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

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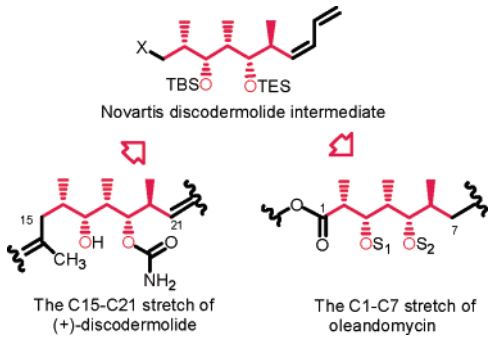
ABSTRACT



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.

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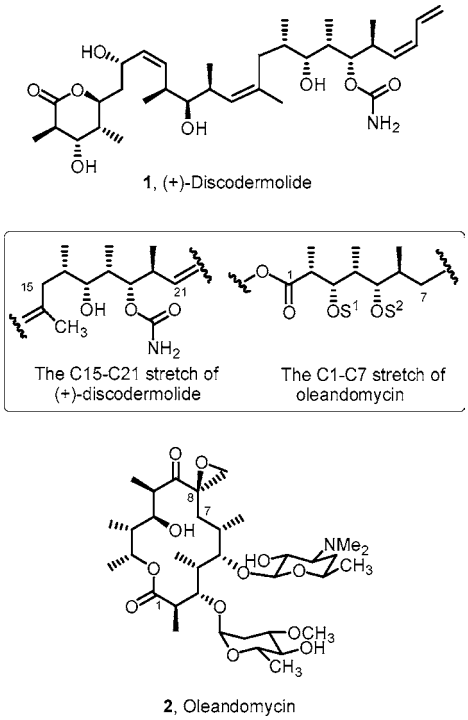


Figure 1. Analysis of the stereopentad substructures of discodermolide and oleandomycin.

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

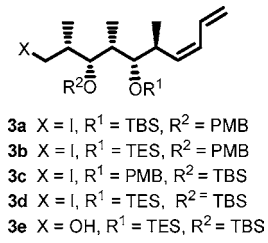


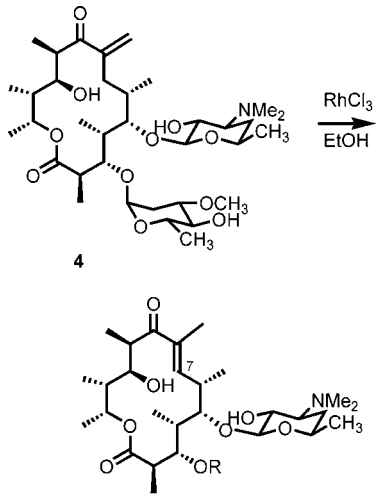
Figure 2. Some known discodermolide stereopentad equivalents.

corresponding alcohol, has served as a key intermediate in a successful total synthesis.[5]

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 $RhCl_3-H_2O$

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



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.

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.

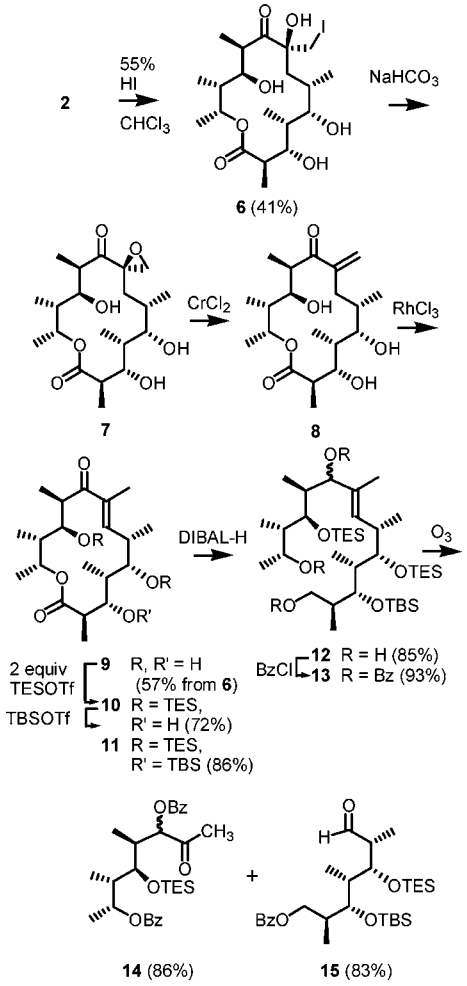
(7) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359.

(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.

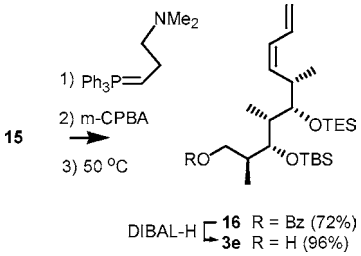
Conversion of iodohydrin **6** to the desirable enone **9** was accomplished by adapting known and newly established chemistry to the aglycon system. Thus, treatment with $NaHCO_3$ afforded the known oleandolide **7**[10] and deoxygenation of the epoxide by the method of Sciavolino[6] provided enone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

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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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