Asymmetric Synthesis Hot Paper

DOI: 10.1002/anie.201405455

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 an inspiration for new reaction development. A new synthesis of discodermolide employs a previously undisclosed stereoselective catalytic diene hydroboration and also establishes a strategy for the alkylation of chiral enolates. Furthermore, this synthesis of discodermolide provides the first examples of the asymmetric 1,4-diboration of dienes and borylative diene–aldehyde couplings in complex-molecule synthesis.*

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 isolation[4] from its natural source, *Discodermia dissoluta,* provides only 7.0 mg of discodermolide from 434 grams of sponge, this natural product 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.[6] Whereas pulmonary toxicity was observed with two patients and prompted the abandonment of discodermolide as a clinical candidate,[1] subsequent studies on the 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 side products.

A short route to discodermolide (see Figure 1 for its structure) that might enable the synthesis[8] of new analogues should be founded upon the enantioselective construction of key chiral building blocks from readily available feedstocks. Considering the specific structural demands presented by the assembly of discodermolide, the construction of the *Z*-configured trisubstituted alkene at the C13–C14 position has proven to be a most challenging task. Indeed, the manufacturing process for clinical trials of discodermolide employed a reaction sequence that occurred in 30% yield for the construction of the C13–C14 region.[6] To enable a rapid synthesis of discodermolide and new analogues, it is most critical to construct this fragment concisely and in an efficient fashion. To accomplish this objective, we considered two key innovations: First, we intended to use a nickel-catalyzed 1,4-diene hydroboration[9] to establish a *Z*-configured trisubstituted alkene bearing an allylic functional group (Figure 1a). Use of this reaction in the construction of discodermolide requires developing a process that results in stereoselective H-atom addition to the prochiral carbon atom at the C12 position. Second, to connect the C16 carbon atom to an electrophile derived from the trisubstituted alkene, we considered an enolate alkylation (Figure 1b). A central requirement for this step was the design of a transformation that allows the stereoselective α-alkylation of an enolate with control by an α′ stereocenter. It is most important in the development of this process that it provides the product with high stereoselectivity and yield without requiring an excess of precious building blocks.

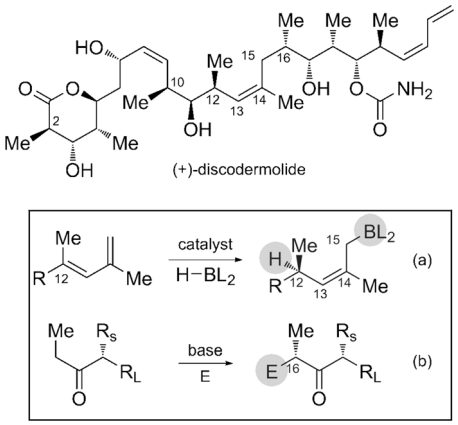

Figure 1. Diastereoselective diene hydroboration (a) and stereoselective alkylation of enolates (b) are advanced to facilitate the synthesis of (+)-discodermolide. R_L = larger substituent, R_S = smaller substituent.

Previous studies in our laboratory have established that the nickel-catalyzed 1,4-hydroboration of 1,3-dienes provides *Z* alkenes with excellent control over the olefin geometry (>20:1 *Z*/*E*).[9,10] The application of this process to the construction of discodermolide required 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**→**B**), and to probe these features, we examined several chiral dienol derivatives. The reaction of an unpro-

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[**] This work was supported by grants from the National Institutes of Health (GM 059417 and GM 064451). Z.Y. and R.J.E. were supported by LaMattina Fellowships.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201405455.

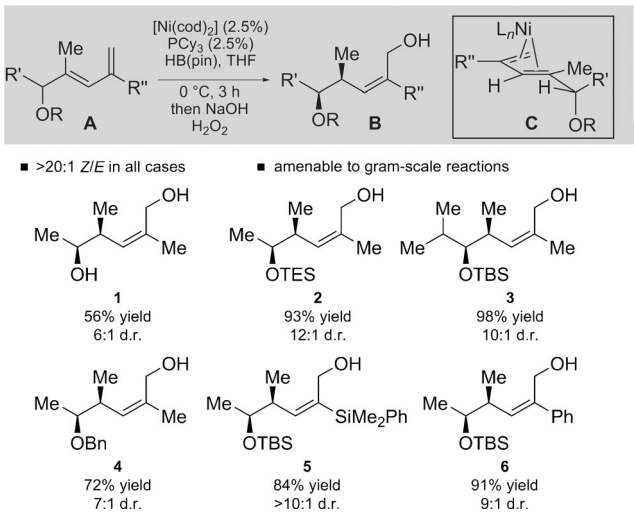


Figure 2. The nickel-catalyzed hydroboration of chiral dienols results in chiral trisubstituted alkenes. Reactions were conducted at a substrate concentration of 0.25 M, and the reaction intermediates were oxidized with H_2O_2 (30%) and NaOH (3 M). The reactions for the synthesis of **5** and **6** were run for 12 hours at RT. Yields refer to isolated purified material, and values denote the average of two experiments. Bn = benzyl, cod = 1,5-cyclooctadiene, Cy = cyclohexyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl.

tected alcohol at 0 °C for three hours with pinacolborane and 2.5% each of $[Ni(cod)_2]$ and PCy_3 followed by oxidative workup furnished the hydroboration product **1** in moderate yield, moderate diastereoselectivity, and excellent olefin *Z* stereoselectivity. Although the alcohol-derived substrate reacted well, a significant improvement in both yield and stereoselectivity was observed upon incorporation of silicon protecting groups. As shown in Figure 2, the use of a TES protecting group furnished the reaction product **2** not only in excellent yield, but also with enhanced selectivity relative to the unprotected substrate (12:1 vs. 6:1 d.r.). The use of larger protecting groups served to enhance selectivity such that with the *tert*-butyldiphenylsilyl (TBDPS)-protected substrate, the product was obtained as a single stereoisomer according to ^{1}H NMR analysis (data not shown). Substrates with other substituents and protecting groups also participated, and the stereoselectivity trends appear to follow the model depicted by **C** (Figure 2, inset). 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* orbital, which enhances backbonding between metal and 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 that is derived from the above-described diene hydroboration. Enolate alkylations that have established this connection in previous syntheses of discodermolide have employed *Z*-configured enolates that engage in chelation with the β-oxygen atom at the C13 position; these reactions proceeded in modest selectivity (6:1 d.r.) and required an excess of electrophile (2 equiv).[5e] Despite important precedents involving *anti* aldol reactions of α-chiral *E* enolates,[12] the use of 1,3-allylic strain to control the α′-alkylation of non-chelated α-chiral ketone enolates remains undeveloped.[13] In line with established strategies for the conformational control of acyclic structures,[14] it was considered that the *E* enolate derived from **D** (Figure 3), in the absence of intervening

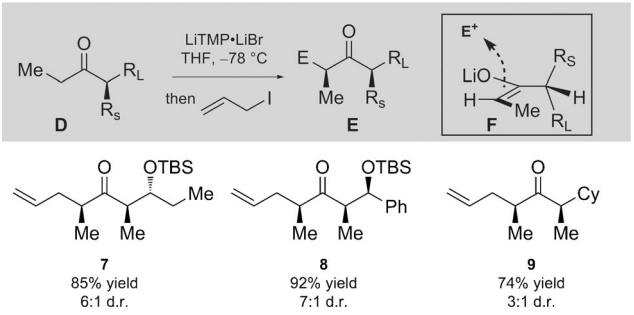
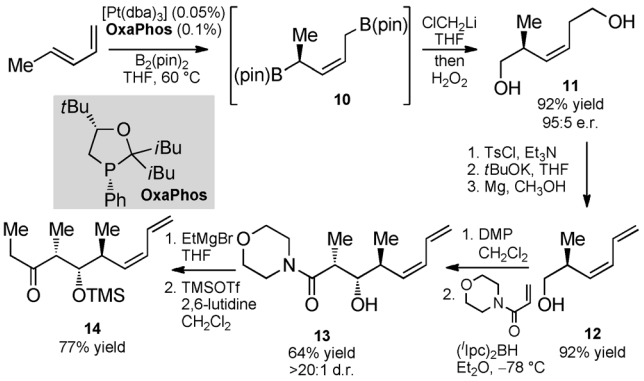


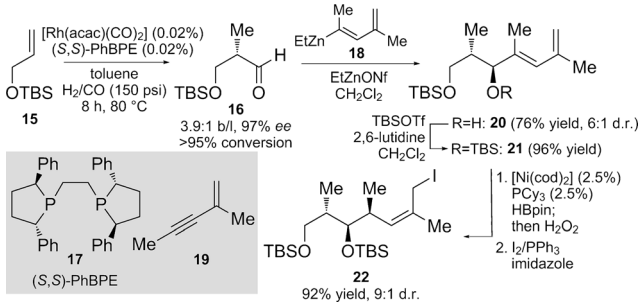
Figure 3. Stereoselective alkylation of α′-chiral *E* enolates. Minimization of 1,3-allylic strain in the *E* enolate derived from **D** establishes a conformation wherein the R_L at the stereocenter impedes approach of a reacting electrophile, which results in stereoselective alkylation. LiTMP = lithium tetramethylpiperidide.

chelation effects, would favor conformer **F**. Subsequent alkylation might occur 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, which are conditions known[15] to generate the *E* enolate even from hindered ketones. Treatment with allyl iodide (1.5 equiv) at −78 °C delivered **7** in excellent yield and in good selectivity. It is of vital importance for an eventual scale-up of complex-fragment couplings that the reaction yield was excellent even when enolate and electrophile were employed in a 1:1 stoichiometry. The selective construction of **8** demonstrates that this alkylation strategy also applies to *syn* aldol products, and the selective formation of product **9** indicates that simple hydrocarbon-derived nucleophiles can react with useful levels of selectivity.

With the central methods in place, construction of discodermolide commenced. To prepare fragment **14**, a reaction sequence involving catalytic enantioselective 1,4-diboration[16] of *trans*-pentadiene followed by in situ homologation[17] and oxidation furnished 1,6-diol **11** in excellent yield and selectivity (Scheme 1). Whereas monoactivation of diol **11** was non-selective, conversion of **11** into 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 the recently developed[18] Roush reductive aldol reaction; subsequent alkylation and TMS protection furnished **14**.



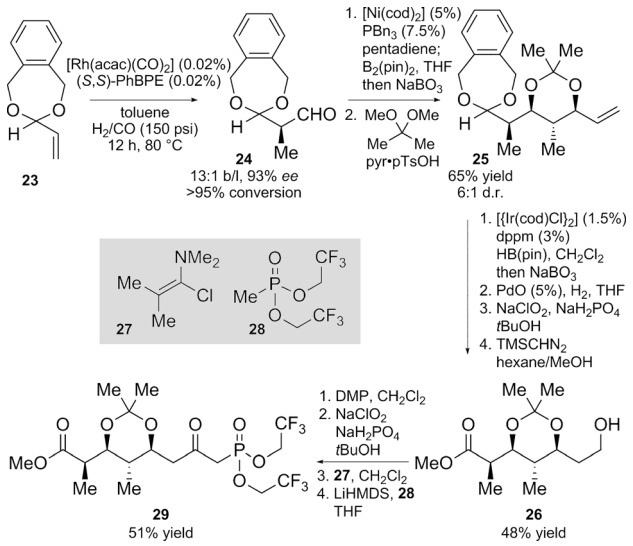
Scheme 1. The synthesis of **14** from pentadiene in eight steps is enabled by catalytic enantioselective tandem diene diboration/homologation/oxidation and reductive aldol reactions. $B_2(pin)_2$ = bis(pinacolato)diboron, dba = (*E*,*E*)-dibenzylideneacetone, DMP = 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, ^{I}Ipc = isopinocampheyl derived from (−)-α-pinene, OTf = trifluoromethanesulfonate, TMS = trimethylsilyl, Ts = *para*-toluenesulfonyl.



Scheme 2. Synthesis of **22** in five steps from TBS-protected allyl alcohol **15**. acac = acetylacetonate, HBpin = pinacolborane, ONf = nonafluorobutanesulfonate.

The 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 et al. using the bisdiazaphos ligand,[19] and similar reactions have been employed by the groups of Burke[20] and Leighton[21] 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 DuPhos[22] ligand family 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 enantioselectivity and yield and with moderate, but useful levels of regiocontrol.[23] Importantly, very low catalyst loadings were effective, and the unpurified reaction product was sufficiently free from contaminants that it could be used directly in subsequent operations. To complete the construction of **22**, aldehyde **16** was subjected to the Walsh conditions for chelation-controlled addition[24] of vinyl zinc species **18**, which is readily available from hydroboration of **19** followed by boron–zinc exchange. Nickel-catalyzed hydroboration and oxidation of **21** followed by iodinolysis furnished **22** in excellent yield and diastereoselectivity.

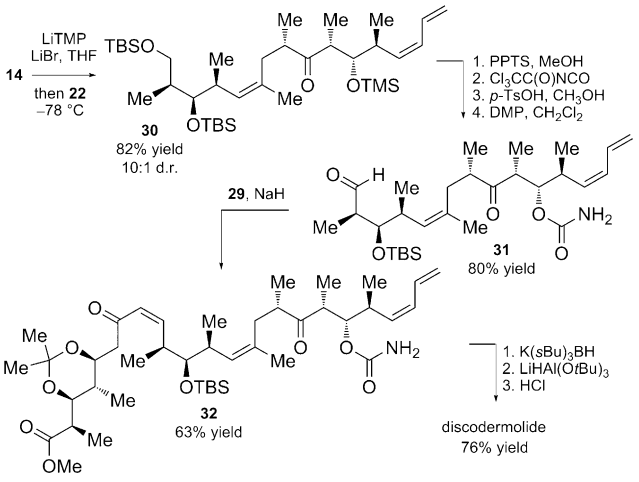
Lastly, construction of fragment **29** employed a sequence involving a catalytic diastereoselective borylative diene–aldehyde coupling (Scheme 3).[25] To begin this sequence,



Scheme 3. Synthesis of **29** from the cyclic *ortho*-xylyl acetal of acrolein (**23**). dppm = bis(diphenylphosphino)methane, pTsOH = *para*-toluenesulfonic acid.

aldehyde **24** was prepared by Rh/PhBPE-catalyzed hydroformylation of the cyclic *ortho*-xylyl acetal[26] of acrolein (**23**). Likely because of the influence of a second electronegative heteroatom at the allylic carbon atom, this hydroformylation occurred with outstanding branched/linear selectivity (b/l = 13:1) and with excellent enantiocontrol, as for the example shown in Scheme 2. Whereas the subsequent borylative diene–aldehyde coupling reaction has precedent in our laboratory using $P(SiMe_3)_3$ as a ligand, it was found that PBn_3 is equally effective and allows for high levels of stereoinduction for the conversion of aldehyde **24** into **25**. Iridium-catalyzed hydroboration and oxidation[27] followed by neutral hydrogenolytic deprotection of the *ortho*-xylyl acetal, oxidation, and esterification furnished **26**. Primary alcohol **26** was converted into 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*-configured enolate derived from **14** (Scheme 4) was treated with allylic iodide **22** (1.0 equiv), which 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



Scheme 4. Stereoselective enolate alkylation to give **30** and conversion into discodermolide. LiTMP = lithium 2,2,6,6-tetramethylpiperidide, PPTS = pyridinium *para*-toluenesulfonate.

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** into discodermolide was accomplished by the three-step reduction and deprotective lactonization sequence depicted in Scheme 4. ^{1}H and ^{13}C NMR spectra, optical rotation values, 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. Whereas it is anticipated that the synthesis strategy described herein will offer access to new discodermolide analogues 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.

Received: May 20, 2014
Published online: July 15, 2014

Keywords: asymmetric catalysis · diboration · discodermolide · hydroboration · total synthesis

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