Total Synthesis of (−)-Discodermolide: An Application of a Chelation-Controlled Alkylation Reaction

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Received May 9, 1997

The polyhydroxylated lactone (+)-discodermolide (*ent*-1) is a potent microtubule-stabilizing agent with antitumor activity similar to that of taxol. In this communication, we describe the total synthesis of (−)-discodermolide (**1**) using chelation-controlled alkylation reaction as the key coupling. Like taxol,[2] *ent*-**1** arrests the cell cycle at the G_2/M boundary and promotes the formation of microtubules.[3] In addition to our own work[4,5] several partial syntheses of discodermolide have appeared.[6] Total syntheses of discodermolide have been described by Schreiber and co-workers[7] and Smith and co-workers.[8]

We adopted a highly convergent strategy to **1**, disconnecting the C-7/8 and C-15/16 bonds to give three key subunits, structures **2**−**4** (Figure 1). The key coupling reaction (C-15/16) was envisioned to occur via a diastereoselective alkylation reaction between the anion of ethyl ketone **4** and allylic iodide **3**. A metal-promoted coupling of a C-8 *Z*-vinyl iodide with a C-7 aldehyde was expected to complete the carbon backbone of **1**.

Chelation of the *β*′-alkoxy moiety in enolate **5** (Figure 2) fixes the enolate in a rotational isomer that displays the α′-methyl group in a position that blocks one face of the enolate. In their synthetic efforts directed toward discodermolide, both Schreiber and co-workers[7] and Heathcock and co-workers[6b] examined the formation of the C-15 to C-16 bond by way of alkylation. They found that for their substrates where P′ was *p*-methoxybenzyl, the alkylation of ethyl ketones analogous to ketone **4** gave the stereochemistry opposite to that required for discodermolide. Both groups overcame this obstacle via a two-step alkylation protocol. Based on our own work[4] and these results, the diastereoselectivity of this type of alkylation is dependent on a number of factors including temperature, solvent, counterion, and protecting group P′ at the *β*′ position of the ketone.

The partners in the chelation-controlled alkylation used for the synthesis of discodermolide were ethyl ketone **7** and allylic iodide **8** (Figure 3). We have previously described syntheses of both **7**[4] and **8**[5] via short sequences starting from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate. We took advantage of the chelating ability of the methoxymethyl protecting group in the key alkylative coupling to form the C-15 to C-16 bond and in the chelation-controlled reduction of the C-17 ketone and to facilitate introduction of the C-19 carbamate late in the synthesis.

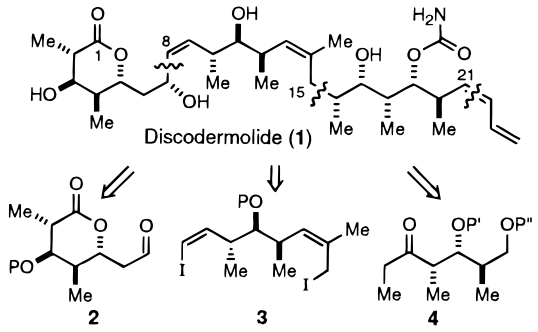

Figure 1.

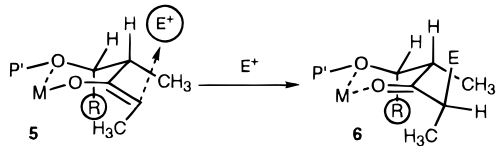

Figure 2.

We found that treatment of **7** with lithium hexamethyldisilazide and 1 equiv of tetramethylethylenediamine in THF at −78 °C followed by addition of allylic iodide **8** led to smooth chelation-controlled alkylation. The diastereoselectivity of this reaction shows a remarkable solvent dependence, affording the desired diastereomer as the major component of a 6:1 mixture, in 70%, using the mixed solvent system 45:55 hexanes:THF. Our assignment of the structure of the major diastereomer was strengthened by the reversal of selectivity (1:18) when using the nonchelating Na^+ counterion during the alkylation. We later established the validity of this assignment via the total synthesis. Using chelation-controlled reduction of ketone **9** with LAH and lithium iodide in ether at −78 °C, we established the C-17 alcohol stereochemistry with >8:1 diastereoselectivity. Silylation of the secondary alcohol (Tips-OTf, TEA) followed by selective hydrogenolysis of the C-9 benzyl ether[9] (Ra/Ni, H_2) then afforded C-9 to C-21 synthon **10** in 71% yield and facilitated separation of all minor diastereomers from **10**.

After extensive investigation into alternative strategies, we found that the Nozaki−Kishi coupling[10] of a C-8 *Z*-vinyl iodide to aldehyde **13** had emerged as the best option. To prepare the required vinyl iodide, we oxidized the C-9 alcohol (**10**) using tetrapropylammonium perruthenate (TPAP) in 10% acetonitrile in CH_2Cl_2.[11] We immediately treated this material with iodomethylene−triphenylphosphorane[12] to obtain the vinyl iodide in 85% yield with *ca.* 20:1 *Z:E* selectivity. Oxidative cleavage

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S0022-3263(97)00809-8 CCC: $14.00

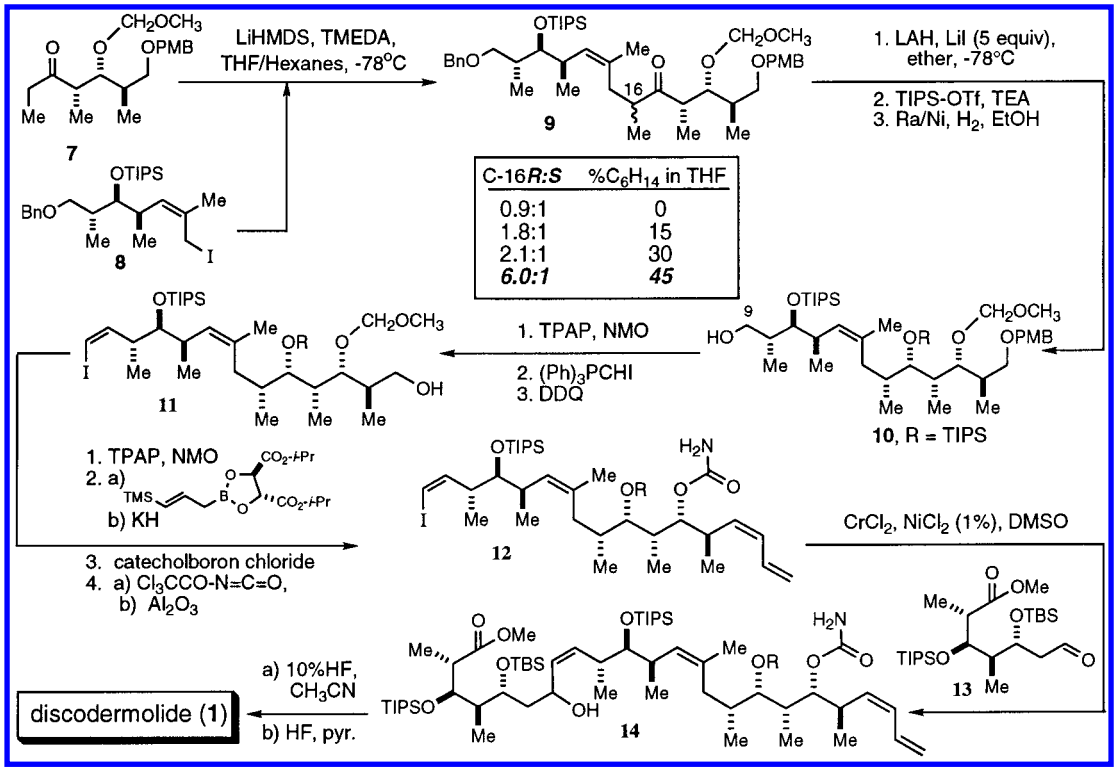

Figure 3.

of the C-21 PMB ether using DDQ proceeded smoothly (87%) to afford alcohol **11**. After TPAP oxidation of alcohol **11** (85%), we prepared the *Z*-diene via a modified Peterson olefination[13] to obtain the desired alkene in >20:1 *Z:E* selectivity in 70% from **11**. After extensive experimentation, we found that 1 equiv of catecholboranyl chloride and 0.5 equiv of H_2O in CH_2Cl_2 led to hydrolysis of the methoxymethyl ether and furnished the desired C-21 alcohol in 60% yield. We prepared carbamate **12** in 80% by treatment of the alcohol with trichloroacetyl isocyanate.[14] The transition metal (1% $NiCl_2$ in $CrCl_2$, DMSO, 5 d) promoted addition of the vinyl iodide of **12** to aldehyde **13**[15] proceeded to afford the C-1 to C-24 fragment **14** of discodermolide in 40% yield as a mixture of C-7 epimers with starting materials **12** and **13** recovered in *ca.* 30% and 30% yield, respectively. The diastereoselectivity of this coupling process is *ca.* 2.5:1. As with diastereoselective alkylation, we did not prove the stereochemistry of the major isomer at this point. We then treated **14** with 10% aqueous HF in acetonitrile for 18 h to remove the C-5 TBDMS ether, effect lactonization, and remove one of the TIPS ethers. Prolonged exposure to these conditions did not lead to further desilylation. Thus, we isolated the monosilyl ether of discodermolide and treated it with HF/pyridine for 18 h to provide stereochemically homogeneous (−)-discodermolide in 40% yield, which could be easily separated from a byproduct believed to be C-7-*epi*-discodermolide, isolated in 20% yield. The (−)-discodermolide obtained from this sequence gave an optical rotation opposite in sign and equal in magnitude to (+)-discodermolide ((−)-**1** $[\alpha]^{22}_D = -14$, $c = 0.28$, MeOH; (+)-**1** $[\alpha]^{22}_D = +14$, $c = 0.50$, MeOH[7b]). Our synthetic (−)-discodermolide was identical in all other respects (^{1}H NMR, ^{13}C NMR, HPLC, IR) to authentic (+)-discodermolide.

This highly convergent synthesis of discodermolide takes advantage of a chelation-controlled alkylation reaction to achieve high selection in the key bond coupling reaction. We have found this method to be highly useful and are applying it to not only to the synthesis of structural analogs of discodermolide but also to the synthesis of other targets.

Acknowledgment. The Alfred P. Sloan Foundation, the University of California, and Pfizer Inc. supported this research. The authors thank Drs. R. E. Longley and S. P. Gunasekera of the Harbor Branch Oceanographic Institution for helpful discussions and for providing (S.P.G.) a sample of (+)-discodermolide, and Mr. T. Lee for help in preparing this manuscript.

Supporting Information Available: Experimental procedures and spectral data for compounds **1**, **9**−**14** (33 pages). information.

JO9708093

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