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Complex Aldol Reactions for the Construction of Dense Polyol Stereoarrays: Synthesis of the C_{33}−C_{36} Region of Aflastatin A

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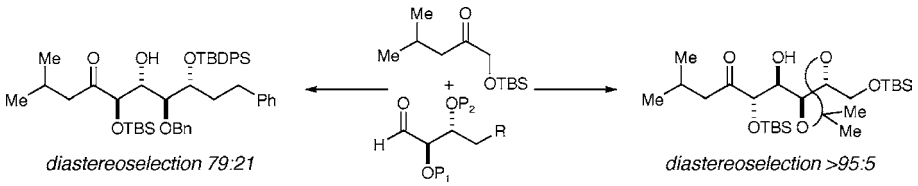
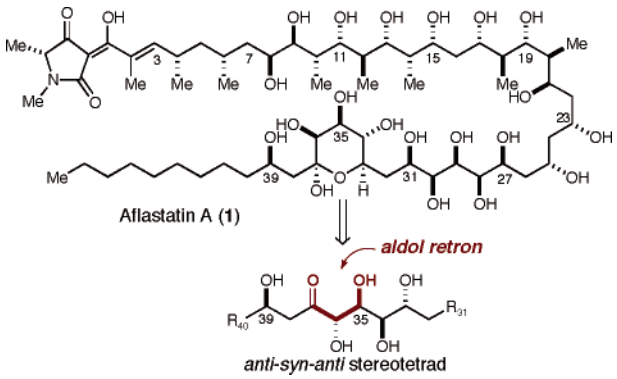
ABSTRACT



Facial selectivity in the addition of boron enolates of α-oxygenated ketones to *anti*-disposed α,*β*-bisalkoxy aldehydes is controlled by the aldehyde vicinal diol protecting group. Protection of the diol as an acetonide results in the exclusive formation of the *anti-syn-anti* stereoarray found in the C_{33}−C_{36} region of aflastatin A.

In 1996, Sukuda and co-workers reported the isolation of aflastatin A from the mycelia of *Streptomyces* sp. MRI 142. This natural product exhibits strong inhibitory activity against aflatoxin production without significantly affecting the growth of *A. parasiticus*.[1] In the initial publication, the structure devoid of stereochemistry was disclosed. The same group later reported the relative and absolute structure of aflastatin A (**1**) (Scheme 1).[2] Examination of the structure reveals two regions possessing dense oxygenation: C_{27}−C_{31} and C_{33}−C_{37}. Our group has had a long-standing interest in the use of aldol reactions for the construction of polyacetate and polypropionate natural products, and this structure presented the possibility of extending this chemistry into the polyol realm. In particular, construction of the C_{33}−C_{37} array in this manner is especially attractive, as examination of this lactol region in the open-chain tautomer reveals the presence of an aldol retron in the correct oxidation state (Scheme 1).

Scheme 1. Aldol Retron Present in Aflastatin A



At the outset, there were a series of concerns to be addressed with C_{35}−C_{36} aldol bond disconnection (Scheme 2): (a) *enolate* regioselectivity−enolization at the α′ position would lead to the formation of undesired α′-alkylation products; (b) *enolate* stereoselectivity−the Zimmerman−Traxler transition state model[3] predicts that the (*E*) enolate will lead to the desired α,*β*-anti adducts, whereas the (*Z*)

(1) Sakuda, S.; Ono, M.; Furihata, K.; Nakayama, J.; Suzuki, A.; Isogai, A. *J. Am. Chem. Soc.* **1996**, *118*, 7855.

(2) Ikeda, H.; Matsumori, N.; Ono, M.; Suzuki, A.; Isogai, A.; Nagasawa, H.; Sakuda, S. *J. Org. Chem.* **2000**, *65*, 438.

(3) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

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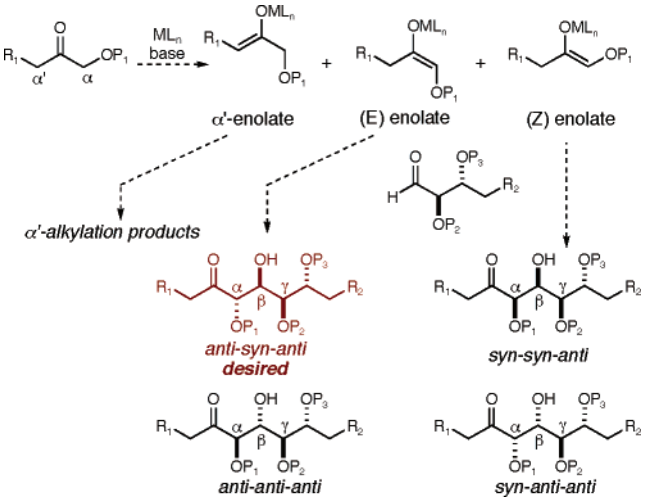
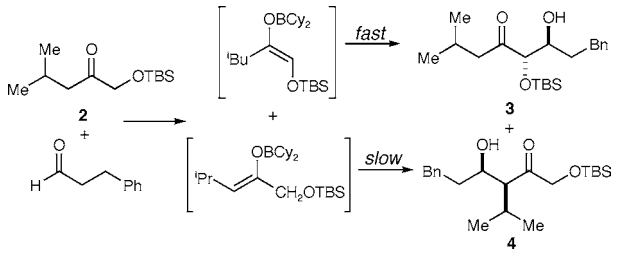
Scheme 2. Regio- and Stereochemical Issues



enolate will lead to the undesired α,*β*-syn adducts; (c) *aldehyde facial selectivity*—anti-Felkin selectivity will lead to the desired *β*,*γ*-*syn* adducts, whereas Felkin selectivity will lead to the undesired *β*,*γ*-*anti* adducts.

Ketone **2** was selected as an appropriate model.[4] To address the issues of enolization selectivity, the aldol additions of boron enolate derived from ketone **2** with dihydrocinnamaldehyde was investigated (Table 1). Dicyclohexylchloroborane was employed, as this reagent generally leads to high selectivity for the desired (*E*) enolate.[5] Enolization at low temperatures (Method A, entry 1)[6] led to low levels of regioselectivity. Enolization at elevated temperatures with extended reaction time (Method B, entry 2)[7] provided the desired aldol adduct in improved regioselection, but the diastereoselectivity was diminished and conversion was low.[8,9] The improved regioselection indicated that the thermodynamic enolization conditions resulted in equilibration to the desired α-enolate, while the diminished diastereoselectivity implied that significant quantities of the undesired α-(*Z*) enolate were also formed under these conditions. However, use of the aldehyde reaction partner as the limiting reagent resulted in formation of the desired aldol adduct with good regio- and diastereoselectivity (entry 3). We thus conclude that whereas enolization of ketone **2** under thermodynamic conditions (Method B) results in the formation of a mixture of enolates, the desired α-(*E*) enolate is the more reactive.[10]

Table 1. Optimization of Enolization Selectivity

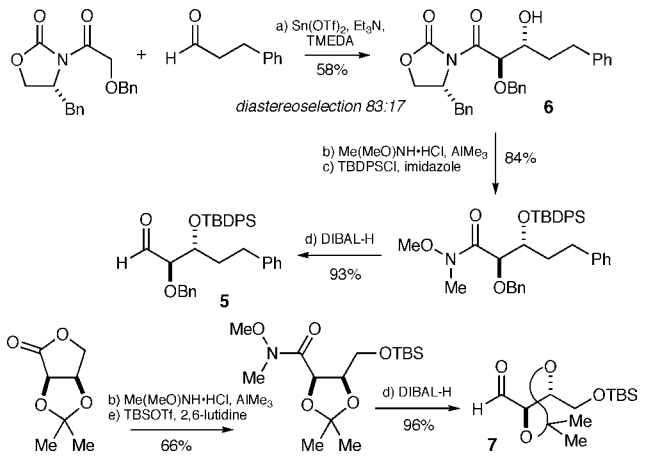


entry	enoliztion method[a]	equiv RCHO	conv [%]	ratio **3**:**4**	*anti*:*syn* (**3**)
1	**A**	1.5	100[b]	36:64	90:10
2	**B**	1.5	60[b]	90:10	80:20
3	**B**	0.5	93[c]	>97:3	92:8

[a] Method A: 1.5 equiv of Cy_2BCl, 1.8 equiv of NEt_3, Et_2O, −78 °C, 1 h. Method B: 1.1 equiv of Cy_2BCl, 2.0 equiv of $EtNMe_2$, pentane, 0 °C to room temperature, 15 h. [b] Based on ketone. [c] Isolated yield based on aldehyde.

To address the issue of aldehyde facial selectivity, two model aldehydes were prepared (Scheme 3). Aldehyde **5** was available using the auxiliary-controlled addition of a Sn(II)-glycolate enolate, which provided adduct **6** with moderate diastereoselection.[11] Aldehyde **7** was prepared from commercially available 2,3-*O*-isopropylidene-D-erythronolactone.

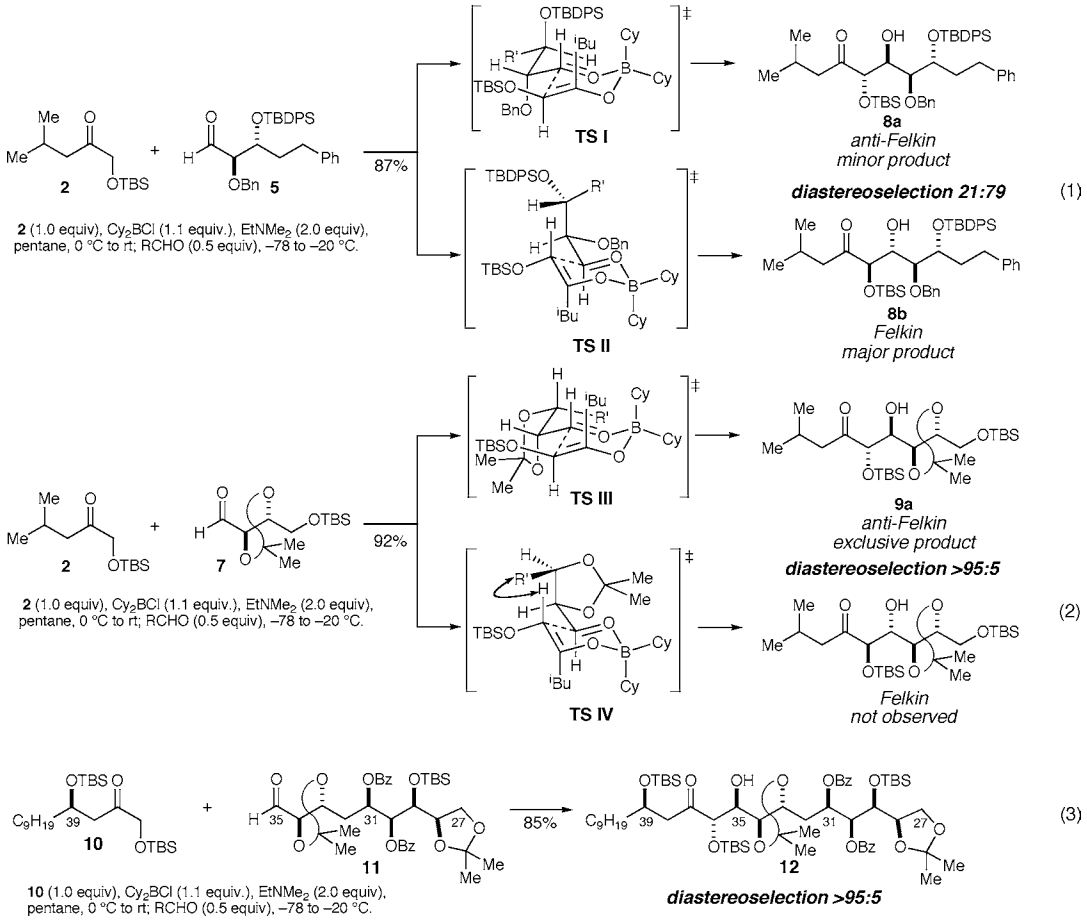
Scheme 3. Syntheses of Model Aldehydes



When the boron enolate derived from ketone **2** was added to these aldehydes under the optimized conditions (Table 1, entry 2), aldol diastereoselectivity was found to be strongly dependent on the choice of protecting groups (Scheme 4). In the case of aldehyde **5**, the undesired Felkin adduct **8b** was obtained as the major product in 79:21 diastereoselection

(4) See Supporting Information for details of the synthesis of **2**.
(5) Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1992**, *33*, 7233.
(6) Marco, J. A.; Carda, M.; Falomir, E.; Palomo, C.; Oiarbide, M.; Ortiz, J. A.; Linden, A. *Tetrahedron Lett.* **1999**, *40*, 1065.
(7) Galobardes, M.; Gascón, M.; Mena, M.; Romea, P.; Urpí, F.; Vilarassa, J. *Org. Lett.* **2000**, *2*, 2599.
(8) Adduct **4** was formed as a single diastereomer, consistent with the formation of the (*Z*) enolate, which is expected for α′-siloxy ketones: Murga, J.; Falomir, E.; Carda, M.; Gonzalez, F.; Marco, J. A. *Org. Lett.* **2001**, *3*, 901.
(9) See Supporting Information for experiments that support all stereochemical assignments.
(10) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. Similarly, it has been noted that (*E*) crotylboronates react faster with aldehydes than the corresponding (*Z*) isomers: Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422.
(11) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, 1961.

Scheme 4. Diastereoselective Aldol Reactions



over the anti-Felkin isomer **8a** (eq 1). When aldehyde **7** was used, however, the desired anti-Felkin isomer **9a** was obtained as a single diasteomer in excellent yield (eq 2).[12] These results demonstrate the ability to control aldehyde diastereofacial selectivity by variation of the protecting groups on neighboring alcohol functionalities. As illustrated in eq 3, the latter reaction has been applied to more complex reaction partners, which resulted in the formation of the fully elaborated $C_{27}-C_{48}$ subunit of aflastatin A.[13]

The divergence in stereoselectivity can be explained by comparison of the Zimmerman−Traxler transition states for these two processes. The free rotation about the $C_\alpha-C_\beta$ bond of aldehyde **5** allows transition states **TS I** and **TS II** to be viable alternatives, leading to the formation of a mixture of adducts **8a** and **8b**. Alternatively, the acetonide protecting group of aldehyde **7** reduces the rotational freedom of the α- and β-positions and results in the development of nonbonding interactions in the transition state leading to the undesired Felkin isomer (**TS IV**).

In conclusion, the $C_{33}-C_{36}$ region of aflastatin has been prepared using a diastereoselective addition of an oxygenated ketone enolate to a α,β-bisoxygenated aldehyde. The general applicability of this method should allow its application to other polyol natural products possessing either stereochemical array. Progress toward a total synthesis of aflastatin A is ongoing and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization of compounds **2**−**9** and **12** and stereochemical proofs for adducts **3**, **4**, **8**, **9** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) In no case were products derived from α′-enolization observed.

(13) The syntheses of compounds **10** and **11** will be reported in due course.