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Diastereoselective Aldol Reactions of β–Silyloxy Ethyl Ketones. Application to the Total Synthesis of Bafilomycin A_1

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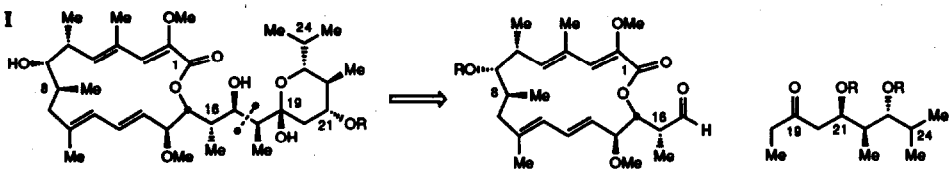
Abstract: Studies directed toward the C_{17}-C_{18} aldol bond construction in the macrolide antibiotic bafilomycin A_1 are described. The effect of the β-substituent in the aldol reactions of α-unsubstituted enolates is documented for various model compounds. The stereoselectivity of this process is critically dependent on the C_{21} and C_{23} oxygen protecting groups. Application of this methodology to the synthesis of bafilomycin A_1 is reported.

Bafilomycin A_1 (1), first isolated and characterized in 1983 by Werner and Hagenmaier,[1a] is a prototypical member of a family of 16- and 18-membered macrolide polyketides which includes the bafilomycins,[1] the concanamycins,[2] and the hygrolidins.[3] The relative stereochemistry of the bafilomycins[1b] and concanamycins[2b] has been established by X-ray diffraction, and the absolute stereochemistry of the concanamycins has been determined by degradation.[2a]

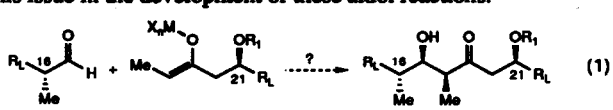
One of the pivotal disconnections that has evolved from a consideration of plausible syntheses of this natural product is the C_{17}-C_{18} aldol transform illustrated below (Scheme I). The purpose of this Letter is to communicate our studies pertaining to the successful development of this complex aldol bond construction.[4]

Scheme I



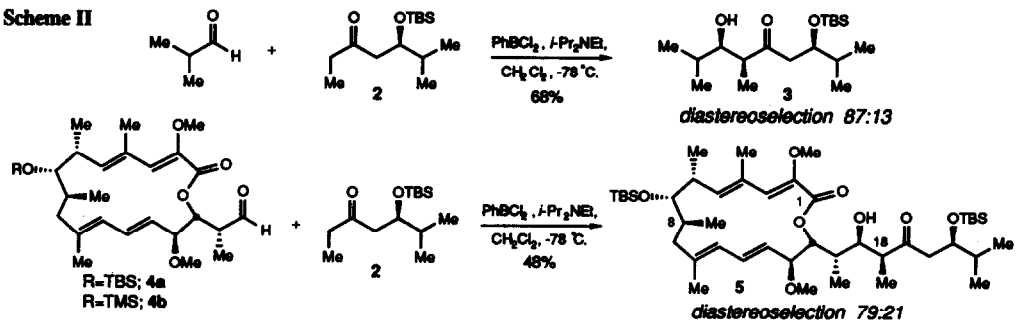
R = H; bafilomycin A_1; (1)
R = flavensomycinate; bafilomycin B_1
R = fumarate; bafilomycin C_1

The aldol reaction suggested by this analysis is undocumented in the literature (eq 1), and some uncertainty is associated with the projected stereochemical outcome of this process. As with double stereodifferentiating reactions of this type, the π-facial selectivities of the aldehyde and enolate reaction partners can be individually analyzed and then combined with reasonable fidelity to predict the stereochemical outcome of the reaction.[5] The addition of most nucleophiles to chiral α-substituted aldehydes is adequately described by the Felkin-Anh paradigm.[6] However, numerous examples have documented that (*Z*) enolates belong to a special class of nucleophiles that exhibit selectivity for the *anti*-Felkin aldehyde diastereoface, a π-facial bias compatible with the desired stereochemical outcome of the projected aldol process.[7] The uncertainty associated with this anticipated bond construction rests with the undetermined facial bias of the enolate coupling partner. The present study was undertaken to address this issue in the development of these aldol reactions.


(1)

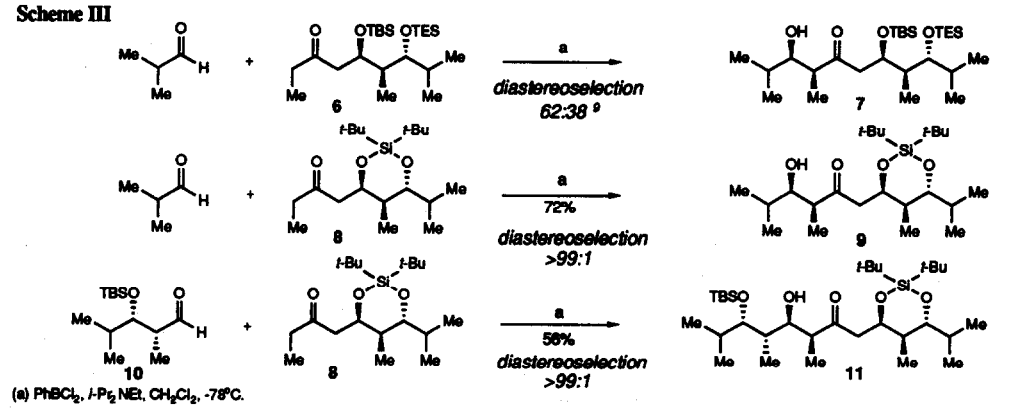
To determine the intrinsic facial selectivity of α-unsubstituted-β-siloxy ethyl ketones, the aldol reactions of ketone **2** with isobutyraldehyde were assayed using the derived *syn*-selective boron and titanium enolates. For these metal enolates the two *syn* aldol adducts were the only products produced with the desired *syn* diastereomer being favored in all cases (Scheme II). Based on selectivity and yield criteria, the little-used chlorophenylboryl enolate[8] was selected for further study. As illustrated below, the desired sense of asymmetric induction was also achieved in the reaction of the boron enolate derived from **2** with the chiral lactone aldehyde **4a**. This more complex double stereodifferentiating reaction would appear to be a matched case; however, the structural complexity of the aldehyde reduces the confidence level of any predictions for aldehyde face selectivity. The minor product was shown to be the C_{18}-epimer of the desired diastereomer. These results suggest that the aldehyde face selectivity exhibited by **4a** is dominant and that the enolate facial bias has been compromised to a minor extent relative to the reference reaction (**2** → **3**).

Scheme II



The aldol reactions of the fully homologated ketones **6** and **8** were examined next (Scheme III).[9] The aldol reaction of **6** with isobutyraldehyde under standard conditions proceeded in low yield and diastereoselectivity. However, the same reaction with **8** exhibited exceptional levels of asymmetric induction to give the desired aldol product **9** as a single diastereomer within the detection limits of GLC. Likewise, the matched double stereodifferentiating union of aldehyde **10** and ketone **8** afforded exclusively the *anti*-Felkin, aldol adduct **11** (>99:1).

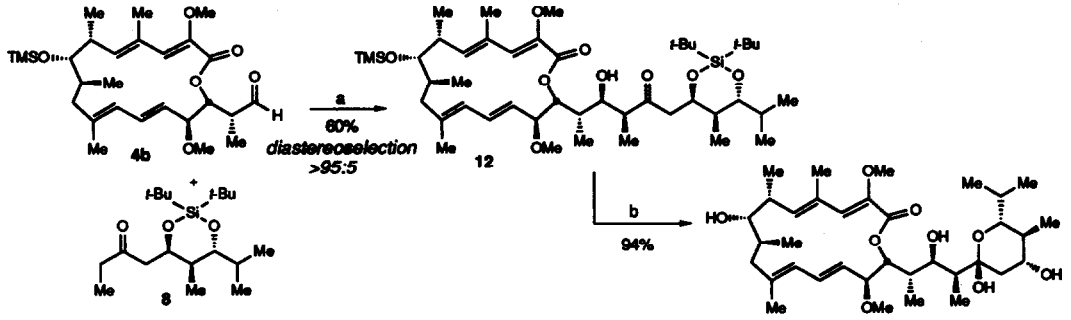
Scheme III



Based on these precedents, the aldol coupling of the bafilomycin aldehyde and ketone fragments **4b** and **8** was then addressed (Scheme IV). In this instance, the indicated reaction afforded the desired aldol adduct **12** (60% yield) as a single diastereomer. Deprotection of **12** under mild conditions afforded bafilomycin A_1 (94%),

which was identical in all respects (^{1}H and ^{13}C NMR; IR; TLC; [α] at several wavelengths) with the natural product.[10] The full details of the synthesis of bafilomycin A_1 will be reported elsewhere.

Scheme IV



(a) $PhBCl_2$, i-Pr_2NEt, CH_2Cl_2, -78°C. (b) HF·pyridine, THF, 25°C.

A Model for Enolate Face Selectivity. A rationalization for the observed sense of induction based on preferred ground state conformations of the enols derived from the various ketones follows. Molecular mechanics calculations[11] indicate that the enols derived from ketones **2** and **8** exist primarily in conformation **A**, while the enol from ketone **6** exists as a mixture of conformers **A** and **B** of comparable energy (Figure 1). By inspection, the *Re* face of enol conformer **A** is more accessible to attack by external electrophiles, while reactions from the opposite enolate diastereoface should be preferred by conformer **B**. The experiments conform to these predictions in that ketones **2** and **8**, which favor conformation **A**, exhibit the *Re* face selectivity while ketone **6**, which does not exhibit a significant conformational bias, is relatively nonselective. The calculations also reveal that destabilizing interactions between the enol moiety and either the C_{22} substituents or the silyl group on the C_{21}-oxygen determine the relative stability of the conformers. The interaction between the enol and the C_{22} substituents is approximately equal for all three enols. However, different torsional angles around the C_{21}-O bond for the different enols leads to varying effective sizes for the silyl group. In ketone **6**, the TES group forces the TBS moiety to rotate forward and the two destabilizing interactions are approximately equal, leading to equal populations of conformations **A** and **B**. In ketone **2**, the silyl group on the C_{21}-oxygen is rotated further away from the enol, diminishing the effective size of this substituent. In this instance, the major destabilizing interaction appears to be between the enol and the C_{22} substituents; consequently, conformation **B** is destabilized relative to **A**. In ketone **8**, the silyl group is rotated even further from the enol, and its effective size is even smaller. To illustrate these effects, the two minimized lowest energy conformers are shown for the enol derived from **8** (Figure 2). As is apparent from these structures, the *Si* face of the enol in conformation **A** is completely shielded by the *tert*-butyl groups. Further calculations and ^{1}H NMR spectroscopic analysis of **2**, **6**, and **8**[12] indicate that the parent ketones follow the same conformational trends.

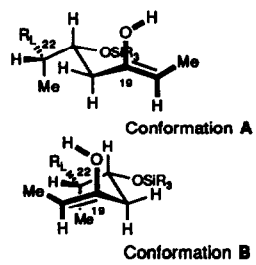


Figure 1. Favored enol conformers of ketones **2** and **8**

In conclusion, it has been demonstrated that the β-center of α-unsubstituted β-silyloxy ethyl ketones can have considerable influence on the diastereoselectivity of the aldol reactions of these substrates. However, the π-facial selectivity of these enolates is highly dependent on the nature of the oxygen protecting group and the local steric environment.

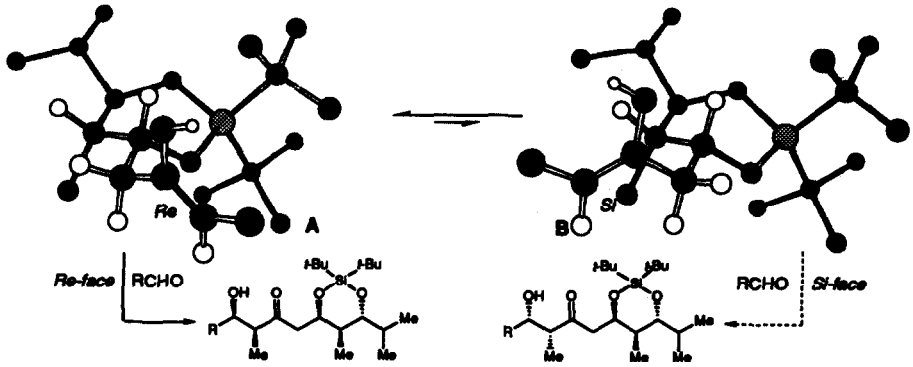


Figure 2. Calculated lowest energy conformers of the enol of **8**

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(8) Hamana, H.; Sasakura, K.; Sugasawa, T. *Chem. Lett.* **1984**, 1729-1732. We have found that optimal enolization conditions involve the addition of $PhBCl_2$ (1.2 equiv) to the ketonic substrate (CH_2Cl_2) followed by the addition of $EtN(i\text{-}Pr)_2$ (1.3 equiv) and subsequent enolization (30 min -78 , 30 min 0 °C). Subsequent aldol reactions were performed at -78 °C.

(9) The stereochemistry of the major adduct **7** was assigned by analogy. The stereochemistry of the minor adduct was not determined.

(10) The ^1H and ^{13}C NMR spectral data was taken from reference 2b. The TLC, IR and optical rotations were performed on an authentic sample of the natural product.

(11) Calculations were performed using the MM3* force field and a montecarlo search routine within the BATCHMIN subprogram of MacroModel. For the enols from ketones **2** and **8**, conformation **A** was ~0.25 kcal/mole more stable than **B**. For the enol from ketone **6**, conformation **B** was <0.1 kcal/mole more stable than **A**.

(12) The ^1H NMR data indicate that **2** and **8** exist almost exclusively in the conformation corresponding to **A**, while **6** exists as a nearly equal mixture of conformations corresponding **A** and **B**. The differences in the magnitude of the C_{20}-H to C_{21}-H coupling constant for the two C_{20} protons were larger for **2** and **8** than for **6** (δ J: 4.1 Hz for **2**, 7.0 Hz for **8**, 1.0 Hz for **6**). The chemical shift differences between the C_{20} protons were also larger in **2** and **8** than in **6** (δ ppm: 0.22 for **2**, 0.32 for **8**, 0.09 for **6**).

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