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

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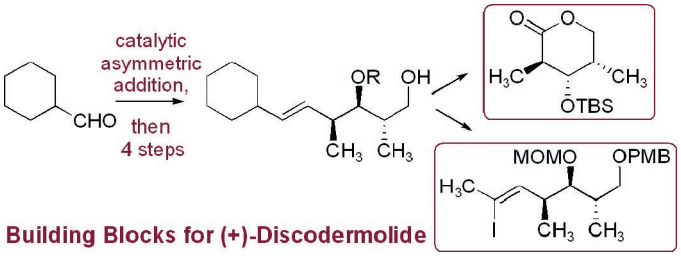
ABSTRACT



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).

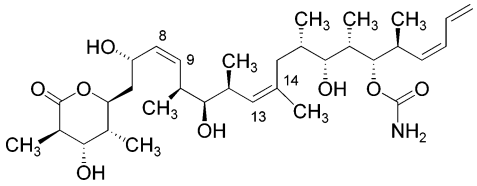


Figure 1. (+)-Discodermolide (**1**).

(+)-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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(2) Related reviews: (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489. (b) Hoffmann, R. W.; Dahmann, G.; Andersen, M. W. *Synthesis* **1994**, 629. (c) Kolodiazhnyi, O. I. *Tetrahedron* **2003**, *59*, 5953.

(3) For a recent review on the occurrence of stereotetrads in natural products and selected examples of stereotetrad building blocks, see: Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev.* **2005**, *34*, 677.

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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.

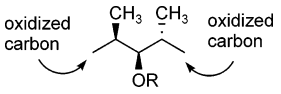

Figure 2. Functionalized syn, anti stereotriad building blocks for polypropionate construction.

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

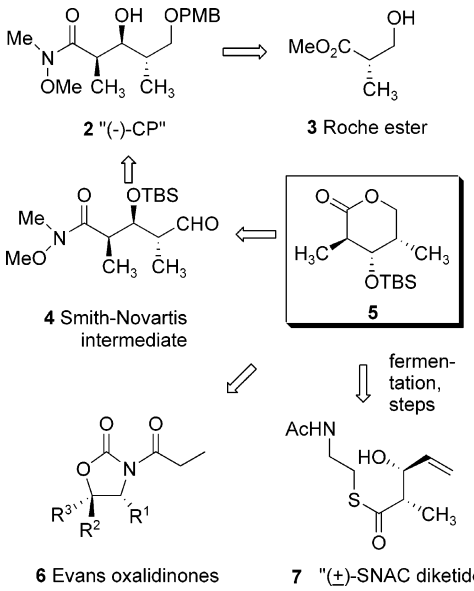

Figure 3. Origins of key building blocks in the chiral pool.

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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

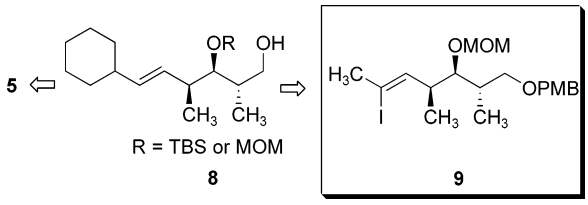


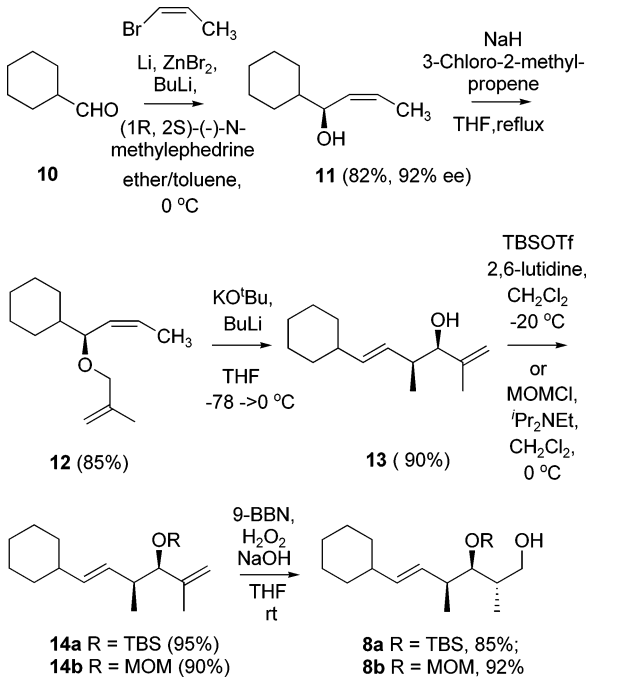
Figure 4. Examples of polypropionate building blocks available from alcohols **8**.

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.

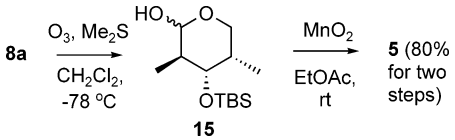
Scheme 1. Asymmetric Catalysis Route to Chiral Stereotriad Building Blocks



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.

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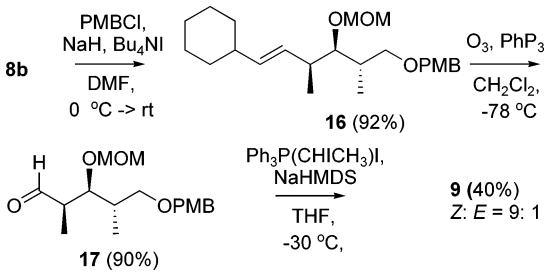
(28) The ee was obtained by Mosher ester analysis; see Supporting Information.

(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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