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Studies Directed toward the Total Synthesis of Discodermolide: Asymmetric Synthesis of the C1–C14 Fragment

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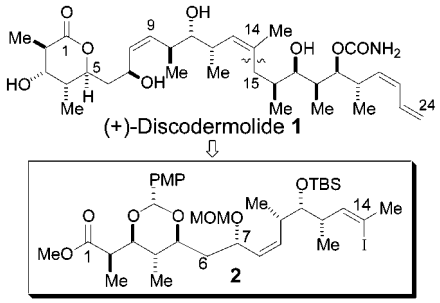
ABSTRACT



A convergent and stereoselective assembly of the C1–C14 subunit of marine natural product (+)-discodermolide has been completed. The approach employs chiral allylsilane bond construction methodology to establish four of the eight stereogenic centers. Key fragment coupling is achieved via an efficient stereoselective acetate aldol reaction between C1–C6 and C7–C14 subunits.

(+)-Discodermolide **1** is a polypropionate-derived marine metabolite, isolated from the Caribbean deep sea sponge *Discodermia dissoluta*.[1,2] The structure of discodermolide, determined through a combination of spectroscopic techniques, was shown to possess a tetrasubstituted δ-lactone ring, a side chain containing four double bonds, and a total of 13 stereocenters. The relative stereochemistry was assigned by X-ray crystallography, while the absolute configuration remained unidentified until Schreiber and co-workers[3] synthesized both antipodes. (+)-Discodermolide was initially shown to be a potent immunosuppressive agent, both in vitro and in vivo, and also an antifungal agent.[4] Further biological studies revealed remarkable cytotoxic activity in a variety of human and murine cell lines. This cytotoxicity is due to binding and stabilizing mitotic spindle microtubules causing cell cycle arrest in the M phase.[5]

The striking biological profile as well as its structural complexity prompted substantial synthetic effort toward the total synthesis of (+)-discodermolide.[6] To date, six total

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syntheses of discodermolide have been reported.[3,7] Herein we report our approach to the C1−C14 fragment **2**, which sets the stage for a convergent synthesis of (+)-discodermolide and its analogues for further structural and biological study.

Our retrosynthetic analysis of (+)-discodermolide **1** is outlined in Figure 1. The first key disconnection at C14−C15 envisions an sp^2-sp^3 type palladium(0)-mediated cross-coupling reaction between C1−C14 vinyl iodide **2** and C15−C24 alkyl iodide **3** fragments. Fragment **2** is derived from propargylic alcohol **4** via Lindlar reduction of the C8−C9 internal acetylene and iododesilylation. Our second disconnection of **4** at C6−C7 yields two subunits **5** and **6**. We projected that the desired stereochemistry of the propagylic alcohol **4** at C7 could be realized utilizing an acetate aldol reaction between the boron enolate of methyl ketone **5** and the propargylic aldehyde **6**. Finally, the stereogenic centers of the polypropinate fragments **5** and **6** could be constructed using chiral (*E*)-crotylsilane bond construction methodology, developed earlier in our laboratories.[8]

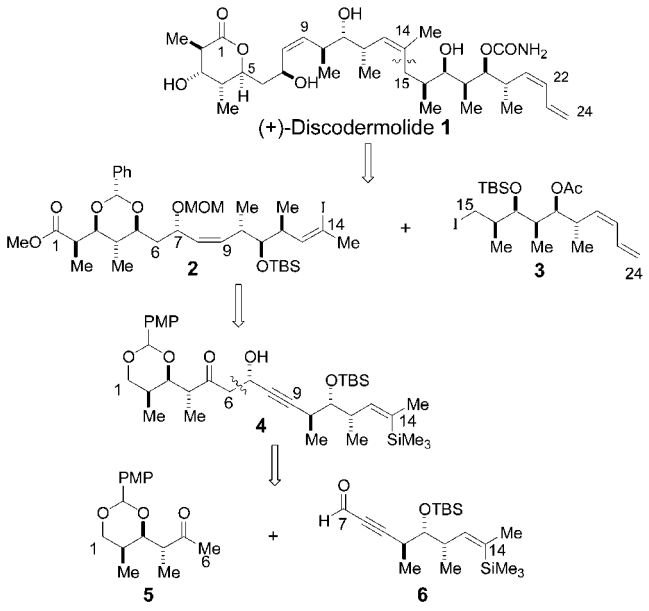
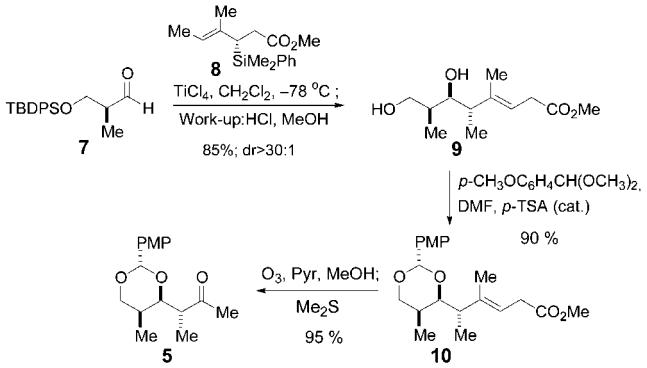


Figure 1. Retrosynthetic analysis of (+)-discodermolide.

Assembly of the methyl ketone **5** started with the double stereodifferentiating crotylation between readily available[9] aldehyde **7** and (*S*)-silane **8** (Scheme 1). Acidic workup removed the silyl protecting group in situ to afford homoallylic alcohol **9** in 85% yield with dr > 30:1 *anti*:*syn*. The resulting diol **9** was converted to the *p*-methoxybenzyl acetal **10** in 90% yield. Subsequent ozonolysis of the double bond in the presence of pyridine provided C1−C6 fragment **5** in 95% yield.

Scheme 1



Synthesis of propargylic aldehyde **6** is outlined in Scheme 2 and was initiated by a double stereodifferentiating reaction between aldehyde **11** and the (*S*)-crotylsilane reagent **12** to give the homoallylic alcohol **13** (85%, dr > 30:1 *syn*:*anti*). Protection of the homoallylic alcohol as the TBS ether (94% yield), followed by the oxidative cleavage of the double bond, and Corey−Fuchs[10] homologation, afforded vinyl dibromide **15** in 84% yield (two steps). Treatment with *n*-BuLi and TMSCl led to acetylene **16** in 79% yield. Hydrozirconation of silylacetylene **16** using Schwartz's reagent[11] [$Cp_2Zr(H)$-Cl] (2.5 equiv, THF, 55 °C, 1 h), followed by quenching with iodine affored iodovinylsilane **17** as a single isomer in 92% yield. Subsequent coupling of **17** with methylzinc species in the presence of a catalytic amount of Pd(0) gave the (*Z*)-vinyl silane **18** in 88% yield. Due to the inherent stability, the vinylsilane functions as a masked vinyl iodide throughout the synthesis until fragments **2** and **3** are ready for the crucial palladium(0)-mediated cross-coupling reaction.

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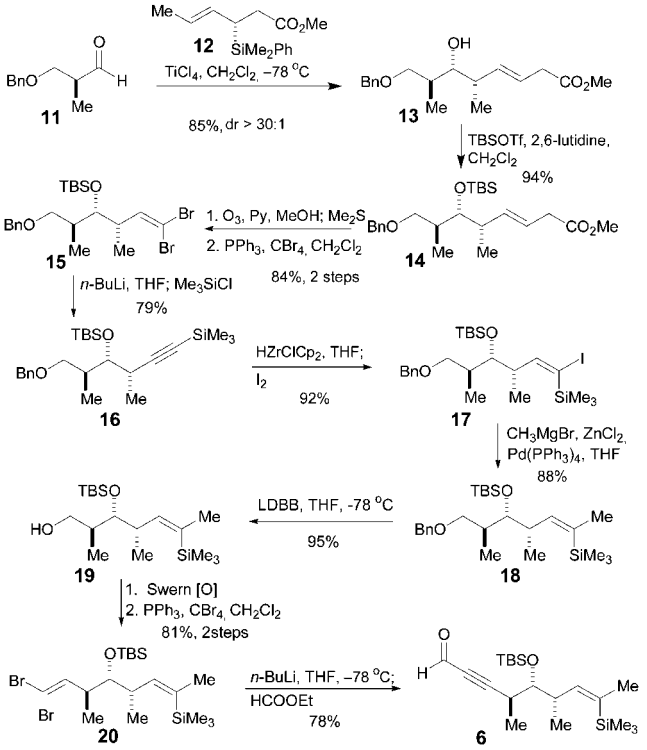
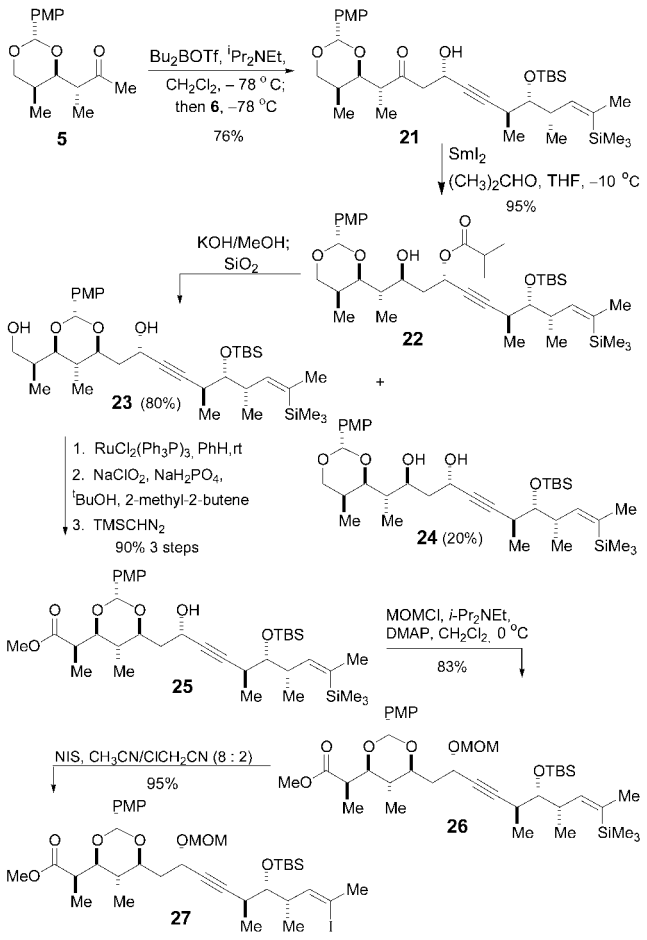
Scheme 2



Scheme 3



The reaction sequence based on the formation (and use) of the geminally substituted iodovinylsilane has been documented[12] to be a useful strategy for the convergent assembly of complex trisubstituted olefins. Our approach provides access to the configurationally pure C13−C14 (*Z*)-olefin of the (+)-discodermolide.

The selective deprotection of the benzyl group (in the presence of the vinylsilane functionality) in **18** was carried out using LDBB reagent[13,14] in 95% yield. Swern oxidation[15] of the deprotected alcohol **19**, followed by the Corey−Fuchs homologation, afforded vinyl dibromide **20** (81% yield, two steps). Subsequent treatment of **20** with *n*-BuLi followed by the addition of ethyl formate furnished the propargylic aldehyde **6** (C7−C14 fragment) in 78% yield.

With the efficient synthetic access to intermediates **5** and **6**, we next examined their union via aldol bond construction (Scheme 3). Analysis of this process dictated the use of enolborinates to establish the desired stereochemistry at C7 via 1,5-*anti* asymmetric induction.[16]

Gratifyingly, the aldol reaction between the dibutylboron enolate, derived from methyl ketone **5** and aldehyde **6** (CH_2Cl_2 [17] at −78 °C), produced the desired adduct **21** as a single diastereoisomer[18] (as determined by ^{1}H NMR analysis) in 76% yield.

A modified Tischenko reduction[19] of the β-hydroxy ketone **21** provided *anti*-1,3 diol **22** in 95% yield, differentiated as the hydroxyisobutyrate. After hydrolysis of the isobutyrate (KOH/MeOH), chromatography on silica gel unexpectedly resulted in acetal rearrangement to afford diol **23** in 80% yield along with the expected diol **24** (20% yield). Diol **24** could be further converted into thermodynamically more stable **23** by stirring with SiO_2 in hexanes or by performing silica gel chromatography with the same conversion (80%).

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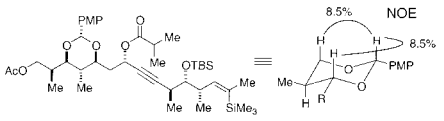
(17) Optimizing the reaction conditions, we found that while the use of both CH_2Cl_2 and Et_2O produced good results on a small scale (70−80% yield on a 20−40 mg scale), increasing the reaction scale using Et_2O led to considerable decrease in yields, due to decomposition of methyl ketone. Use of CH_2Cl_2 as a solvent allowed us to upscale the aldol reaction and run it with reproducibly good yields on a 20−500 mg scale.

(18) The relative stereochemistry was assigned by NOE analysis of the acetal, derived from **22**:



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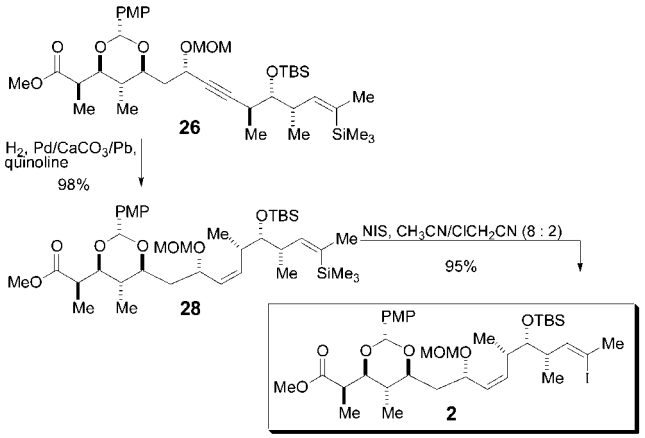
Since we planned to deprotect the primary hydroxyl of the anticipated acetal **24** later (for eventual conversion to a methyl ester for the subsequent lactonization step), this rearrangement could save a step at this advanced point in synthesis. To use the acetal rearrangement in our favor, however, we needed to find the reagent system able to selectively oxidize the primary hydroxyl to an aldehyde, in the presence of the secondary propargylic alcohol. To determine the feasibility of this approach, a variety of oxidative conditions were explored at this point. The use of modified Ley's oxidation protocol[20] (TPAP/NMO, CH_3CN; then H_2O) as well as the use of 4-MeO-TEMPO/NaOCl oxidation conditions[21] caused decomposition of the substrate. Fortunately, selective oxidation of **23** worked extremely well using $RuCl_2(Ph_3P)_3$ [22] in benzene. Treatment with buffered sodium chlorite,[23] followed by (trimethylsilyl)diazomethane, furnished methyl ester **25** with 90% overall yield. The choice of protecting group for the C7 hydroxyl proved to be crucial for the subsequent Lindlar reduction step. Our preliminary studies indicated that bulky protecting groups inhibited the hydrogenation of the alkyne in a similar system. For this reason, we protected the C7 hydroxyl as MOM ether **26** (83% yield).

Having only two steps left before the end of the fragment synthesis, we initially decided to proceed with iododesilylation first, leaving the Lindlar reduction as the last step. We argued that having a triple bond within the molecule during the iododesilylation (electrophilic addition of the I^+) was a safer option than having the (Z)-olefin, which may be prone to isomerization. To this end, we have screened several iododesilylation conditions and learned that I_2/CH_2Cl_2 [24] promoted decomposition of **26** while the use of NIS/THF[25] gave back the starting material. Application of Kishi protocol[26] (NIS, $CH_3CN/ClCH_2CN$) resulted in a clean transformationto vinyl iodide **27** in a 95% yield. Unfortunately, the Lindlar reduction of this product led to hydrogenolysis of the vinyl iodide. To circumvent this problem, the order of the iododesilylation/Lindlar reduction sequence was reversed (Scheme 4). Hydrogenation under Lindlar conditions afforded (*Z*)-olefin **28** in 98% yield. The use of Kishi iododesilylation conditions (95% yield) completed the synthesis of the C1−C14 fragment **2**.

Scheme 4



In conclusion, the synthesis of the fully elaborated C1−C14 fragment of (+)-discodermolide was completed in 21 steps in approximately 14% yield. The approach is convergent and proceeds with high levels of stereocontrol throughout. With the vinyl iodide **2** in hand, we are now in position to explore the final steps of the synthesis. Progress toward the total synthesis continues and will be reported in due course.

Acknowledgment. This work has been financially supported by the National Institute of Health (GM55740).

Supporting Information Available: Experimental procedures and spectroscopic characterization (IR, HRMS, ^1H NMR and ^{13}C NMR data) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.

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