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Remarkable Long Range Effects on the Diastereoface Selectivity in an Aldol Condensation

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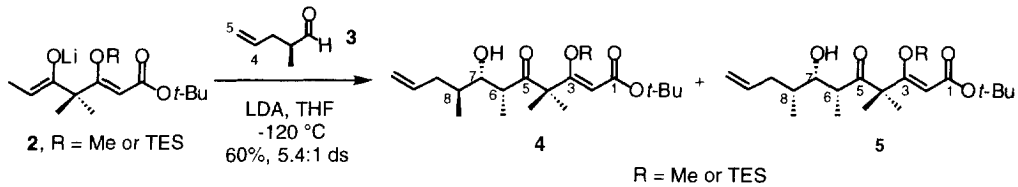
Abstract: The stereochemical results in an aldol reaction between the enolate **2** and various α-methyl aldehydes indicates a stabilizing through space interaction between C_4-C_5 unsaturation and the formyl group. This interaction leads to a reaction conformation which favors a C_7-C_8 (epothilone numbering) *anti*-relationship in the aldol products. Included is an extensive study that identifies steric and electronic effects of various α-methyl aldehydes in the aldol diastereoselection.

Keywords: Epothilone B, aldol, anti-Cram

Recently, we completed a semi-practical total synthesis of 12,13-desoxyepothilone B.[3,4] In the communication describing this syntheses, we reported the development of tricarbonyl dianion synthons and the unusual face selectivity observed in their aldol condensation with the chiral α-methyl aldehyde **3** (eq 1).



The aldol reactions proceed through the intermediacy of a *Z*-lithium enolate with the expected topographic selectivity. The major product has the C_6-C_7 *syn* relationship shown in **4** (by *ul* addition). Surprisingly, but fortunately, the C_7-C_8 relationship of the principal product was anti (by *lk* addition).[5] Superficially the relative face selectivity exhibited in the aldol condensation seems to be contrary to the predicted models for double stereodifferentiation encompassed in the Felkin rules.[6] Our results were rationalizable in the context of a perception originally suggested by Roush to account for attrition in *anti* selectivity with certain aldehydes.[7] As a

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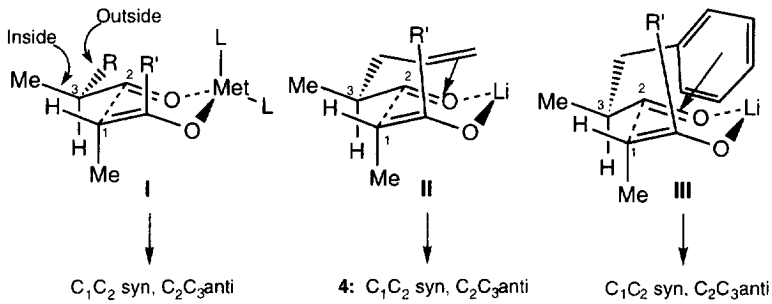
result of his study, a model was proposed in which the R group (larger group) of the aldehyde is distanced from the R' group of the enolate (**I**) to avoid an unfavorable, developing syn-pentane interaction. The crux of the Roush formulation focuses on minimization of steric hindrance between the largest functions of the enolate and the α-branched aldehyde in the reacting ensemble.



Our observations using aldehyde **3** (Table 1) and related congeners were quite unique in that our substrate aldehydes lack the usual resident protected alcohol derivative such as is usually involved in fashioning *anti* diastereoface selectivity.[8] Rather, the conformational bias in our substrates is dependent on a particular relationship between the unsaturated site in the pendant side chain and the formyl moiety. We identified an important consequence in the tether length between the unsaturation and the formyl group. Thus reduction of the double bond of the side chain led to a sharply diminished selectivity affording a 1.3:1 mixture of diastereomeric products (entry b). Also, lengthening of the tether beyond that found in **3** led to a 2:1 ratio of diastereomers (entry c). By contrast, benchmark 2-phenylpropionaldehyde (entry d) gave strong *syn* diastereoface selectivity consistent with previous findings with this particular aldehyde. The results of entry e, in which similar steric factors are virtually equivalent (propyl *versus* allyl at the branching site) demonstrate a small, but clear preference for the C_7-C_8 *anti* product, presumably reflecting the special effect of the olefin-aldehyde interaction.

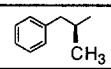
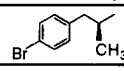
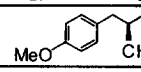
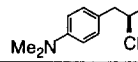
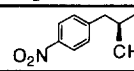
Table 1. Results of aldol reaction of **2** and various acyclic aldehydes, RCHO.

Entry	Aldehyde, R =	Ratio (C_7-C_8, *syn:anti)*	
a		1	5.4
b		1	1.3
c		1	2.0
d		11	1.0
e		1	2.0

Further experimentation revealed that the unsaturation site could be encompassed in the context of a properly positioned benzo linkage. We first examined the effects of *para*-positioned functional groups on the resultant C_7-C_8 relationship (Table 2).

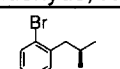
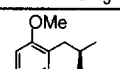
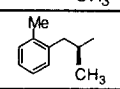
Some minor slippage in the *anti*:*syn* ratio is seen in the *para*-bromo substrate (entry b). The benchmark ratio (entry a) is restored with the *para*-methoxy substrate (entry c) while a small improvement was realized with the *para*-dimethylamino derivative (entry d). By contrast, in the *para*-nitrophenyl substrate, the C_7-C_8 *anti* selectivity is abrogated. Clearly, the "aryl effect" is closely coupled to the electron donating ability of the ring.

Table 2: Results of aldol reaction of **2** and various aromatic aldehydes, RCHO.

Entry	Aldehyde, R =	Ratio (C_7-C_8, *Syn*:*Anti*)	
a		1	5.0
b		1	4.2
c		1	5.0
d		1	5.4
e		1	1.2

By contrast with the reconcilable data observed with *para*-substituted substrates, a range of *ortho* substituents (Table 3) all resulted in significant weakening of the C_7-C_8 *anti* selectivity. We take these data to suggest that *ortho* substitution results in some steric inhibition of the rotamer in which the faces of the aromatic ring and formyl group are parallel (see structure **III**).

Table 3: Diastereoface selectivity in the aldol reaction of **2** and various *ortho*-substituted aromatic aldehydes, RCHO.

Entry	Aldehyde, R =	Ratio (C_7-C_8, *Syn*:*Anti*)	
a		1	2.1
b		1	1.2
c		1	2.8

In summary, our data point to a stabilizing through-space interaction[9] of a donor olefinic linkage with the formyl function as the likely source of preference of conformers **II** and **III** leading to the sense of attack anticipated by the Roush model.[7] Further explorations based on probing this theme are planned.

Acknowledgments

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References and Notes

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2 Present address: Eli Lilly Corporate Research Center, Indianapolis, IN 46285

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9 An alternate view, suggested by a reviewer of this manuscript, postulates that the unsaturation acts as a ligand on a second lithium atom complexed to the aldehyde group. We thank the referee for proposing this argument.