

Formal Synthesis of (+)-Discodermolide

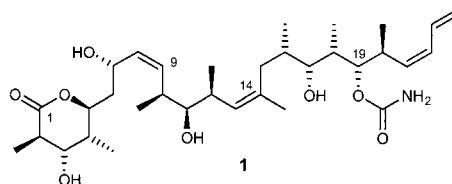
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ABSTRACT

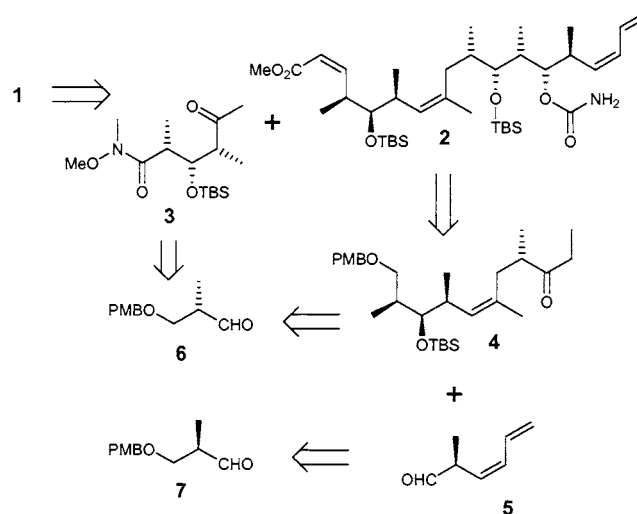


Herein we report the formal total synthesis of (+)-discodermolide in 21 steps (longest linear sequence) from commercially available Roche ester. This synthesis features the assembly of C_{9–18} and C_{19–24} fragments via a metal-chelated aldol coupling reaction.

(+)-Discodermolide (**1**) is a potent microtubule stabilizing agent isolated from the Caribbean sponge *Discodermia dissoluta*.¹ Discodermolide is a potent inhibitor of tumor cell growth in vitro and is not cross-resistant with paclitaxel or epothilone-resistant cells.² Discodermolide also demonstrates significant human tumor growth inhibition in hollow fiber and xenograft mouse models (including paclitaxel-resistant tumors).³ Discodermolide is currently undergoing Phase I clinical trials. Drug supply needs have been met using total synthesis.⁴ To address the drug supply needs of advanced clinical trials, further synthesis refinements are necessary. Herein we describe a hybrid of several reported syntheses

that features a novel assembly of C_{9–18} and C_{19–24} fragments via a metal-chelated aldol coupling reaction.⁵

Scheme 1



Key synthesis disconnections as outlined in the retrosynthetic analysis of **1** (Scheme 1) include formation of the bond

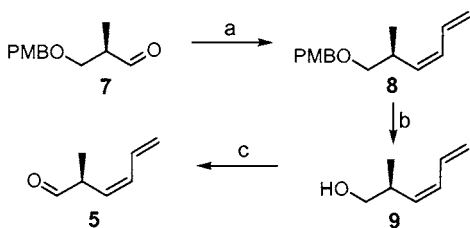
(1) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912. Additions and corrections: Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1991**, *56*, 1346.

(2) (a) Jordan, M. A. *Curr. Med. Chem.: Anti-Cancer Agents* **2002**, *2*, 1. (b) Altmann, K. H. *Curr. Opin. Chem. Chem. Biol.* **2001**, *5*, 424. (c) He, L. F.; Orr, G. A.; Horwitz, S. B. *Drug Discovery Today* **2001**, *6*, 1153. (d) He, L.; Chia-Ping, H. Y.; Horwitz, S. B. *Mol. Cancer Ther.* **2001**, *1*, 3. (e) Kowalsky, R. J.; Giannakakou, P.; Gunasekera, S. P.; Longley, R. E.; Day, B. W.; Hamel, E. *Mol. Pharmacol.* **1997**, *52*, 613.

(3) Kinder, F. R., Jr.; Bair, K. W.; Chen, W.; Florence, G.; Francavilla, C.; Geng, P.; Gunasekera, S.; Guo, Q.; Lassota, P. T.; Longley, R. E.; Palermo, M. G.; Paterson, I.; Pomponi, S.; Ramsey, T. M.; Rogers, L.; Sabio, M.; Sereinig, N.; Sorensen, E.; Wang, R. M.; Wright, A. *Abstracts of Papers*, 224th National Meeting of the American Chemical Society, Boston, MA, August 18–22, 2002; American Chemical Society: Washington, DC, 2002; MEDI-236.

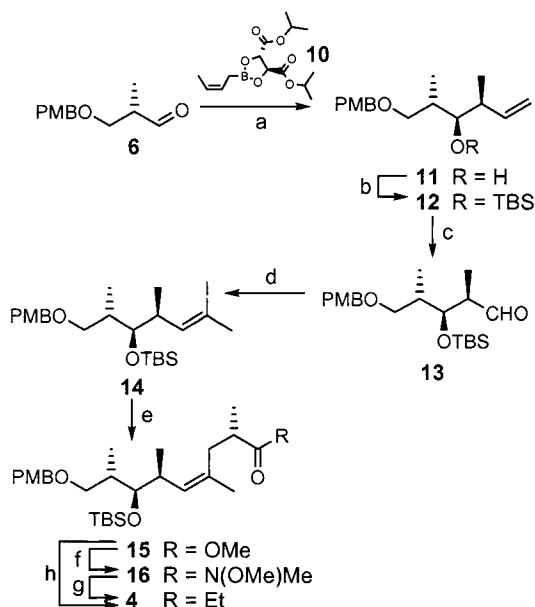
(4) Detailed account of the synthesis of the Phase I batch of discodermolide by the Novartis Pharma Chemical and Analytical Development group will be reported elsewhere.

(5) For a review, see: Kaleese, M. *ChemBioChem* **2000**, *1*, 171.

Scheme 2^a

^a Reaction conditions: (a) CrCl₂, (1-bromo-2-propenyl)trimethylsilane, THF, 0 °C → rt, 18 h; then 6 M KOH, methanol, 25 °C, 1 h, 57%. (b) DDQ, water, rt, 1 h, 81%. (c) Dess–Martin periodinane, DCM, rt, 4 h, 73%.

at C_{6–7} via chiral boron-mediated aldol reaction with the corresponding aldehyde prepared from **2** and ketone **3** as described by Paterson.⁶ Intermediate **2** was prepared by elaboration of the metal-chelated aldol (vide infra) product from ketone **4** and aldehyde **5**. Both intermediates **3** and **4** were prepared from aldehyde **6** via common stereotriad intermediate **13** (see Scheme 3). The remarkably stable aldehyde **5** was prepared in three steps from aldehyde **7**.

Scheme 3^a

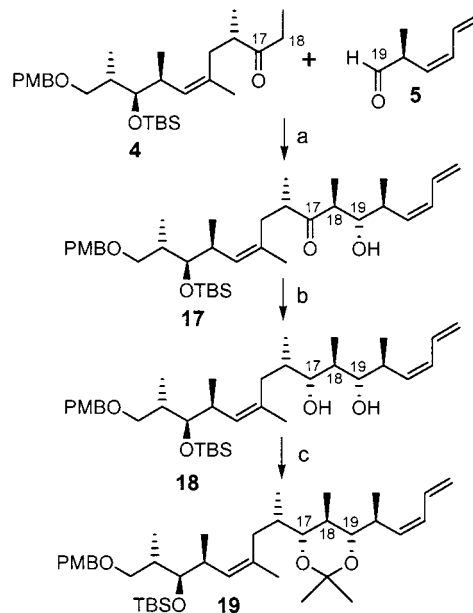
^a Reaction conditions: (a) **10**, toluene, 4 Å molecular sieves, –78 °C, 18 h. (b) TBSOTf, 2,6-lutidine, THF, 0 °C, 1.5 h, 95%. (c) (i) MNO, OsO₄, acetone, *t*-BuOH, water, rt, 18 h; (ii) NaIO₄, water, THF, rt, 2 h, 71%. (d) Ph₃PEtI, BuLi, 0 °C, 10 min; then 0.1 M I₂ in THF, –78 °C, 15 min; then NaHMDS, THF, –23 °C, 10 min; then **13**, –33 °C, 30 min, 36%. (e) (*R*)-(+)-3-Methoxy-2-methyl-3-oxopropylzinc bromide, Pd(PPh₃)₄, THF, rt, 18 h, 87%. (f) *N,O*-Dimethylhydroxylamine hydrochloride, toluene, 2.0 M AlMe₃ in hexanes, 0 °C, 30 min; then **15** in toluene, 80 °C, 2 h, 91%. (g) EtMgBr, THF, 0 °C, 1 h, 75%. (h) *N,O*-Dimethylhydroxylamine hydrochloride, EtMgBr, THF, –10 °C → rt, 2 h, 90%.

Aldehyde **7** (Scheme 2), which was obtained from a three-step procedure from methyl (*R*)-3-hydroxy-2-methylpropi-

onate,⁷ was subjected to a one-pot combination⁸ of Nozaki–Hiyama⁹ and Peterson-type syn elimination¹⁰ reactions, which gave only the (*Z*)-diene **8**. This was followed by deprotection to provide alcohol **9** and a Dess–Martin oxidation¹¹ to give **5**.

Aldehyde **6** (Scheme 3), obtained from methyl (*S*)-3-hydroxy-2-methylpropionate, was subjected to crotyl-boration¹² to give **11** (via Roush chiral auxiliary¹³ **10**). Silylation of the alcohol **11** and oxidative cleavage of the alkene **12** provided aldehyde **13**. Utilizing the chemistry developed by Zhao and co-workers,¹⁴ **13** and an α-iodoalkyl ylide gave the 2-iodo-2-alkene **14**. The high *Z*:*E* ratio was attributed to the removal of the iodo-betaine intermediate, which would ultimately form the (*E*)-olefin, through formation of an epoxide via a Darzan reaction.¹⁵ A Negishi cross-coupling of the Riecke organozinc compound¹⁶ and **14** gave the methyl ester **15**.

Originally, the ethyl ketone **4** was synthesized in a two-step procedure by formation of the Weinreb amide¹⁷ **16**, followed by nucleophilic attack by EtMgBr. Later, it was found that this two-step procedure could be easily done in one pot¹⁸ using 6–10 equiv of EtMgBr and *N,O*-dimethylhydroxylamine hydrochloride.

Scheme 4^a

^a Reaction conditions: (a) LDA, THF, –78 °C, 2 h; then **5**, –78 → –19 °C, 19 h, 77% (based on 73% recovered starting material). (b) DIBAL-H, THF, –100 °C, 4 h, 88%. (c) 2,2-Dimethoxypropane, CSA, rt, 5 h, 69%.

An aldol coupling with ethyl ketone **4** (Scheme 4) and aldehyde **5** formed a lithium-chelated six-membered ring intermediate to give the undesired stereochemistry in **17**. The

(6) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. J. *Am. Chem. Soc.* **2001**, *123*, 9535.

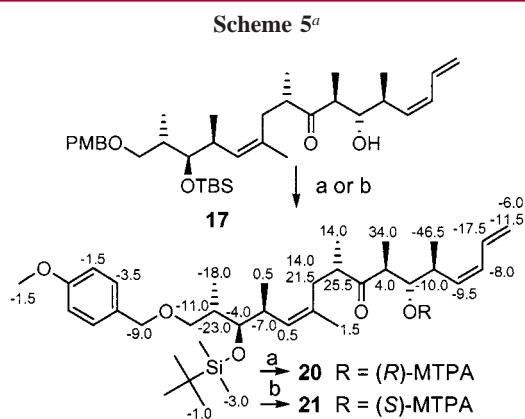
(7) Smith, A. B., III; Qiu, Y.; Kaufman, M.; Arimoto, H.; Jones, D. R.; Kobayashi, K. U.S. Patent 6 031 133, 2000.

opposite stereogenic center at C₁₈ was suspected due to the sluggishness of the aldol reaction, which required an unusually high temperature and long reaction time. We speculate that equilibration of the (*Z*)-enolate to the (*E*)-enolate would give the anti-configuration. To investigate, we performed reactions that would help identify which stereocenters were obtained at C₁₈ and C₁₉ for compound **17**.

To determine if the anti-relationship was present, the acetal **19** was synthesized (Scheme 4). Through a C₁₉-hydroxy-directed reduction, the carbonyl was stereoselectively reduced to diol **18**. The acetal was formed by treatment of the diol with 2,2-dimethoxypropane and CSA.

The suspected relationship was determined upon measurement of the coupling constants as well as performing a NOE experiment. One methyl of the acetal had a NOE with the C₁₇ hydrogen, C₁₉ hydrogen, and C₁₈ methyl hydrogens. Additionally, the other acetal methyl had a NOE with the C₁₈ hydrogen.

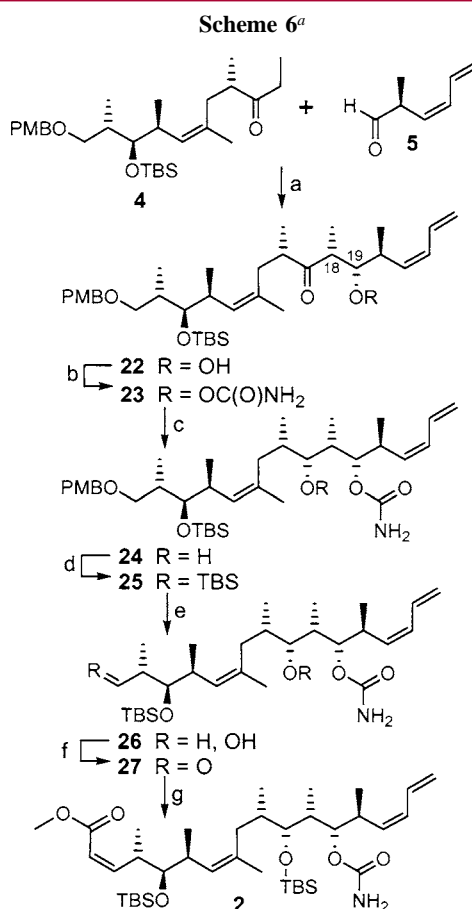
To determine the absolute stereochemistry, both (*R*)- and (*S*)-Mosher esters¹⁹ were synthesized (Scheme 5). Subtraction of the chemical shifts for each ¹H NMR signal in compound **20** from that of compound **21** gave a value for each in hertz. These values provided evidence to deduce the stereochemistry of compound **17**.



^a Reaction conditions: (a) (*R*)-(-)- α -Methoxy- α -(trifluoromethyl)phenylacetyl chloride, DMAP, pyridine, DCM, rt, 24 h, 86%. (b) (*S*)-(-)- α -Methoxy- α -(trifluoromethyl)phenylacetyl chloride, DMAP, pyridine, DCM, rt, 24 h, 86%.

An aldol coupling, using magnesium as the chelation metal (Scheme 6), proved to be effective at increasing the reaction

- (8) Paterson, I.; Schlapbach, A. *Synlett* **1995**, 498.
 (9) Cintas, P. *Synthesis* **1992**, 248.
 (10) Hudrlik, P. F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, 97, 1464.
 (11) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, 48, 4155.
 (12) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, 112, 6348.
 (13) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, 112, 6339.
 (14) Chen, J.; Wnag, T.; Zhao, K. *Tetrahedron Lett.* **1994**, 35, 2827.
 (15) Arimoto, H.; Kaufman, M. D.; Kobayashi, K.; Qiu, Y.; Smith, A. B., III. *Synlett* **1998**, 765.
 (16) Available through Aldrich, catalog no. 49,949-8.
 (17) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, 22, 3815.
 (18) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.; Grabowski, E. J. *J. Tetrahedron Lett.* **1995**, 36, 5461.



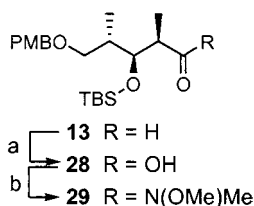
^a Reaction conditions: (a) LDA, THF, -78°C , 1.5 h; then MgBr_2 , **5**, -78°C , 18 h, 35% (based on 74% recovered starting material). (b) Trichloroacetyl isocyanate, DCM, rt, 1 h; then neutral alumina, rt, 4 h, 93%. (c) $\text{Li}(t\text{-BuO})_3\text{AlH}$, THF, -78°C , 1 h, 91%. (d) 2,6-lutidine, TBSOTf, DCM, rt, 1 h, 93%. (e) DDQ, water, DCM, rt, 1 h, 92%. (f) TEMPO, BAIB, rt, 2 h, 97%. (g) $(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}_2\text{C}(\text{O})\text{OCH}_3$, K_2CO_3 , 18-crown-6, -20°C \rightarrow 0°C , 2 h, 83%.

rate and hindered the equilibration to the (*E*)-enolate. Analysis of the new diastereomer by synthesis of the (*R*)- and (*S*)-Mosher esters and the acetal derivatives showed that the desired stereochemistry was obtained.

The reason for the significant amount of recovered starting material was most likely due to the presence of water in the aldehyde. This was seen in the NMR spectrum of **5**. In addition, we observed that an increase in the number of equivalents of **5** resulted in increased recovery of starting material (**4**). The diastereoselectivity of this reaction was 11:1:0:0, albeit in low overall yield.

The alcohol **22** was converted to the carbamate **23**. Using the carbamate as a directing group²⁰ allowed stereoselective reduction of the carbonyl to the corresponding alcohol **24**

- (19) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, 113, 4092. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, 95, 512. (c) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, 38, 2143.
 (20) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, 118, 11054.

Scheme 7^a

^a Reaction conditions: (a) NaClO₂, NaH₂PO₄, *t*-BuOH, 2,3-dimethyl-2-butene, rt, 1 h, 91%. (b) 2-Chloro-4,6-dimethoxy-1,3,5-triazine, NMM, THF, 0 °C, 1 h; then *N,O*-dimethylhydroxylamine hydrochloride, NMM, 0 °C \rightarrow rt, 19 h, 87%.

to be accomplished with a 30:1 selectivity. The C₁₇ alcohol was silylated to provide **25**. Subsequent oxidative deprotection of the C₇ alcohol provided **26**. Alcohol **26** was oxidized²¹ to aldehyde **27**, followed by Still–Gennari olefination²² to give the (*Z*)-olefin **2**.

To complete the synthesis of **1**, ketone **3** was prepared from aldehyde **13** (Scheme 7). Aldehyde **13** was oxidized

(21) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.

(22) Still, W. C.; Gennari, C. *Tetrahedron* **1983**, *24*, 4405.

to carboxylic acid **28**, followed by an amide coupling reaction to obtain the corresponding Weinreb amide **29**. The conversion of **29** to **3** has been reported.²³ Completion of the total synthesis of **1** using intermediates **2** and **3** has been reported elsewhere.^{3,4,23}

In conclusion, we have described a 21-step linear synthesis (34 total steps) of discodermolide that features a magnesium-chelated aldol coupling reaction of two major fragments to establish the carbon–carbon bond at C_{18–19}. Furthermore, key components of several previously published discodermolide syntheses were utilized in the present synthesis.^{6,20,24–26}

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

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(23) *Process for preparing discodermolide and analogues thereof*. Kinder, F. R. (Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.). PCT Int. Appl. 22 pp. CODEN: PIXXD2 WO 0212220 A2 20020214, 2002.

(24) Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qui, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654.

(25) Filla, S. A.; Song, J. J.; Chen, L.; Masamune, S. *Tetrahedron Lett.* **1999**, *40*, 5449.

(26) Yang, G.; Myles, D. C. *Tetrahedron Lett.* **1994**, *35*, 2503.