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An Alkylative Strategy to the C-13 to C-21 Sector of Discodermolide

*Ge Yang and David C. Myles**

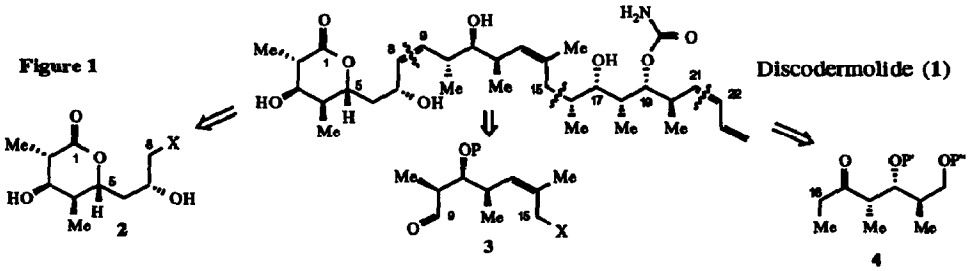
Department of Chemistry and Biochemistry, UCLA
Los Angeles, CA 90024-1569

Abstract: An approach to the C-13 to C-21 sector of the immunosuppressive marine natural product discodermolide (1) is described. The C-15 to C-16 bond is formed by diastereoselective alkylation of a ketone enolate. Either diastereomer of alkylation can be obtained by selecting the appropriate counter ion. The C-16 to C-21 subunit is prepared in two steps from **11**.

The heightened interest in understanding the subtleties of the human immune system has placed new emphasis on the discovery and characterization of new immunologically active natural products. Cyclosporin A and FK-506 are two such compounds which have been used to minimize the immunological consequences of organ transplantation. Recently, Gunasekera and coworkers revealed that the organic extracts of the marine sponge *Discodermia dissoluta* displayed antileukemic and immunosuppressive activity.[1] The polyhydroxylated lactone discodermolide (1) was found to have activity against P388 murine leukemia cells and in a two-way mixed-lymphocyte response (MLR) assay while displaying low cytotoxicity. More recently, this *in vitro* activity was demonstrated *in vivo* in mice.[2,3]

We chose to adopt a highly convergent strategy to the synthesis of discodermolide (1), disconnecting the carbon backbone at the C-8,9 Z-alkene and C-15,16 allylic bond, thus dividing the target into three key subunits, structures **2**, **3**, and **4**. In this letter we describe the enantio- and diastereoselective synthesis synthons for **4** and investigations into the alkylative coupling of this fragment to form the C-13 to C-21 sector of discodermolide.[4]

Figure 1



Structure **5** (Figure 2) depicts enolates of an alkoxy ketone similar to **4**, possessing similar stereochemistry at the α and β carbons. Chelation of the β-alkoxy function would serve to organize the enolate prior to alkylation (structure **5**).[5] The two factors which will determine the stereochemical outcome of the

alkylation are the diastereofacial selectivity of alkylation and the enolate geometry. Examination of **5** leads to the expectation that alkylation will occur via transition state A from the less hindered top face of the enolate, away from the α and β substituents. The trajectory of disfavored transition state B would place the alkylating agent in a *syn*-pentane like relationship with the α methyl group of **5**. The *Z* enolate of **5** (X=Me, Y=H) reacting through transition state A would form adduct **7**. Alkylation of the *E* enolate via transition state B would lead to **8**. Partial structure **9** shows that the required sense of the stereocenter set in the alkylation step is analogous to that in **7**, the product of alkylation of a *Z* enolate via transition state A. Alternatively, the stereochemical outcome of the alkylation of non-chelated enolate **6** should be governed by avoidance of A strain between the enolate and the stereocenter in the α position.[6] Thus, alkylation takes place on the bottom face of the enolate via transition state D, away from the adjacent large alkyl side chain (R").

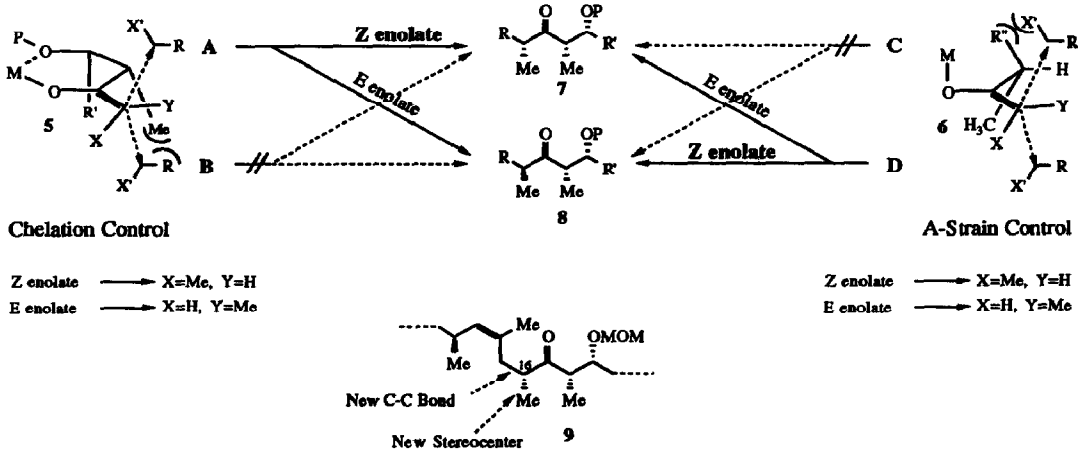


Figure 2

As a model for the key diastereoselective coupling reaction, we examined the alkylation of **12** by allyl iodide (Figure 3). Ethyl ketone **12** was prepared directly by aldol condensation of the lithium anion of 3-pentanone and *R*-3-benzyloxy-2-methylpropionaldehyde (77%),[7] followed by protection of the resulting alcohol as the methoxymethyl ether (73%).[8] The selection of the methoxymethyl protecting group for the alcohol β to the ketone was expected to promote the desired chelation of the metal counter ion of the enolate. In addition, this protecting group will facilitate introduction of the C-19 carbamate function at a late stage in the synthesis. As a model for the C-9 to C-15 synthon, we chose allyl iodide. Although allyl iodide can alkylate via S_N2 and S_N2' mechanisms, we felt that it would be a suitable alkylating agent for the model experiments.

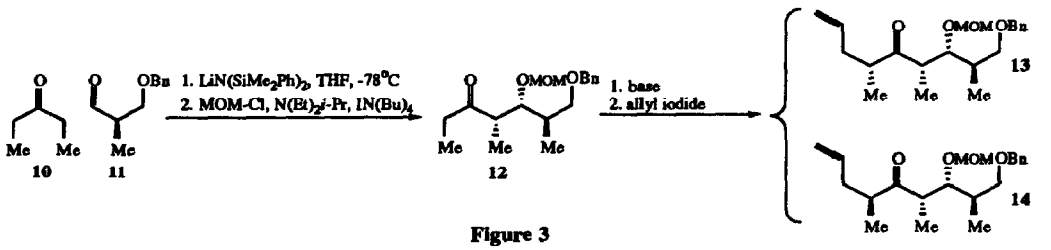


Figure 3

After investigating several sets of conditions for the alkylation, we found that treatment of **12** with lithium diisopropylamide and hexamethylphosphoramide in THF at -78°C followed by 2.5 equivalents of allyl iodide afforded alkylated products in a diastereomeric ratio of 1.8:1.0 in 65% yield favoring the desired alkylation product **13** as the major product (*vide infra*). Interestingly, treatment of **12** with NaHMDS in THF followed by allyl iodide resulted in reversal of the diastereoselection, affording **14** as the major product. Thus, by selecting the counter ion, either diastereomer of alkylation is easily accessible. We are currently optimizing reaction conditions and investigating the generality of these processes (Table 1).

Table 1. Alkylation of Ketone **12**

Base	Equiv Allyl Iodide	13/14	Yield
LDA	2.5	1.8:1.0	65%
$LiN(SiMe_2Ph)_2$	2.5	1.7:1.0	71%
NaHMDS	2.5	1.0:3.5	68%

Chelation controlled reduction of the ketone with LAH and lithium iodide in ether at -100°C established the C-17 alcohol stereochemistry with excellent diastereoselectivity and facilitated separation of all minor diastereomers from the major product (Figure 3).[9] Acid promoted cyclization of hydroxyl acetal **16** allowed for unequivocal determination of the facial selectivity of the reduction by examination of the ^1H NMR coupling constants of protons at C-17 and C-18.[10] Hydroboration (9-BBN) of the alkenes of **16** followed by cycloetherification of the corresponding tosylate afforded pyrans **17**. Examination of ^1H NMR coupling constants between protons at C-16 and C-17 of these materials proved the stereochemistry of the alkylations.[11]

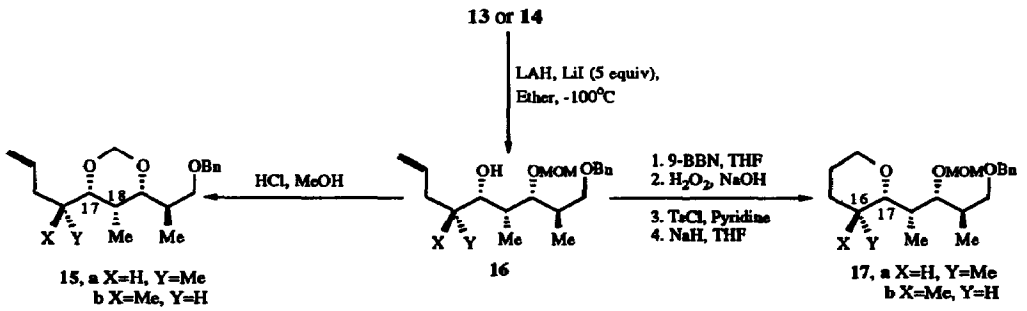


Figure 4

In conclusion, we have found that in the presence of a methoxymethyl ether at the β position, modest chelation controlled alkylation of the lithium enolate of ketone **12** can be obtained. In addition, the sodium enolate of **12** showed good diastereoselctivity for alkylation presumably through a non-chelated intermediate. Thus by selection of the counterion, either diastereomer of alkylation could be obtained. Conversion of the alkylation products to cyclic materials allowed for unambiguous assignment of the stereochemistry of alkylation reactions. We are currently investigating the generality of this alkylation process and optimizing conditions for chelation controlled alkylation.

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References and Notes

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8. Aldehyde **11** is prepared from methyl (S)-(+)-3-hydroxy-2-methylpropionate (Aldrich) via the following sequence: 1. DHP, CH_2Cl_2, TsOH; 2. LAH, ether; 3. benzyl bromide, NaH, THF, IN(Bu)4; 4. EtOH, TsOH; 5. oxalyl chloride, DMSO, TEA, CH_2Cl_2.

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10. ^1H NMR couplings for **15a**: (discodermolide numbering is used) $J_{(H17\text{-}H18)}$ = 2.0 Hz. For **15b**: $J_{(H17\text{-}H18)}$ = 2.0 Hz. Spectra were recorded in $CDCl_3$ at 360 MHz on a Brucker spectrometer.

11. ^1H NMR couplings for **17a**: (discodermolide numbering is used) $J_{(H16\text{-}H17)}$ = 1.9 Hz. For **17b**: $J_{(H16\text{-}H17)}$ = 9.6 Hz. Spectra were recorded in $CDCl_3$ at 360 MHz on a Brucker spectrometer.

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