J|A|C|S
ARTICLES
Published on Web 03/26/2005

Crotylsilane Reagents in the Synthesis of Complex Polyketide Natural Products: Total Synthesis of (+)-Discodermolide

Alexander Arefolov† and James S. Panek*

Contribution from the Department of Chemistry and Center for Chemical Methodology and Library Development, Metcalf Center for Science and Engineering, 590 Commonwealth Avenue, Boston University, Boston, Massachusetts 02215

Received November 12, 2004; E-mail: panek@chem.bu.edu

Abstract: An efficient, highly convergent stereocontrolled synthesis of (+)-discodermolide has been achieved with 2.1% overall yield (27 steps longest linear sequence). The absolute stereochemistry of the C1−C6 (**12**), C7−C14 (**13**), and C15−C24 (**11**) subunits was introduced using asymmetric crotylation methodology. Key elements of the synthesis include the use of hydrozirconation−cross-coupling methodology for the construction of C13−C14 (*Z*)-olefin, acetate aldol reaction to construct the C6−C7 bond and install the C7 stereocenter with high levels of 1,5-*anti* stereoinduction, and the use of palladium-mediated sp^2-sp^3 cross-coupling reaction to join the advanced fragments, which assembled the carbon framework of discodermolide.

Introduction

Discodermolide (**1**) is a polyketide natural product that was first isolated in 1990 from extracts of the rare Caribbean marine sponge *Discodermia dissoluta* by the researchers at Harbor Branch Oceanographic Institution (HBOI).[1] Its gross structure was determined by extensive spectroscopic studies, including a combination of 1-D and 2-D NMR techniques; the relative stereochemistry was subsequently assigned by X-ray crystallography.[1] Structurally, discodermolide incorporates a linear 24-membered polyketide backbone bearing 13 stereogenic centers, a tetrasubstituted δ-lactone (C1−C5), one di- and one trisubstituted (*Z*)-double bond, an adjunct carbamate moiety (C19), and a terminal (*Z*)-diene (C21−C24). The absolute configuration of discodermolide was established by Schreiber and co-workers later on by their initial syntheses of both (+)- and (−)-antipodes.[2]

(+)-Discodermolide was initially found to be a potent immunosuppressive agent, both in vivo and in vitro, as well as displaying antifungal activity.[3] It inhibited T-cell proliferation with an IC_{50} of 9 nM and graft versus host disease in transplanted mice. (+)-Discodermolide also suppressed both the two-way mixed-lymphocyte reaction and the concanavalin A-induced mitogenesis of murine splentocytes in vitro (IC_{50} 0.24 and 0.19 mM, respectively) with no associated cytotoxicity. These findings have stimulated considerable interest in discodermolide as a possible immunosuppressant and suggested that it may be developed as an alternative drug to cyclosporine A, which has demonstrated remarkable clinical success over the past two decades in both organ and bone marrow transplantation.

Further biological studies revealed the remarkable cytotoxic activity of (+)-discodermolide in a variety of human and murine cell lines, causing cell cycle arrest in the G2/M phase by binding and stabilizing mitotic spindle microtubules,[4] thus resembling the clinically proven anticancer agent paclitaxel[5a] (**2**)—another member of a small, but structurally diverse, family of microtubule-stabilizing natural products (Figure 1) discovered over the past decade. This family also includes epothilones A and B (**3**, **4**),[5b] eleutherobin (**5**),[5c] sarcodictyin (**6**),[5d] laulimalide (**7**),[5e] and the most recently isolated (−)-dictyostatin (**8**),[5f] which is thought to be biogenetically related to (+)-discodermolide. Interestingly, the (−)-antipode of discodermolide was also reported to possess considerable antiproliferative activity, although acting by a different mechanism—blocking the cell cycle in the S phase.[6] The similarity between the cell growth inhibitory effects of (+)-discodermolide and paclitaxel has been confirmed by Day and co-workers.[7] Significantly, the binding

† Current address: PTC Therapeutics, South Plainfield, NJ.

(1) (a) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912−4915. Additions and corrections: *J. Org. Chem.* **1991**, *56*, 1346. (b) Gunasekera, S. P.; Pomponi, S. A.; Longley, R. E. U.S. Patent No. US5840750, Nov 24, 1998. (c) Gunasekera, S. P.; Paul, G. K.; Longley, R. E.; Isbrucker, R. A.; Pomponi, S. A. *J. Nat. Prod.* **2002**, *65*, 1643−1648.

(2) (a) Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621−12622. (b) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054−11080.

(3) (a) Gunasekera, S. P.; Cranick, S.; Longley, R. E. *J. Nat. Prod.* **1989**, *52*, 757−761. (b) Longley, R. E.; Caddigan, D.; Harmody, D.; Gunasekera, M.; Gunasekera, S. P. *Transplantation* **1991**, *52*, 650−655. (c) Longley, R. E.; Caddigan, D.; Harmody, D.; Gunasekera, M.; Gunasekera, S. P. *Transplantation* **1991**, *52*, 656−661.

(4) (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.

(5) (a) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15−44. (b) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325−2333. (c) Long, B. H.; Carboni, J. M.; Wasserman, A. J.; Cornell, L. A.; Casazza, A. M.; Jensen, P. R.; Lindel, T.; Fenical, W.; Fairchild, C. R. *Cancer Res.* **1998**, *58*, 1111−1115. (d) Ciomei, M.; Albanese, C.; Pastori, W.; Grandi, M.; Pietra, F.; D′Ambrosio, M.; Guerriero, A.; Battistini, C. *Proc. Am. Cancer Res.* **1997**, *38*, 5. (e) Mooberry, S. L.; Tien, G.; Hernandez, A. H.; Plubrukarn, A.; Davidson, B. S. *Cancer Res.* **1999**, *59*, 653−660. (f) Paterson, I.; Britton, R.; Delgado, O.; Meyer, A.; Poullennec, K. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4629−4633.

(6) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *Chem. Biol.* **1994**, *1*, 67−89.

10.1021/ja043168j CCC: $30.25

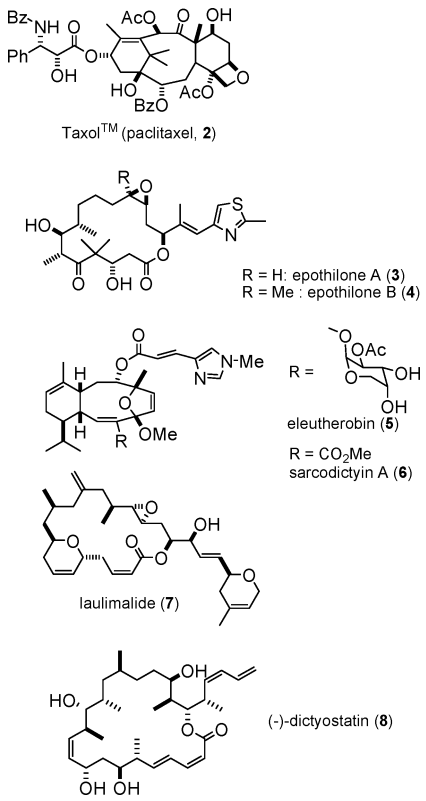


Figure 1. Microtubule-stabilizing natural products.

activity to microtubules is higher for (+)-discodermolide. (+)-Discodermolide also displays potent activity against multi-drug-resistant carcinoma cell lines, including paclitaxel-resistant ovarian and colon cancer cell lines, with an IC_{50} of 2.5 nM.[8] In the comparative studies of discodermolide, epothilones, and eleutherobin against a paclitaxel-dependent human lung carcinoma cell line (A549-T12),[9] it was found that discodermolide could not replace paclitaxel, whereas the natural products epothilone A and B and eleutherobin could substitute for paclitaxel and thus maintain the viability of the cell line. Importantly, the paclitaxel-dependent cell line proved to be almost 20-fold more sensitive to discodermolide in the presence of low concentrations of paclitaxel than in its absence. This synergistic effect, however, was not observed with combinations of the epothilones or eleutherobin with paclitaxel.

The highly interesting biological profile of discodermolide makes it a promising candidate for clinical development as a chemotherapeutic agent, either on its own or in combination with paclitaxel, for treatment of paclitaxel-resistant breast, ovarian, and colon cancer, as well as other multi-drug-resistant cancers. Currently, discodermolide is undergoing phase I clinical trials for pancreatic cancer at the Cancer Therapy & Research Center in San Antonio, TX, as it is being developed as an anticancer drug by Novartis Pharmaceuticals Corp. (Francavilla, C.; Chen, W. C.; Kinder, K. R. *Org. Lett.* **2003**, *5*, 1233−1236).

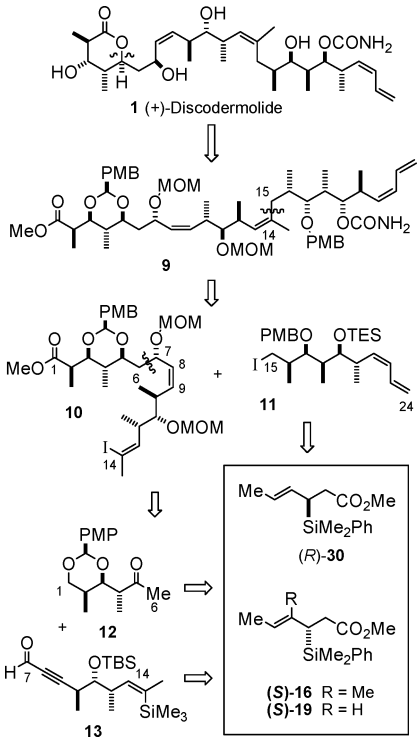
The remarkable biological activity and challenging structure of discodermolide, as well as the growing interest in providing useful quantities of this compound for preclinical research and development, stimulated considerable synthetic effort resulting in six total syntheses[2,10] and numerous fragment syntheses.[11] In the present paper we report full details of the development of a total synthesis of (+)-discodermolide based on an asymmetric crotylation methodology developed in our laboratories.

Results and Discussion

Synthesis Plan. The synthetic plan developed for (+)-discodermolide was guided by the principles of convergency, flexibility of modifications in case of pitfalls, and the use of similar precursors for the construction of key intermediates. At the outset, we planned to take full advantage of the chiral crotylsilane-based C−C bond construction methodology, developed earlier in our laboratories,[12] allowing us to efficiently build polypropionate-like stereochemical arrays. In the context of acyclic stereocontrol, these reaction processes rely on the

(7) Balachandran, R.; ter Haar, E.; Welsh, M. J.; Grant, S. G.; Day, B. W. *Anti-Cancer Drugs* **1998**, *9*, 67−78.
(8) Kowalski, R. J.; Giannakakou, P.; Gunasekera, S. P.; Longley, R. E.; Day, B. W.; Hamel, E. *Mol. Pharm.* **1997**, *52*, 613−622.
(9) Martello, L. A.; McDiad, H. M.; Regl, D. L.; Yang, C. H.; Meng, D.; Pettus, T. R.; Kaufman, M. D.; Arimoto, H.; Danishefsky, S. J.; Smith, A. B., III; Horwitz, S. B. *Clin. Cancer Res.* **2000**, *6*, 1978−1987.
(10) (a) Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011−12012. (b) Smith, A. B., III; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823−1826. (c) Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y. P.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654−8664. (d) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 377−380. (e) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereing, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535−9544. (f) Harried, S. S.; Yang, G.; Strawn, M. A.; Myles, D. C. *J. Org. Chem.* **1997**, *62*, 6098−6099. (g) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885−7892. (h) 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.; Loo, M.; Prasad, K.; Repič, O.; Shieh, W.-C.; Wang, R.-M.; Waykole, L.; Xu, D. D.; Xue, S. *Org. Process Res. Dev.* **2004**, *8*, 92−100. (i) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Grimler, D.; Koch, G.; Daeffler, R.; Osmani, A.; Hirni, A.; Schaer, K.; Gamboni, R.; Bach, A.; Chaudhary, A.; Chen, S.; Chen, W.; Hu, B.; Jagoe, C. T.; Kim, H.-Y.; Kinder, F. R.; Liu, Y.; Lu, Y.; McKenna, J.; Prasad, M.; Ramsey, T. M.; Repič, O.; Rogers, L.; Shieh, W.-C.; Wang, R.-M.; Waykole, L. *Org. Process Res. Dev.* **2004**, *8*, 101−106. (j) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Koch, G.; Kuesters, E.; Daeffler, R.; Osmani, A.; Seeger-Weibel, M.; Schmid, E.; Hirni, A.; Schaer, K.; Gamboni, R.; Bach, A.; Chen, S.; Chen, W.; Geng, P.; Jagoe, C. T.; Kinder, F. R.; Lee, G. T.; McKenna, J.; Ramsey, T. M.; Repič, O.; Rogers, L.; Shieh, W.-C.; Wang, R.-M.; Waykole, L. *Org. Process Res. Dev.* **2004**, *8*, 107−112. (k) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Seger, M.; Schreiner, K.; Daeffler, R.; Osmani, A.; Bixel, D.; Loiseleur, O.; Cercus, J.; Stettler, H.; Schaer, K.; Gamboni, R. *Org. Process Res. Dev.* **2004**, *8*, 113−121. (l) Mickel, S. J.; Niederer, D.; Daeffler, R.; Osmani, A.; Kuesters, E.; Schmid, E.; Schaer, K.; Gamboni, R.; Chen, W.; Loeser, E.; Kinder, F. R.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Repič, O.; Wang, R.-M. *Org. Process Res. Dev.* **2004**, *8*, 122−130. (m) Mickel, S. J.; Daeffler, R.; Prikoszovich, W. *Org. Process Res. Dev.* **2005**, *9*, 113−120.
(11) (a) Clark, D. L.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 5878−5879. (b) Evans, P. L.; Golec, J. M. C.; Gillespie, R. J. *Tetrahedron Lett.* **1993**, *34*, 8163−8166. (c) Paterson, I.; Schlapback, A. *Synlett* **1995**, 498−500. (d) Miyazawa, M.; Oonuma, S.; Maruyama, K.; Miyashita, M. *Chem. Lett.* **1997**, 1191−1192. (e) Miyazawa, M.; Oonuma, S.; Maruyama, K.; Miyashita, M. *Chem. Lett.* **1997**, 1193−1194. (f) Marshall, J. A.; Lu, Z. H.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817−823. (g) Misske, A. M.; Hoffman, H. M. R. *Tetrahedron* **1999**, *55*, 4315−4324. (h) Evans, D. A.; Halstead, D. P.; Allison, B. D. *Tetrahedron Lett.* **1999**, *40*, 4461−4462. (i) Filla, S. A.; Song, J. J.; Chen, L. R.; Masamune, S. *Tetrahedron Lett.* **1999**, *40*, 5449−5453. (j) Paterson, I.; Florence, G. J. *Tetrahedron Lett.* **2000**, *41*, 6935−6939. (k) Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; Scott, J. P.; Sereing, N. *Org. Lett.* **2003**, *5*, 35−38. (l) Shin, Y.; Choi, N.; Balachandra, R.; Madiraju, C.; Day, B. W.; Curran, D. P. *Org. Lett.* **2002**, *4*, 4443−4446. (m) Day, B. W.; Kangani, C. O.; Avor, K. S. *Tetrahedron: Asymmetry* **2002**, *13*, 1161−1165. (n) Arefolov, A,; Panek, J. S. *Org. Lett.* **2002**, *4*, 2397−2400. (o) Curran, D. P.; Furukawa, T. *Org. Lett.* **2002**, *4*, 2233−2235. (p) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 3995−3998. (q) Arjona, O.; Menchaca, R.; Plumet, J. *Tetrahedron* **2001**, *57*, 6751−6755. (r) Yadav, J. S.; Abraham, S.; Reddy, M. M.; Sabitha, G.; Sankar, A. R.; Kunwar, A. C. *Tetrahedron Lett.* **2001**, *42*, 4713−4716. (s) Kiyooka, S.; Shahid, K. A.; Goto, F.; Okazaki, M.; Shuto, Y. *J. Org. Chem.* **2003**, *68*, 7967−7978.
(12) (a) Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12475−12476. (b) Jain, N. F.; Cirillo, P. F.; Pelletier, R.; Panek, J. S. *Tetrahedron Lett.* **1995**, *36*, 8727−8730. (c) For a review, see: Masse, C. E.; Panek. J. S. *Chem. Rev.* **1995**, *95*, 1293−1316. (d) Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1993**, *58*, 809−811. (e) Panek, J. S.; Cirillo, P. F. *J. Org. Chem.* **1993**, *58*, 294−296. (f) Panek, J. S.; Beresis, R. T.; Xu, F.; Yang, M. *J. Org. Chem.* **1991**, *56*, 7341−7344.

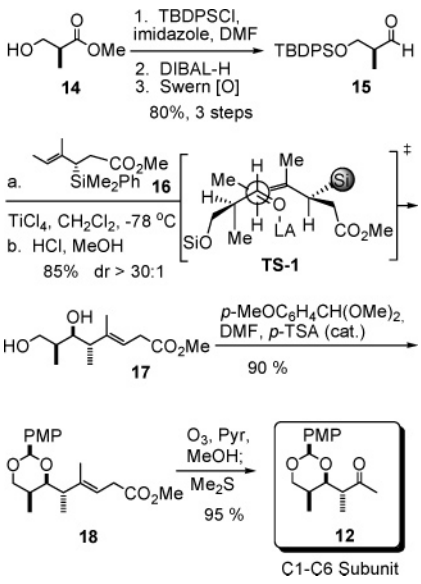
Scheme 1. Retrosynthetic Analysis of (+)-Discodermolide



use and proper choice of the chiral crotylsilane reagents and Lewis acids to deliver the anticipated relative and absolute stereochemical relationships.

Our synthetic plan for (+)-discodermolide is outlined in Scheme 1. Our strategy identifies methyl ester **9** as a key intermediate from which (+)-discodermolide would be generated. Thus, it was anticipated that formation of the sensitive lactone moiety would take place during the last step of the synthesis in concert with total deprotection of the fully assembled C1−C24 fragment **9**. Our first retrosynthetic disconnection of the C14−C15 bond generated two fragments: the C1−C14 vinyl iodide **10** and the C15−C24 alkyl iodide **11**. In the synthetic direction, this operation corresponds to a Pd(0)-mediated sp^2-sp^3 type cross-coupling reaction.[13] It was envisioned that the sensitive vinyl iodide functionality would be masked as a vinyl silane[14] throughout the synthesis, allowing it to be carried through a number of steps. The C8−C9 (*Z*)-double bond would come from the Lindlar hydrogenation of the internal acetylene. Further disconnection of the C6−C7 bond yield the C1−C16 fragment **12** and the C7−C14 fragment **13**. We projected that the desired stereochemistry of the propargylic alcohol at C7 could be realized utilizing an acetate aldol reaction between the boron enolate of methyl ketone **12** and the propargylic aldehyde **13** via 1,5-*anti* asymmetric induction.[15]

Scheme 2. Synthesis of C1−C6 Subunit **12**



Our retrosynthetic analysis yielded three principal fragments, **11**, **12**, and **13**, of approximately equal complexity. Identification of *syn*- and *anti*-related oxygen−methyl vicinal stereochemical relationships at C2−C4, C10−C12, and C16−C20 suggested that the three advanced polypropionate-like subunits **11**, **12**, and **13** could be constructed through double stereodifferentiating crotylation reactions, a valuable extension of chiral organosilane methodology developed in our laboratories.[12]

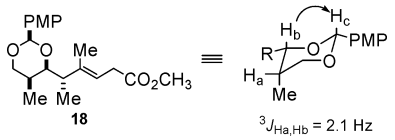
Synthesis of the C1−C6 Subunit 12. The reaction sequence started with the formation of α-chiral silyl-protected aldehyde **15** from the commercially available methyl (*S*)-2-methyl-3-hydroxypropionate, (*S*)-**14** (Scheme 2). Protection as the *tert*-butyldiphenylsilyl ether followed by DIBAL-H reduction with subsequent Swern oxidation afforded aldehyde **15** (80% yield, three steps). This aldehyde was used without further purification in a diastereoselective condensation reaction with (*S*)-crotylsilane **16** promoted by $TiCl_4$ as the Lewis acid. Treatment of the crude product with a solution of 2% HCl in MeOH removed the TBDPS protecting group to afford diol **17** with overall 85% yield as a single diastereoisomer. This first asymmetric crotylation proceeds through a synclinical transition state (**TS-1**), where the observed stereochemistry is consistent with the *anti*-S_E' mode of addition with Felkin induction. The use of silane **16**, bearing an additional methyl group, allowed for the introduction of a trisubstituted olefin, which was used as a methyl ketone equivalent through an oxidative cleavage. To this end, diol **17** was protected as *p*-methoxybenzyl acetal **18** with 90% yield under standard conditions (*p*-methoxybenzaldehyde dimethyl acetal in the presence of catalytic amounts of *p*-TsOH in DMF).[16] Ozonolytic cleavage of the double bond of acetal **18** furnished the desired methyl ketone subunit **12** with 95% yield.

(13) (a) Hyashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158−163. (b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298−3299. (c) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314−321.

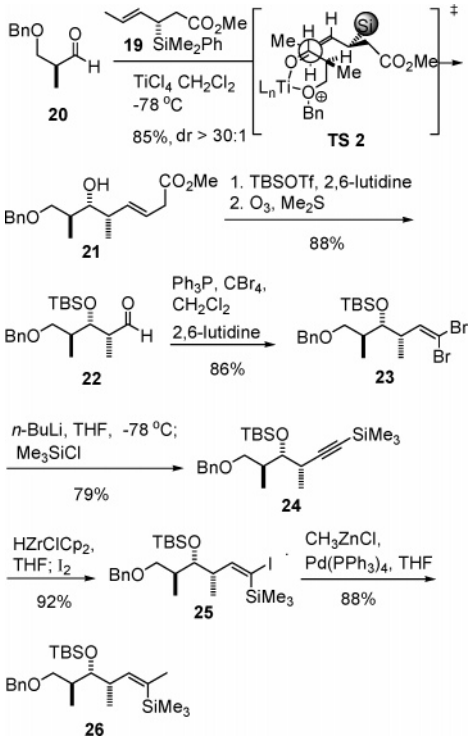
(14) A similar strategy was adopted in Nicolaou's synthesis of rapamycin. See: Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419−4420. (b) Piscopio, A. D.; Minowa, N.; Chakraborty, T. K.; Koide, K.; Bertinato, P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1993**, 617−619. (c) Nicolaou, K. C.; Bertinato, P.; Piscopio, A. D.; Chakraborty, T. K.; Minowa, N. *J. Chem. Soc., Chem. Commun.* **1993**, 619−622.

(15) (a) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788−789. (b) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585−8588.

(16) The relative stereochemistry of the crotylation product was confirmed at this point by the analysis of the vicinal coupling constant and NOE measurements of PMB acetal **18**:



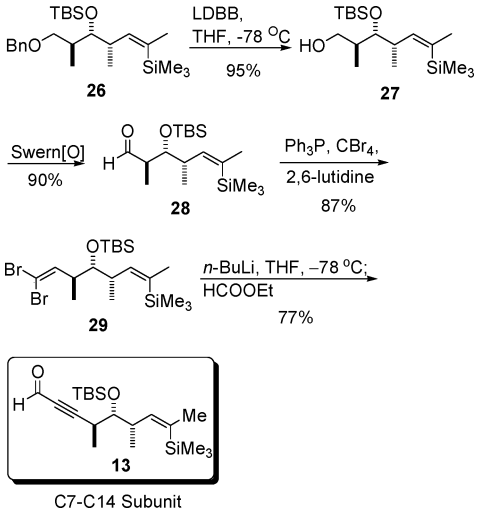
Scheme 3. Synthesis of C7−C14 Subunit **13**



Synthesis of the C7−C14 Subunit 13. Synthesis of this intermediate was initiated with the addition of (*S*)-silane **19** to the benzyl-protected aldehyde **20**[17] in the presence of $TiCl_4$ as the Lewis acid (Scheme 3) to afford homoallylic alcohol **21** with 85% yield as a single stereoisomer.[18] The high diastereoselectivity of the reaction results from the matched case[19] of chelation control and the *syn* addition mode of the crotylsilane. Homoallylic alcohol **21** was protected as a TBS ether in quantitative yield. Ozonolytic cleavage of the resultant alkene furnished aldehyde **22** with 88% yield, which was then converted to alkynylsilane **24** via a two-step reaction sequence. First, **22** was subjected to Corey−Fuchs olefination[20] to obtain vinyl dibromide **23** with 86% yield. Second, treatment of the vinyl dibromide **23** with *n*-butyllithium followed by trapping of the intermediate lithium acetylide with trimethylsilyl chloride afforded the desired silylacetylene **24** with 79% yield.

One of the most challenging problems in the synthesis of (+)-discodermolide has been the efficient introduction of the C13−C14 trisubstituted (*Z*)-olefin. Earlier approaches have used conventional phosphorus-based olefination methods[10c,g,i] which produced variable yields and selectivities. Our plan utilized a hydrozirconation−cross-coupling approach[21] which allows convergent assembly of complex trisubstituted olefins.

Scheme 4. Synthesis of C7−C14 Subunit **13**

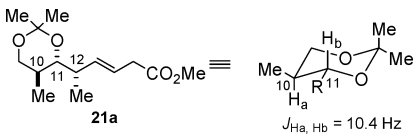


Accordingly, hydrozirconation of silylacetylene **24** using Schwartz's reagent[22] was followed by quenching of the resultant alkenylzirconium species with iodine to afford the geminal iodovinylsilane **25** as a single regio- and stereoisomer in 92% yield. Subsequent coupling of **25** with methylzinc chloride in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) gave the (*Z*)-vinylsilane **26** in 88% yield. In this approach, the vinylsilane functions as a masked vinyl iodide[23] throughout the synthesis until fragments **10** and **11** are ready for the crucial palladium(0)-mediated cross-coupling reaction. Lithium di-*tert*-butylbiphenyl radical anion (LDBB) reagent[24] in THF at −78 °C selectively removed the benzyl ether without affecting the C13−C14 double bond nor the labile C11 silyl ether, providing **27** in 95% isolated yield (Scheme 4). The resultant alcohol **27** was converted to aldehyde **28** using Swern conditions[25] in 90% yield. Aldehyde **28**, prone to epimerization, was immediately converted to vinyl dibromide **29** utilizing the Corey−Fuchs homologation protocol in 87% yield. Subsequent treatment of **29** with *n*-BuLi was followed by the addition of ethyl formate to furnish the propargylic aldehyde **13** (C7−C14 fragment) in 77% yield.

Synthesis of the C15−C24 Subunit 11. Synthesis of the C15−C24 fragment started with the diastereoselective addition of (*R*)-silane **30** to the silyl-protected aldehyde **15** promoted by $TiCl_4$ as the Lewis acid (Scheme 5). In this situation, the reaction partners represented a matched case, giving a *syn*,*syn* stereochemical triad that is consistent with a Felkin mode of addition. Treatment of the crude reaction mixture with methanolic HCl promoted cleavage of the silyl protecting group, affording diol **31** as a single diastereoisomer with a 90% yield.[26] This diol was protected as di-*tert*-butylsilylene derivative **32** using $^tBu_2Si(OTf)_2$ and 2,6-lutidine[27] in CH_2Cl_2 at −78 °C with 95% yield. Ozonolysis of the (*E*)-olefin of **32** successfully gave aldehyde

(17) For the preparation of the (*S*)-3-(benzyloxy)-2-methylpropanal, see: (a) Ireland, R. E.; Thaisrivongs, S.; Dussault, P. H. *J. Am. Chem. Soc.* **1988**, *110*, 5768−5779. (b) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1988**, *48*, 5180−5184.

(18) The relative stereochemistry of the addition product **21** was confirmed by conversion to acetonide **21a** and analysis of the ^1H NMR vicinal coupling constant:



(19) Masamune, S.; Ali, S. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557−558.

(20) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1792**, *13*, 3769−3772.

(21) Arefolov, A.; Langille, N. F.; Panek, J. S. *Org. Lett.* **2001**, *3*, 3281−3284.

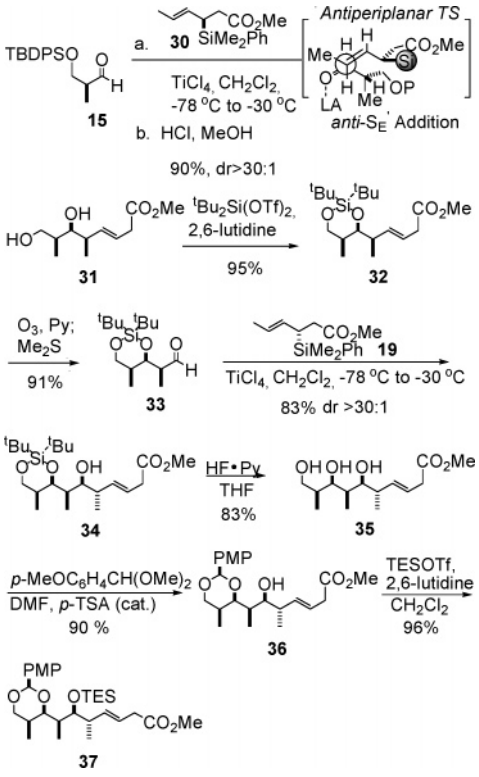
(22) (a) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115−8116. (b) Buchwald, S. L.; La Maire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895−3898.

(23) For the regio- and stereospecific transformations of vinylsilanes to vinyl iodides, see: (a) Koenig, K. E.; Weber, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 3416−3418. (b) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857−873.

(24) (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924−1930. (b) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854−860.

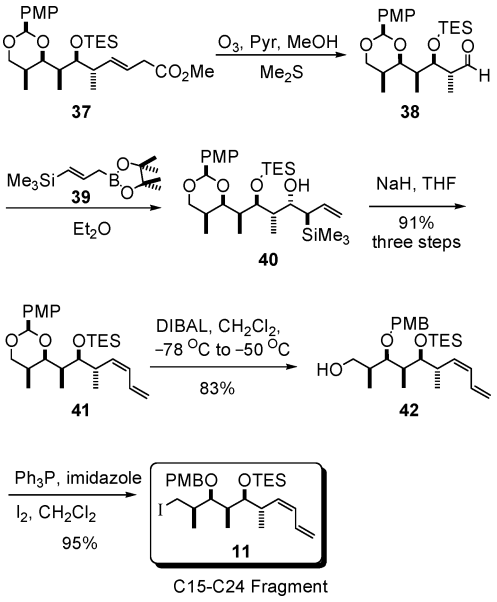
(25) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

Scheme 5. Synthesis of C15−C24 Subunit **11**



33 in 91% yield. This material was used in a double stereodifferentiating *anti* crotylation reaction with silane (*S*)-**19**. The $TiCl_4$-promoted condensation reaction between aldehyde **33** and (*S*)-silane **19** produced the *anti* homoallylic alcohol **34** (diastereoselection >30:1, 83% yield),[28,29] which was deprotected using HF·Py reagent in THF to afford triol **35** with 83% yield. This triol was selectively protected as *p*-methoxybenzyl acetal **36** with 90% yield under standard conditions (*p*-methoxybenzaldehyde dimethyl acetal in the presence of catalytic amounts of *p*-TsOH in DMF).[30] The selectivity of this reaction resulted, presumably, from the difference in nucleophilicity between the primary and secondary hydroxyl groups. Homoallylic alcohol **36** was further protected as triethylsilyl ether **37** utilizing (TES)OTf and 2,6-lutidine in CH_2Cl_2 with 96% yield.

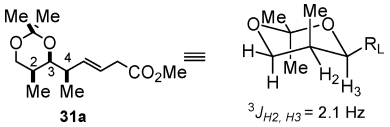
Scheme 6. Synthesis of C15−C24 Subunit **11**



Next, the C21−C24 terminal (*Z*)-diene was installed in a three-step sequence (Scheme 6). First, olefin **37** was oxidatively cleaved with ozone. The resultant aldehyde **38** was used unpurified in the reaction with 2 equiv of 1-trimethylsilyl-1-propene boronate **39**[31] in diethyl ether to afford *anti*-silylhydroxyalkene **40** as a single diastereoisomer. Silyl alcohol **40** was used without purification to undergo a Peterson *syn* elimination[32] using sodium hydride in THF to give (*Z*)-diene **41** as a single isomer in 91% yield over three steps starting from **37**. The *p*-methoxybenzylidene acetal **41** was regioselectively opened under reductive conditions[33] (DIBAL-H at −50 °C) to afford alcohol **42** with 83% yield. The fragment synthesis was completed by iodination of the primary hydroxyl using Ph_3P/I_2/imidazole to produce iodide **11** in 95% yield.

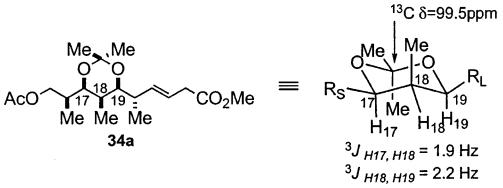
C6−C7 Bond Construction and Elaboration of the C1−C14 Fragment. With efficient synthetic access to intermediates **12** and **13**, we next examined their union via aldol bond construction methodology (Scheme 7). At the inception of this project, very few precedents existed for highly stereoselective acetate aldol reactions where a methyl ketone component alone is controlling the stereochemical outcome. In studies toward the total synthesis of spongistatin 1, Paterson and co-workers discovered that boron enolates of β-oxygenated methyl ketones gave good to excellent levels of 1,5-*anti* asymmetric induction with achiral aldehydes, leading to the efficient synthesis of 1,3-polyol chains.[34] In related studies directed toward the total synthesis of altohyrtin C, Evans and co-workers reported similar findings and extended these results to the additions with chiral aldehydes.[35]

(26) The relative stereochemistry of the addition product **31** was confirmed by conversion to acetonide **31a** and analysis of the ^{1}H NMR vicinal coupling constant:



(27) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 4871−4874.

(28) The relative stereochemistry of the addition product **34** was confirmed by conversion to acetonide **34a** and analysis of the ^{1}H NMR vicinal coupling constant as well as ^{13}C NMR analysis of the acetonide, which were consistent with the reported data: see ref 29.



(29) For the use of ^{13}C NMR to assign the relative stereochemistry of 1,3-diols, see: (a) Rychnovsky, S. D.; Roger, B.; Yang, G. J. *J. Org. Chem.* **1993**, *58*, 3511−3515. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099−7103.

(30) For an example of a similar triol protection selectivity, see: Evans, D. A.; Ng, H. P. *Tetrahedron Lett.* **1993**, *34*, 2229−2233.

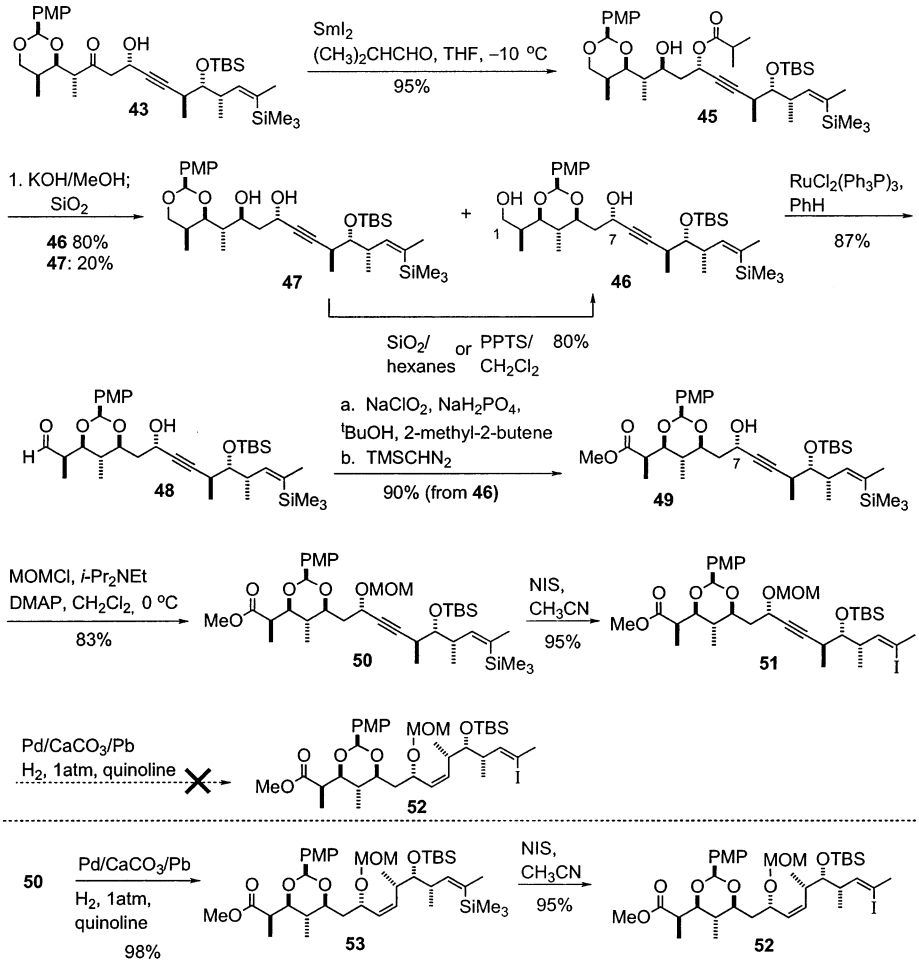
(31) Tsai, D. J. S.; Matteson, D. S. *Tetrahedron Lett.* **1981**, *29*, 2751−2752.

(32) Hudrlik, P. F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1464−1468.

(33) (a) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593−1597. (b) Sviridov, A. F.; Ermolenko, M. S.; Yaskunsky, D. V.; Borodkin, V. S.; Koshetkov, N. K. *Tetrahedron Lett.* **1987**, *28*, 3835−3843. (c) Marotta, E.; Pagani, I.; Righi, P.; Rosini, G.; Bortolasi, V.; Medici, A. *Tetrahedron: Asymmetry* **1995**, *6*, 2319−2324.

(34) (a) Paterson, I.; Collett, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187−1191. (b) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585−8588.

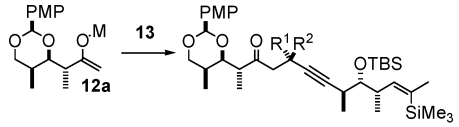
Scheme 7. Synthesis of C1−C14 Subunit **10**



In Paterson's and Evans' investigations, methyl ketone components lacked substitution in the α-position to the carbonyl. In the case of discodermolide, however, there is a methyl group at the α-position to the C5 carbonyl of the C1−C6 subunit. Having no precedent to help us anticipate the influence of this substitution pattern on the stereochemical outcome of the aldol condensation, we set out to investigate the levels and sense of selectivity of boron enolates derived from subunit **12** in our system (Table 1). Gratifyingly, the dialkylboron enolates displayed good levels of asymmetric induction, consistently favoring the 1,5-*anti* product **43**. Dicyclohexylboron enolate (entry 1) was less selective than dibutylboron enolate (entries 2−4), the latter providing the desired alcohol **43** as a single diastereoisomer, as determined by ^{1}H NMR analysis of the crude reaction product.

After successful coupling of **12** and **13** subunits, we turned our attention to the synthesis of the C1−C14 fragment (Scheme 7). First, Evans−Tischenko reduction[36] of the *β*-hydroxy ketone **43** provided *anti*-1,3-diol **45** in 95% yield.[37] Hydrolysis of *β*-hydroxyisobutyrate **45** was carried out with KOH in methanol. Unexpectedly, purification of the crude reaction mixture by chromatography on SiO_2 resulted in acetal rearrangement to afford the internal acetal **46** in 80% yield along with the expected 1,3-diol **47** (20% yield). The minor diol **47** could be further converted into thermodynamically more stable internal acetal **46** by stirring with SiO_2 in hexanes or using a catalytic amount of PPTS in CH_2Cl_2.[38]

Table 1. 1,5 Induction with Boron Enolates



43 : R^1 = OH, R^2 = H
44 : R^1 = H, R^2 = OH

entry	M/base[a]	*T* (°C)	solvent	yield[b] (%)	**43**/**44**[c]
1	Cy_2B/Et_3N	−78	CH_2Cl_2	83	90:10
2	$Bu_2B/i\text{-}Pr_2NEt$	−78	Et_2O	76	>30:1
3	$Bu_2B/i\text{-}Pr_2NEt$	−78	CH_2Cl_2	86	>30:1
4	$Bu_2B/i\text{-}Pr_2NEt$	−115	CH_2Cl_2	88	>30:1

[a] The enolates were formed from the corresponding boron triflates. [b] Yields of the unseparable mixture of diastereoisomers **43** + **44** isolated after chromatography on SiO_2. [c] Ratios determined by ^{1}H NMR analysis of the unpurified reaction mixture.

Since we planned to deprotect the primary hydroxyl of the anticipated acetal **47** at a later stage of the synthesis (for the eventual conversion to a methyl ester for the subsequent lactonization step), this acetal rearrangement could save a step at this advanced point in the synthesis. To use this rearrangement in our favor, however, we needed to selectively oxidize the primary hydroxyl at C1 to an aldehyde in the presence of the

(35) (a) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671−8726. (b) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788−789.
(36) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449.

C7 secondary propargylic alcohol. To determine the feasibility of our approach, we screened a variety of conditions and reagents. The use of modified Ley's oxidation protocol[39] (TPAP/NMO, CH_3CN, then H_2O) as well as the use of 4-MeO-TEMPO/NaOCl oxidation conditions[40] caused undesirable side reactions. Fortunately, selective oxidation of **46** was carried out using Oshima's reagent—$RuCl_2(Ph_3P)_3$[41] in benzene. The crude aldehyde **48** was further treated with buffered sodium chlorite[42] to afford a carboxylic acid, which, without purification, was converted to methyl ester **49** utilizing (trimethylsilyl)diazomethane[43] with 81% yield over three steps starting from diol **46**. The choice of a protecting group for the C7 hydroxyl group proved to be crucial for the following Lindlar reduction step. Our initial choice of TES ether as a protecting group precluded the hydrogenation of the C8−C9 alkyne under Lindlar conditions. For this reason, the C7 hydroxyl was protected as MOM ether **50** (83% yield).

Having only two steps left before the end of the fragment synthesis, we initially decided to proceed with iododesilylation, leaving the Lindlar reduction as the last step. We argued that having a triple bond within the molecule during the iododesilylation (electrophilic addition of I^+) was a safer option than having the (*Z*)-olefin, which may be prone to isomerization. To this end, we have screened several iododesilylation conditions and learned that I_2/CH_2Cl_2[44] promoted decomposition of **50**, while the use of NIS/THF[45] gave back unreacted starting material. Fortunately, application of the modified Kishi protocol (NIS, CH_3CN)[46] resulted in a clean transformation to vinyl iodide **51** in a 95% yield. Subsequent Lindlar reduction[47] of the vinyl iodide **51**, however, proved problematic, leading to the decomposition of the substrate due to hydrogenolysis of the vinyl iodide.

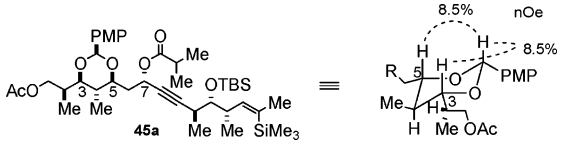
To circumvent this problem, the order of the iododesilylation/Lindlar reduction sequence was reversed (Scheme 7). Accordingly, hydrogenation under Lindlar conditions with a catalytic amount of quinoline[48,49] afforded (*Z*)-olefin **53** in 98% yield. The use of Kishi iododesilylation conditions completed the synthesis of the C1−C14 fragment **52** in 95% yield.

Coupling of the C1−C14 and C15−C24 Fragments. We have now reached a crucial point in these synthetic studies: formation of a σ-bond between subunits **11** and **52**. At the outset, we had planned to employ a palladium-catalyzed cross-coupling reaction methodology. An analogous approach was employed by Smith and co-workers, who coupled a C9−C14 vinyl iodide with a C15−C21 vinyl iodide utilizing modified Negishi conditions.[10c] Utilizing a similar strategy but at a later stage of the synthesis, Marshall and Johns joined C1−C14 vinyl iodide with C15−C24 alkyl iodide subunits under Suzuki conditions.[10g]

We attempted cross-coupling of alkyl iodide **11** and vinyl iodide **52**, trying both Negishi[50] and Suzuki[51] coupling conditions (Scheme 8). To our disappointment, both coupling conditionsfailed to afford the desired coupling product **54**. After considerable experimentation and further model studies, we realized that the protecting group at C11 (TBS ether) was preventing cross-coupling reaction, presumably by sterically blocking the oxidative addition step of vinyl iodide **52**. For this reason, we decided to replace the C11 TBS ether with a smaller protecting group. Removal of the C11 TBS ether proceeded smoothly with TBAF/AcOH,[52] while reprotection of the resultant alcohol as a MOM ether was achieved using standard conditions (MOMCl, Hünig's base in the presence of DMAP in CH_2Cl_2) to furnish **10** with 68% yield over two steps. Fragment **10** was tried as a coupling partner with C15−C24 fragment **11** (Scheme 8). Alkyl iodide **11** was converted to the trialkyl boronate **55** by lithiation and subsequent addition of *B*-methoxy-9-BBN. Suzuki cross-coupling with vinyl iodide **10** in the presence of $PdCl_2$(dppf) as a catalyst provided the desired coupling product **57** in 82% yield. In an alternate approach, we were also able to generate the C14−C15 bond through the Negishi cross-coupling of the organozinc species **56** (derived from iodide **11**) with vinyl iodide **10**. Thus, advanced intermediate **57** was produced in 64% yield in the presence of catalytic amounts of tetrakis(triphenylphosphine)palladium (0). When the two cross-coupling processes were compared, the Negishi coupling gave minor amounts of impurities in the final product and the reproducibility of the reaction was often a problem. The Suzuki reaction, on the other hand, provided consistently cleaner product with reproducibly higher yields.

After having solved the problems with our final cross-coupling reaction, we were pleased to find that the final steps of our synthesis proceeded uneventfully. Triethyl silyl ether **57** was cleanly deprotected using *p*-TsOH in MeOH to give alcohol **58** with 77% yield (Scheme 9). The carbamate derivative **9** was

(37) For assignment of the relative stereochemistry of aldol adduct **43**, alcohol **45** was converted to acetal **45a**. A C3−C5 *syn* relationship was confirmed by NOE measurement. Since the relationship between C5 and C7 hydroxyl groups is *anti* (see ref 36), the C3 and C7 hydroxy groups are also in an *anti* relationship to each other.



(38) We assume that the observed thermodynamic stability of **46** over **47** results from the C2-methyl in **47** adopting an axial position, whereas the C4-methyl in **46** adopts an equatorial position.

(39) For a review, see: Ley, S.; Norman, J.; Griffith, W.; Marsden, S. *Synthesis* **1994**, 639−666.

(40) For reviews, see: (a) DeNooy, A. E. J.; Basemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153−1174. (b) Anelli, P. L.; Biffi, C.; Montanarie, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559−2562. (c) Ireland, R. E.; Gleason, J. L.; Gegnas, L. D.; Highsmith, T. K. *J. Org. Chem.* **1996**, *61*, 6856−6872.

(41) Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605−1608.

(42) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096.

(43) (a) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475−1478. (b) Hirai, Y.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1989**, *111*, 3062−3064.

(44) Chan, T. H.; Fleming, I. *Synthesis* **1979**, *10*, 761−786.

(45) Piscopio, A. D.; Minowa, N.; Chakraborty, T. K.; Koide, K.; Bertinato, P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1993**, 617−618.

(46) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647−8650.

(47) (a) Lindlar, H.; Dubuis, R. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 880−883. (b) Rajaram, J.; Narula, A. P. S.; Chawla, H. P. S.; Dev, S. *Tetrahedron* **1983**, *39*, 2315−2318. (c) McEven, A. B.; Guttieri, M. J.; Maier, W. F.; Laine, R. M.; Shvo, Y. *J. Org. Chem.* **1983**, *48*, 4436−4438.

(48) In the absence of quinoline, over-reduction to an alkane was observed.

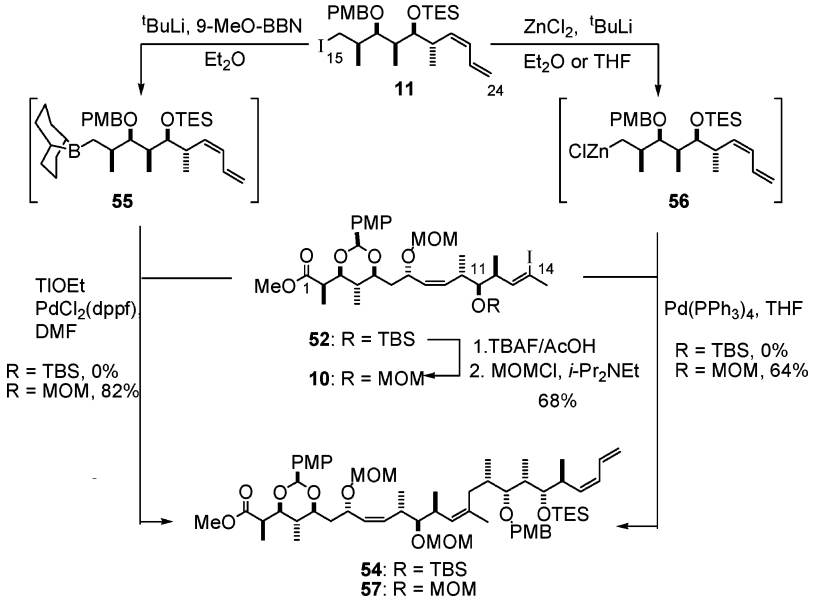
(49) For a powerful example of the use of quinoline as a Lindlar catalyst poison, see: (a) Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc.* **1982**, *104*, 5558−5560. (b) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5560−5563.

(50) For a review, see: Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley: New York, 2002; Part III, pp 215−1119.

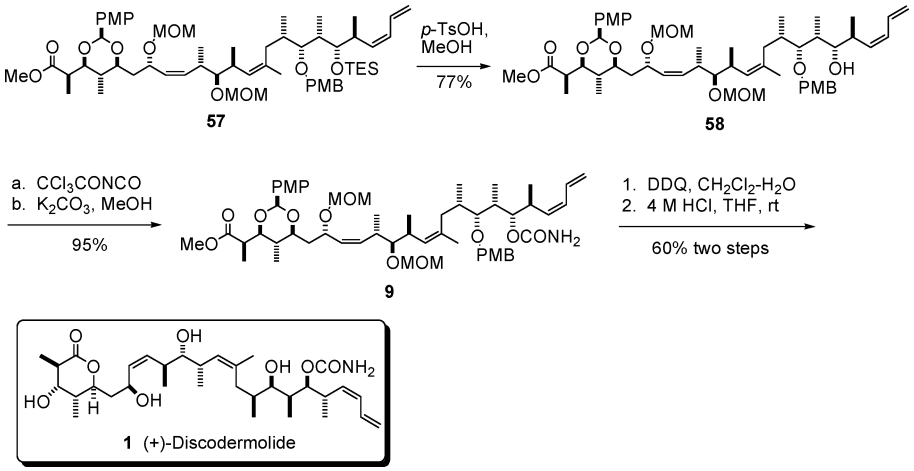
(51) For reviews, see: (a) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(52) (a) All other reagent systems surveyed including HF·Py, TBAF, HF, and $LiBF_4$ failed to deprotect the C11 hydroxyl. (b) For an example of using TBAF/AcOH to remove a TBS ether, see: Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935−3948.

Scheme 8. Cross-Coupling of C1−C14 and C15−C24 Fragments



Scheme 9. Completion of the Synthesis of (+)-Discodermolide



obtained through addition of trichloroacetyl isocyanate[53] and in situ cleavage of the derived trichloroacetyl derivative with methanolic K_2CO_3 in 95% yield. Next, the PMB protecting group at C17 was removed by oxidative cleavage utilizing DDQ in aqueous CH_2Cl_2.[54] Prolonged exposure (70 h) of the resultant alcohol to 4 M HCl solution in THF effected cleavage of the MOM protecting groups and the *p*-methoxybenzyl acetal with concomitant lactonization, in accordance with the earlier precedents.[10e,g] Purification of the crude product by flash chromatography (10% $CH_3OH-CH_2Cl_2$) afforded (+)-discodermolide (**1**) as a stable amorphous solid in 60% yield over the two steps. The spectroscopic and analytical properties of this material (^{1}H NMR, ^{13}C NMR, $[\alpha]_D$, IR, FAB-HRMS) proved identical in all respects with the data reported earlier.

Summary. An enantioselective total synthesis of (+)-discodermolide has been achieved in a highly convergent manner. A salient feature of the synthesis is that 11 out of 13 stereocenters within the target molecule were established using asymmetric crotylation reactions. Highlights of the synthesis include the use of hydrozirconation−cross-coupling methodology for the construction of C13−C14 (*Z*)-olefin, acetate aldol reaction to construct the C6−C7 bond and install the C7 stereocenter with high levels of 1,5-*anti* stereoinduction, and the use of palladium-mediated sp^2-sp^3 cross-coupling reaction to join the advanced fragments at the late stage of the synthesis. Our synthetic strategy provides access to natural (+)-discodermolide in a total of 42 steps with 2.1% yield based on the longest linear sequence (27 steps).

Acknowledgment. Financial support was obtained from NIH Grant GM55740. J.S.P. is grateful to Johnson & Johnson, Merck Co., Novartis, Pfizer, and GSK for financial support of our program. Drs. Gwilherm Evano, Fredrik Lake, and Neil Langille are acknowledged for their help with the manuscript preparation.

Supporting Information Available: Experimental procedures and characterization data for all synthetic intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA043168J

(53) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521−5524.
(54) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885−888.