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Synthesis of (+)-Discodermolide by Catalytic Stereoselective Borylation Reactions**

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Abstract

The marine natural product (+)-discodermolide was first isolated in 1990 and, to this day, remains a compelling synthesis target. Not only does the compound possess fascinating biological activity, but it also presents an opportunity to test current methods for chemical synthesis and provides a forum for the inspiration of new reaction development. In this manuscript, we present a synthesis of discodermolide that employs a previously undisclosed stereoselective catalytic diene hydroboration and also establishes a strategy for chiral enolate alkylation. In addition, this synthesis of discodermolide provides the first examples of diene 1,4-diboration and borylative diene-aldehyde couplings in complex molecule synthesis.

Keywords

discodermolide; total synthesis; asymmetric catalysis; hydroboration; diboration

Discodermolide is a marine natural product that is a highly potent microtubule stabilizing agent.¹ Notably, it exhibits activity against paclitaxel-resistant cell lines and has been found to possess synergism with paclitaxel in human carcinoma cells.^{2,3} Because of these promising features and because isolation⁴ from its natural source, *Discodermia dissoluta*, provides only 7.0 mg from 434 grams of sponge, discodermolide has been the subject of many total synthesis efforts.⁵ Most notably, a group at Novartis prepared 64 g of synthetic material to support clinical trials.⁵ While pulmonary toxicity was noted among two patients and prompted abandonment of discodermolide as a clinical candidate,¹ subsequent studies on metabolism of the drug found near-complete oxidation after one hour in the presence of human liver microsomes.⁷ Currently, it is unknown whether the pulmonary toxicity alluded to above arises from discodermolide itself or from metabolic byproducts.

A short route to discodermolide (Figure 1 for structure) that might enable new analog synthesis⁸ should be founded upon enantioselective construction of key chiral building

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blocks from readily available feedstocks. In considering specific structural demands presented by the assembly of discodermolide, construction of the *Z*-trisubstituted alkene at C13-C14 has proven to be a most challenging task. Indeed, the manufacturing process for clinical trials of discodermolide employed a reaction sequence that occurs in 30% yield for construction of the C13-C14 region.⁶ To enable a rapid synthesis of discodermolide and new analogs, it is most critical to construct this element concisely and in an efficient fashion. To accomplish this objective, we considered two key innovations: first, we considered use of Ni-catalyzed 1,4-diene hydroboration⁹ to establish a *Z* trisubstituted alkene bearing an allylic functional group (eq. 1). Use of this reaction in the construction of discodermolide requires developing a process that results in stereoselective H-atom addition to the prochiral carbon at C12. Second, to connect C16 with an electrophile derived from the trisubstituted alkene, we considered an enolate alkylation (eq. 2). A central requirement for this technology was the design of a transformation that allows stereoselective α -alkylation of an enolate with control by an α' stereocenter. Most important in the development of this process is that it provides the product in high stereoselection and yield, without requiring an excess of precious building blocks.

Previous studies in our laboratory established that Ni-catalyzed 1,4-hydroboration of 1,3-dienes provides *Z*-alkenes with excellent control over the olefin geometry (>20:1 *Z:E*).^{9,10} Application of this process to the construction of discodermolide requires the reaction of prochiral diene substrates such as in **A** (Figure 2). A critical question thus arises as to the influence of neighboring stereocenters on the diastereoselectivity of the reduction process (**A** $\rightarrow$ **B**) and to probe these features, we examined several chiral dienol derivatives. Reaction of an unprotected alcohol at 0 °C for 3 h with pinacolborane and 2.5% each of Ni(cod)₂ and PCy₃, followed by oxidative workup furnished the hydroboration product **1** in moderate yield, moderate diastereoselection and excellent olefin *Z* stereoselectivity. While the alcohol-derived substrate reacted well, a significant improvement in both yield and stereoselection was observed upon incorporation of silicon protecting groups. As depicted in Table 1, use of a TES protecting group furnished the reaction product **2** in not only excellent yield, but also in enhanced selectivity relative to the unprotected substrate (12:1 vs. 6:1 dr). Use of larger protecting groups served to enhance selectivity such that with the TBDPS-protected substrate (data not shown), the product was obtained as a single stereoisomer according to ¹H NMR analysis. Substrates with other substituents and protecting groups also participated and the stereoselectivity trends appear to follow the model depicted by **C** (inset, Figure 2). We reason that the Ni complex associates with the diene in a manner that positions the metal complex antiperiplanar with respect to the adjacent oxygen atom. This orientation allows the π system of the diene to mix with the C-O σ^* and enhance backbonding between the metal and the alkene.¹¹ A conformation such as **C**, wherein the carbinol hydrogen atom is directed towards the metal complex and the carbinol substituent directed away, serves to minimize steric interactions with the catalyst and leads to a stereocontrolled reaction.

To establish the C15–C16 linkage in discodermolide, we considered alkylation of a ketone enolate with an electrophile derived from the above-described diene hydroboration. Enolate alkylations that establish this connection in previous syntheses of discodermolide have

employed *Z*-enolates that engage in chelation with the β -oxygen at C13; these reactions proceed in modest selectivity (6:1 d.r.) and require an excess of electrophile (2 equivalents).^{5e} Important precedents involving *anti* aldol reactions of α -chiral *E* enolates¹² notwithstanding, the use of A(1,3) strain to control the α' -alkylation of non-chelated α -chiral ketone enolates remains undeveloped.¹³ In line with established strategies for acyclic conformational analysis,¹⁴ it was considered that the *E* enolate derived from **D** (Figure 3), in the absence of intervening chelation effects between neighboring functional groups and the metal enolate might favor conformer **F** such that alkylation occurs preferentially from the *Re* face. In a preliminary experiment aimed at addressing this issue, alkylation to give **7** was accomplished by subjecting the corresponding ethyl ketone starting material to deprotonation with lithium tetramethylpiperidide in the presence of lithium bromide, conditions known¹⁵ to generate the *E*-enolate even from hindered ketones. Treatment with 1.5 equivalents of allyl iodide at $-78\text{ }^{\circ}\text{C}$ delivered **7** in excellent yield and in good selectivity. Of vital importance for eventual scale-up of complex fragment couplings, the reaction yield was excellent even when a 1:1 stoichiometry of enolate:electrophile was employed. Selective construction of **8** demonstrates that this alkylation strategy applies to *syn* aldol products, and selective formation of product **9** indicates simple hydrocarbon-derived nucleophiles can exhibit useful levels of selectivity.

With central technology in place, construction of discodermolide commenced. To prepare fragment **14**, a reaction sequence involving catalytic enantioselective 1,4-diboration¹⁶ of *trans*-pentadiene followed by *in situ* homologation¹⁷ and oxidation furnished 1,6-diol **11** in excellent yield and selectivity (Scheme 1). While monoactivation of diol **11** was non-selective, conversion of **11** to diene **12** was readily accomplished by bis(tosylation), selective elimination with a hindered basic alkoxide (potassium *tert*-butoxide), and detosylation. Importantly, this simple three-step sequence could be accomplished in excellent yield. Oxidation of **12** by the Dess-Martin periodinane, was followed by use of the recently-developed¹⁸ Roush reductive aldol reaction; subsequent alkylation and TMS protection furnished **14**.

Construction of fragment **22** was accomplished in four synthesis steps from chiral aldehyde **16** (Scheme 2). In designing this route, it was considered that access to **16** by hydroformylation of protected allyl alcohol derivatives would be an ideal strategy. Hydroformylation of this substrate class has been addressed by Landis using the bisdiazaphos ligand¹⁹ and similar reactions have been employed by Burke²⁰ and Leighton²¹ for the construction of polypropionate arrays. Unfortunately, the bisdiazaphos ligands are not readily available. Expecting that related electron-rich bidentate diphosphines might provide sufficient selectivity, alternative ligands were examined in the hydroformylation of TBS-protected allyl alcohol **15**. The electronic and steric properties of the commercially available DuPhos²² family of ligands appeared ideally suited to the task and it was found that phenyl-substituted bis(phospholano)ethane (PhBPE, **17**) was most effective, delivering chiral aldehyde **16** in outstanding levels of enantioselection and yield, and with moderate-but-useful levels of regiocontrol.²³ Importantly, very low catalyst loadings are effective and the unpurified reaction product is sufficiently free from contaminants that it may be used directly in subsequent operations. To complete construction of **22**, aldehyde **16** was

subjected to Walsh chelation-controlled addition²⁴ of vinyl zinc **18**, which is readily available from hydroboration of **19** followed by boron-zinc exchange. Ni-catalyzed hydroboration/oxidation of **21** followed by iodinolysis furnished **22** in excellent yield and diastereoselection.

Lastly, construction of fragment **29** employed a sequence involving catalytic diastereoselective borylative diene-aldehyde coupling (Scheme 3).²⁵ To begin this sequence, aldehyde **24** was prepared by Rh/PhBPE catalyzed hydroformylation of the cyclic *o*-xylyl acetal²⁶ of acrolein (**23**). Likely due to the influence of a second electronegative heteroatom at the allylic carbon, this hydroformylation occurred with outstanding branch:linear selectivity (b:l = 13:1) and, like the example in Scheme 2, with excellent enantiocontrol. While the subsequent borylative diene-aldehyde coupling reaction has precedent in our laboratory using P(SiMe₃)₃ as a ligand, it was found that PBN₃ is equally effective and allows for high levels of stereoinduction from aldehyde **24** in conversion to **25**. Iridium-catalyzed hydroboration/oxidation²⁷ followed by neutral hydrogenolytic deprotection of the *o*-xylyl acetal, oxidation, and esterification furnished **26**. Primary alcohol **26** was converted to fragment **29** by oxidation, chlorination and carbonyl substitution employing a phosphoryl anion derived from **28**.

In line with the enolate alkylation reactions described above, the *E*-enolate derived from **14** (Scheme 4) was treated with 1.0 equivalent of allyl iodide **22** and this furnished **30** in excellent yield and stereoselectivity. After replacement of the TMS protecting group in **30** with a requisite primary carbamate, the primary TBS protecting group was removed and the product alcohol oxidized to give aldehyde **31**. The reaction sequence for completion of the target molecule was influenced by expertise developed in the course of reported prior syntheses.^{5d,28} Thus **31** was subjected to Still-Gennari olefination with **29** to give **32**.²⁹ Final conversion of **32** to discodermolide was accomplished by the three-step reduction and deprotective lactonization sequence depicted in Scheme 4. ¹H and ¹³C NMR spectra, optical rotations and mass spectral data were identical to those reported for the natural product.

Overall, the synthesis of discodermolide was accomplished in a total of 36 steps with a longest linear sequence of 17 steps (13% yield) from commercially available materials. While it is anticipated that the synthesis strategy described herein will offer access to new discodermolide analogs that may address biological limitations of the natural product itself, it is also anticipated that the synthetic methods developed to address this structure may have value in other ventures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Diastereoselective diene hydroboration (eq. 1) and stereoselective alkylation of enolates (eq. 2) are advanced to facilitate the synthesis of (+)-discodermolide.

■ >20:1 Z:E in all cases

■ amenable to gram-scale reaction

Figure 2.

Ni-catalyzed hydroboration of chiral dienols results in chiral trisubstituted alkenes.

Reactions were conducted at [substrate] = 0.25 M and oxidized with 30% H₂O₂ and 3 M NaOH. Yields refer to isolated yield of purified material and values are an average of two experiments. TES=triethylsilyl, TBS=*tert*-butyldimethylsilyl.

Figure 3.

Stereoselective alkylation of α' -chiral *E*-enolates. Minimization of allylic (1,3) strain in the *E*-enolate derived from **D**, establishes a conformation wherein the R_L at the stereocenter impedes approach of a reacting electrophile and results in a stereoselective alkylation.

Scheme 1.

Synthesis of **14** from pentadiene in 8 steps is enabled by catalytic enantioselective tandem diene diboration/homologation/oxidation and reductive aldol methods. DMP=1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one, TMS=trimethylsilyl.

Scheme 2.

Synthesis of **22** in 5 steps from TBS-protected allyl alcohol **15**. TBSOTf=*tert*-butyldimethylsilyl trifluoromethane sulfonate, HBpin=pinacolborane, ONf=nonafluorobutane sulfonyl.

Scheme 3.

Synthesis of **29** from acrolein cyclic *o*-xylyl acetal **23**. B₂(pin)₂=bis(pinacolato)diboron, pTsOH=*para*-toluene sulfonic acid, dppm=bis(diphenylphosphino)methane, cod=1,5-cyclooctadiene.

Scheme 4.

Stereoselective enolate alkylation to give **30** and the conversion to discodermolide.

LiTMP=lithium 2,2,6,6-tetramethylpiperamide, PPTS=pyridinium *para*-toluene sulfonate,

p-TsOH=*para*-toluene sulfonic acid,