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Formal Synthesis of (+)-Discodermolide

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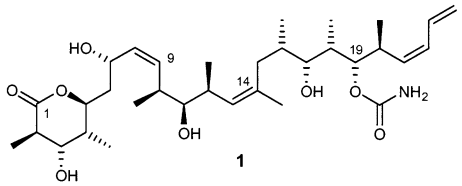
ABSTRACT



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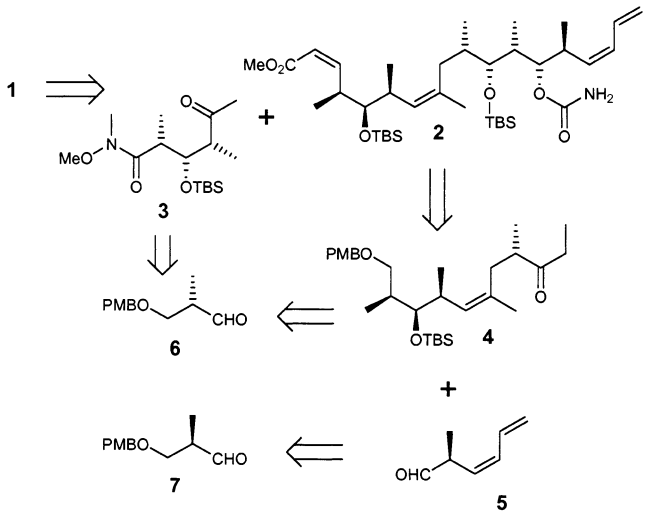
Herein we report the formal total synthesis of (+)-discodermolide in 21 steps (longest linear sequence) from commercially available Roche ester. This synthesis features the assembly of C_{9-18} and C_{19-24} fragments via a metal-chelated aldol coupling reaction.

(+)-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 1 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 1 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.

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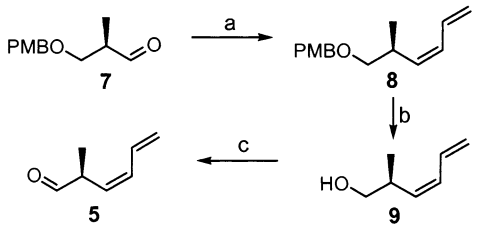
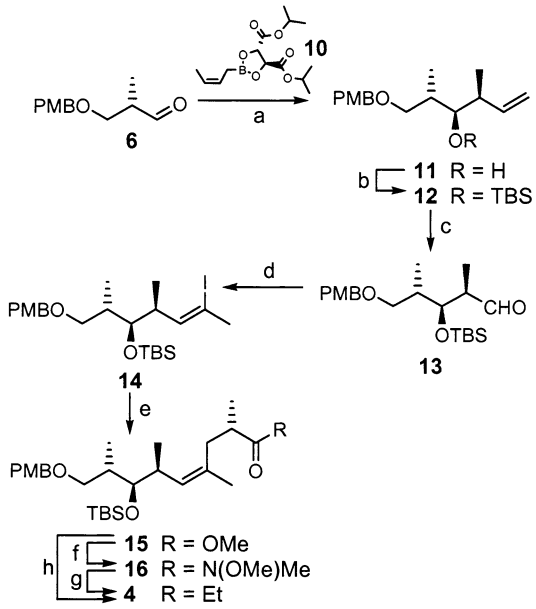
Scheme 2[a]



[a] Reaction conditions: (a) $CrCl_2$, (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]



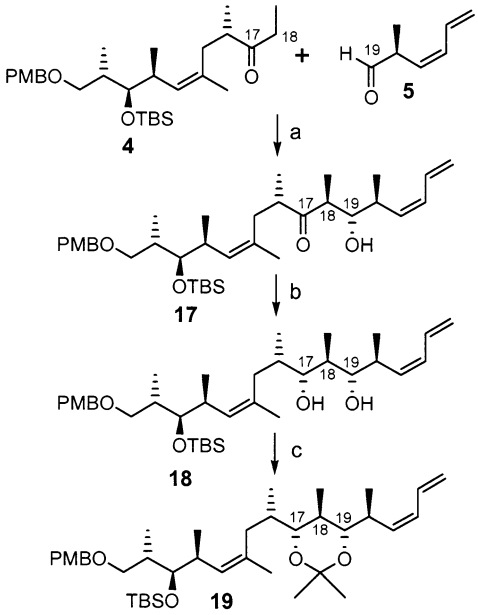
[a] Reaction conditions: (a) **10**, toluene, 4 Å molecular sieves, −78 °C, 18 h. (b) TBSOTf, 2,6-lutidine, THF, 0 °C, 1.5 h, 95%. (c) (i) MNO, OsO_4, acetone, *t*-BuOH, water, rt, 18 h; (ii) $NaIO_4$, water, THF, rt, 2 h, 71%. (d) Ph_3PEtI, BuLi, 0 °C, 10 min; then 0.1 M I_2 in THF, −78 °C, 15 min; then NaHMDS, THF, −23 °C, 10 min; then **13**, −33 °C, 30 min, 36%. (e) (*R*)-(+)-3-Methoxy-2-methyl-3-oxopropylzinc bromide, $Pd(PPh_3)_4$, THF, rt, 18 h, 87%. (f) *N*,*O*-Dimethylhydroxylamine hydrochloride, toluene, 2.0 M $AlMe_3$ 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-methylpropionate,[7] was subjected to a one-pot combination[8] of Nozaki−Hiyama[9] and Peterson-type syn elimination[10] reactions, which gave only the (*Z*)-diene **8**. This was followed by deprotection to provide alcohol **9** and a Dess−Martin oxidation[11] to give **5**.

Aldehyde **6** (Scheme 3), obtained from methyl (*S*)-3-hydroxy-2-methylpropionate, was subjected to crotyl-boration[12] to give **11** (via Roush chiral auxiliary[13] **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 compound[16] and **14** gave the methyl ester **15**.

Originally, the ethyl ketone **4** was synthesized in a two-step procedure by formation of the Weinreb amide[17] **16**, followed by nucleophilic attack by EtMgBr. Later, it was found that this two-step procedure could be easily done in one pot[18] 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.

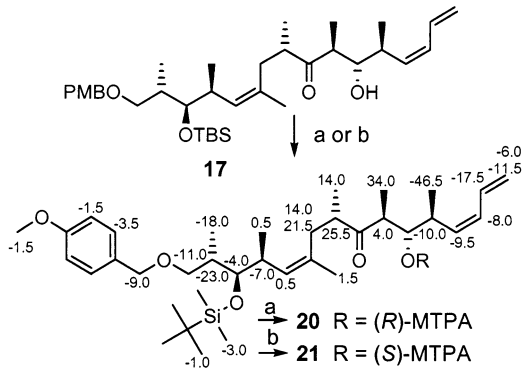
opposite stereogenic center at C_{18} was suspected due to the sluggishness of the aldol reaction, which required an unusually high temperature and long reaction time. We speculate that equilibration of the (*Z*)-enolate to the (*E*)-enolate would give the anti-configuration. To investigate, we performed reactions that would help identify which stereocenters were obtained at C_{18} and C_{19} for compound **17**.

To determine if the anti-relationship was present, the acetal **19** was synthesized (Scheme 4). Through a C_{19}-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 C_{17} hydrogen, C_{19} hydrogen, and C_{18} methyl hydrogens. Additionally, the other acetal methyl had a NOE with the C_{18} hydrogen.

To determine the absolute stereochemistry, both (*R*)- and (*S*)-Mosher esters[19] were synthesized (Scheme 5). Subtraction of the chemical shifts for each ^{1}H 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**.

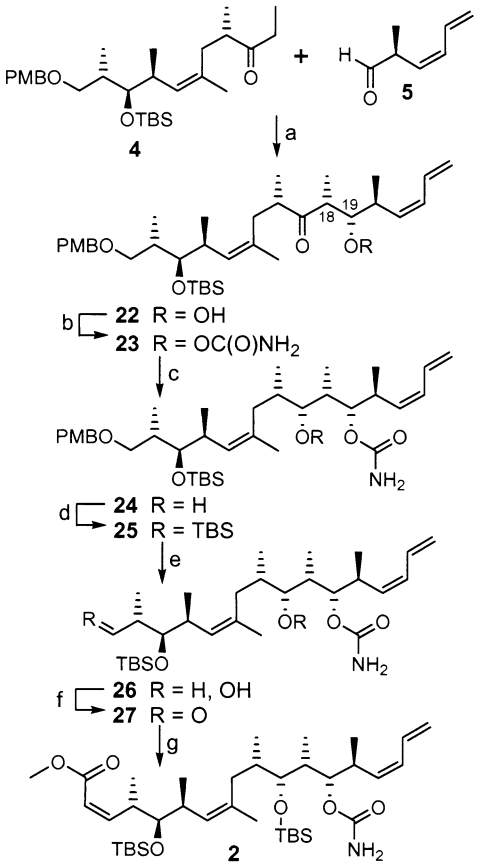
Scheme 5[a]



[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 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.

Scheme 6[a]



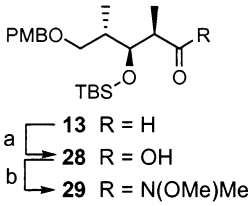
[a] Reaction conditions: (a) LDA, THF, −78 °C, 1.5 h; then $MgBr_2$, **5**, −78°C, 18 h, 35% (based on 74% recovered starting material). (b) Trichloroacetyl isocyanate, DCM, rt, 1 h; then neutral alumina, rt, 4 h, 93%. (c) Li(*t*-BuO)$_3$AlH, THF, −78 °C, 1 h, 91%. (d) 2,6-lutidine, TBSOTf, DCM, rt, 1 h, 93%. (e) DDQ, water, DCM, rt, 1 h, 92%. (f) TEMPO, BAIB, rt, 2 h, 97%. (g) $(CF_3CH_2O)_2P(O)CH_2C(O)OCH_3$, K_2CO_3, 18-crown-6, −20 °C → 0 °C, 2 h, 83%.

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 group[20] allowed stereoselective reduction of the carbonyl to the corresponding alcohol **24**

(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.
(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) $NaClO_2$, NaH_2PO_4, *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 → rt, 19 h, 87%.

to be accomplished with a 30:1 selectivity. The C_{17} alcohol was silylated to provide **25**. Subsequent oxidative deprotection of the C_7 alcohol provided **26**. Alcohol **26** was oxidized[21] to aldehyde **27**, followed by Still−Gennari olefination[22] 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 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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(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.
(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.