)- to (*E*)-olefin was 33:67. However, in DMSO, the (*E*)-alcohol **(*E*)-11a** (inversion of the double bond) was obtained almost exclusively (Table 2).

Table 2: Solvent Effect on Iododesilylation of 5,6-Dihydro-2*H*-1,2-oxasiline **9**



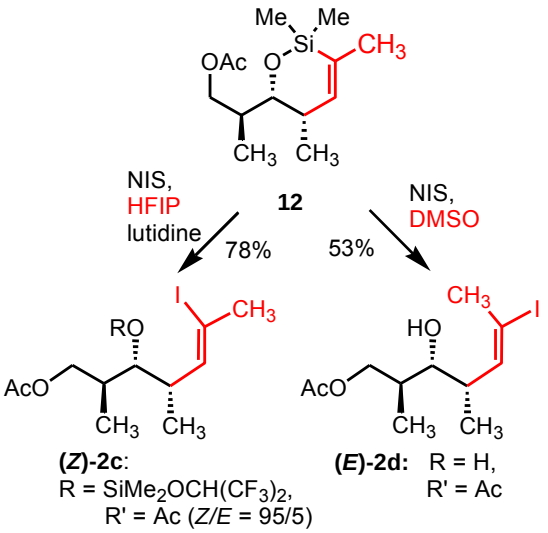
Yield (Z:E ratio) *Rxn time (hr)*		
HFIP	**MeCN/ClCH$_2$CN (1:4)**	**DMSO**
62% (Z only)[a] *68*	*65% (33:67)*[b] *18*	*63% (2:98)*[b] *93*

a. Isolated as the silyloxy derivative, **(*Z*)-11e**
b. Isolated as the alcohols **(*Z*)-11a** and **(*E*)-11a**

An extension of these results to a complex substrate was straightforward (Scheme 6). Thus, treatment of the protected dihydrooxasiline **12** (see Supporting Information for synthesis) with NIS in HFIP containing lutidine gave the (*Z*)-olefinic silyl ether **(*Z*)-2c** (R = $SiMe_2OCH(CF_3)_2$, R' = Ac) [14] in 78% yield after 3 days.

On the other hand, treatment of the substrate **12** with 4 equivalents of NIS in DMSO gave only 9% conversion to iodoolefinic product after 3 days. Increasing the amount of NIS to 15 equivalents led to complete conversion, affording (*E*)-vinyl iodide **(*E*)-2d** (R = H, R' = Ac) as the only product in 53% yield after 7 days.

Scheme 6



Thus, the iododesilylation of dihydrooxasilines like that of vinyl silanes, is subject to stereochemical control by solvent, HFIP leading to the (Z)-olefinic hexafluoroisopropoxysilyl ether and DMSO effecting inversion of geometry to give the (E)-olefinic homoallylic alcohol. The results of both protocols are consistent with the general principles put forth by Tamao[9] for the halodesilylation of vinyl silanes and they highlight the utility of dihydrooxasilines as direct precursors of vinyl iodides.

In summary, both unhindered and chain-substituted (Z)-vinyl silanes (**10** and **1a** respectively) give (Z)-vinyl iodides under the HFIP conditions; however, only the unhindered compounds were efficiently converted to (*E*)-vinyl iodides in DMSO. Both unhindered and chain-substituted (*E*)-vinyl iodides were obtained directly from the NIS / DMSO reaction of the dihydrooxasiline (**(9)** -> **(*E*)-11a** and **12** -> **(*E*)-2d**).

Acknowledgment. This work was supported by the Army Breast Cancer Initiative (BC 051816), the National Institutes of Health (GM 74776), and the National Science Foundation (CHE-0131146, NMR instrumentation).

Supporting Information Available: Detailed descriptions of the experimental procedures and complete analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) Partial removal of the unusual silyl ether group was effected by treatment with acetic acid in methanolic dichloromethane.

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Functional Group Compatibility. Propargyl Alcohol Reduction in the Presence of a Vinyl Iodide

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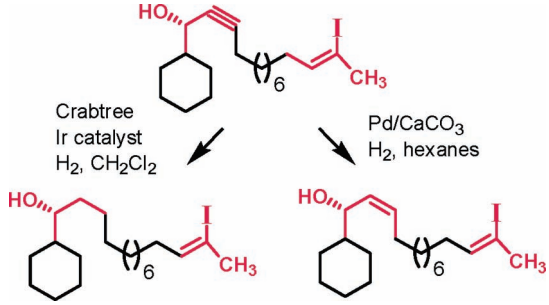
ABSTRACT



Vinyl iodides are stable to the reduction of propargyl alcohols to cis allylic alcohols by hydrogen over $Pd/CaCO_3$ in hexane. They are also stable to the reduction of propargyl alcohols to saturated alcohols by hydrogen over Crabtree's iridium catalyst in CH_2Cl_2.

Our interest in designing and implementing optimally convergent schemes for the synthesis of polyketide antibiotics led us to consider the possibility of directly reducing the alkyne bond of a propargyl alcohol system to a cis olefin in the presence of a vinyl iodide. Vinyl iodides are generally believed to be incompatible with conditions that would reduce an alkyne to an olefin or to a saturated carbon−carbon bond.[1]

The particular system of interest to us was the conversion of propargyl alcohol **3** to cis allylic alcohol **2**, an advanced intermediate in a projected short synthesis of discodermolide **1** (Scheme 1).[2] Olefin **2** would need only a protection step before linkage to a stereopentad-containing synthon, a key step that would complete the construction of the carbon skeleton of the target. The ability of the vinyl iodide to withstand the reduction conditions was essential to the optimal convergence of the synthesis.

In order to test conditions that might effect the key transformation, we needed a model system for which the substrate and product would be nonvolatile and easily handled. Furthermore, we desired a model substrate that could be prepared easily from commercially available materials by a short sequence. We believed that the substrate requirements would be met by propargyl alcohol **9** (Scheme 2), which we considered the addition product of alkyne **7** and cyclohexanecarboxaldehyde (**8**). Iodoolefinic alkyne **7** might be conveniently prepared from the inexpensive 10-undecenal (**4**). Therefore, we converted aldehyde **4** to the iodo olefin **5** and then cleaved the unsubstituted terminal double bond with OsO_4 followed by $NaIO_4$ to obtain aldehyde **6**. Treatment of this compound with the Ohira−Bestmann reagent[3] afforded alkyne **7**. Addition of the

(1) (a) de Lemos, E.; Poree, F.-H.; Bourin, A.; Barbion, J.; Agouridas, E.; Lannou, M.-I.; Commercon, A.; Betzer, J.-F.; Pancrazi, A.; Ardisson, J. *Chem.−Eur. J.* **2008**, *14*, 11092. (b) Arefolov, A.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 5596. (c) Arefolov, A.; Panek, J S. *Org. Lett.* **2002**, *4*, 2397.

(2) For related work, see: (a) Cao, H.; Parker, K. A. *Org. Lett.* **2008**, *10*, 1353. (b) Xie, Q.; Denton, R. W.; Parker, K. A. *Org. Lett.* **2008**, *10*, 5345. (c) Parker, K. A.; Wang, P. *Org. Lett.* **2007**, *9*, 4793.

(3) Roth, G. J.; Liepold, B.; Muller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59; Corrigendum: *Synthesis* **2004**, 640.

10.1021/ol900927a CCC: $40.75
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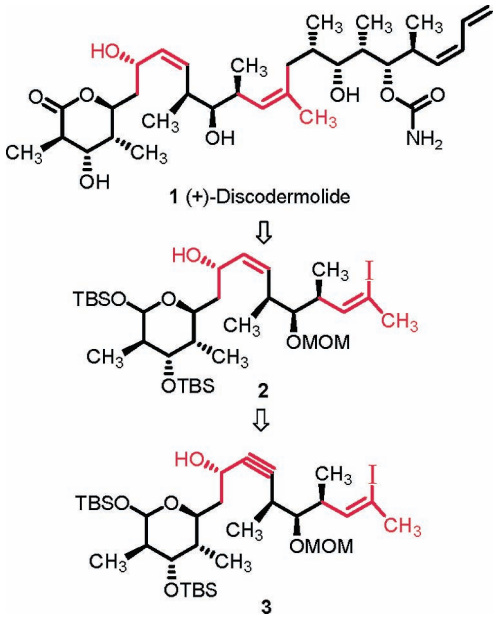
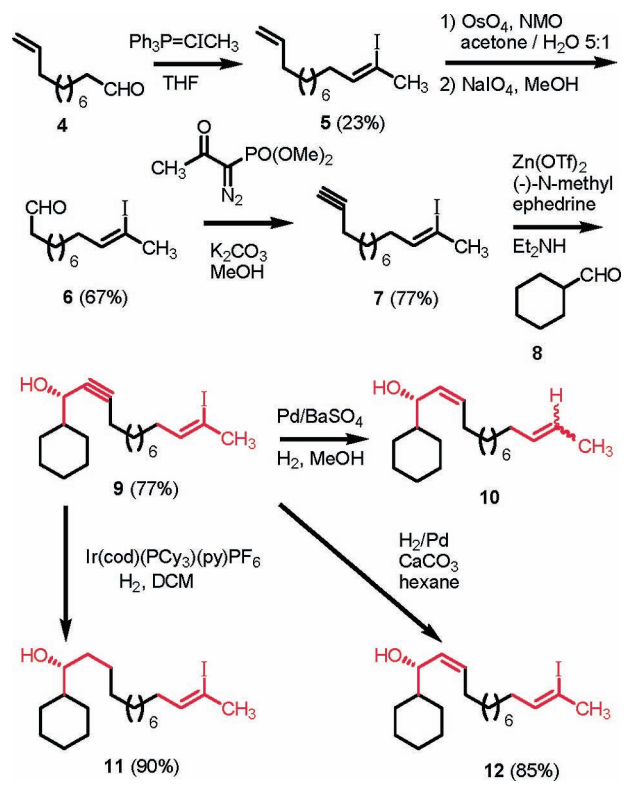
Scheme 1



Scheme 2



corresponding Carreira reagent[4] to aldehyde **8** afforded substrate **9** for our feasibility studies.

We then proceeded to survey reaction conditions. Treatment of alcohol **9** with 1 atm of hydrogen gas in the presence of commercially obtained "Lindlar catalyst" (Fluka)[5] resulted in the recovery of starting material. Likewise, application of the recently introduced method of Wu [$Pd(OAc)_2$, Ph_3P, methoxide in methanol][6] returned alcohol **9**. Treatment of substrate **9** with hydrogen in the presence of 5% $Pd/BaSO_4$ resulted in the recovery of allylic alcohol **10** in which the iodo olefin had also been reduced. More interesting was the reaction in methylene chloride in the presence of Crabtree's iridium catalyst [$Ir(cod)(PCy_3)(py)PF_6$].[7] This gave 90% of alcohol **11** in which the vinyl iodide was still intact but the alkyne bond had been completely reduced to the saturated system. Although the survival of the vinyl iodide during reduction of alkynol to alkanol was not our goal in this study, we suspect that this protocol will find applications in schemes directed toward other targets.

Some of the desired alcohol **12** was obtained by treatment of substrate **10** with diimide. However, the reaction was difficult to control, and conversion was always less than 50%. Hydrogenation over $Pd/CaCO_3$ in methanol gave a mixture of the desired **12** and over-reduced alcohol **10** (ratio ≈ 1/6). However, modification of the catalyst system by the substitution of hexanes for methanol as solvent led to encouraging mixtures of starting material and alcohol **12**. Optimization of these conditions provided the target alcohol **12** in 86% yield.

The selective reductions described herein, (**9** → **11**) and (**9** → **12**), offer the chemist new latitude in the design of schemes for the synthesis of complex molecules. The pursuit of some of these opportunities is underway in our laboratory.

Acknowledgment. This work was supported by the Army Breast Cancer Initiative (BC 051816), the National Institutes of Health (GM 74776), and the National Science Foundation (CHE-0131146, NMR instrumentation).

Supporting Information Available: Detailed descriptions of the experimental procedures and complete analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813.

(5) Approximately 5% $Pd/CaCO_3$, poisoned with lead.

(6) Wei, L.-L.; Wei, L.-M.; Pan, W.-B.; Leou, S.-P.; Wu, M.-J. *Tetrahedron Lett.* **2003**, *44*, 1979.

(7) (a) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655. (b) Crabtree, R. H.; Felkin, H.; Fillebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183.