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EFFECT OF METAL COUNTERIONS ON THE STEREOSELECTIVITY OF ALDOL REACTIONS USED TO ASSEMBLE THE SECO ACID BACKBONE OF ERYTHROMYCIN B

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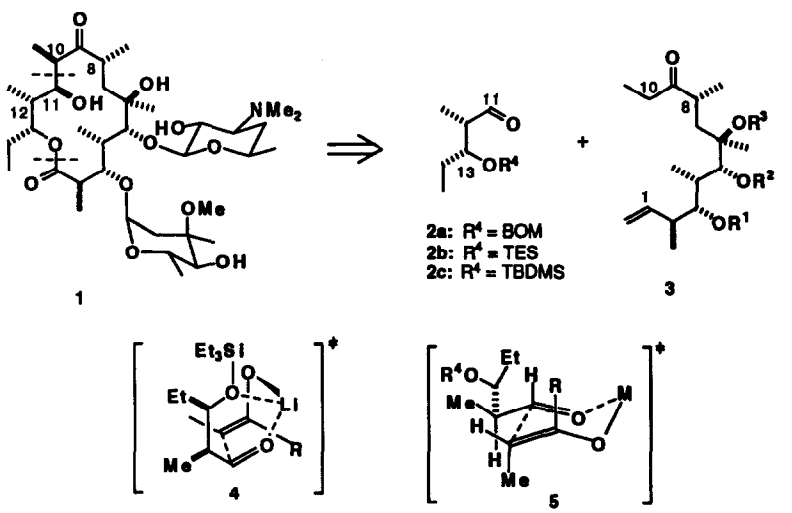
Abstract. The diastereofacial selectivity of the aldol reactions of the enolates derived from the ketones **11**, **15**, and **19** with the aldehyde **2a** depended upon whether the counterion was lithium or titanium. For lithium enolates the stereoselectivity appeared to be controlled by the stereochemistry alpha to the carbonyl group of the aldehyde partner, whereas the stereochemistry at the α'-carbon of the enolate was important for the titanium enolate.

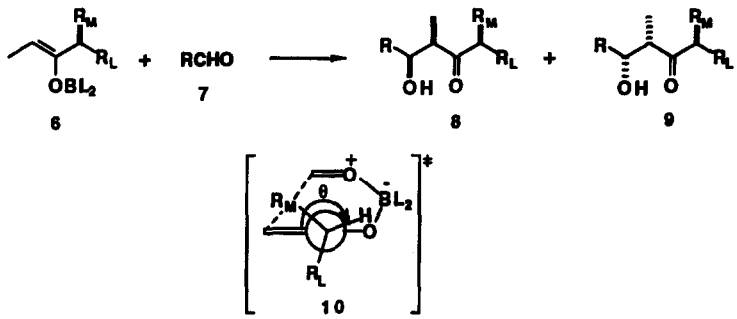
One of the key steps in our strategy for completing an efficient asymmetric total synthesis of erythromycin B (**1**)[1] was a stereoselective aldol reaction[2] between protected aldehydes **2a** and **2b** and ketones related to **3** to establish the C(10)-C(11) carbon-carbon bond and the attendant stereocenters (Scheme 1). We observed that the reactions of enolates derived from a ketone of general type **3** with the protected aldehydes **2a** and **2b** gave the requisite (10*R*, 11*S*) stereochemistry present in erythromycin B. In addition to our own work in this area, it should be noted that similar constructions involving enolates derived from ketones related to **3** have been reported by Masamune[3] using **2b** and by Kochetkov[4] using **2c**. Masamune rationalized the anti Felkin-Anh diastereofacial selectivity obtained with **2b** by invoking the bicyclic three-point chelated transition state **4**. That we found the aldol reaction of **2a** was more stereoselective than that involving the silyl protected aldehyde **2b** (*i.e.*, 6:1 vs 3:1) is consistent with a chelation transition state such as **4**, although other mechanisms are possible.[5,6] For example, Roush has rationalized such anti Felkin-Anh stereoselectivity by invoking a gauche-pentane transition state **5**.[7] The

Scheme 1



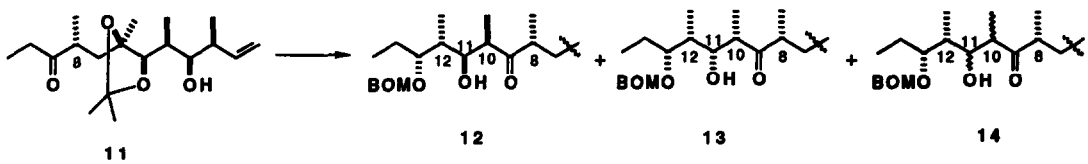
asymmetric center adjacent to the carbonyl carbon of an enolate such as **6** is also known to influence the diastereoselectivity of an aldol reaction with an achiral aldehyde (Scheme 2).[2,8] In such processes, a ketone enolate **6** preferentially adds to achiral aldehydes to give the adducts **8**, and a recent study[9] has suggested the general model **10** (θ = 133-173°) to rationalize the facial selectivity of such reactions. This model is consistent with transition states that have been previously proposed by Evans[10] and Paterson.[8d,11]

Scheme 2

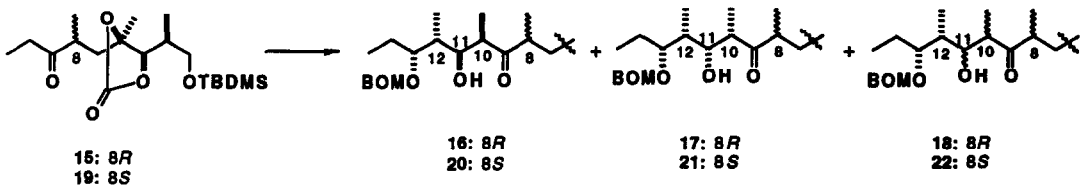


One of the experimental parameters that may be varied to improve the stereoselection in aldol reactions is the metal counter ion. In this context, we noted that titanium enolates have been employed in highly diastereoselective aldol reactions.[8e,10,12-14] The stereoselectivity of some of these reactions has been rationalized by invoking a titanium bound to the enolate and aldehyde carbonyl oxygens in a classical Zimmerman-Traxler transition state together with an additional oxygen ligand present on the enolate moiety.[13,14] However, we were unaware of any examples wherein the titanium was coordinated in a bicyclic transition state such as **4** in which the third oxygen that chelated with the titanium was present in the aldehyde reaction partner. Since the O-Ti bond (1.62-1.73 Å) is shorter than O-Li bond (1.92-2.00 Å), it occurred to us that using titanium in place of lithium in the directed aldol reaction of ketone enolates related to **3** with the aldehyde **2a** might enhance the diastereoselection of these additions. We thus undertook a series of studies to evaluate this hypothesis (Schemes 3 and 4).

Scheme 3



Scheme 4



The lithium enolates of **11**, **15**, and **19** were generated with lithium hexamethyldisilazide (2-3 equiv.) in THF at -78 °C according to Masamune,[3] and the corresponding titanium enolates were generated by metal exchange with chlorotitanium triisopropoxide as reported by Thornton.[12a] The aldol reactions of these enolates with **2a** were executed at -78 °C and warmed to 0 °C before quenching. The *syn* or *anti* stereochemistry of all of the adducts was assigned based on their ^{13}C NMR spectra according to the trends identified by Heathcock.[15,16] The structure of **12** was based upon an X-ray study,[17] and the structures of the other *syn* adducts were assigned based upon comparisons of their spectral (^1H and ^{13}C NMR) data with those observed for **12** and **13**.

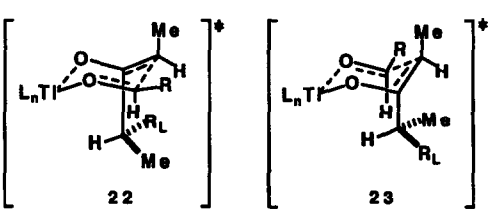
An inspection of the results summarized in Table 1 reveals that the stereochemical outcome of the aldol reactions of **11**, **15** and **19** with **2a** varies considerably with the metal counter ion. Changing the metal from lithium to titanium resulted in a reversal of diastereofacial selectivity in the aldol reactions of the enolates derived from the 8*R* ketones **11** and **15** (entries 1-4). Clearly different stereochemical control elements and transition states are operative depending upon whether the metal ion is lithium or titanium.

Table 1. Diastereoselectivity of Aldol Reactions of Ketones 11, 15, and 19.

Entry	Ketone	M	C(10)/C(11)-*syn*[a] (10*R*, 11*S*) : (10*S*, 11*R*)			C(10)/C(11)-*anti*
1	**11**	Li	(**12**) 6	:	(**13**) 1	-
2	**11**	Ti	(**12**) 1	:	(**13**) 4	4[b]
3	**15**	Li	(**16**) only[c]	:	(**17**) -	-
4	**15**	Ti	(**16**) 1	:	(**17**) 9	-
5	**19**	Li	(**20**) 1	:	(**21**) -	1.8[d]
6	**19**	Ti	(**20**) only[c]	:	(**21**) -	-

(a) All ratios were determined by isolated yield of pure isomer except entry 4 in which the ratio was determined by the ^1H NMR integration. (b) Only one anti aldol adduct was isolated. (c) Only one product could be isolated and identified. (d) Two anti aldol products were isolated in a 1.2:1 ratio.

When lithium was used as the counter ion of the enolate, the preferred diastereofacial selection appears to be dictated by the stereochemistry at the carbon alpha to the aldehyde carbonyl group so that the "anti Felkin-Anh" products **12**, **16** and **20** will be the dominant *syn* adducts. Both of the transition states **4** (chelated bicyclic) or **5** (gauche-pentane interaction) are consistent with this observation. Although our original hypothesis was that titanium might enhance addition via a chelated transition state as **4**, such an array does not appear operative in the present reactions. Rather the diastereofacial selection seems to be controlled by the chiral center at C(8), which is α to the carbonyl carbon of the ketone enolate. The stereochemical outcome of the reactions of the titanium enolates may then be rationalized by the transition state depicted in **10** in which the large group occupies a position antiperiplanar to the incipient bond with the hydrogen oriented toward the metal to minimize interactions with its associated ligands as in



22 **23**

22 (for **13** and **17**) and **23** (for **20**). We tentatively speculate that the formation of the *anti* adducts (entries 2 and 5) arises from the isomerization of the less reactive (*Z*) enolate to the (*E*) enolate prior to the aldol addition,[9] but we presently have no data either to support this conjecture or exclude other possibilities.

These experiments indicate that depending upon whether lithium or titanium is employed as the metal counterion in the directed aldol reactions of enolates derived from the ketones **11**, **15**, and **19**, one may obtain preferentially products whose stereochemistry is controlled by the chirality of the either aldehyde or the ketone, respectively. Probing the generality of this observation is the subject of current investigations, the results of which will be reported in due course.

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