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Total Synthesis of (+)-Discodermolide: A Highly Convergent Fourth-Generation Approach

Amos B. Smith, III,* B. Scott Freeze, Ming Xian, and Tomoyasu Hirose

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

smithab@sas.upenn.edu

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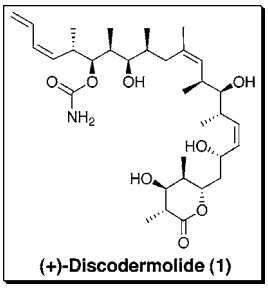
ABSTRACT



A highly convergent, fourth-generation total synthesis of (+)-discodermolide (1), with a longest linear sequence of 17 steps and an overall yield of 9.0%, has been achieved. Highlighting the strategy is the efficient construction and sequential, bidirectional union of a linchpin comprising the C(9)–C(14) Wittig salt-vinyl iodide (–)-18. Importantly, Wittig salt generation proceeded in excellent yield under ambient pressure.

In 1990, Gunasekera and co-workers reported the isolation and structural elucidation of (+)-discodermolide (**1**, Figure 1), derived from the deep sea marine sponge *Discodermia*

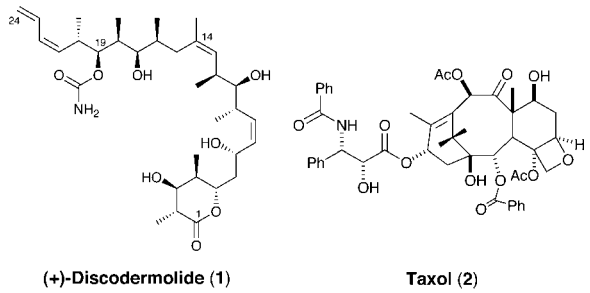


Figure 1.

dissoluta.[1] Subsequently, ter Haar and co-workers[2a] and Schreiber et al.[2b] independently revealed that (+)-discodermolide possesses potent antimitotic activity, akin to the clinically proven anticancer agent Taxol (**2**), with a similar mechanism of action that entails binding to, and stabilization of, microtubules. Importantly, (+)-discodermolide displays significant tumor cell growth inhibitory activity against a wide range of known cancer cell lines, including Taxol-resistant cells,[3] is synergistic with Taxol with respect to tumor cell growth inhibition,[4] and displays effective in vivo activity in mice. The limited availability of (+)-discodermolide from natural sources, however, has greatly compromised access to practical quantities of this promising natural product and analogues thereof. Fortunately, a number of synthetic approaches have been achieved;[5] however, only a handful

(1) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912−4915; (correction) *J. Org. Chem.* **1991**, *56*, 1346.

(2) (a) 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*, 243−250. (b) Hung, D. T.; Chen, J.; Schreiber, S. L. *Chem. Biol.* **1996**, *3*, 287−293.

(3) Kowalski, R. J.; Giannakakou, P.; Gunasekera, S. P.; Longley, R. E.; Day, B. W.; Hamel, E. *Mol. Pharm.* **1997**, *52*, 613−622.

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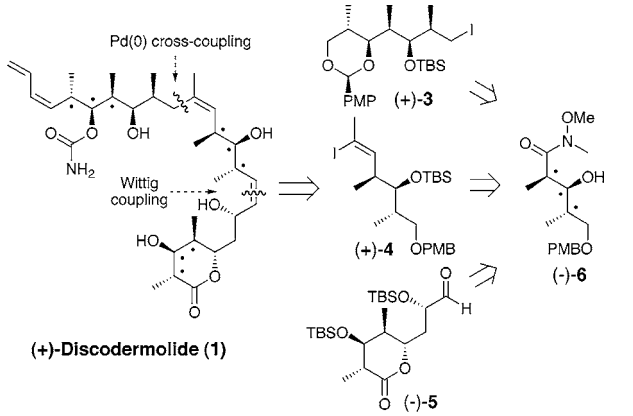
Scheme 1

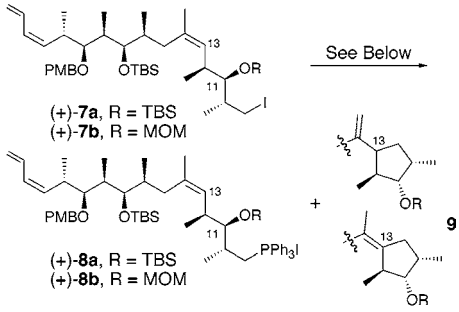


possess the degree of efficiency and scalability necessary for the required large-scale production to permit clinical development.

Our initial approach to (+)-discodermolide (Scheme 1), later improved to encompass a practical (i.e., scalable) total synthesis, called for construction of three advanced subtargets [(+)-**3**, (+)-**4**, and (−)-**5**] from a common precursor [(−)-**6**] possessing the triad of stereogenicity that appears in each subtarget. Ultimately, this process led to the generation of over 1 g of the natural product.[5e,h] Subsequently, Novartis Pharmaceuticals licensed the University of Pennsylvania synthesis and, employing a hybrid of this approach and the effective endgame of Paterson,[5g] produced over *60 g* of (+)-discodermolide, a feat that afforded the natural product in an overall yield of 1%, with a longest linear sequence of 26 steps.[5m] More recently, Paterson disclosed a significantly improved (third-generation-Paterson) synthesis, exploiting a Still−Gennari Horner−Wadsworth−Emmons olefination as the key improvement, to furnish (+)-discodermolide in an overall yield of 11.1% over a 21 step linear sequence.[5n] In this letter, we disclose our fourth-generation synthesis, which evolved from the successful one-gram approach; the synthesis now proceeds with a longest linear sequence of 17 steps and 9.0% overall yield.

The first major improvement to the gram-scale approach was to eliminate the ultra-high-pressure reaction that was required to minimize cyclopentane byproduct formation that occurred during generation of Wittig salt **8a** from the corresponding iodide (Scheme 2, entry A).[5h] As previously reported,[5l] replacement of the sterically encumbering C(11) TBS moeity with a less bulky MOM group significantly reduced cyclopentane ring formation, thereby permitting formation of **8** at ambient pressure (entries B and C).

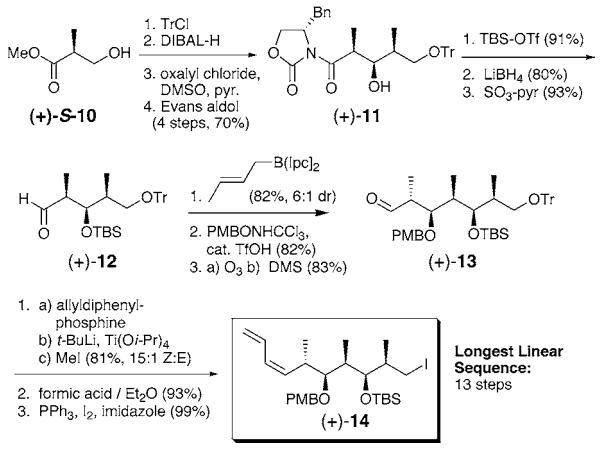
Scheme 2



	R	conditions	Yield 8	Yield 9
A	TBS	PPh_3, DIPEA, 12.8 kBar	75%	20%
B	TBS	PPh_3, DIPEA, 100 °C	35%	63%
C	MOM	PPh_3, DIPEA, 100 °C	69%	24%

To increase the convergence of the overall synthetic route, the fully elaborated C(15)−C(24) dienyl alkyl iodide (+)-**14** (Scheme 3) was designed as a replacement for acetal (+)-**3** and employed in a Pd(0)-catalyzed cross-coupling reaction, a tactic exploited to great advantage by the Novartis

Scheme 3



(4) (a) Martello, L. A.; McDaid, H. M.; Regl, D. L.; Yang, C.-P. H.; Meng, D.; Pettus, T. R. R.; Kaufman, M. D.; Arimoto, H.; Danishefsky, S. J.; Smith, A. B., III; Horwitz, S. B. *Clin. Cancer Res.* **2000**, *6*, 1978−1987. (b) Honore, S.; Kamath, K.; Braguer, D.; Horwitz, S. B.; Wilson, L.; Briand, C.; Jordan, M. A. *Cancer Res.* **2004**, *64*, 4957−4964.

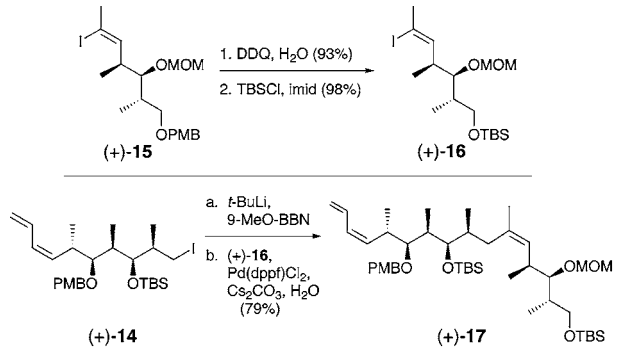
(5) (a) Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621−12622. (b) Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011−12012. (c) Harried, S. S.; Yang, G.; Strawn, M. A.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6098−6099. (d) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885−7892. (e) Smith, A. B., III; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823−1826. (f) Halstead, D. P., Ph.D. Thesis, Harvard University, 1999. (g) Paterson, J.; Florence, G. J.; Gerlach, K.; Scott, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 377−380. (h) Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654−8664. (i) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535−9544. (j) Harried, S. S.; Lee, C. P.; Yang, G.; Lee, T. I. H.; Myles, D. C. *J. Org. Chem.* **2003**, *68*, 6646−6660. (k) Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; Scott, J. P.; Sereinig, N. *Org. Lett.* **2003**, *5*, 35−38. (l) Smith, A. B., III; Freeze, B. S.; Brouard, I.; Hirose, T. *Org. Lett.* **2003**, *5*, 4405−4408. (m) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Daeffler, R.; Osmani, A.; Schreiner, K.; Seeger-Weibel, M.; Bérod, B.; Schaer, K.; Gamboni, R.; Chen, S.; Chen, W.; Jagoe, C. T.; Kinder, F. R., Jr.; Loo, M.; Prasad, K.; Repic, O.; Shieh, W.-C.; Wang, R.-M.; Waykole, L.; Xu, D. D.; Xue, S. *Org. Process Res. Dev.* **2004**, *8*, 101−130 and references therein. (n) Paterson, I.; Lyothier, I. *Org. Lett.* **2004**, *6*, 4933−4936.

group. Although (+)-**14** could be readily derived from intermediates produced en route to (+)-**3**, a shorter sequence was ultimately chosen beginning from (+)-*S*-Roche's ester [(+)-**10**].

To this end, protection of (+)-*S*-**10** as the trityl ether, followed by reduction and oxidation, furnished the corresponding aldehyde,[6] which was reacted with the boron enolate derived from (+)-*N*-propionyl-4-(phenylmethyl)-2-oxazolidinone to provide alcohol (+)-**11** in excellent overall yield. Pleasingly, only a single chromatographic purification was necessary in this four-step sequence. Protection of the secondary alcohol as the TBS ether, followed by reductive removal of the chiral auxiliary and oxidation then afforded aldehyde (+)-**12**. The two remaining stereocenters were installed via Brown crotylation, and the resulting secondary alcohol was protected as the PMB ether. Oxidative cleavage of the terminal olefin provided aldehyde (+)-**13**, at which point the C(21)−C(24) diene subunit could be readily incorporated employing the conditions reported by Yamamoto and co-workers.[7] Acid-mediated removal of the trityl ether and iodination completed construction of the desired dienyl alkyl iodide (+)-**14** in 19% overall yield, with a longest linear sequence of 13 steps.

With alkyl iodide (+)-**14** in hand, we turned to the Pd(0)-catalyzed cross-coupling employed by Novartis, with an appropriately protected vinyl iodide partner [e.g., (+)-**16**, Scheme 4]. To access (+)-**16**, the PMB moiety in (+)-**15**[5l]

Scheme 4



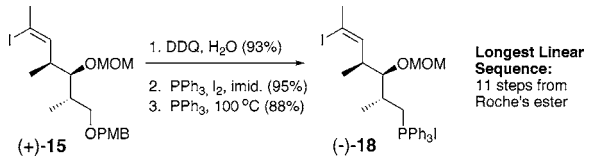
was removed under oxidative conditions and the resultant alcohol reprotected as the TBS ether, a tactic designed to avoid later selectivity problems emanating from the C(19) PMB ether. Union of the two fragments proceeded smoothly under modified Suzuki conditions[5d,m] to afford triene (+)-**17**, a known advanced intermediate, previously converted in eight steps to (+)-discodermolide (**1**).[5l] Construction of (+)-**17** therefore constitutes a formal total synthesis of (+)-discodermolide, requiring a longest linear sequence of 21 steps, with an overall yield of 5.5%.

(6) (a) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035−1038. (b) Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S.; Sasaki, A.; Sunagawa, M. *Tetrahedron Lett.* **1986**, *27*, 6241−6244.

(7) Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 723−730.

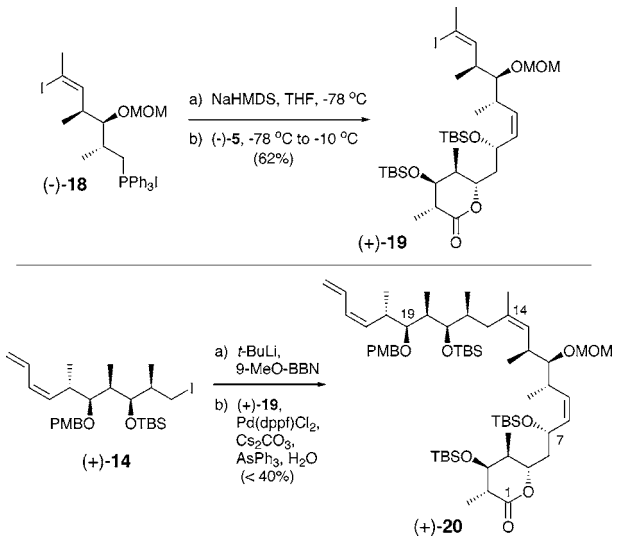
The next major advance vis-à-vis the overall efficiency of our fourth-generation approach was the discovery that vinyl iodide (+)-**15** could be readily converted via a highly efficient three-step sequence to the corresponding Wittig salt (−)-**18**, without concomitant cyclopentane formation (Scheme 5).

Scheme 5



The availability of bifunctional (−)-**18** immediately suggested the possibility that this intermediate might serve as a synthetic linchpin, providing the basis for a highly convergent, bidirectional construction of (+)-discodermolide (**1**), via sequential coupling, first with known aldehyde (−)-**5** and then with alkyl iodide (+)-**14**. In the event, slow, dropwise addition of NaHMDS (1.0 M in THF) to a THF solution of the Wittig salt [(−)-**18**] at −78 °C promoted efficient formation of the corresponding phosphonium ylide, while minimizing β-elimination of the vinyl iodide. Subsequent addition of a precooled THF solution of aldehyde (−)-**5** to the derived ylide and warming to −10 °C, followed by an aqueous quench (saturated aqueous ammonium chloride) and workup, led to vinyl iodide (+)-**19** in 62% yield (Scheme 6). Initial attempts at Suzuki cross-coupling with alkyl iodide

Scheme 6

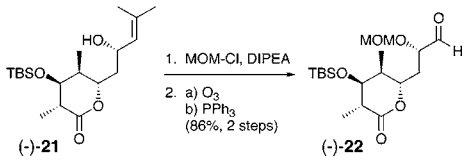


(+)-**14**, however, proved troublesome, typically proceeding in less than 40% conversion as judged by ^{1}H NMR, in conjunction with multiple byproducts that proved inseparable from the desired tetraene.

Success with linchpin (−)-**18**, albeit modest, prompted further investigation of the bidirectional tactic. Empirical

observation of the crystal structure of (+)-discodermolide[1] reveals that the stereogenicity of the C(10)−C(12) methyl-hydroxyl-methyl triad imparts a turn-structural bias to the backbone, which serves to place C(7) in close spatial proximity to C(14). Reasoning that this structural motif might also exist in the truncated fragment (+)-**19** (Scheme 6), we speculated that replacement of the C(7) TBS ether with a smaller protecting group might serve to alleviate steric hindrance to approach of the alkyl boronate in the Suzuki reaction. To this end, aldehyde (−)-**22** (Scheme 7), possessing a MOM ether at C(7), was prepared in two straightforward steps from known alcohol (−)-**21**.[5h]

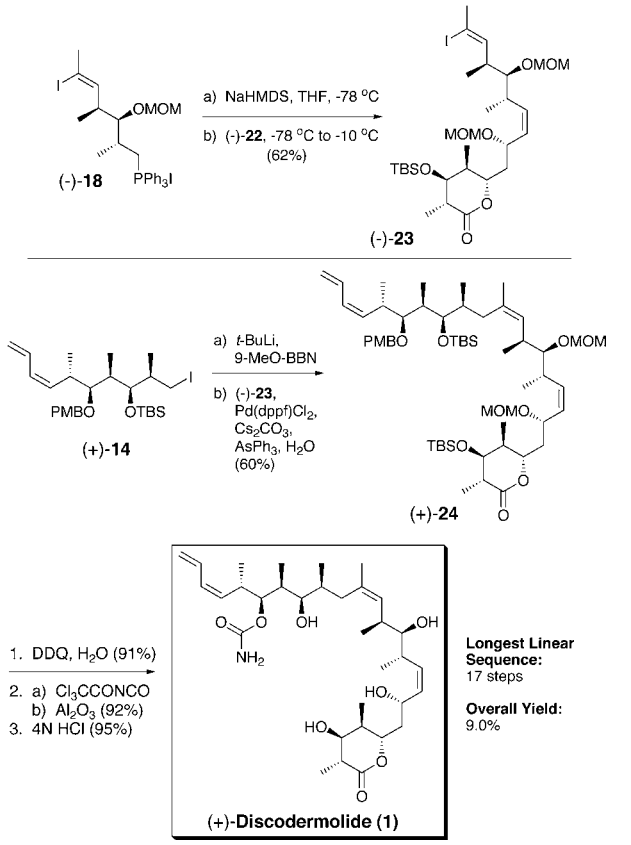
Scheme 7



The linchpin coupling was then explored. Wittig union of phosphonium salt (−)-**18** with aldehyde (−)-**22** furnished vinyl iodide (−)-**23** (Scheme 8). Pleasingly, (−)-**23** proved to be a superior substrate for the requisite Suzuki reaction, affording the desired tetraene (+)-**24** in an isolated yield of 60%. Installation of the C(19) carbamate and global deprotection then afforded totally synthetic (+)-discodermolide (**1**) in an overall yield of 9.0% and with a longest linear sequence of 17 steps. Importantly, this synthesis entails the shortest linear sequence reported to date for this important lead natural product.

In summary, an effective (i.e., short), highly convergent synthesis of (+)-discodermolide (**1**) has now been achieved. Highlighting this, our fourth-generation synthesis, is the construction and sequential, bidirectional union of the C(9)−C(14) Wittig salt/vinyl iodide (−)-**18**. Importantly, generation of the Wittig salt proceeds in excellent yield under ambient pressure conditions.

Scheme 8



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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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