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1,6-Asymmetric Induction in Boron-Mediated Aldol Reactions: Application to a Practical Total Synthesis of (+)-Discodermolide

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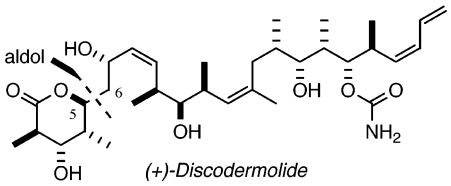
ABSTRACT



(+)-Discodermolide

By relying solely on substrate-based stereocontrol, a practical total synthesis of the microtubule-stabilizing anticancer agent (+)-discodermolide has been realized. This exploits a novel aldol bond construction with 1,6-stereoinduction from the boron enolate of (*Z*)-enone 3 in addition to aldehyde 2. The 1,3-diol 7 is employed as a common building block for the C_1–C_5, C_9–C_{16}, and C_{17}–C_{24} subunits.

(+)-Discodermolide (**1**) is a unique cytotoxic polyketide isolated from the Caribbean deep-sea sponge *Discodermia dissoluta*.[1,2] Biological screening demonstrated cell cycle arrest at the G2/M phase in a variety of human and murine cancer cell lines.[3] Discodermolide is now recognized as a member of a group of antimitotic agents (including Taxol, epothilones, eleutherobin, and laulimalide) known to act by microtubule stabilization,[4] which makes it a highly promising candidate as a new chemotherapeutic agent for the treatment of Taxol-resistant breast, ovarian, and colon cancer and other multi-drug-resistant cancers.

At present, total synthesis provides the only viable means of accessing useful quantities of discodermolide, and several syntheses,[5] including one by our group,[6] have been completed. Despite these efforts, there continues to be a pressing demand for developing a more practical and scaleable route to enable clinical development. With our existing total synthesis in hand,[6] we sought further refinements by inter alia reducing the total number of steps, eliminating the use of any chiral reagents or auxiliaries, and exploring a novel endgame strategy. By exploiting remote 1,6-asymmetric induction in boron-mediated aldol reactions of (*Z*)-enones, we now report a highly convergent and practical total

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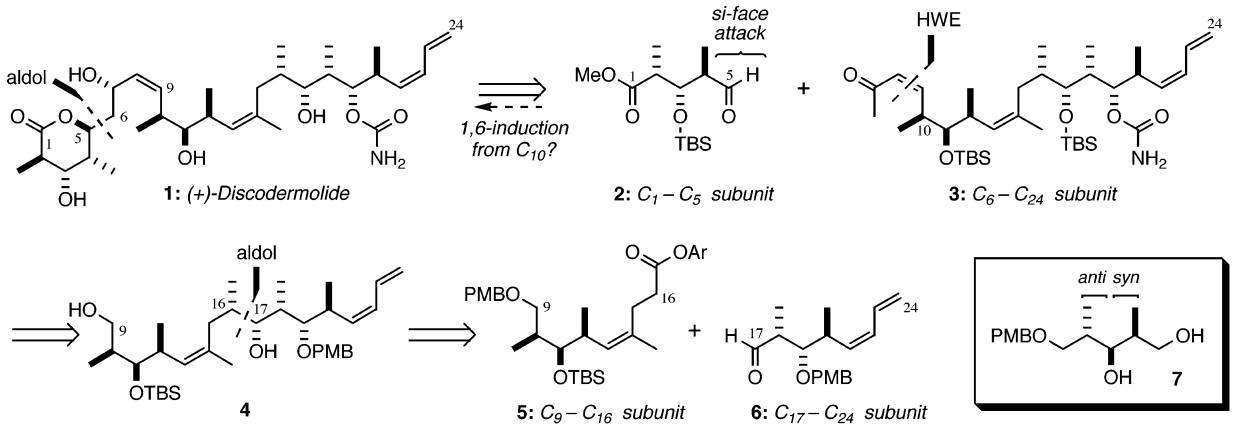
Scheme 1

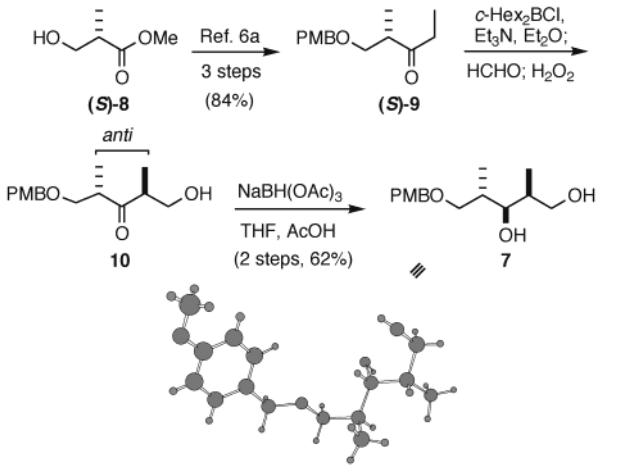


synthesis of (+)-discodermolide that depends solely on substrate-based stereocontrol and makes use of a common building block to access the three main subunits.

Our synthetic plan is outlined in Scheme 1. An aldol disconnection across C_5-C_6 reveals aldehyde **2** and (*Z*)-enone **3** having a γ-stereocenter at C_{10}. We speculated that such a remote center might induce *Si*-face attack (in the anti-Felkin sense) on the aldehyde component to set up the required (5*S*)-configuration in discodermolide. Further disconnection of **3** leads back to alcohol **4**,[6] an advanced intermediate in our previous synthesis assembled by the aldol coupling of ester **5** and aldehyde **6**. Recognizing the repeating *anti*,*syn*-stereotriad present in **2**, **5**, and **6**, we sought to access these three key subunits from 1,3-diol **7** as a common building block.

In contrast to the chiral reagent-based approaches adopted by other groups,[5] we chose to use substrate control to prepare stereotriad **7** from Roche ester (*S*)-**8** (Scheme 2). This

Scheme 2

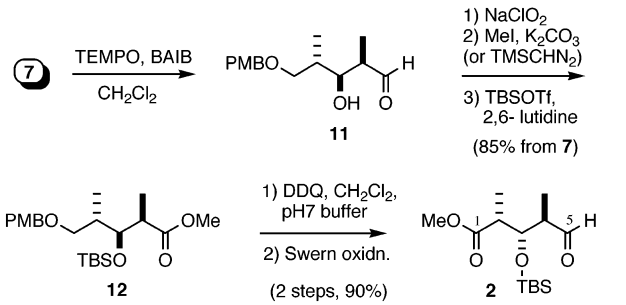


exploits the highly diastereoselective aldol chemistry of the (*E*)-enol dicyclohexylborinate derivative of ketone (*S*)-**9**,[6a,7] which is applied here to addition to formaldehyde. Thus (*E*)-enolization of **9** with *c*-Hex_2BCl/Et_3N and addition of an ethereal solution of formaldehyde[8] (−78 °C) gave aldol adduct **10** (96%, 95:5 dr) with the required 1,3-*anti*-configured methyl groups.

Reduction of ketone **10** with $NaBH(OAc)_3$[9] then gave the 1,3-diol **7** (90:10 dr), which could be conveniently isolated in stereochemically pure form in 62% yield from **9** by crystallization (mp 71−72 °C). The relative configuration of **7** was confirmed by single-crystal X-ray analysis. Starting from ester (*S*)-**8**, this efficient five-step sequence can be performed routinely on a multigram scale without any chromatography.

The synthesis of the C_1-C_5 aldehyde **2** (Scheme 3) from

Scheme 3



the common building block **7** proceeded in 76% overall yield. It began with a selective TEMPO/BAIB oxidation[10] of the primary hydroxyl to give β-hydroxy aldehyde **11**, which was

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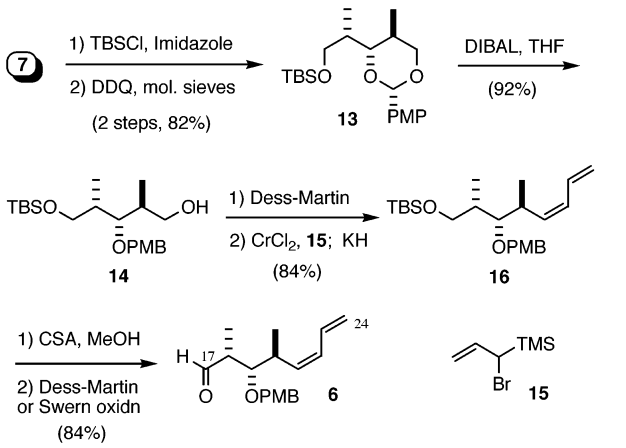
immediately oxidized to the acid ($NaClO_2$)[11] and then converted into the methyl ester (MeI, K_2CO_3, DMF; or $TMSCHN_2$). Protection of the secondary hydroxyl as the TBS ether **12**, PMB deprotection (DDQ) followed by Swern oxidation, then gave the C_1-C_5 subunit **2**.

The preparation of the $C_{17}-C_{24}$ aldehyde **6** from the common 1,3-diol **7** required sequential protecting group manipulations (Scheme 4). Selective TBS protection of the

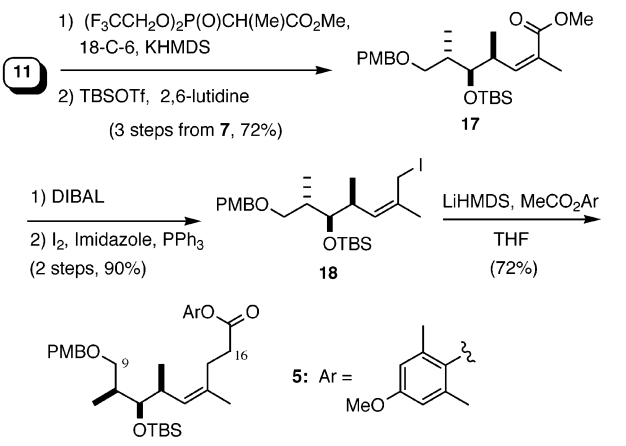
Scheme 4



primary hydroxyl and treatment with anhydrous DDQ[12] afforded PMP acetal **13** (82%). Regioselective acetal opening with DIBAL,[13] followed by Dess−Martin oxidation of the resultant primary hydroxyl and installation of the (*Z*)-diene, following our previously established protocol,[14] gave the known intermediate **16**,[6a] which was routinely converted into aldehyde **6**.

The synthesis of the remaining C_9-C_{16} subunit **5** started out from the already prepared β-hydroxy aldehyde **11** (Scheme 5), where Still−Gennari HWE olefination[15a] and

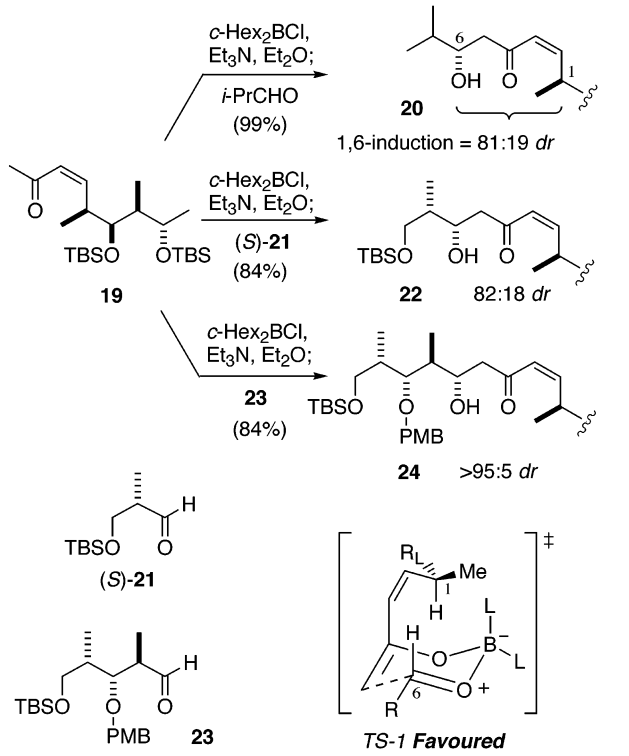
Scheme 5



hydroxyl protection gave TBS ether **17** (72% from **7**). Following reduction of ester **17** with DIBAL, the resulting alcohol was converted into iodide **18** (I_2, imidazole, PPh_3) and treated with the lithium enolate of 2,6-dimethyl-4-methoxyphenyl acetate (LiHMDS, THF) to produce aryl ester **5** (65% over three steps).[16]

We next sought to explore the potential influence of the γ-stereogenic center at C_{10} of methyl ketone **3** (Scheme 1) in the proposed C_5-C_6 aldol coupling to access discodermolide. Our previous studies of related reactions of γ-chiral (*Z*)-enals[6c] led us to speculate that such a remote center would indeed act as a stereodeterminant in boron-mediated aldol additions. Model studies with (*Z*)-enone substrate **19** indicated a useful level of remote 1,6-stereoinduction was achievable (Scheme 6). Enolization of **19** (*c*-Hex_2BCl, Et_3N)

Scheme 6



and addition of *i*-PrCHO (−78 °C) gave 81:19 dr in favor of adduct **20**.[17] A similar addition to α-chiral aldehyde **21** gave **22** with comparable selectivity (82:18 dr). For chiral aldehyde **23** (from oxidation of **14**), the adduct **24** was isolated with >95:5 dr (84%), indicative of matched double

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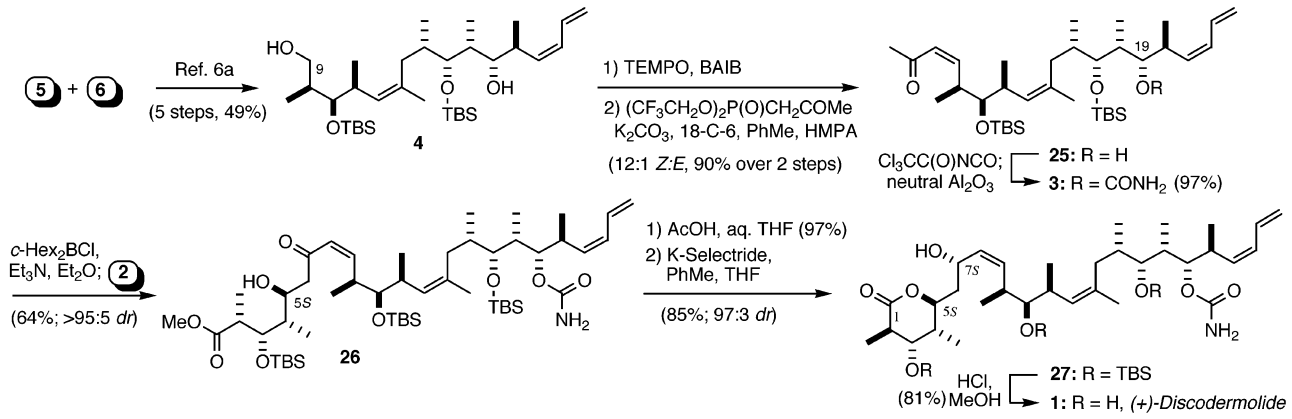
(16) To achieve an efficient alkylation with iodide **18**, incorporation of an electron-donating 4-methoxy group into the aryl acetate was required. The subsequent aldol coupling of **5** with **6** and ester reduction steps proceeded in comparable yield to that obtained previously for the corresponding Heathcock aryl ester (ref 6a).

Scheme 7



diastereoface selection. This outcome, in the anti-Felkin sense with respect to the aldehyde, correctly introduces the C_2-C_5 stereotetrad sequence for the δ-lactone of discodermolide. Our working model for rationalizing *Si*-face attack on all these aldehydes invokes the preferred chair transition structure ***TS-1***, in which the dienolate is constrained in the lower energy *s-trans* conformation, A(1,3) strain is minimized, and other steric clashes are avoided.

With these supportive results in hand, the C_5-C_6 bond formation for discodermolide itself was now addressed (Scheme 7). The aldol coupling of the C_9-C_{16} and $C_{17}-C_{24}$ subunits **5** and **6** and elaboration into alcohol **4** was realized in an analogous manner[16] to that described previously.[6a] In our new route, selective olefination of the derived aldehyde (TEMPO, BAIB, CH_2Cl_2)[6a,10] under modified Still−Gennari HWE conditions[15b] gave (*Z*)-enone **25** in 90% yield from **4** (12:1 *Z/E*). Carbamate installation[18] then gave the required C_6-C_{24} subunit **3** (97%). As expected from the model studies, enolization of methyl ketone **3** (*c*-Hex_2BCl, Et_3N, Et_2O) and addition of aldehyde **2** (1.3 equiv, −78 °C) gave adduct **26** in 64% isolated yield with a high level of control over the (5*S*)-center (≥92:8 dr).[19] In comparison, the reversed aldol coupling at C_6-C_7 used in our original route[6] depends on stereoinduction from a chiral boron reagent to overturn the substrate bias and at best proceeds with 84:16 dr.

Up to this point, we had successfully configured all of the new stereocenters by relying on only substrate control. However, reduction at C_7 of β-hydroxy ketone **26** proved troublesome, affording mixtures of epimeric alcohols with a variety of reagents. Gratifyingly, reduction of the readily derived δ-lactone (AcOH, aq THF) with K-Selectride[5c] proceeded cleanly in favor of the desired (7*S*)-configuration in **27** (85%, 97:3 dr). Global deprotection of **27**[6a,b] then gave (+)-discodermolide (**1**) in 81% yield, which was identical to an authentic sample in all respects.

In summary, we have completed a highly convergent and practical total synthesis of (+)-discodermolide (5.1% over 24 linear steps, with 35 steps in total), making use of 1,3-diol **7** as a readily prepared common building block. In contrast to other reported syntheses of discodermolide that start out from the Roche ester,[5a−g,6] the present route relies solely on substrate control to configure all of the remaining stereocenters. The exploitation of remote 1,6-asymmetric induction in the boron-mediated aldol reactions of γ-chiral (*Z*)-enones, as used in **3** → **26**, is also notable. This new route should be applicable to the preparation of multigram quantities, enabling further biological and clinical studies of discodermolide, and provide access to further novel analogues for SAR studies.

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Supporting Information Available: Spectroscopic data for all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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(18) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521.

(19) To date, we have performed this key aldol coupling on a gram scale. In contrast, by using the lithium enolate from **3**, the addition proceeds under Felkin-Anh induction from the aldehyde **2** and leads to exclusively the undesired (5*R*) configuration.