Studies on the Alkylation of Chiral Enolates: Application toward the Total Synthesis of Discodermolide

David L. Clark and Clayton H. Heathcock*

Department of Chemistry, University of California, Berkeley, California 94720

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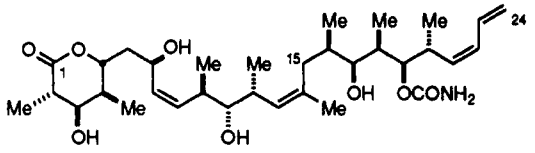
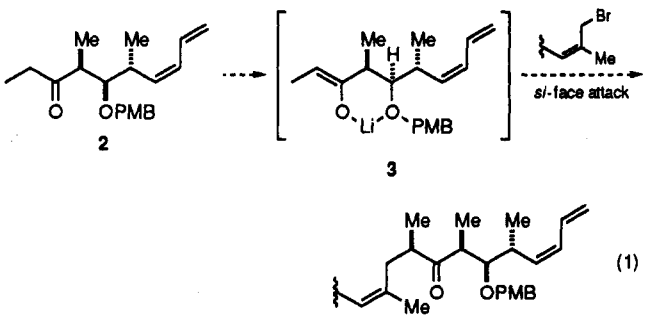
Summary: The alkylation of chiral enolates related to the C-16 to C-24 portion of discodermolide has been studied.

Discodermolide (1) is a polypropionate-derived natural product recently isolated[1] from the marine sponge *Discodermia dissoluta*. It is a potent *in vivo* immunosuppressive agent, with potential clinical applications, rivaling cyclosporine or FK506 in activity.[2]



Discodermolide 1

In addition, discodermolide represents a challenge to present methods for the synthesis of stereochemically complex molecules. We have begun studies aimed at the total synthesis of discodermolide. It was thought that the lithium *Z* enolate derived from ketone **2** might be selectively alkylated on the less hindered *si*-face through the intermediacy of an internally chelated enolate, such as **3** (eq 1). If successful, this maneuver would allow the

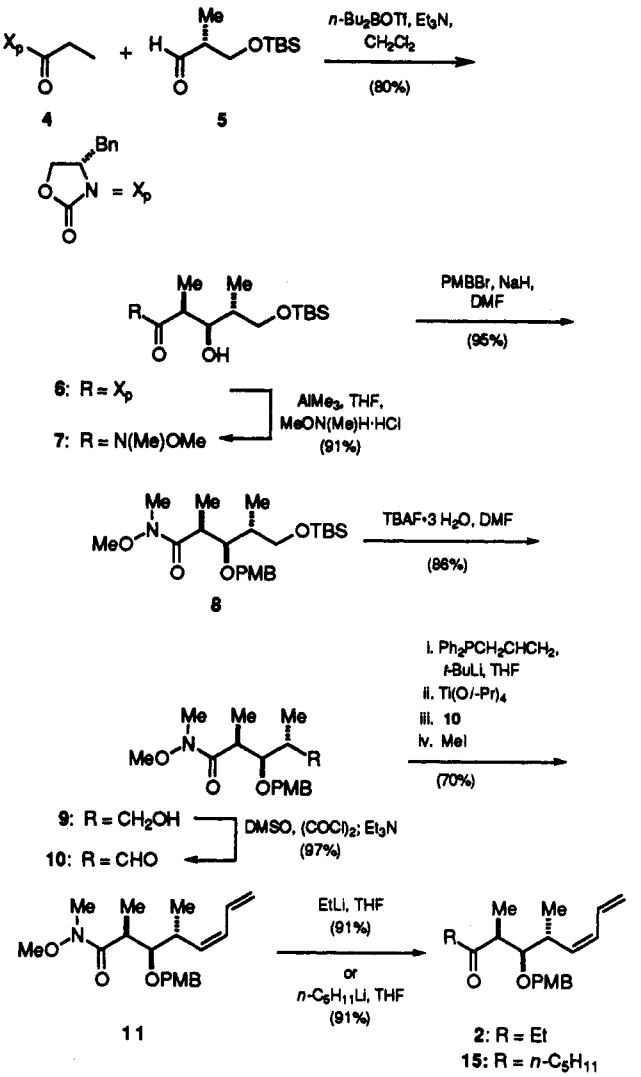


(1)

convergent assembly of two complex subunits with the control of the stereochemistry at C-16. We report here our studies toward this goal.

The synthesis of ketone **2** is shown in Scheme I. Reaction of imide **4**[3] with aldehyde **5**,[4] according to the procedure of Evans,[3] provided aldol **6**, which could be converted to the corresponding *N*-methoxy-*N*-methylamide[5] **7** in 73% overall yield. Protection of the alcohol as the *p*-methoxybenzyl ether **8** occurred without incident. Extensive experimentation was required to find conditions suitable

Scheme I



for the desilyation of **8**.[6] Eventually it was found that treatment of **8** with tetrabutylammonium fluoride trihydrate in DMF at 0 °C provided the labile alcohol **9**, which could be oxidized[7] to give aldehyde **10** in 83% overall yield. The *Z* diene was created according to the method of Yamamoto.[8] Reaction of aldehyde **10** with the species generated from titanium(IV) isopropoxide and lithiated allyldiphenylphosphine, followed by addition of methyl

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(6) Deprotection of **8** under basic conditions (TBAF, THF) resulted in β-elimination at a rate competitive with desilylation. Under acidic conditions (AcOH, THF, H_2O or HF, pyridine), or upon standing, alcohol **9** under went cyclization to the corresponding δ-valerolactone.

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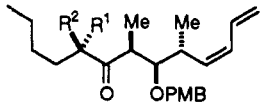
Table I

ketone	electrophile	yield (%)	ratio of 12:13[a]
2	*n*-BuI	77	89:11
15	MeI	97	12:88

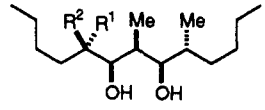
[a] Product ratios were determined by hydrogenation with 5% Pt–C followed by HPLC analysis.

iodide, gave diene 11 in 70% yield with 10:1 *Z*/*E* selectivity. Reaction of amide 11 with ethyllithium provided ketone 2 in 91% yield.

With ketone 2 in hand, the key alkylation reaction could be studied. Enolization[9] of 2 with lithium bis(dimethylphenylsilyl)amide, at −78 °C, followed by addition of *n*-butyl iodide and warming to 0 °C, gave adducts 12 and 13 in a ratio of 89:11 (Table I). The stereochemical outcome of the alkylation was determined by a four-step conversion to diol 14,[10] which exhibited a ^{13}C NMR spectrum containing only nine peaks, as predicted for the meso compound. Thus, alkylation occurs on the *re*-face. To amend the situation for application in a synthesis of discodermolide, two tactics might be employed: (1) the alkylation could be performed on the *E* enolate, or (2) the electrophile and enolate substituent could be exchanged. The latter option was chosen. Enolization of ketone 15, with lithium bis(dimethylphenylsilyl)amide, followed by addition of methyl iodide and warming to −35 °C, gave the same two ketones in a ratio of 12:88 (Table I). Confirmation of the relative configuration was obtained by transforming 13, to diol 16, which displayed 16 ^{13}C NMR signals.



12: R^1 = Me, R^2 = H
13: R^1 = H, R^2 = Me



14: R^1 = Me, R^2 = H
16: R^1 = H, R^2 = Me

These results suggest that the alkylation does not proceed through a chelated species such as 3. This observation is consistent with those made in earlier studies[9b] on the aldol reaction of related lithium enolates. However, by reversing the order of substituent introduction, it is possible to obtain the desired stereochemical outcome necessary for application to a total synthesis of discodermolide.

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Supplementary Material Available: Experimental procedures and analytical data for all new compounds reported in this manuscript (12 pages). This material is contained in 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.

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(10) The sequence consisted of the following: (1) hydrogenation of the diene with 5% Pt–C; (2) HPLC separation of the C-5 methyl epimers; (3) removal of the PMB group with DDQ; and (4) reduction of the β-hydroxy ketone to the *syn*-diol with Et_2BOMe and $NaBH_4$.[11] Consult the supplementary material for more details.

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