Total Synthesis of the Immunosuppressive Agent (–)-Discodermolide

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Scientists at the Harbor Branch Oceanographic Institute have recently reported their discovery and structural characterization of the marine natural product discodermolide.[1] In addition, their demonstration that the compound inhibits the proliferation of cultured lymphocytes[2] has suggested that it may be a candidate for use in immunosuppressive therapy. However, the inability to collect significant samples of the natural product from its native source (the sponge *Discodermia dissoluta*) has prevented a detailed investigation of its cellular specificity and mechanism of growth inhibition. We now report the first total synthesis of the (–)-antipode of discodermolide. The synthesis provides access to significant quantities of both antipodes of the natural product,[3] thereby facilitating mechanistic investigations of this molecule.[4]

The plan for the synthesis hinged on the recognition that three fragments of roughly equal complexity are separated by olefinic units in discodermolide (Figure 1). These fragments contain a common stereochemical triad that we planned to prepare from the homoallylic alcohols **6** and **7**. These simple compounds are readily derived in high diastereomeric excess from methyl (*R*)-(–)-3-hydroxy-2-methylpropionate using a procedure reported by Roush and co-workers.[5,6]

The homoallylic alcohol **7** was oxidatively cleaved and homologated to the (*Z*)-alkene using the Still–Gennari reagent (Scheme I).[7] After reduction and protection, **8** was homologated to an acetylene using Gilbert's reagent[8] and then to the iodoacetylene **3** by the method of Goekjian and Kishi.[9] **7** was also converted to the ketones **4** and **5** by first adding the appropriate Grignard reagent to an aldehyde derived from **7**. After deprotection, the diols **9** and **10** were oxidized to their corresponding keto aldehydes with subsequent selective homologation, via intermediate (*Z*)-iodoalkenes, to the dienes **4** and **5** by a palladium-catalyzed coupling with vinylzinc bromide.[10]

In accord with the recent findings of Evans and Gauchet-Prunet,[11] an internal Michael addition of a presumed hemiacetal intermediate derived from the *trans*-enoate corresponding to **6** proceeded with complete stereoselectivity to provide, after deprotection, the acetal **11**. The acetal was transformed into the third target fragment **2** by a six-step procedure.

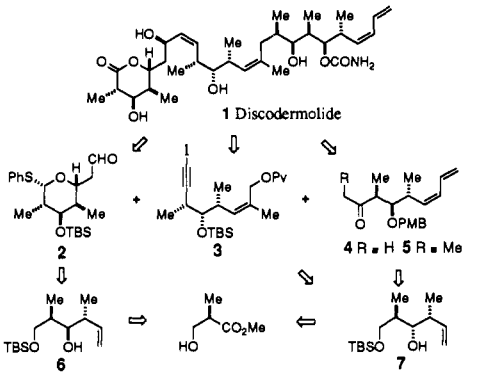
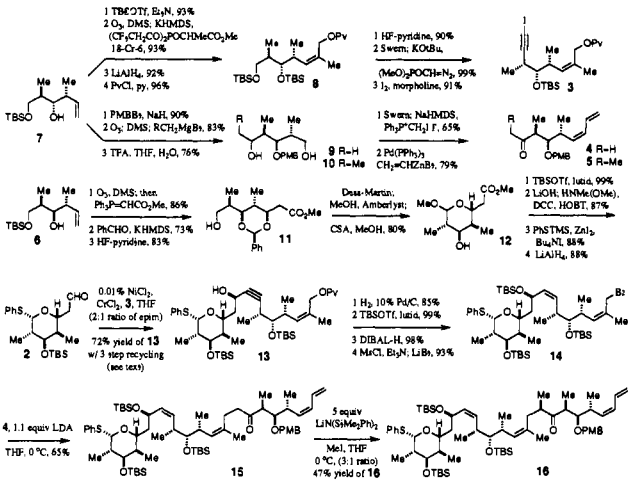


Figure 1. Retrosynthetic analysis of discodermolide.

Scheme I



After many attempts to couple fragments related to and including **2** and **3**, we eventually found that the $NiCl_2$–$CrCl_2$-promoted addition of iodoacetylenes to aldehydes developed by Kishi and colleagues provided effective results.[12] The reaction provides a 2:1 mixture of **13** and its propargylic isomer.[13] The major isomer was formed in 48% yield from the coupling reaction, but the minor isomer could be recycled to the desired epimer for an overall yield of 72%. The minor isomer was efficiently converted into **13** by a Swern oxidation (98% yield) to a propargylic ketone, which was subjected to Corey's asymmetric reduction (catecholborane and catalytic *B*-butyloxazaborolidine derived from L-proline, –20 °C) (81% yield).[14] Following a semihydrogenation of the acetylene in **13**, the pivaloyloxy group was converted to a bromide, resulting in the formation of **14**.

The final coupling reaction involved a stereoselective enolate alkylation. In the course of our synthetic investigations, we studied the coupling of the lithium (*Z*)-enolate derived from the ethyl

(1) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E. *J. Org Chem.* **1990**, *55*, 4912; Correction: *J. Org Chem.* **1991**, *56*, 1346.

(2) (a) Longley, R. E.; Caddigan, D.; Harmody, D.; Gunasekera, M.; Gunasekera, S. P. *Transplantation* **1991**, *52*, 650. *In vivo* studies were also performed: (b) Longley, R. E.; Caddigan, D.; Harmody, D.; Gunasekera, M.; Gunasekera, S. P. *Transplantation* **1991**, *52*, 656.

(3) Hung, D. T., Nerenberg, J. B., Schreiber, S. L., submitted.

(4) For discussions of the use of natural products as probes of cellular processes, see: (a) Rosen, M. K.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 384. (b) Schreiber, S. L. *Chem. Eng. News* **1992**, *70*(43), 22.

(5) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(6) Since the absolute stereochemistry of discodermolide was not known at the outset of these studies, we arbitrarily chose the enantiomer depicted, which required the use of the (*R*)-enantiomer of the starting methyl isobutyrate derivative.

(7) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405. See also experimental modifications in Wang, Z. Ph.D. Thesis, Yale University, 1988.

(8) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997.

(9) Goekjian, P. G. Ph.D. Thesis, Harvard University, 1990.

(10) Gardette, M.; Jabri, N.; Alexakis, A.; Normant, J. F. *Tetrahedron* **1984**, *40*, 2741.

(11) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, 58, 2446.

(12) (a) Aicher, T. D.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 3463. (b) Takai, K.; Kuroda, T.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5585. Addition of the acetylide to electrophiles ranging from aldehydes to methyl iodide proved to be problematic due to an apparent lack of nucleophilicity. Formation of the acetylide with bases such as LDA was confirmed by its deuteration with CD_3OD.

(13) Assigned by the method of: (a) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51* 2370. (b) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58* 3511. In the enantiomeric series, the coupling products *enant*-**13** and its minor epimer were converted to *anti*- and *syn*-1,3-diols, respectively, by hydrolysis of the thiophenyl acetals and reduction of the resulting lactols with $NaBH_4$. Formation of the ^{13}C-labeled acetonides of the 1,3-diols wiih $(^{13}CH_3)_2CO$ provided the two derivatives for stereochemical analysis. The acetonide of the major isomer had ^{13}C resonances at 23.83 and 28.15 ppm, whereas the acetonide of the minor isomer had ^{13}C resonances at 19.78 and 30.03 ppm.

(14) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem Soc.* **1987**, *109*, 5551. (b) Link, J. O. Ph.D. Thesis, Harvard University, 1992.

0002-7863/93/1515-12621$04.00/0

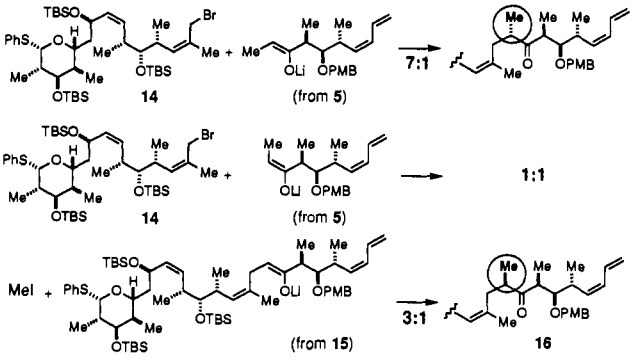
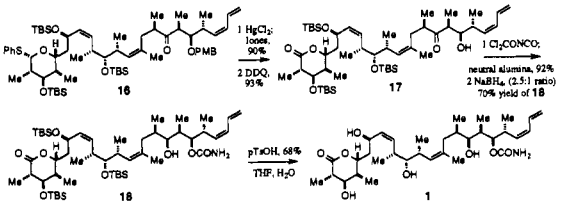


Figure 2. Stereoselectivity in enolate coupling reactions.

Scheme II



ketone **5** (prepared by enolization of **5** with $LiN(SiMe_2Ph)_2$)[15,16] with **14** (Figure 2). The reaction provided a 7:1 mixture of isomers, with the undesired isomer predominating. In an attempt to reverse the stereochemical outcome of the coupling, the lithium (*E*)-enolate derived from **5** (prepared by enolization of **5** with lithium tetramethylpiperidide)[15,17] was examined next. This enolate reacted with **14** to provide a 1:1 mixture of epimers. A more satisfactory solution takes advantage of the diastereofacial selectivity observed with the (*Z*)-enolate. Methylation of the lithium (*Z*)-enolate of **15** was expected to proceed wtih the same sense of facial selectivity observed with **5** and therefore should yield the desired isomer **16** as the predominant product. **15** was obtained by the alkylation of the lithium enolate of the methyl ketone **4** with bromide **14**. Enolization of **15** with $LiN(SiMe_2Ph)_2$ and alkylation with methyl iodide provided a 3:1 mixture of isomers, with the desired isomer **16** predominating.[18] The stereochemical outcome of these reactions can be rationalized by the less-hindered approach of the electrophile to the low-energy conformation of a β-chelated lithium enolate. Alkylation occurs from the face shielded by the methyl group rather than the face shielded by the methine group.

The completion of the synthesis of discodermolide is outlined in Scheme II. Hydrolysis of the thiophenyl acetal in **16**, oxidation of the resultant lactol to the lactone, and deprotection of the *p*-methoxybenzyl ether provided the β-hydroxy ketone **17**. Although **17** can be reduced to a *syn*-1,3-diol with excellent selectivity by the Prasad–Narasaka protocol,[19] the most expeditious synthesis of discodermolide entailed converting the alcohol into its carbamate[20] and reducing the ketone with $NaBH_4$. This procedure provided a 2.5:1 mixture of **18** and its alcohol epimer, separable by SiO_2 column chromatography. A final, complete deprotection of **18** afforded totally synthetic (–)-discodermolide ($[\alpha]^{20}_D = -13.0$ ($c = 0.6$, methanol)). The relative stereochemistry of **1** is identical to that of natural discodermolide as judged by a comparison of the ^1H and ^{13}C NMR data.[21] The signs of the optical rotations of synthetic (determined in this study) and natural (lit.[1] $[\alpha]^{20}_D = +7.2$ ($c = 0.72$, methanol)) discodermolide are opposite; however, their small absolute values diminished the confidence with which we could claim that the two samples are enantiomeric. In addition, the synthetic (–)-antipode has been shown to be a potent inhibitor of cell proliferation.[22]

The first total synthesis of discodermolide (3.2% overall yield, 36 total steps; longest linear sequence = 24 steps) reported herein has several significant features. It has been used to prepare useful quantities of stereoisomers of the natural product.[21,22] In addition, the late-stage introduction of the C17 hydrogen with $NaBH_4$ has provided a means to prepare a tritiated sample of the natural product. This reagent is proving to be of value in our efforts to characterize the cellular target(s) of discodermolide.

Acknowledgment. These investigations have been supported by a grant from Hoffmann-La Roche (awarded to S.L.S.) and fellowships to P.K.S. (American Cancer Society) and D.T.H. (NIH-MSTP and Life and Health Insurance Medical Reseach Fund). We are grateful to Dr. Jeff Tilley, Dr. Bob Guthrie, and Mr. Frank Mennona of Hoffmann-La Roche for providing samples of synthetic intermediates and to Dr. Ross Longley for providing spectral data on the natural product. Mass spectral data were obtained by Dr. A. Tyler, Ms. L. Romo, and Mr. R. Valentekovich at the Harvard University Mass Spectrometry Facility. We acknowledge the NIH BRS Shared Instrumentation Grant Program (1 S10 RR01748-01A1) and NSF (CHE88-14019) for providing NMR facilities.

Supplementary Material Available: Complete physical and spectral data for compounds **1–5**, **8–13**, **15–18**, and (–)-discodermolide; ^1H NMR data for intermediate 14; comparison ^1H NMR spectra of natural and synthetic discodermolide (28 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(15) The lithium enolates were trapped with trimethylsilyl chloride, and the resulting silyl alkenyl ethers were analyzed by ^1H NMR to confirm the anticipated configurational outcome of the deprotonation reactions.[16,17]

(16) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.

(17) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571.

(18) The methyl epimers of **16** were separated by HPLC (Rainin Microsorb column, 10.0 × 250.0 mm², 2% EtOAc/hexane, 5 mL/min).

(19) (a) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155. (b) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233.

(20) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521–5524.

(21) Without access to an authentic sample, we were unable to make a more complete comparison of natural and synthetic discodermolides. However, three nonnatural diastereomers of discodermolide were also synthesized (derived from the diastereomeric products of the final alkylation and reduction). These isomers provide ^1H NMR spectra that are readily distinguished from that of natural discodermolide.

(22) We have recently synthesized both enantiomers of discodermolide [(+)-**1**, $[\alpha]^{20}_D = +14.0$ ($c = 0.6$, methanol)] and investigated their effects on three different cell lines. Both inhibit cell proliferation, yet at different concentrations and by different mechanisms. For example, they arrest cells in different phases of the cell cycle. Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L., submitted.