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

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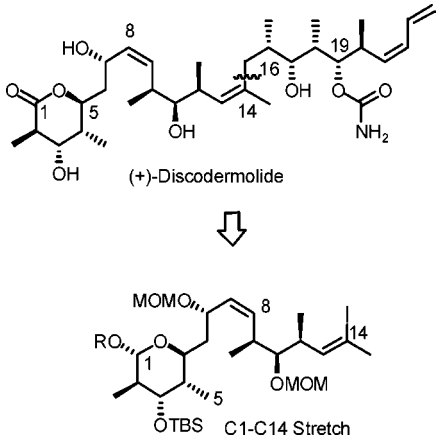
ABSTRACT



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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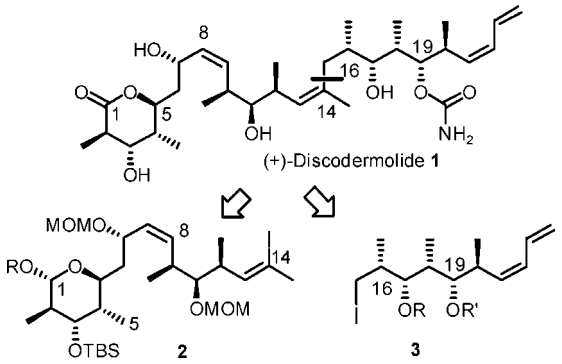


Figure 1. First disconnect for the retrosynthesis of (+)-discodermolide.

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).

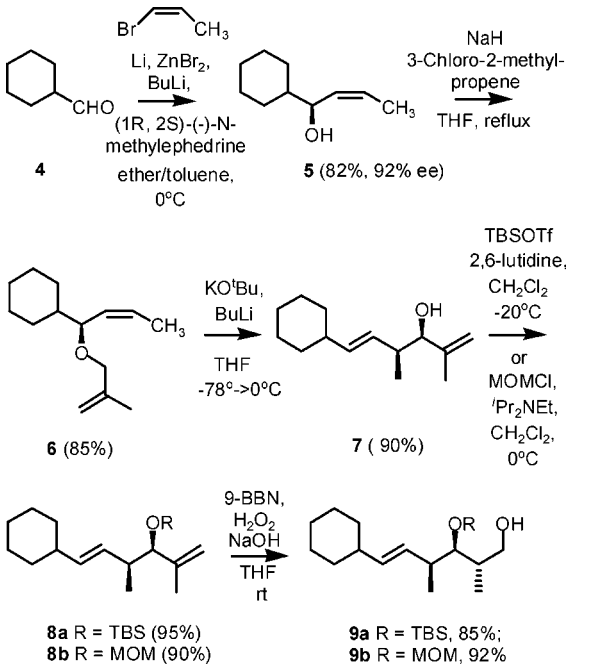
For the preparation of key intermediate **2**, we initially examined an approach based on the pseudosymmetry of the C1−C13 stretch.[11] Although this early model study has not yet been extended to total synthesis, the further pursuit of the pseudosymmetry strategy[12] highlighted the need for inexpensive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

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(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.

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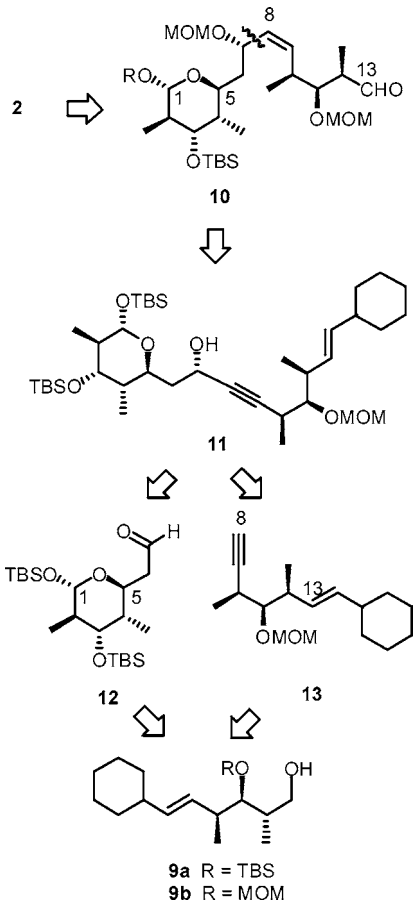
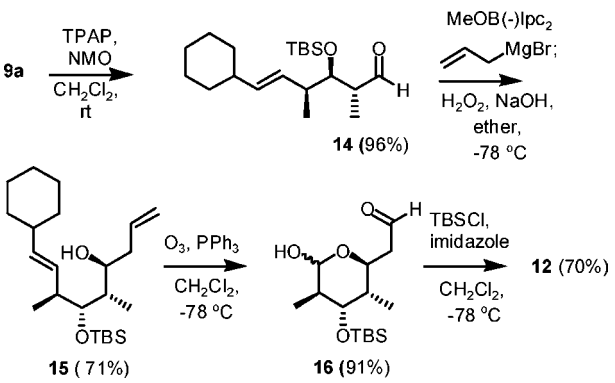


Figure 2. Retrosynthesis of key intermediate **2** to building blocks **9a** and **9b**.

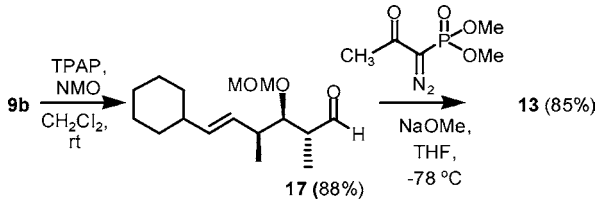
Cleavage of the two double bonds in diene **15** by ozonolysis accompanied by cyclization gave lactol **16** (a 1:1 mixture of β and α anomers as indicated by NMR analysis). This mixture was subjected to silylation to afford the protected hemiacetal **12** as the α anomer in 70% yield after silica gel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



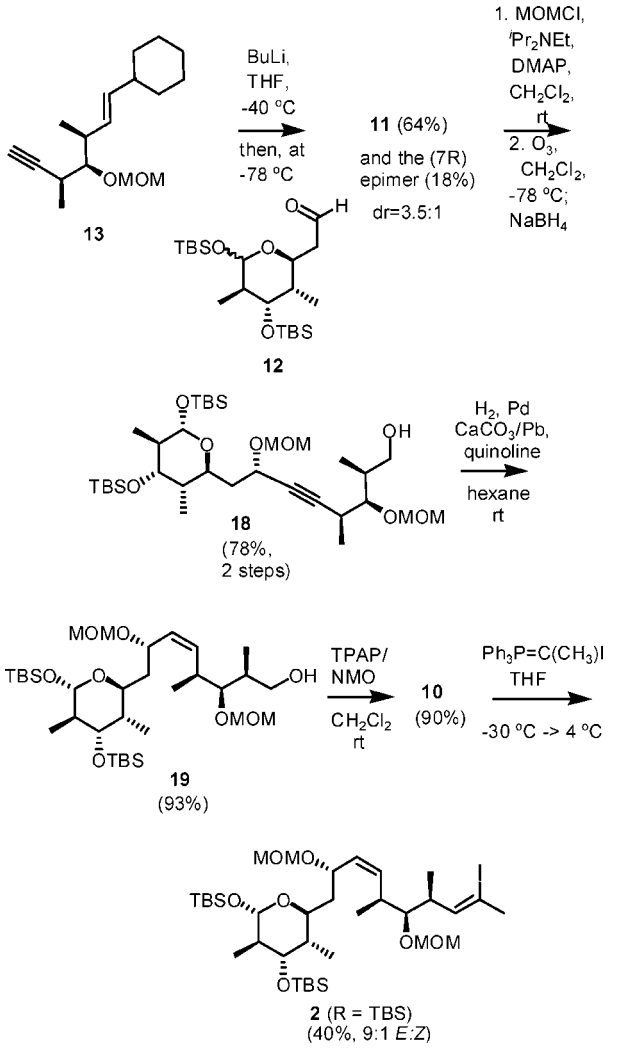
Scheme 3. Elaboration of Building Block **9b** to Intermediate **13**



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.

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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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