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Gram-Scale Synthesis of (+)-Discodermolide

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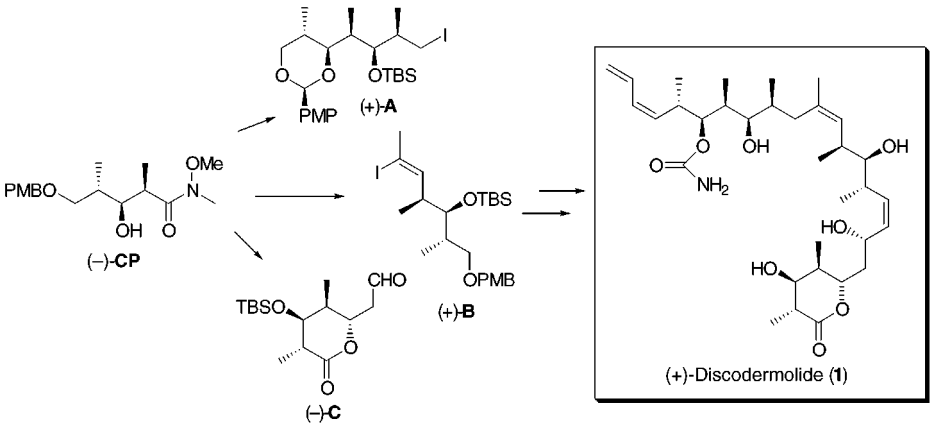
ABSTRACT



A triply convergent, highly efficient second-generation synthesis of the potent antimitotic agent (+)-discodermolide (1) has been achieved on a 1-g scale.

In 1990, Gunasekera and co-workers at the Harbor Branch Oceanographic Institute reported the isolation of (+)-discodermolide (**1**) from the deep-water Caribbean sponge *Discodermia dissoluta*.[1] Early studies indicated that **1** possesses substantial immunosuppressive activity. More recent investigations have revealed **1** to be a potent antimitotic agent,[2] possessing a mode of action similar to that of the clinically proven anticancer agent paclitaxel (Taxol).[3] Both natural products arrest the cell cycle at the M phase, promote microtubule formation, and have similar inhibitory effects (IC_{50}) against breast cancer carcinoma [2.4 nM (**1**) and 2.1 nM (paclitaxel)].[2] Importantly, **1** is also potent against multidrug resistant (MDR) carcinoma cell lines.[4]

The biological data obtained to date indicate that (+)-discodermolide holds great promise as a new chemotherapeutic agent for the treatment of cancer. Unfortunately, the supply of **1** is severely limited; the reported isolation yield is only 0.002% (w/w from frozen sponge), resulting in the acquisition of only 7 mg of natural product from 434 g of sponge.[1] Thus, total synthesis is an attractive and, to date, the only economical means of producing the quantities of **1** required for further biological evaluation.[5] To satisfy this need, we set out to improve our first generation synthesis[5b] of *ent*-**1**. Herein we report a second-generation synthesis which has been utilized to produce 1.043 g of totally synthetic, crystalline (+)-discodermolide (**1**).

(1) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912; (correction) **1991**, *56*, 1346.

(2) (a) Hung, D. T.; Chen, J.; Schreiber, S. L. *Chem. Biol.* **1996**, *3*, 287. (b) ter Haar, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243.

(3) Schiff, P. B.; Frant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665.

(4) Kowalski, R. J.; Giannakakou, P.; Gunasekera, S. P.; Longley, R. E.; Day, B. W.; Hamel, E. *Mol. Pharmacol.* **1997**, *52*, 613.

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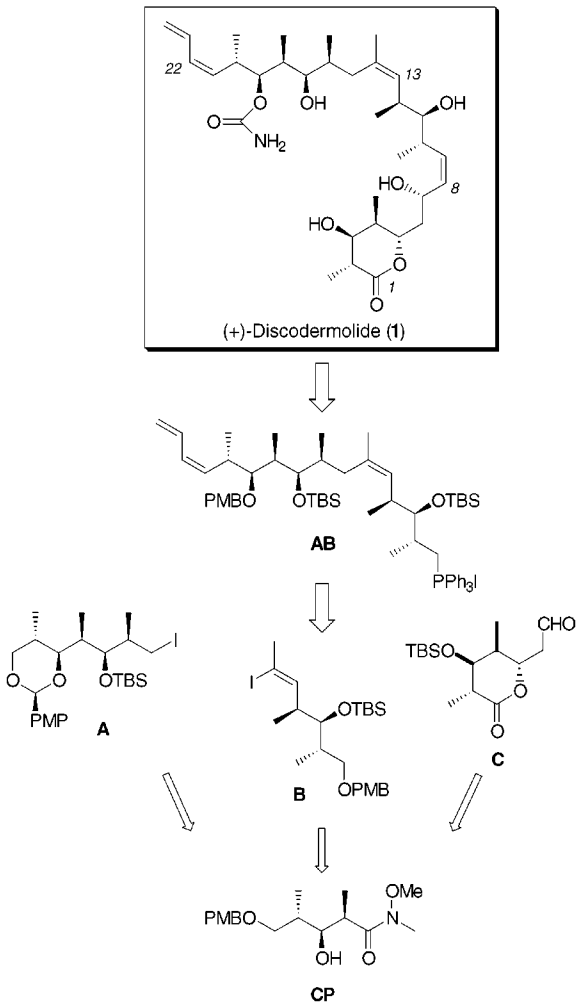
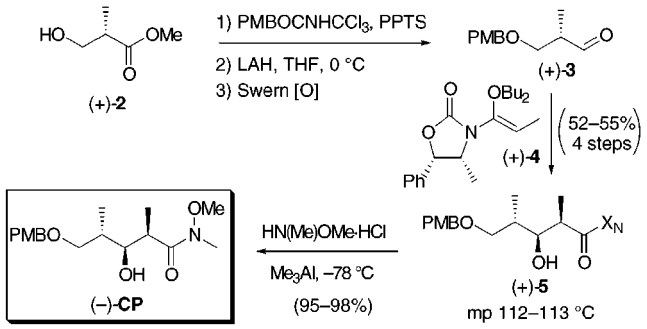
From the synthetic perspective (Scheme 1), we maintained the triply convergent approach utilized in our first-generation synthesis, dissecting the natural product at the C(8−9) and C(13−14) alkenes to generate subunits **A**−**C**, each to be prepared from a common precursor (**CP**). In contrast to our first-generation approach, we chose to maintain the lactone oxidation state in fragment **C**, in anticipation of a chemoselective Wittig olefination with phosphonium salt **AB**, the latter comprising the C(9−24) carbons of the natural product. Such a second-generation approach would greatly simplify the end-game of the synthesis and thus facilitate material throughput for large-scale synthesis.

Scheme 1



Our point of departure entailed protection of (+)-**2** as the PMB ether, followed by reduction (LAH), oxidation (Swern),[6] and reaction with oxazolidinone (+)-**4**[7] to furnish the highly crystalline aldol (+)-**5**[8] in 52−55% yield from (+)-**2** (Scheme 2). In practice, the first three intermediates of this sequence can be carried forward without purification and the aldol product (+)-**5** crystallized from the crude reaction mixture. Transamidation of (+)-**5** then gave (−)-**CP**[9] in excellent yield. Purification of (−)-**CP** was facilitated by isolation of the recyclable oxazolidinone auxiliary (80−90%) by efficient crystallization from the reaction mixture. Importantly, this concise, five-step sequence required only one chromatographic purification and could be performed routinely on a 60-g scale.

Scheme 2



Fragments (+)-**A** and (+)-**B** were next prepared in large scale, upon optimization of the chemistry developed in our first-generation synthesis (Scheme 3).[5b] The synthesis of (+)-**A** (20-g scale) proceeded in six steps (55% overall), and all intermediates en route proved crystalline. The (*Z*)-vinyl iodide (+)-**B** (30-g scale) was prepared in 40−46% from (−)-**CP** and required only a single chromatographic purification.

Preparation of the C(1−8) fragment (−)-**C** began with silylation (TBSOTf) of (−)-**CP**, removal of the PMB group [H_2, $Pd(OH)_2$], and oxidation (SO_3·Pyr)[10] to furnish crystalline aldehyde (−)-**8**[9] (Scheme 3). Addition of silyl enol ether **9**[11] to a premixed solution of (−)-**8** and $TiCl_4$ at −78 °C then afforded, after acid-catalyzed lactonization of the corresponding hydroxy amide, lactone (−)-**10**.[9] Importantly, this Mukaiyama aldol proceeded with 20:1 selectivity, favoring the desired anti-Felkin product. Reduction of enone (−)-**10** with K-Selectride then furnished the corresponding allylic alcohol with 9:1 selectivity, favoring the desired α-isomer (not shown). The structure of this alcohol was secured by single-crystal X-ray analysis. Silylation of the hydroxyl (TBSCl) and oxidative cleavage of the trisubstituted alkene (O_3; PPh_3) completed the synthesis of crystalline aldehyde (−)-**C**. [9]

We are pleased to note that this second-generation route to (−)-**C** eliminated seven steps from our original fragment

(5) Total syntheses of **1** and *ent*-**1** to date: (a) Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621. (b) Smith, A. B., III.; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011. (c) Harried, S. S.; Yang, G.; Strawn, M. A.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6098. (d) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885.

(6) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(7) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77.

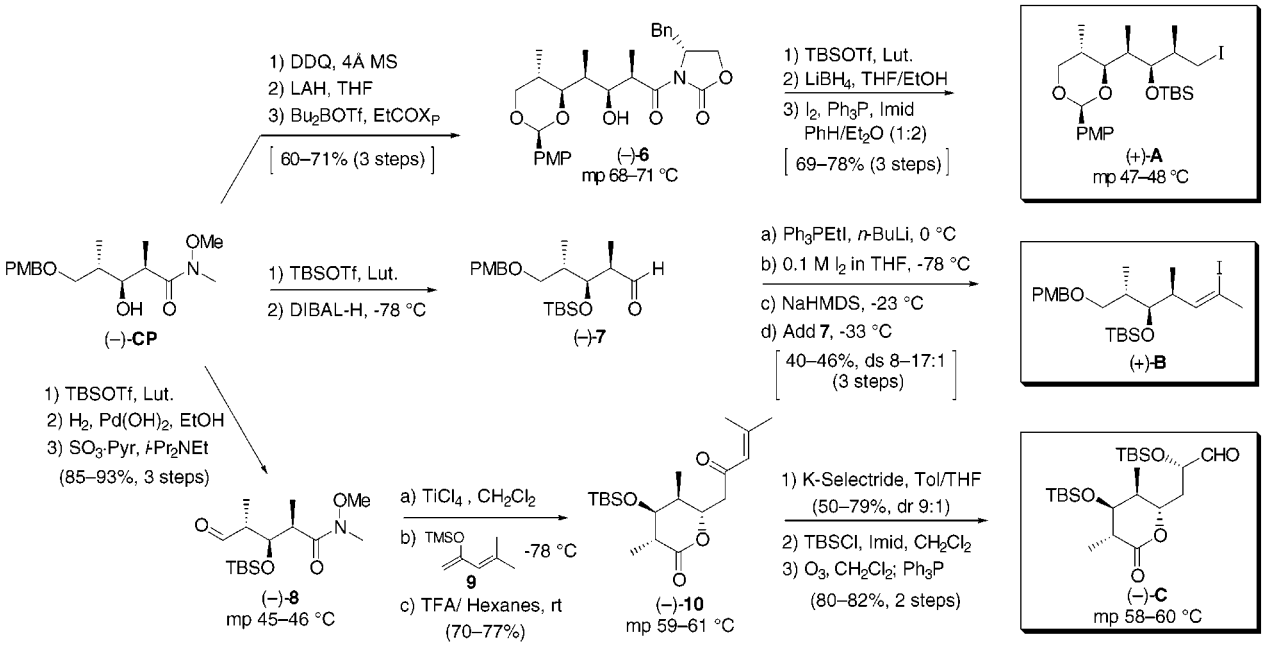
(8) Walkup, R. D.; Kahl, J. D.; Kane, R. R. *J. Org. Chem.* **1998**, *63*, 9113.

(9) The structure assigned to each new compound is in accord with its infrared, 500-MHz ^{1}H NMR, and 125-MHz ^{13}C NMR spectra, as well as appropriate ion identification by HRMS.

(10) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(11) Paterson, I. *Tetrahedron Lett.* **1979**, 1519.

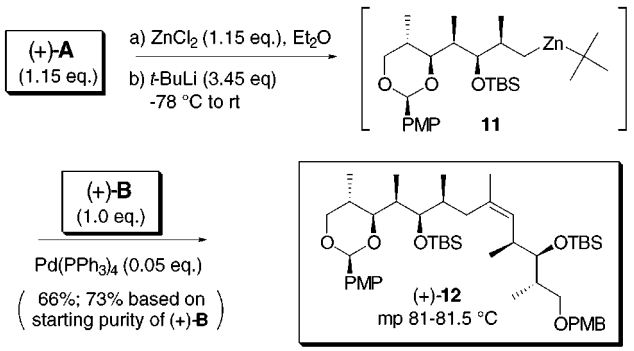
Scheme 3



"**C**" synthesis and that five of the seven intermediates were crystalline, again facilitating large-scale synthesis.

With fragments **A**−**C** in hand, attention turned to the palladium-catalyzed cross-coupling of fragments (+)-**A** and (+)-**B** (Scheme 4). Optimal results were obtained by addition

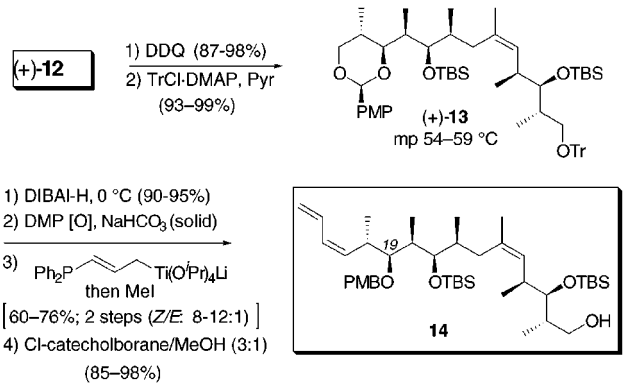
Scheme 4



of *t*-BuLi to a solution of (+)-**A** and $ZnCl_2$ in Et_2O at −78 °C, followed by warming the reaction mixture to room temperature. Addition of this solution via cannula to an intimate mixture of (+)-**B** and $Pd(PPh_3)_4$ (5 mol %) furnished (+)-**12** in 66% yield. The use of 3 equiv of *t*-BuLi for each equivalent of (+)-**A** was imperative; use of lesser amounts resulted in greatly diminished yields and partial recovery of (+)-**A**. We speculate that the mixed alkyl zinc species **11** is the reactive alkyl donor in this coupling reaction. It is noteworthy that this cross-coupling reaction is highly efficient, requiring only 1.15 equiv of (+)-**A** to obtain synthetically useful yields, whereas most cross-couplings require at least 1.5 equiv of alkyl iodide for comparable efficiency.[5d] Currently we are investigating the scope of this modification of the Negishi coupling.[12] Crystallization of (+)-**12** furnished diastereomerically homogeneous material.

Introduction of the diene moiety at this stage required a protecting group exchange to facilitate eventual discrimination of the C(19)-PMB ether. Accordingly, the PMB ether (+)-**12** was removed chemoselectively (DDQ)[5b] and replaced with a trityl ether (Scheme 5). Reductive opening of the

Scheme 5



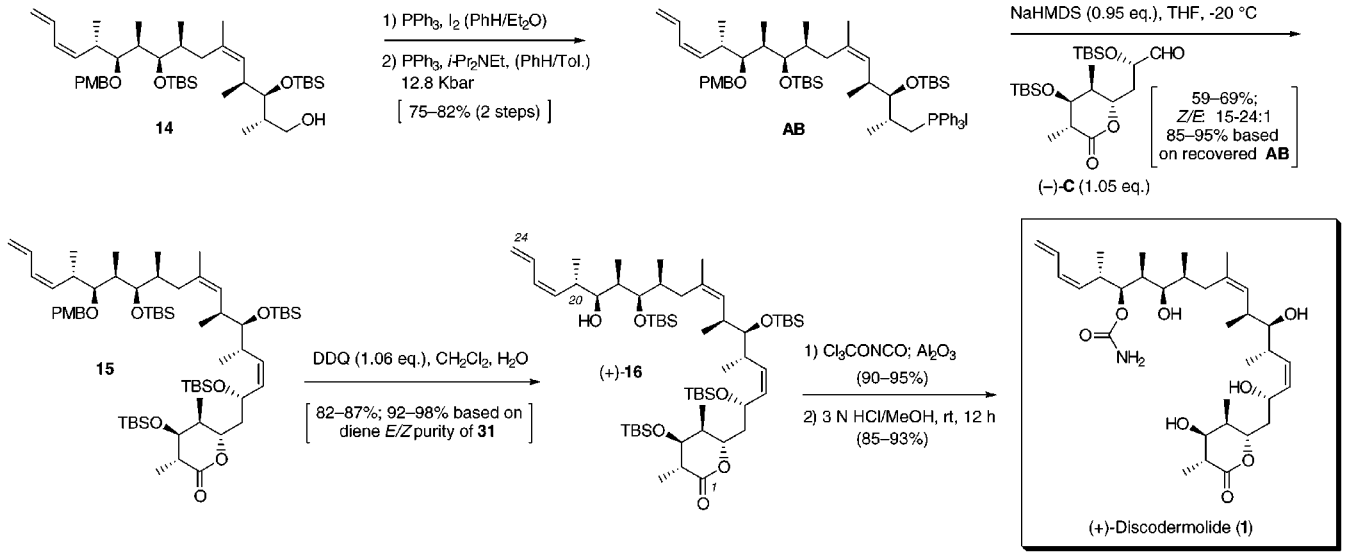
acetal (DIBAl-H)[13] liberated a primary alcohol, which in turn was oxidized (DMP)[14] and subjected to the Yamamoto

(12) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298.

(13) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593.

(14) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

Scheme 6



protocol.[15] While the diene *E/Z* ratio was only 8−12:1, we were able to remove easily the unwanted *E* isomer at a later stage of the synthesis by taking advantage of the differing reactivity of the *E* and *Z* dienes (vide infra).[16] Removal of the trityl group[17] then furnished **14** in excellent overall yield.

Construction of Wittig salt **AB** (Scheme 6) began with conversion of alcohol **14** to the corresponding iodide by employing our modification of the Corey protocol (PPh_3, I_2, PhH/Et_2O);[5b] subjection of the resultant unstable iodide to excess PPh_3 at ultrahigh pressure (12.8 Kbar)[18] in a buffered, nonpolar medium (Hünig's base, toluene/benzene) reliably delivered **AB** on a multigram scale. In our first-generation synthesis, formation of a similar phosphonium salt was plagued by competitive cyclization of the trisubstituted olefin with the primary iodide to yield a cyclopentene byproduct.[19]

Chemoselective addition of the ylide derived from **AB** to aldehyde (−)-**C** afforded **15** in good yield with excellent *Z/E* selectivity (15−24:1). Having completed the assembly of the discodermolide carbon skeleton, treatment of **15** with DDQ provided (+)-**16** as a single diastereomer along with an easily separable byproduct (not shown) resulting from a fortuitous Diels−Alder reaction between the *E* diene impurity and DDQ.[20] Completion of the discodermolide synthesis then entailed installation of the carbamate via the Kocovsky protocol ($Cl_3CCONCO$; Al_2O_3)[21] and final deprotection (3 N HCl, MeOH). The bulk of the (+)-discodermolide prepared (1.06 g) was crystallized from acetonitrile to afford 1.043 g of totally synthetic, crystalline (+)-discodermolide, identical in all respects with the natural material (single-crystal X-ray analysis, 500-MHz ^1H and 125-MHz ^{13}C NMR in both $CDCl_3$ and CD_3CN, IR, HRMS, optical rotation).

In conclusion, we have developed a second-generation synthesis of (+)-discodermolide that is both highly efficient, proceeding in 6% overall yield, and amenable to gram-scale production of this potentially important natural product. Notable features of the synthesis include triple convergency, with each of the three advanced subtargets derived from a common precursor (**CP**), a modified Negishi coupling, efficient synthesis of phosphonium salt **AB** via ultrahigh pressure, and a chemoselective Wittig coupling reaction.

Acknowledgment. M.D.K. and T.J.B. thank the NIH for postdoctoral fellowships. We also thank Novartis for financial support and for supplying spectral data for (+)-discodermolide in CD_3CN and Dr. Patrick Carroll for the X-ray crystallographic analysis of synthetic (+)-discodermolide and other intermediates.

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

OL9910870

(15) (a) Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 723. (b) This protocol was first used in synthetic studies toward **1** by Heathcock and co-workers. See: Clark, D. L.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 5878.

(16) Compounds listed without an optical rotation sign are a mixture of *E/Z* diene isomers; the major isomer is that depicted.

(17) Boeckman, R. K., Jr.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.

(18) Dauben, W. G.; Gerdes, J. M.; Bunce, R. A. *J. Org. Chem.* **1984**, *49*, 4293.

(19) Qiu, Y. Ph.D. Dissertation, University of Pennsylvania, Philadelphia, PA, 1997.

(20) The *E* isomer can adopt the *S-cis* conformation needed to undergo cycloaddition with DDQ, whereas the *Z* isomer is prohibited from adopting the requisite *S-cis* conformation due to significant steric interaction between the C(24) vinyl and C(20) methine protons.

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