Total Synthesis of (−)-Discodermolide

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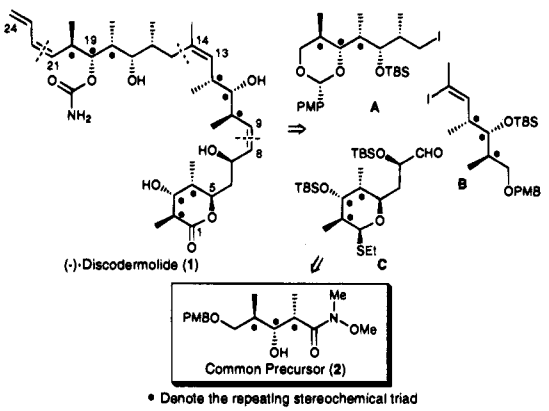
In 1990 discodermolide emerged as an extremely promising immunosuppressive agent, comparable with FK506 and rapamycin.[1,2] The exceptional pharmacological potential and extreme scarcity of the natural material [0.002% (w/w) from frozen marine sponge] have stimulated intensive synthetic effort,[3] including a total synthesis of both the unnatural and natural antipodes [i.e., (−)- and (+)-**1**] by Schreiber and co-workers,[4] which also elucidated the absolute stereochemistry.

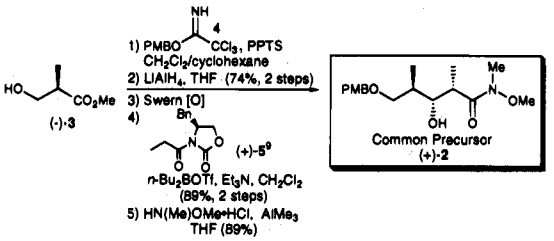
From the retrosynthetic perspective, we and others recognized the repeating stereochemical triad embedded in the discodermolide backbone (Scheme 1). This observation suggested dissection of the skeleton into fragments **A**, **B**, and **C**, each to

Scheme 1



derive from a common precursor **2**. Union of the fragments at the olefinic linkages and introduction of the terminal diene moiety would exploit a combination of stereocontrolled σ- and π-bond constructions, the former noteworthy as an innovative unifying strategem in our immunosuppressant synthetic program.[5] Herein we report a highly convergent and stereoselective total synthesis of (−)-discodermolide (**1**).[6]

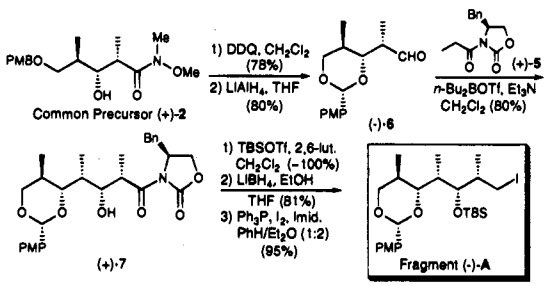
Scheme 2



As our point of departure, ester (−)-**3** (Scheme 2) was protected as the PMB ether;[7] LAH reduction, Swern oxidation,[8a] Evans syn aldol addition of (+)-**5**,[9] and Weinreb transamidation[10] then afforded the common precursor (+)-**2**.[11] The overall yield for this five-step sequence, conveniently executed on a 50-g scale, was 59%.

Elaboration of the C(15−21) fragment **A** began with DDQ oxidation[8b] of (+)-**2** (Scheme 3). LAH reduction gave aldehyde (−)-**6**,[11] which underwent syn aldol addition of (+)-**5**[9] to furnish (+)-**7**;[11] the structure and stereochemistry were confirmed by single-crystal X-ray analysis.[12] Hydroxyl protection as the TBS ether, reductive ($LiBH_4$)[13] removal of the chiral auxiliary without epimerization, and iodination via a variation of the Corey protocol[14] [I_2, PPh_3, imidazole, PhH/Et_2O (1:2)] then afforded (−)-**A**.[11]

Scheme 3



The C(9−14) fragment **B**, a vinylic halide initially conceived as the bromide **9**, likewise derived from (+)-**2**, beginning with protection (TBS) and DIBAL reduction[15] (Scheme 4). Treatment of the resultant aldehyde (+)-**8**[11] with the Wittig reagent $Ph_3PCBrCO_2Et$[16] gave predominantly (8.5:1) the expected *Z* unsaturated ester. A second DIBAL reduction, mesylation, and displacement with Super-Hydride then furnished vinyl bromide (−)-**9**.[11] After considerable experimentation, the corresponding vinyl iodide (−)-**B**[11] proved to be a more effective substrate for cross coupling (vide infra). The iodide was generated from (−)-**9** with catalytic Zn, $NiBr_2$, and excess KI (HMPA/DMF,

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(6) At the start of our work, the absolute stereochemistry was unknown.

(7) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.

(8) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505. (c) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.

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(11) All synthetic compounds were purified by flash chromatography on silica gel. The structure assigned to each new compound is in accord with its infrared, 500-MHz ^1H NMR, and 125-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry. In addition, compounds (+)-**2**, (+)-**7**, (+)-**10**, (−)-**14**, and (−)-**A** gave satisfactory combustion analyses.

(12) Carroll, P. J., University of Pennsylvania, unpublished results.

(13) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307.

(14) Corey, E. J.; Pyne, S. G.; Su, W.-G. *Tetrahedron Lett.* **1983**, *24*, 4883. We obtained superior results with the less polar solvent system PhH/Et_2O (1:2).

(15) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(16) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1980**, *102*, 7146.

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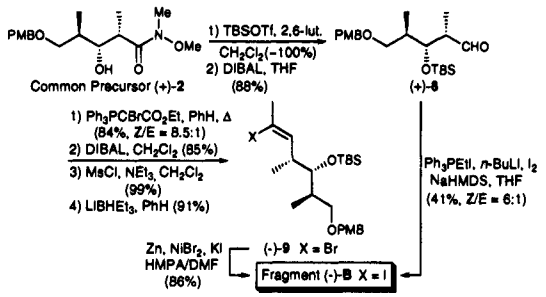
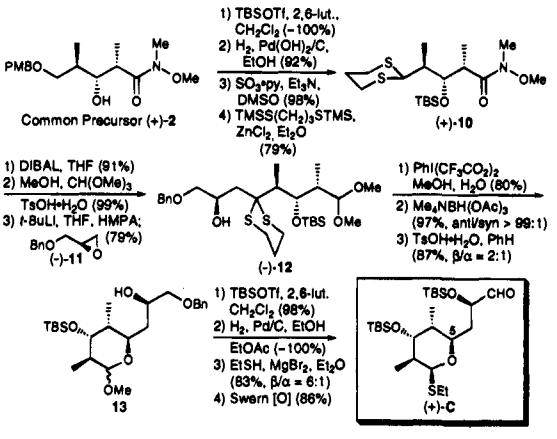
Scheme 4



90 °C, 86% yield);[17] alternatively **B** could be prepared in one step from aldehyde (+)-**8** (41%, 6:1 *Z*/*E*) via the procedure of Zhao.[18]

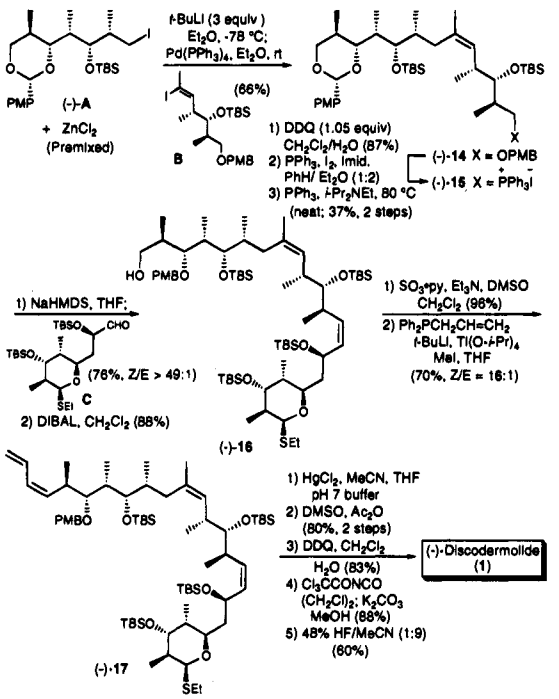
Preparation of the C(1−8) fragment **C** began with hydroxyl protection (TBSOTf) and removal of the PMB group in common precursor **2** [H_2, $Pd(OH)_2$/C, EtOH], followed by oxidation with SO_3·py[8c] and conversion to dithiane (+)-**10**[11,19] (Scheme 5). DIBAL reduction, formation of the dimethoxy acetal, and addition of the derived dithiane anion to benzyl (*R*)-(−)-glycidyl ether (**11**) then furnished (−)-**12**.[11] The latter transformation manifests a central strategy of our immunosuppressant synthetic program, the stereospecific generation of protected aldol linkages via dithiane−epoxide coupling.[5] Dithiane cleavage,[20] Evans directed reduction [$Me_4NBH(OAc)_3$],[21] and chemoselective cyclization led to the methyl pyranosides **13**.[11,22] Silylation, debenzylation (H_2, Pd/C), ethyl thioacetal formation,[23] and Swern oxidation furnished (+)-**C**.[11] The stereochemical assignments for C(5) and the anomeric center derived from NMR decoupling and NOE studies of the penultimate alcohol.

Scheme 5



With fragments **A**, **B**, and **C** in hand, we turned to assembly of the discodermolide backbone. Initially we explored the cross coupling of fragment (−)-**A** with bromide (−)-**9**; under a variety of conditions, the highest yield of (−)-**14**[11] was only 14% [$MgBr_2$, $PdCl_2$(dppf)].[24] In contrast, reaction of vinyl iodide (−)-**B** with the organozinc derivative of (−)-**A** (prepared via the alkyllithium)[25] and $Pd(PPh_3)_4$ as catalyst[26] afforded (−)-**14** in 66% yield (Scheme 6). Selective removal of the PMB group [DDQ (1.05 equiv), CH_2Cl_2, H_2O] then provided the primary alcohol with less than 2% overoxidation of the benzylic acetal. Conversion to the corresponding iodide proved unexpectedly difficult; eventually our modification of the Corey protocol [Ph_3P, I_2, imidazole, PhH/Et_2O (1:2)][14] did provide the unstable iodide,[27] which in turn furnished the requisite Wittig reagent (−)-**15**[11] upon heating (80 °C) with Ph_3P (15 equiv) and *i*-Pr_2NEt (3 equiv).

Scheme 6



Union of fragment (+)-**C** with the ylide derived from (−)-**15** (Scheme 6) and reductive opening of the acetal ring (DIBAL) gave primary alcohol (−)-**16**,[11] which was oxidized (SO_3·py) to the corresponding aldehyde. Yamamoto olefination[28] then generated *Z* diene (−)-**17**,[11] comprising the complete discodermolide backbone.[29] Hg(II)-mediated thioacetal hydrolysis followed by oxidation (DMSO, Ac_2O) introduced the C(1) lactone.[30] Completion of the discodermolide synthetic venture entailed removal of the PMB group (DDQ), carbamate introduction via the Kocovsky protocol ($Cl_3CCONCO$; imide hydrolysis),[31] and final deprotection (HF, CH_3CN); synthetic (−)-**1** was identical to (−)-discodermolide (500-MHz ^1H and 125-MHz ^{13}C NMR, IR, HRMS, optical rotation, and TLC in four solvent systems).[32]

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Supporting Information Available: Spectroscopic and analytical data for **1**, **2**, **6**−**10**, **12**−**17**, and **A**−**C** as well as selected experimental procedures (15 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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