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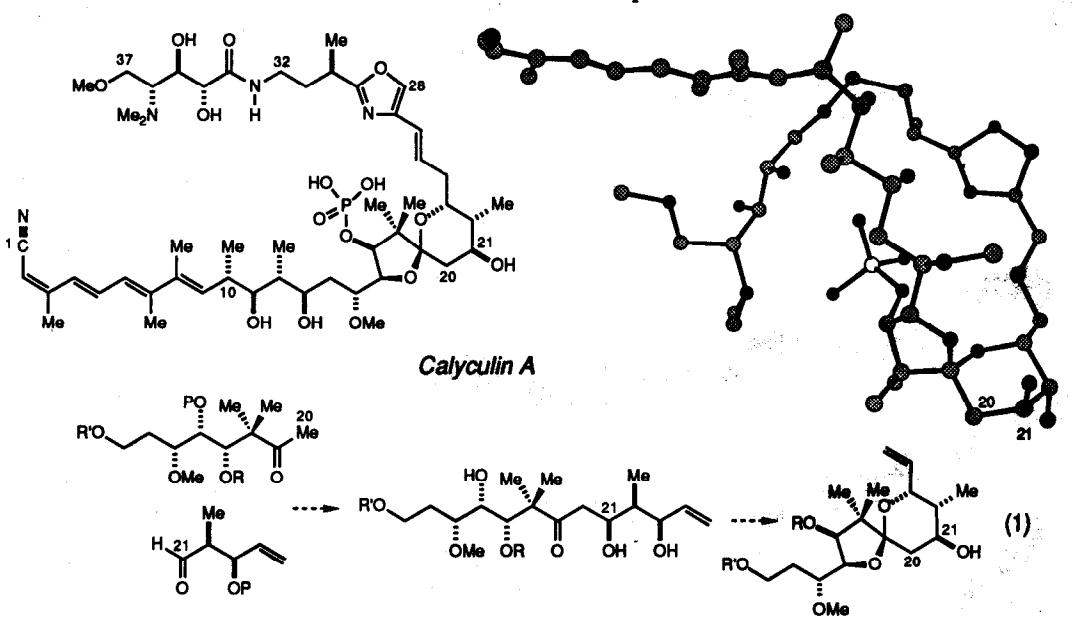
Reversal of Aldehyde Diastereofacial Selectivity in a Methyl Ketone Aldol Reaction. Application to the Synthesis of the Calyculin Spiroketal

David A. Evans* and James R. Gage[1]

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Abstract: It has been observed that aldehyde diastereofacial selectivity in a methyl ketone aldol reaction can be fully regulated under appropriate conditions. Addition of the lithium enolate provided the product derived from apparent chelation control, while Lewis acid-promoted addition of the derived silyl enol ether afforded the Felkin-Anh diastereomer. Application of this methodology to the ongoing synthesis of calyculin A is presented.

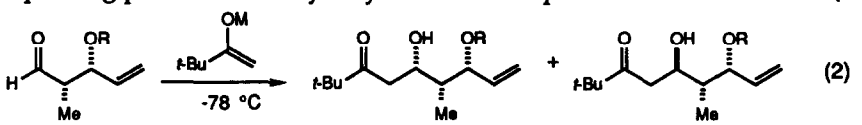
We recently undertook studies directed towards the synthesis of the calyculins, bioactive metabolites isolated from the sponge *Discodermia calyx*.[2] At the core of these richly functionalized natural products lies a spiroketal bearing an array of six stereogenic centers.[3] Our plans for the assemblage of this portion of calyculin A call for construction of the C_{20}-C_{21} bond through the illustrated Felkin-Anh selective aldol addition reaction (eq 1).[4]



Literature analogies for related aldol reactions suggested that the desired diastereomer might be obtained by reaction of a lithium enolate with a suitably protected aldehyde.[5,6] Accordingly, studies were undertaken to investigate the stereochemical details of this bond construction. In the initial phases of the study the illustrated methyl ketone was modeled by pinacolone (eq 2). In

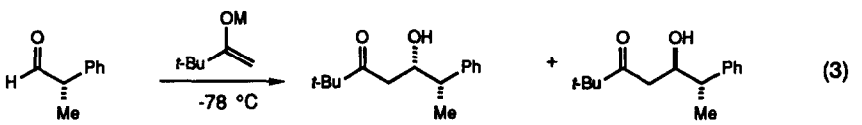
each of the reactions the diastereomeric aldol adducts were chromatographically separated and transformed to their respective 1,3-diol acetonides. The relevant ^1H NMR NOE experiments performed on these derivatives allowed for unambiguous assignment of stereochemistry for the diastereomeric aldol adducts **2** and **3**.[7]

To our surprise, the reaction of aldehyde **1a** with the lithium enolate of pinacolone produced predominantly the anti-Felkin aldol adduct **3a** (Table, entry 1). The selectivity could not be turned over by varying the nature of the silyl ether protecting group (entries 2 and 3). The preference for these aldehydes to undergo anti-Felkin addition is in accord with a subsequently reported effort to perform a similar bond construction en route to a calyculin synthon.[8] Addition of the corresponding pinacolone dibutylboryl enolate to **1b** proved to be nonselective (entry 4).



1a R = Si-Et$_3$ (TES)
b R = Si-Me$_2$*t*-Bu (TBS)
c R = Si-*i*-Pr$_3$ (TIPS)

2 (Felkin-Anh) **3**



4 **5** (Felkin-Anh) **6**

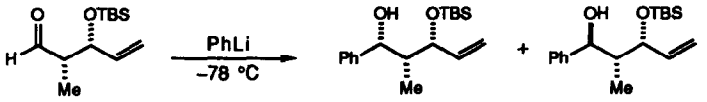
Table. Aldol Diastereoselection Versus Enolate and Aldehyde Structure.

Entry	M	Aldehyde	Ratio[a] 2:3 (or 5:6)
1	Li	**1a**	18:82[b]
2	Li	**1b**	12:88
3	Li	**1c**	20:80
4	BBu_2	**1b**	50:50
5	TBS, $BF_3{\cdot}OEt_2$	**1a**	98:2[c]
6[d]	Li	**4**	80:20
7[d]	TBS, $BF_3{\cdot}OEt_2$	**4**	96:4

[a]Determined by ^1H NMR analysis except where noted. [b]Partial epimerization of the aldehyde occurred. [c]Determined by capillary GLC. [d]Taken from reference 11.

Although the unexpected stereochemical outcome of the aldol reaction with the lithium enolate may be rationalized by invoking chelation control, we think that this explanation is unlikely for three reasons. First, silyl ethers, especially *tert*-butyldimethylsilyl and triisopropylsilyl ethers, usually preclude chelate organization of the type under discussion.[9] Second, no clear dependence of selectivity on the size of the protecting group is observed (entries 1-3). Third, addition of

phenyllithium to aldehyde **1b** afforded a mixture of alcohols with the expected syn (Felkin) adduct predominating in a ratio of 71:29 (eq 4). We have not at present settled on a satisfactory rationalization for this behavior.

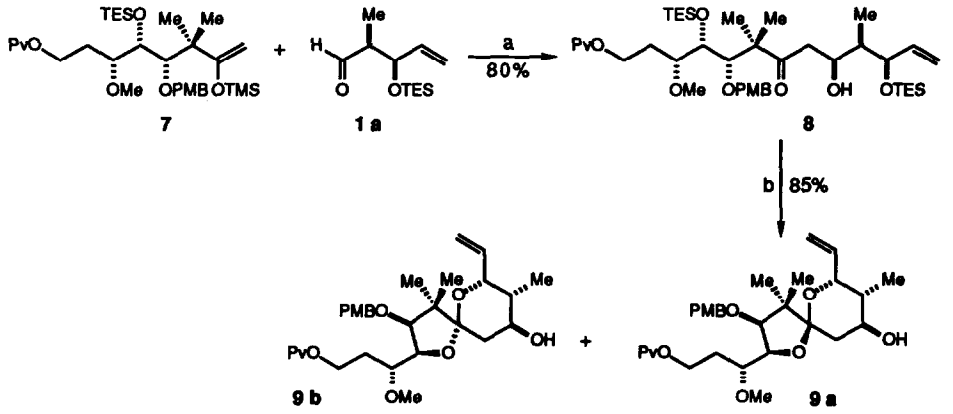


(4)

diastereoselection 71 : 29

In an effort to reverse the stereochemical outcome of the aldol reaction to give the desired aldol adduct **2**, the Lewis acid promoted addition of a pinacolone silyl enol ether was investigated.[10] Heathcock and Flippin have shown that the boron trifluoride etherate promoted addition of a silyl enol ether to 2-phenylpropanal gives enhanced levels of Felkin selectivity relative to the addition of the corresponding lithium enolate (Table, entries 6 and 7).[11] To our satisfaction, the reaction of the *tert*-butyldimethylsilyl enol ether of pinacolone with aldehyde **1a** in the presence of boron trifluoride etherate (1.1 equiv, CH_2Cl_2, -78 °C, 15m) afforded the desired Felkin aldol adduct **2a** with exceptional selectivity (entry 5). Notably, the silyl ether protecting group survived the reaction intact. Thus, choice of appropriate conditions allows for the selective formation of either aldol diastereomer **2** or **3** without recourse to chiral enolates.

We then proceeded to apply the boron trifluoride etherate promoted aldol reaction to the calyculin problem. Treatment of aldehyde **1a** and silyl enol ether **7** with an excess of this Lewis acid (10 equiv $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 °C, 10 h) afforded hydroxyketone **8** as a single diastereomer in 80% yield. This aldol adduct could be transformed to an equilibrium mixture (5:1) of spiroketals **9a** and **9b** in 85% yield by treatment with 48% aqueous HF/acetonitrile/water (5:86:9, 25 °C, 4 h). The two spiroketals were readily separated by column chromatography, and the undesired, minor diastereomer could be recycled by resubmission to the reaction conditions. The stereochemical assignments of each of the diastereomeric spiroketals followed from an unambiguous set of ^1H NOE experiments. Further studies on the total synthesis of the calyculins will be reported in due course.



(a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 °C, 10h. (b) 48% aq. HF:MeCN:water (5:86:9), 25 °C, 4h.

As a caveat to the preceding discussion, the aldol bond constructions described in this study are also relevant to related stereochemical issues in projected syntheses of the aplysiatoxin spiroketal.[12]

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(1) National Science Foundation Predoctoral Fellow, 1986-1989.

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