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A Practical Improvement, Enhancing the Large-Scale Synthesis of (+)-Discodermolide: A Third-Generation Approach

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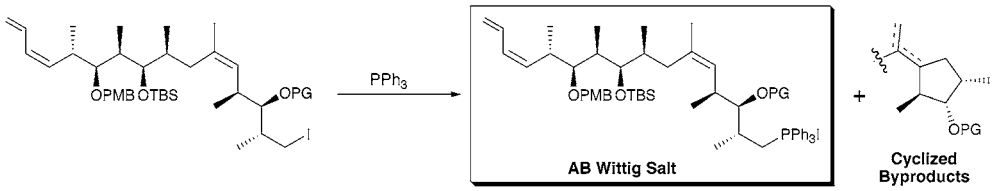
ABSTRACT



A significant improvement to the Penn one-gram synthesis of (+)-discodermolide (1) has been achieved. Specifically, reduction of the steric bulk of the C(11) hydroxyl protecting group permits formation of the requisite AB Wittig salt at the expense of the undesired intramolecular cyclization upon treatment with PPh_3 at ambient pressure.

(+)-Discodermolide (**1**, Figure 1), an architecturally intriguing marine sponge natural product[1] possessing significant antitumor activity,[2] is currently undergoing clinical trials.[3] The mechanism of action, similar to that of the epothilones (**2**), the eleutherobins, and the clinically proven anticancer drug Taxol (**3**), entails stabilization of mitotic spindle microtubules.[2] Importantly, (+)-discodermolide (**1**) is effective against Taxol-resistant cell lines.[4] In addition, (+)-discodermolide (**1**) displays the unusual property of synergy with Taxol.[5] Not surprisingly, the promise of therapeutic use, in conjunction with the interesting architecture of (+)-**1**, has led to a number of total syntheses,[6] including our development of a preparative-scale approach, which in 1999 culminated in the synthesis of over 1 g of the natural product.[6d] The latter was sufficient to permit extensive preclinical pharmacological studies leading to Phase 1 clinical trials by the Novartis Pharmaceutical Corp.

The continued need for an even more efficient, practical synthesis of (+)-discodermolide, however, has prompted us to reinvestigate what we saw as a significant limiting step in the ultimate scalability of our gram-scale approach, namely the requirement to employ ultrahigh-pressure conditions (ca.

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(3) Novartis Pharmaceuticals.

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

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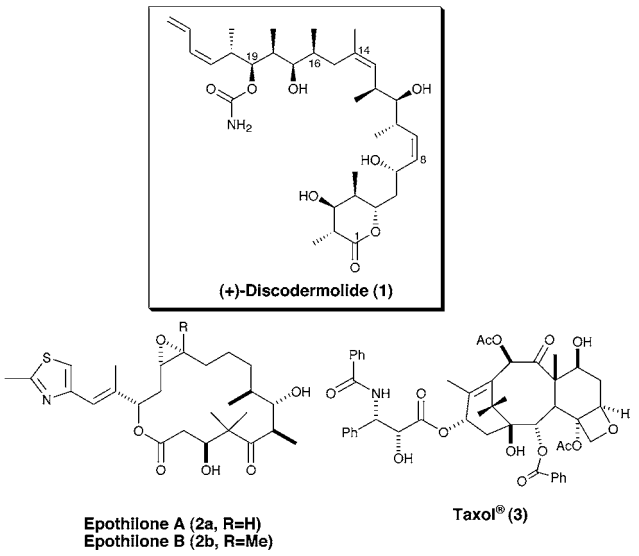
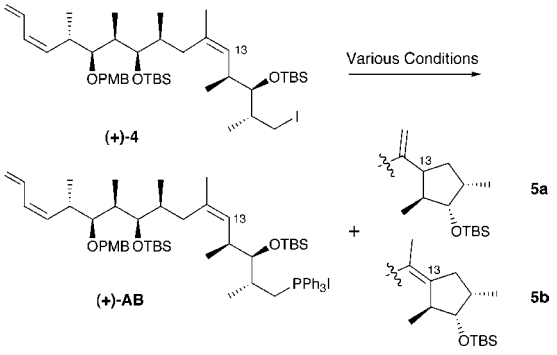


Figure 1. Representative microtubulin-stabilizing natural products.

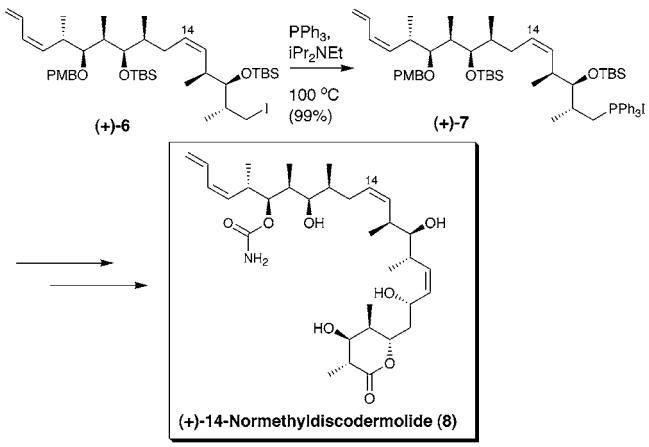
12.8 kbar) to generate the Wittig salt (+)-**AB** (Scheme 1). Standard conditions, involving heating a mixture of PPh_3 and iodide (+)-**4** in solvents of varying polarity, at best furnished only modest amounts of the requisite Wittig salt. Detailed ^1H NMR studies revealed that the bulk of the material was instead a mixture of **5a** and **5b**, the result of five-membered ring formation[6e] involving the electron-rich C(13,14) olefin. Olefin-assisted cyclizations are of course well precedented.[7] In addition, some decomposition occurred, presumably due to the HI generated via the requirement to heat the PPh_3−iodide mixture.

Scheme 1



In contrast to this observation, heating a mixture of the corresponding primary iodide (+)-**6**, possessing a disubstituted instead of the more electron-rich trisubstituted olefin at C(13,14), with PPh_3 and diisopropylethylamine proceeded readily to furnish (+)-**7**, with essentially no cyclopentane formation (Scheme 2). This reaction permitted construction

Scheme 2

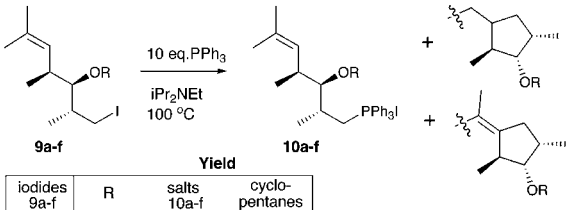


of (+)-14-normethyldiscodermolide **8**, a congener of (+)-discodermolide (**1**) displaying similarly potent in vivo cytotoxicity.[8]

To circumvent the impass in the construction of Wittig salt (+)-**AB**, we exploited high pressure conditions, known to accelerate dramatically the alkylation of phosphines at room temperature.[9] To this end, pressurizing a benzene/toluene solution of iodide (+)-**4** and PPh_3 at 12.8 kBar for 10−14 days at ambient temperature furnished the desired (+)-**AB** Wittig salt in 75% yield. Although reaction scales of up to 2 g were readily accommodated by the Leco High-Pressure Cell,[10] these conditions were by no means optimal, especially in the context of an industrial-scale synthesis.

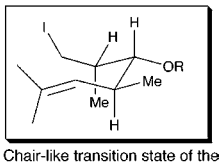
In an attempt to understand the formation of cyclic products upon treatment with PPh_3 at ambient pressure, we examined the chairlike transition state (Scheme 3). This

Scheme 3



Yield

iodides 9a-f	R	salts 10a-f	cyclo-pentanes
a	Ac	59%	41%
b	SEM	63%	34%
c	BOM	69%	30%
d	MOM	69%	24%
e	H	62%	38%
f	TBS	35%	63%



Chair-like transition state of the olefin-assisted cyclization

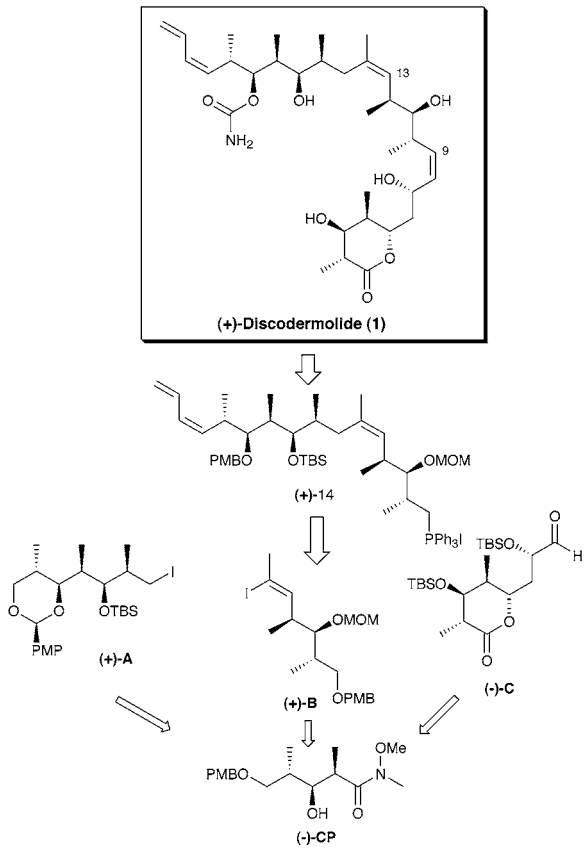
analysis suggested that the bulky TBS ether might promote a turn-structural bias to the ground-state conformation of the

(7) (a) Johnson, W. S.; Bailey, D. M.; Owyang, R.; Bell, R. A.; Jaques, B.; Crandall, J. K. *J. Am. Chem. Soc.* **1964**, *86*, 1959. (b) Johnson, W. S.; Owyang, R. *J. Am. Chem. Soc.* **1964**, *86*, 5593.

primary iodide (+)-**4**, thereby inducing a predisposition toward intramolecular cyclization. We reasoned that this "reactive rotamer effect"[11] might be suppressed by replacement of the large protecting group with a sterically less demanding one. Indeed, reaction of several readily prepared model iodides (**9a**−**f**) incorporating less encumbered protecting groups (Scheme 3) demonstrated the anticipated trend; less encumbered protecting groups increased the ratio of Wittig salt formation at ambient pressure versus cyclization.[12] Best results were obtained with the MOM protecting group.

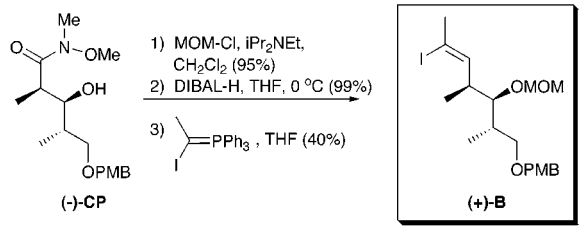
With these observations in hand, we returned to our triply convergent approach to (+)-discodermolide (**1**),[13] now with a MOM protecting group incorporated at C(11) in fragment (+)-**B** (Scheme 4).

Scheme 4



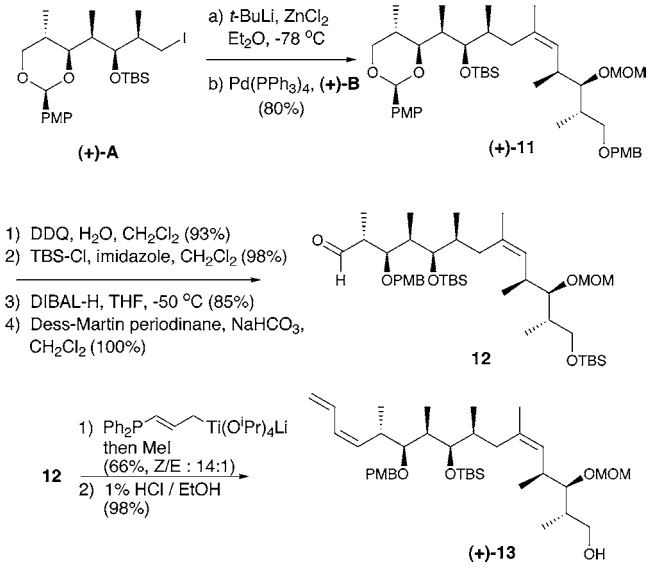
Toward this end, fragment (+)-**B** possessing the MOM group was prepared in three steps from the common precursor (−)- **CP** (Scheme 5).

Scheme 5



Union of fragments (+)-**A** and (+)-**B** via a modified Negishi coupling,[14] followed by elaboration to the corresponding dienyl alcohol (+)-**13**, then proceeded efficiently under conditions similar to our earlier gram-scale synthesis (Scheme 6).[6e]

Scheme 6



Gratifyingly, heating a mixture of the primary iodide derived from (+)-**13** with PPh_3 in the presence of *i*-Pr_2NEt at 100 °C furnished the requisite Wittig salt (+)-**14** in 70% yeild, with only modest cyclopentane formation. Subsequent Wittig union with aldehyde (−)-**C**, removal of the secondary PMB group, and installation of the carbamate at C(19), followed by global deprotection (Scheme 7) led to synthetic (+)-discodermolide (**1**), identical in all respects to the natural material (500-MHz ^1H NMR and 125-MHz ^{13}C NMR in CD_3CN, HRMS, optical rotation).

In conclusion, we have developed a third-generation synthesis for (+)-discodermolide which does not require ultrahigh pressure to access the Wittig salt required for construction of the C(8,9) disubstituted olefin. This approach,

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(9) Dauben, W. G.; Gerdes, J. M.; Bunce, R. A. *J. Org. Chem.* **1984**, *49*, 4293. For reviews on the use of high pressure in organic synthesis, see: (a) *Organic Synthesis at High Pressure*; Matsumoto, K., Morrin Acheson, R., Eds.; John Wiley: New York, 1991. (b) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1. (c) Matsumoto, K.; Sera, A. *Synthesis* **1985**, 999.

(10) Model PG-200-HPC, Leco Corp., Bellefonte, PA.

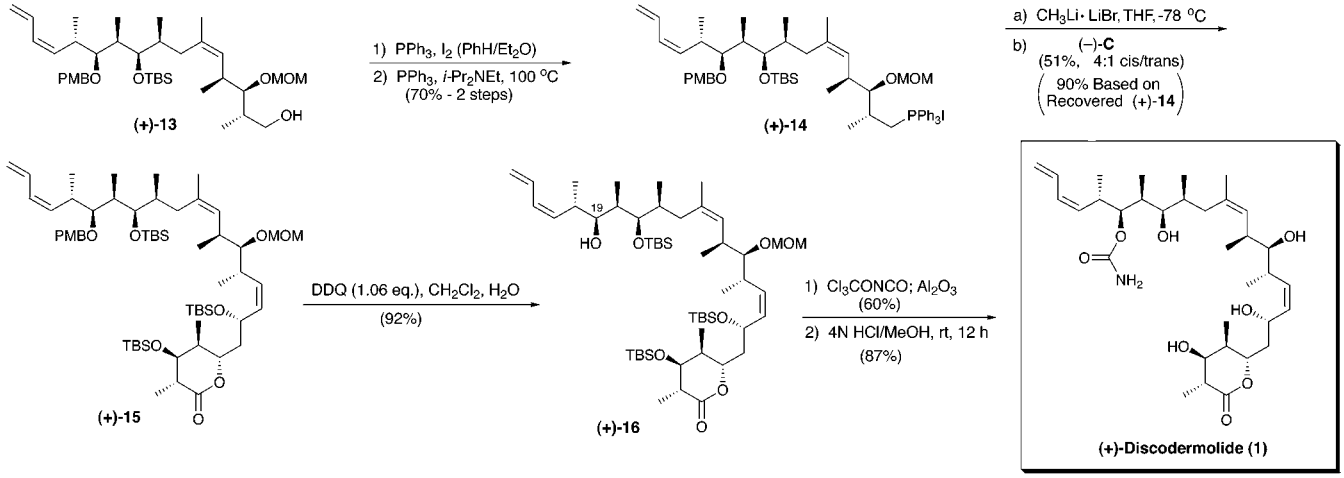
(11) Jung, M. E.; Dervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224.

(12) An alternative explanation, kindly suggested by one reviewer, is that smaller protecting groups selectively increase the rate of SN_2 displacement by PPh_3 by increasing the population of the SN_2 reactive conformer.

(13) For reference, our original retrosynthetic scheme can be found in ref 6d.

(14) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. For our modified conditions, see ref 6d.

Scheme 7



we believe, now holds the promise of an efficient, scalable, and practical synthetic route to this potentially important antitumor agent.

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

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