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Total Synthesis of (+)-Discodermolide: An Improved Endgame Exploiting a Still–Gennari-Type Olefination with a C1–C8 β-Ketophosphonate Fragment†

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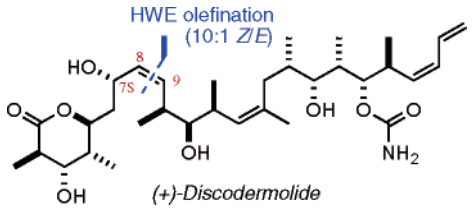
ABSTRACT



An improved, third-generation, total synthesis of (+)-discodermolide, a potent microtubule-stabilizing anticancer agent of marine sponge origin, is achieved in 11.1% yield over 21 steps. Key steps include a Still–Gennari HWE olefination, performed using NaH as the base, between C1–C8 β-ketophosphonate 7 and C9–C24 aldehyde 8, introducing the (8*Z*)-alkene with 10:1 selectivity, and K-Selectride reduction of the derived enone 16, installing the (7*S*)-configuration.

As a structurally unique antimitotic agent that is a potent inhibitor of cell proliferation, discodermolide (**1**) represents a promising candidate for development in cancer chemotherapy.[1−3] While sharing the same microtubule-stabilizing mechanism of action as paclitaxel (Taxol), discodermolide is a comparatively poor substrate for the P-glycoprotein drug efflux pump and thus circumvents the problem of multidrug resistance. Moreover, discodermolide induces significant growth inhibition of paclitaxel-refractory tumors in hollow fiber and xenograft mouse models, such that it has recently moved into human clinical trials. Despite considerable progress over the past decade in refining synthetic routes to discodermolide,[4−7] there remains a supply problem, hampering its development as a new-generation anticancer drug.[8]

† Dedicated to Professor Amos B. Smith on the occasion of his 60th birthday.

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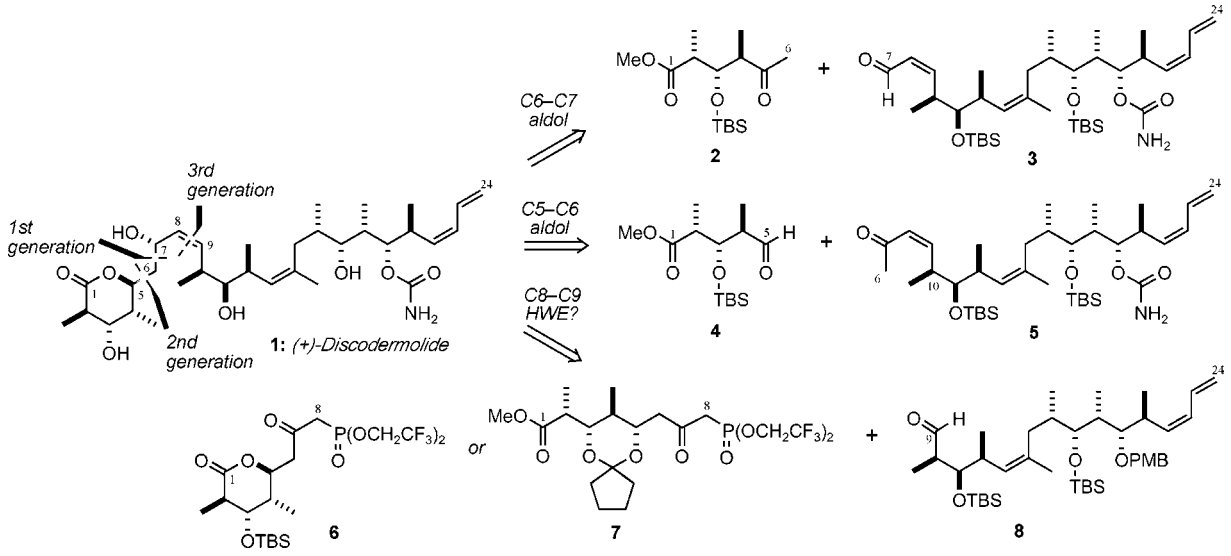
Scheme 1

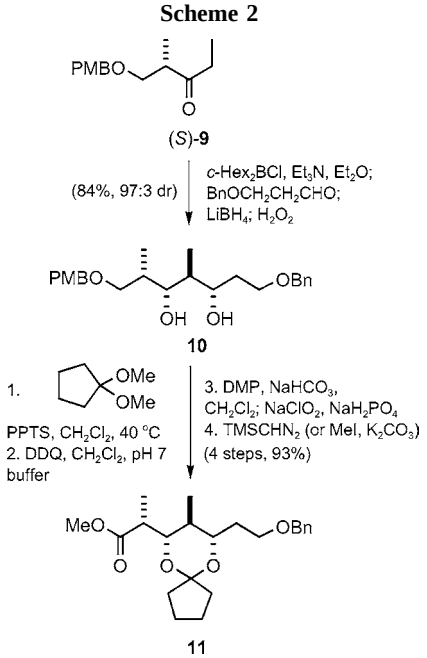


At present, due to the low isolation yield from the deep-sea sponge source,[1] total synthesis offers the only viable means of supply to support its clinical development. Within the pharmaceutical industry, Novartis chemists have recently reported the large-scale synthesis of over 60 g of discodermolide (for Phase I) based on a Smith−Paterson hybrid route,[8] where the need for developing a more practical and robust synthesis to potentially become a manufacturing process was highlighted. Following on from our previous work,[5] we now disclose a highly convergent, third-generation, total synthesis of (+)-discodermolide based on a novel endgame strategy. By exploiting an experimentally straightforward Still−Gennari-type fragment union using an advanced C1−C8 β-ketophosphonate, a more practical process is realized relative to existing synthetic routes.

In considering the options for devising an improved synthetic plan, we sought a simple and convenient fragment union to assemble the carbon skeleton in a convergent manner, followed by a small number of straightforward steps to arrive at discodermolide (Scheme 1). Previously, we have reported completed total syntheses of discodermolide based on pivotal boron-mediated aldol coupling reactions performed, at a late stage, either at C5−C6 or at C6−C7. In the latter case,[5a,b] the reagent-controlled fragment union of ketone **2** and (*Z*)-enal **3** sets up the required (7*S*)-configuration, overturning the intrinsic facial bias of the aldehyde partner. In our second-generation synthesis,[5c,d] a reversed C5−C6 aldol coupling between aldehyde **4** and ketone **5**, exploiting 1,6-asymmetric induction from the remote C10 stereocenter, sets up the required (5*S*)-configuration under substrate control. In light of perceived technical difficulties in performing such complex aldol couplings on an industrial scale, where the quality of organoboron reagents from commercial suppliers is variable and arduous chromatographic isolation of the product is required,[8] we sought to simplify the key coupling step and further streamline our synthesis. This led us to propose a more convenient endgame, involving a challenging Still−Gennari-type HWE olefination at C8−C9 to connect an advanced β-ketophosphonate such as **6** or **7** with the aldehyde **8**, leading directly to the carbon skeleton of discodermolide.

The synthesis of the linear C1−C8 β-keto phosphonate **7** (Scheme 2) commenced from the ethyl ketone (*S*)-**9**, readily obtained from the Roche ester in three steps as described

Scheme 2



(7) See ref 5d for a recent comprehensive listing of discodermolide fragment syntheses and other synthetic studies in progress.

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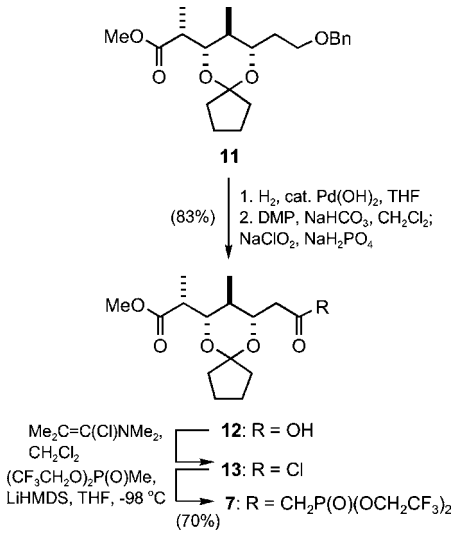
Scheme 3

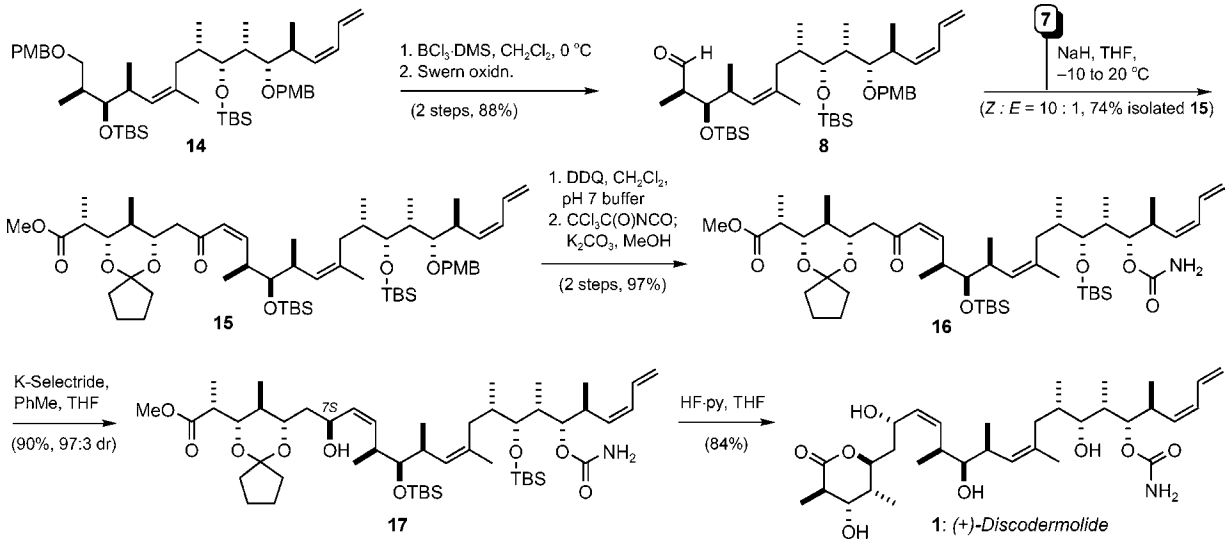


previously.[5] To install the stereotetrad sequence correctly, we exploited the highly diastereoselective *anti*-aldol chemistry of the derived (*E*)-enol dicyclohexylborinate, which is applied here to addition to 2-benzyloxypropanal followed by in situ reduction of the intermediate aldolate with $LiBH_4$,[9] giving 1,3-*syn*-diol **10** in 84% yield (97:3 dr). Conversion of diol **10** into a cyclopentylidene acetal was then followed by PMB ether cleavage (DDQ), where subsequent transformation of the resulting alcohol into methyl ester **11** proved to be straightforward (four steps, 93%).

With the correct stereochemistry and oxidation states now in place for the C1−C6 segment, we now focused on installing the CF_3CH_2O-substituted phosphonate moiety (Scheme 3), required for the Still−Gennari modified HWE olefination.[10] Following hydrogenolysis of benzyl ether **11**, oxidation to the corresponding acid **12** (Dess−Martin periodinane or Swern; $NaClO_2$) was realized. Without purification, acid **12** was treated with the Ghosez reagent ($Me_2C{=}C(Cl)NMe_2$)[11] to generate acyl chloride **13**, which was immediately reacted with a solution of $(CF_3CH_2O)_2P(O)CH_2Li$ at −98 °C.[12] Pleasingly, this acylation reaction proceeded smoothly, providing *β*-ketophosphonate **7** in 70% yield from **12**. Starting from ketone (S)-**9**, this sequence can be performed conveniently on a multigram scale in 45.4% overall yield.

With the C1−C8 *β*-ketophosphonate **7** in hand, we now required the C9−C24 aldehyde **8** (Scheme 4), which should be accessible from the common intermediate **14** employed in our two preceding discodermolide syntheses.[5] Thus, selective cleavage of the primary PMB ether proceeded on treatment of **14** with $Cl_3B{\cdot}SMe_2$ complex at 0 °C, followed by Swern oxidation of the resulting alcohol to give aldehyde **8** in readiness for exploring the viability of the pivotal fragment assembly. Gratifyingly, when phosphonate **7** was treated with NaH in THF at 0 °C for 30 min, followed by the addition of aldehyde **8**, a clean HWE olefination occurred. Analysis of the crude product by ^1H NMR spectroscopy indicated that the desired (*Z*)-enone **15** was formed selectively (*Z*:*E* = 10:1), which was then isolated in 74% yield after a simple chromatographic separation. Notably, this constitutes one of the first examples of a (*Z*)-selective *intermolecular* Still−Gennari olefination employing such an elaborate *β*-ketophosphonate.[13] Furthermore, this coupling also proceeds satisfactorily by simply using NaH as a base under experimentally undemanding conditions, without resorting to expensive crown ether additives (important for minimizing the cost of goods in scaling up).[10] This mild coupling method for highly functionalized and sterically encumbered fragments, as in **7** + **8** → **15**, may well prove to be useful in other complex natural product synthesis. However, in contrast to the success achieved using the linear *β*-ketophosphonate **7**, the preparation of the alternative

Scheme 4

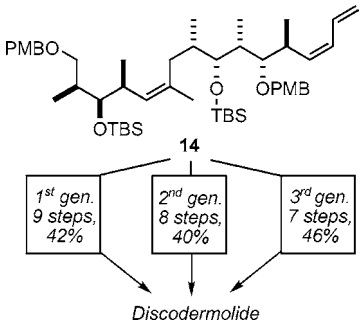


fragment **6** (see Scheme 1), already containing the δ-lactone ring of discodermolide, proved to be problematic.[14]

With the carbon backbone of discodermolide now in place, all that remained was to install the carbamate moiety at the C19 hydroxyl, followed by stereocontrolled reduction of the C7 ketone and deprotection. First, PMB ether **15** was cleaved oxidatively with DDQ (99%), subsequent treatment of the resulting alcohol with trichloroacetyl isocyanate[15] and methanolysis of the intermediate trichloroacetyl adduct (K_2CO_3, MeOH) then gave **16** in 98% yield. Following our second-generation route,[5c,d] we treated (*Z*)-enone **16** with K-Selectride in PhMe/THF at −78 °C. Gratifyingly, this led to a highly selective 1,2-reduction, providing the required (7*S*)-alcohol **17** (97:3 dr) in 90% yield. Finally, global deprotection and concomitant δ-lactonization proceeded cleanly on treatment with HF·py to provide (+)-discodermolide (**1**), which was identical to an authentic sample in all respects.

In summary, we have completed a highly convergent synthesis of discodermolide from the advanced intermediate **14**, which represents a significant improvement over our previous synthetic routes both in terms of efficiency (see comparison in Scheme 5) and ease of performing the key fragment coupling step. This third-generation synthesis exploits a late-stage Still−Gennari-type HWE coupling using phosphonate **7** under experimentally undemanding conditions and proceeds in 11.1% yield over 21 steps (longest linear sequence) from the Roche ester.[16] By avoiding some of the problematic steps associated with earlier syntheses,[8] this new endgame should be more applicable to the preparation of larger quantities of discodermolide, enabling further biological and clinical studies.

Scheme 5



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

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(13) For another example of a complex fragment coupling by a Still−Gennari HWE olefination, see: Paterson, I.; Britton, R.; Delgado, O.; Meyer, A.; Poullennec, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 4629.

(14) Our initial plan was to use phosphonate **6** (Scheme 1); however, its synthesis proved to be troublesome due to the propensity for β-elimination across C5−C6 with opening of the lactone ring under mild acidic or basic conditions.

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(16) This is based on our first-generation synthesis of intermediate **14** (ref 5b); the overall yield is 9.5% over 23 steps following our second-generation synthesis (ref 5c,d).