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Concerning the Diastereofacial Selectivity of Aldol Reactions of Chiral Methyl Ketone Enolates: Evidence for Remote Chelation in the Bafilomycin Aldol Reaction

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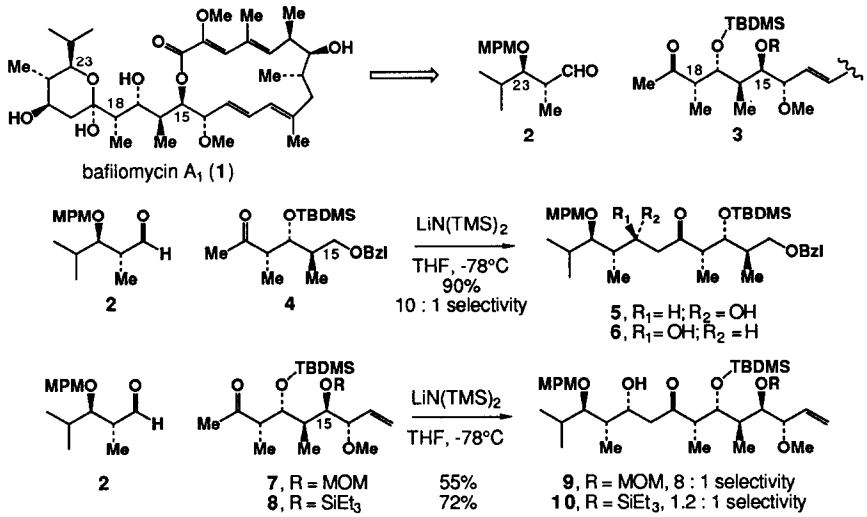
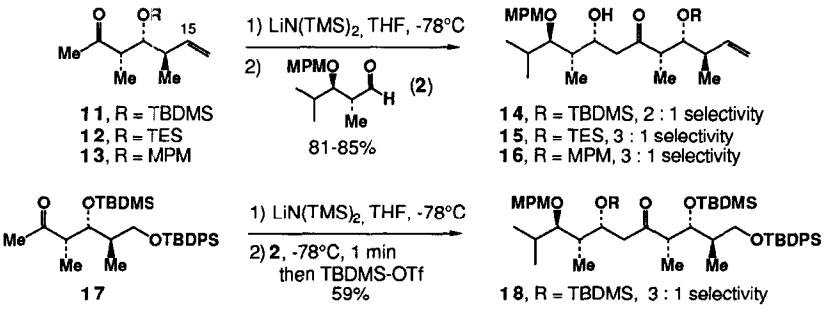
*Abstract. Evidence is presented that the aldol reactions of the lithium enolates of **4** and **7** proceed preferentially by way of chelated transition structure **19**.*

One of the key steps in our synthetic approach to bafilomycin A_1 (**1**)[2] is the aldol reaction between the chiral aldehyde **2** and a chiral methyl ketone represented by partial structure **3**. We recently reported that the aldol reaction of **2** and methyl ketone **4** provides aldol **5** with up to 10 : 1 selectivity, but that the product ratio is highly dependent on the metal counter ion and solvent additives.[3] We also reported that the aldol reaction of **2** and the lithium enolate of **7** is reasonably selective (8 : 1) for the Felkin aldol **9**, but that the reaction of **8** possessing a triethylsilyl ether at the remote C(15) position is not.[3] In view of the increasing importance of fragment assembly aldol reactions of chiral ketone enolates and chiral aldehydes in natural products synthesis[3,4] and the need to define more fully the factors that influence the diastereofacial selectivity of chiral enolates,[5,6] we report herein additional investigations of the bafilomycin aldol reaction and our conclusion that chelation involving the C(15)-alkoxy substituents of **4** and **7** plays an especially important role in the reactions of the lithium enolates.



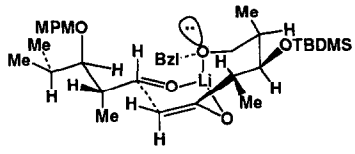
Aldol reactions of **11-13** and **17** were examined to provide further insight into the influence of the C(17) and C(15) substituents on the aldol diastereoselectivity. These reactions were performed by treating the methyl ketones with 1.2 equiv. of $LiN(TMS)_2$ in THF at -78°C followed by adding a solution of **2** in THF.

The reactions with **11-13** were quenched 30-120 sec later with pH 7 buffer solution and products isolated by standard procedures. The mixture of aldols obtained from the reaction of **17** were unstable with respect to retro aldolization during silica gel chromatography, so the reaction of **2** and **17** was quenched after 1 min with TBDMS-OTf to give the TBDMS protected aldol **18** and its C(21)-epimer. Each of these reactions provided 2-3 : 1 mixtures of the two diastereomers, with the Felkin isomer (**14-16**, **18**) predominating in each case.[7,8]

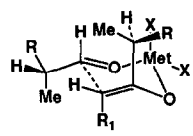


These data show that while the C(17) alkoxy group has almost no influence on the stereochemistry of the reaction, the C(15) alkoxy group is strongly implicated as an important stereochemical control element since the only lithium enolate aldol reactions in this series that give synthetically useful levels of diastereoselectivity are with **4** and **7** which possess Lewis basic C(15)-alkoxy groups.[9] This prompts us to suggest that the reactions of **2** with **4** and **7** proceed by way of a chelated transition state such as **19**.[10,11] While remote chelation effects are rarely observed,[12] this hypothesis is consistent with the following observations: (i) the lithium enolates prepared from methyl ketones **8** and **17** possess C(15)-silyl ethers that should disfavor participation in a chelated transition state like **19**;[13] (ii) enolates deriving from **11-13** lack a C(15)-alkoxy group and are incapable of reacting by way of such a highly ordered, chelated transition structure; and (iii) the aldol reactions of **2** with the sodium and boron enolates of **4**, as well as with the lithium enolate in the presence of HMPA, are non-selective (ca. 1 : 1),[3] since chelates involving the C(15)-alkoxy group are less likely (Na enolate) or are impossible (B enolate) under these conditions. It is inferred that in the absence of a highly organized, chelated transition structure such as **19**, several other transition structures must be accessible, the combination of which leads to poor diastereoselectivity in the aldol reactions of **8**, **11-13** and **17**. Our working hypothesis is that the non-chelated aldol reactions proceed by way of transition structures **20** and **21** which exhibit opposite selectivity for addition of the enolates to the aldehyde. We expect that the diastereofacial selectivity of aldol reactions that proceed by way of non-chelated chair-like transition states should favor the Felkin diastereomer (e.g., **14-18** via **20**), in view of Evans' observation that the aldol reactions of chiral ethyl ketone Z(O)-enolates are also highly diastereoselective by way of t.s. **22**.[5e] Replacement of R_1 = Me in **22** by R_1 = H in **20** should not significantly decrease the diastereofacial selectivity of the chiral enolate in **20** vs. **22**. However, it is well known that boat-like transition structures are often significant contributors in aldol reactions of acetate or methyl ketone enolates.[5d,14] This implies that the boat-like transition structure **21** must favor the "anti-Felkin" aldol diastereomers (e.g., **6**). Examination of molecular models of **21** suggests that the indicated anti-Felkin rotamer should be favored in order to minimize non-bonded interactions between the α-substituents on the aldehyde and the chiral methyl ketone which are cis in **21**, but trans in **20**. This hypothesis provides a basis for rationalizing an example of a highly anti-Felkin selective methyl ketone aldol reaction reported by

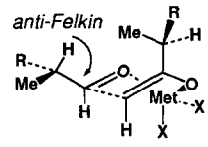
Evans, assuming that the boat t.s. is considerably lower in energy than the chair in this case.[15] Thus, according to this analysis, the high selectivity aldol reactions of **4** and **7** benefit from the involvement of **19** which is lower in energy than either **20** or **21**. In cases where **19** is not involved (e.g., **8**, **11-13** and **17**), selectivity ranges from approximately 1 : 1 to 3 : 1 since **20** and **21** are comparable in energy.



19

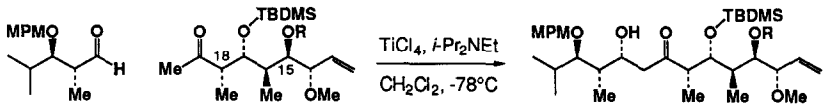


20, R_1 = H
22, R_1 = Me



21

While the data presented above strongly implicate chelation involving the C(15)-alkoxy substituent in the reactions of the lithium enolates, we close by noting that this substituent is unimportant in aldol reactions of the chlorotitanium enolates. For example, the aldol reactions of **2** and the Ti^{+4} enolates of **8** with **23**, which were generated by using Evans' procedure,[5e] provide the Felkin aldols **10** and **24** with excellent diastereoselectivity (≥94 : 6). Because a chelated transition state analogous to **19** seems unlikely under these conditions, the excellent diastereoselectivity may be a consequence of the shorter Ti-O bond lengths that maximize non-bonded interactions in the boat-like transition state,[4h] thereby raising its energy so that the vast majority of the reaction proceeds by way of the chair-like transition structure **22** (Met = Ti).



2

8, R = $SiEt_3$
23, R = COPh

74%
81%

10, R = $SiEt_3$, ≥96 : 4 selectivity
24, R = COPh, 94 : 6 selectivity

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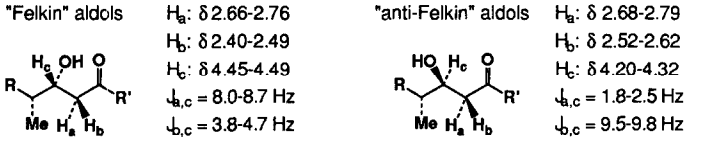
7. The spectroscopic properties (high field ^{1}H NMR, IR, high resolution mass spectroscopy and/or C,H analytical data) of all new compounds were in complete agreement with the assigned structures.
8. The stereochemistry of many of the aldols generated in this study were assigned by ^{1}H NMR analysis of the p-methoxybenzylidene acetals generated by DDQ oxidation of the aldols (for several examples, see ref. 3). However, we also noticed a strong correlation between the assigned stereochemistry and the ABX pattern for the three spin system shown. We have correlated over 10 pairs of methyl ketone aldols by this method, and feel that it can be used for making reliable stereochemical assignments.



9. We established that the aldol reaction of **2** and **4** proceeds under kinetic control by treating **6** (the minor product of this reaction) with 1.1 equiv. of $LiN(TMS)_2$ in THF at -78°C for 15 min, and also with $Li(NTMS)_2$ in THF-HMPA at -78°C for 15 min, to regenerate the lithium aldolate. The "Felkin" diastereomer **5** was not observed in either case, indicating that equilibration does not occur under the reaction conditions. Similarly, the minor product of the aldol reaction of **2** and **12** did not equilibrate with **15** when resubjected to the reaction conditions.
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11. It is well appreciated that lithium enolates exist as aggregates in solution, and that the dimeric forms are believed to be the most reactive species (Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624). The chelation event implied by our data can be accommodated in a dimeric structure, and it is also conceivable that that the C(15)-alkoxy substituent could be chelated to a second lithium cation in an aggregate. We represent transition structures **19-21** as monomers simply for convenience.
12. For several examples of remote chelation effects in carbonyl addition reactions: (a) Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 6335. (b) Frenette, R.; Monette, M.; Bernstein, M. A.; Young, R. N.; Verhoeven, T. R. *J. Org. Chem.* **1991**, *56*, 3083.
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