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The Synthesis of the C-9 to C-21 Sector of Discodermolide: An Efficient Route to the C13-14 *Z*-Trisubstituted Alkene.

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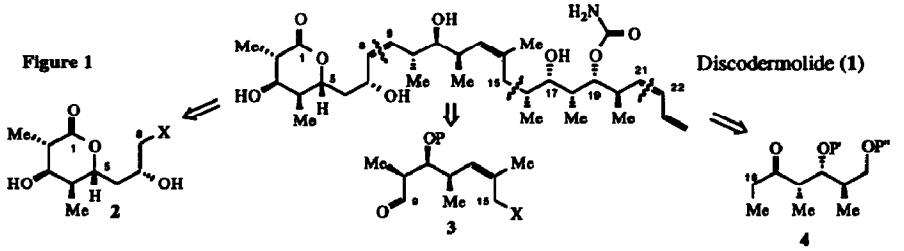
Abstract: The synthesis of the C-9 to C-21 sector of the immunosuppressive marine natural product discodermolide is described. The C-9 to C-15 subunit is synthesized in five steps from aldehyde **5** using the diene aldehyde cyclocondensation reaction. Diastereoselective alkylation of the previously synthesized C-16 to C-21 subunit by a suitably functionalized C-9 to C-15 synthon (**3**) leads to the C-9 to C-21 sector of discodermolide.

We have recently reported a strategy for the synthesis of the C-13 to C-21 sector of the immunosuppressive agent discodermolide (1).[1,2,3,4] The critical C-15 to C-16 bond was established via a diastereoselective alkylation of the lithium enolate of ketone **4**. In this letter we detail the synthesis of the central C-9 to C-15 fragment **3** of discodermolide and the use of this *Z*-trisubstituted alkene in a similar alkylative coupling reaction to afford the C-9 to C-21 sector of the target molecule.

Figure 1



The C-9 to C-15 synthon was prepared via a short sequence of operations described in Figure 2. It was our plan to take advantage of a cyclic structure to enforce the *Z*- geometry in the alkene. Subsequent cleavage of the ring would then furnish the desired acyclic compound. Dihydro-4-pyrone **7** has been obtained via the diene-aldehyde cyclocondensation reaction of diene **6** and aldehyde **5**.[5,6] Dihydropyrone **7** serves as the template for the establishment of the required Z-trisubstituted alkene of discodermolide. In addition, the cyclocondensation

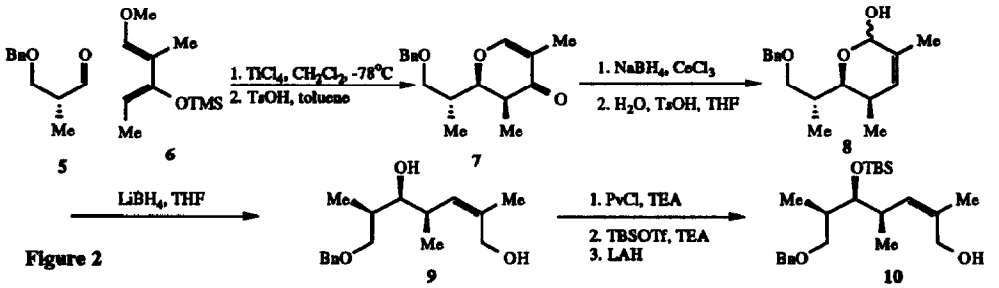


Figure 2

reaction establishes the three stereogenic centers in **3**. Setting the stage for the cleavage of the heterocycle, reduction of the carbonyl of pyrone **7** using sodium borohydride in the presence of cerium trichloride[7] afforded the corresponding alcohol as a mixture of diastereomers. This material was isomerized[8] to hemiacetal **8** with aqueous p-toluenesulfonic acid in refluxing THF. Reductive opening of the pyran ring with lithium borohydride

afforded the desired Z-allylic alcohol **9** in 62% yield from pyrone **7**. Acylation of the primary allylic alcohol (pivaloyl chloride, TEA, DMAP, CH_2Cl_2) followed by silylation of the secondary (TBS-OTf, TEA, CH_2Cl_2) and reductive cleavage of the ester afforded allylic alcohol **10** in 69% yield from **9**.

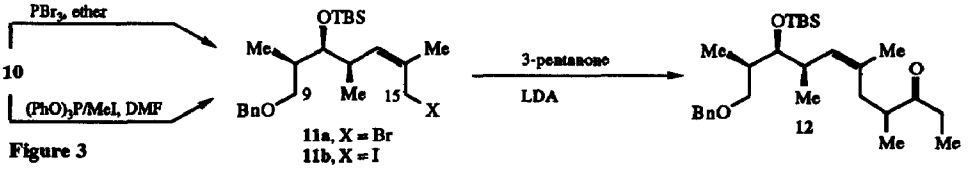


Figure 3

Activation of the allylic alcohol set the stage for alkylation experiments. Conversion of the allylic alcohol to its corresponding bromide (PBr_3, ether) or iodide ($(PhO)_3P/MeI$, DMF)[9] afforded C-9 to C-15 synthons **11a** and **11b**. We next examined the alkylation of the lithium anion of 3-pentanone by **11**. Treatment of 3-pentanone with LDA and HMPA in THF at -78°C followed by allyl bromide **11a** lead to no alkylated product. However under the same conditions, iodide **11b** led to smooth alkylation to afford ketones **12** and establish the C-15 to C-16 bond.

We are investigating the application of this strategy to the coupling of **11b** and **13**[1] for the synthesis of the C-9 to C-21 section of discodermolide. In a preliminary experiment, treatment of the lithium enolate of ketone **13** with HMPA and iodide **11b** at -78°C in THF resulted in alkylation to afford ketones **14**, the C-9 to C-21 fragment of discodermolide in 23% yield with recovered starting material. This alkylation showed little diastereoselectivity (*ca.* 1.1:1). In addition to the expected products, we also observed in 20% yield the product resulting from the elimination of the methoxymethyl ether at C-19 following alkylation. We are currently optimizing conditions and investigating the stereochemical outcome of the alkylative coupling reaction (Fig. 4).

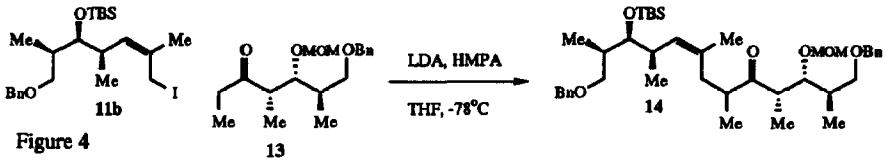


Figure 4

In summary, we have developed an efficient diastereo- and enantioselective strategy for the synthesis of the C-9 to C-15 Z-trisubstituted alkene of the discodermolide (1) backbone. We have found that allylic iodide **11b** will alkylate simple ketone enolates and have examined the coupling of two key fragments of **1** via the diastereoselective alkylation of the enolate of **13**.

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