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# Synthesis of the C(3)-C(15) Segment of Rutamycin B via a C(8)-C(9) Fragment Assembly Aldol Reaction: Metal Dependence of the Aldehyde and Enolate Diastereofacial Selectivities

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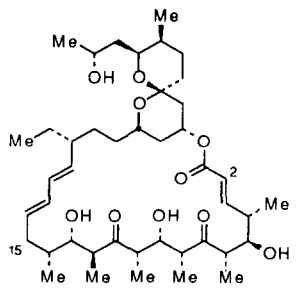
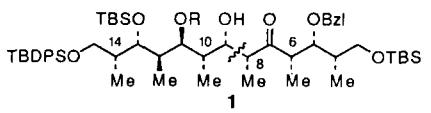
*Abstract: The diastereofacial selectivities of aldehyde **2b** and ketone **3** are metal dependent, and their fragment assembly aldol coupling is a matched double asymmetric reaction when a chlorotitanium enolate is used.*

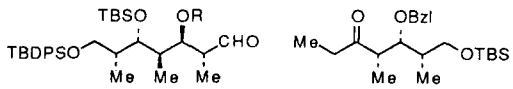
In connection with our long standing interest in the development of highly stereoselective C-C bond forming reactions and their application to the synthesis of polyhydroxylated and polypropionate natural products, we have investigated a fragment assembly aldol approach to the synthesis of the C(3)-C(15) segment of rutamycin B.[2] We were particularly interested in the stereochemical course of the aldol coupling of the chiral aldehyde **2** and the chiral methyl ketone **3**. Based on literature precedent, we expected that the diastereofacial bias of a Z(O)-chlorotitanium or dialkylboron enolate derived from **3** would favor the syn relationship between the C(6) and C(8) methyl groups of **1**.[3] However, we expected that the intrinsic diastereofacial bias of chiral aldehyde **3** would favor production of the anti-Felkin aldol with an anti relationship between the C(8) and C(10) methyl groups, whereas a C(8)-C(10) syn relationship is required in **1**.[4] We therefore anticipated that the aldol coupling of **2** and **3** would be a mismatched double asymmetric reaction,[5] and it was not obvious at the outset which of the chiral reactants, if either, would dominate the stereochemical course of this reaction. While our studies were in progress,[1a] Evans reported a total synthesis of rutamycin B and White described a synthesis of the C(1)-C(15) segment.[6,7] Both groups employed fragment assembly aldol reactions to construct the C(8)-C(9) bond, and both demonstrated that the aldol coupling was highly stereoselective for the desired diastereomer (c.f., **1**) when chlorotitanium enolates were used. We now provide evidence that the diastereofacial preferences of **2** and **3** are metal dependent, and that the fragment assembly aldol reaction is a stereochemically matched pair in the chlorotitanium enolate series.




rutamycin B




**1**

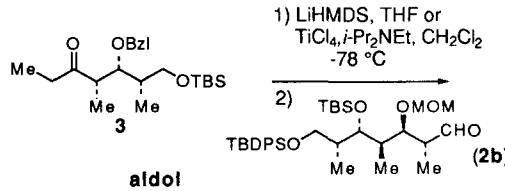



**2a**, R = TES
**2b**, R = MOM

**3**

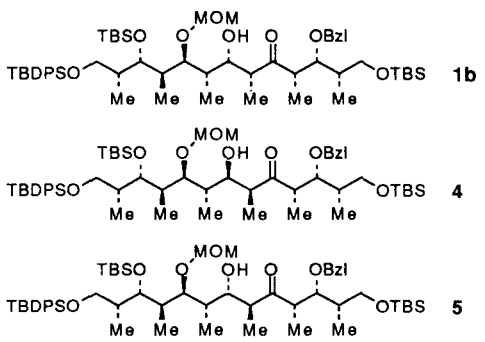
We initially studied the aldol reaction of **2a** and **3**, but found that complex mixtures of products were produced when either lithium or titanium enolates were used.[8] In subsequent experiments, we observed that the aldol reaction of **2b** with the chlorotitanium enolate of **3** is highly selective for the desired diastereomer **1b**, in agreement with the observations of Evans and White.[6,7] In contrast, the anti-Felkin aldol **4** was slightly favored from experiments performed with the lithium enolate of **3** for short reaction times. However, the 8,9-anti aldol **5** is the major product from reactions performed for longer periods at -78°C or at higher reaction temperatures, indicating

that lithium aldolate equilibration occurs under these conditions.[9] In fact, treatment of HPLC purified aldol **1b** with LiHMDS in THF at -78°C for 2 min provided a 62 : 25 : 13 mixture of **1b**, **4** and **5**, respectively, along with aldehyde **2b** and ketone **3**. Thus, although we infer that **4** is the kinetic product of the lithium enolate aldol reactions, the data reported even for the 2 min reaction reflect partial product equilibration. Although the evidence indicates that **1b** is the kinetic product of the $TiCl_4$ aldol reaction, it appears that the titanium aldolates may also partially equilibrate at -78°C, since the amounts of **4** and **5** are greater in reactions performed for 5.5 h than for a 3 h period.[10] Finally, attempts to perform the aldol reaction with a dialkylboron enolate generated from **3** (9-BBN-OTf, *i*-$Pr_2NEt$, $CH_2Cl_2$) were unsuccessful.[11]

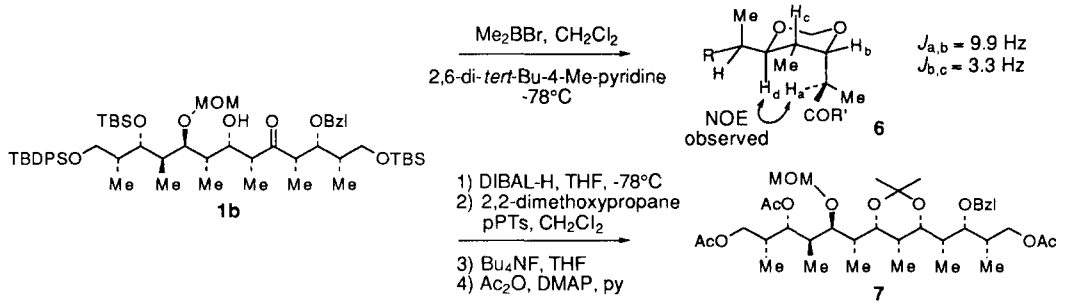



| aldol enolate | conditions | 1a | 4 | 5 | yield |
|---|---|---|---|---|---|
| $TiCl_4$ | -78°C, 3 h | 91 | 6 | 3 | 60%* |
| $TiCl_4$ | -78°C, 5.5 h | 82 | 12 | 6 | 88% |
| LiHMDS | -78°C, 2 min | 23 | 47 | 20 | 63%* |
| LiHMDS | -78°C, 30 min | 9 | 17 | 74 | 42%* |
| 9-BBN-OTf | -78°C, 5 h | – | – | – | poor conv. |

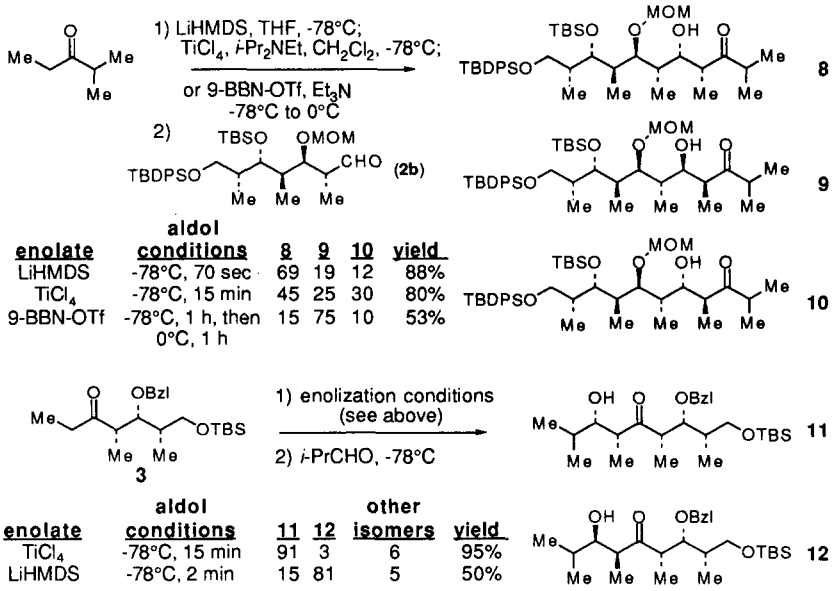
*Products isolated by preparative HPLC




The stereostructure of aldol **1b** was assigned as follows. First, treatment of **1b** with $Me_2BBr$ in $CH_2Cl_2$ at -78°C in the presence of 2,6-di-*tert*-butyl-4-methylpyridine provided methylene acetal **6**,[12] $^1H$ NMR analysis of which confirmed the 9,10-syn relationship in **1b**. Second, 1,3-syn selective reduction[13] of **1b** with DIBAL (81%) followed by acetonide formation, removal of all silyl protecting groups and peracetylation then provided **7**, $^1H$ and $^{13}C$ NMR analysis of which confirmed that **1b** has the expected 8,9-syn stereochemistry.[14] The stereostructures of subsequently described aldols were assigned by analogous methods.



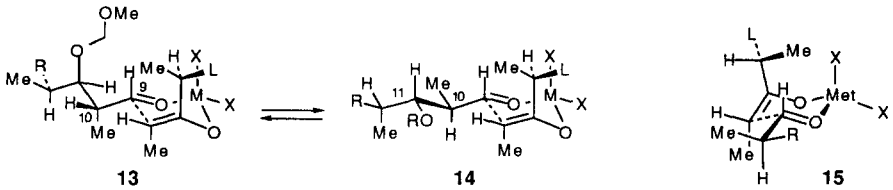

Aldol reactions of **2b** and **3** with achiral partners were performed in order to gain further insight into the factors that govern the kinetic diastereoselectivity of the rutamycin fragment assembly aldol reaction. Interestingly, the results of these experiments indicate that the diastereofacial selectivity preferences of both fragments are dependent on the enolate metal. Thus, whereas the Felkin aldol **8** is favored in the reaction of aldehyde **2b** with the lithium enolate of ethyl isopropyl ketone (**8** : **9** = 69 : 19), the anti-Felkin aldol **9** is the major product from the aldol reaction with the 9-BBN enol borinate (**8** : **9** = 15 : 75). The reaction of **2b** with the chlorotitanium enolate of ethyl isopropyl ketone is intermediate in selectivity, providing a 45 : 25 : 30 mixture of the three aldols among which the




Felkin aldol **8** is slightly favored. Caution must be exercised in interpreting these data, since control experiments established that the lithium aldolates corresponding to **8** and **9** equilibrate under the reaction conditions.[15a] Nevertheless, the data support the conclusion that **8**, and not **9**, is kinetically favored in the lithium enolate aldol reaction. The diastereofacial selectivity of ketone **3** is also dependent on the metal: the reaction of the chlorotitanium enolate of **3** with isobutyraldehyde favors the 3,5-syn aldol **11** (**11** : **12** = 91 : 3), whereas the reaction with the lithium enolate of **3** favored the 3,5-anti aldol **12** (**11**: **12** = 15 : 81).[15b] The reversal of selectivity with the lithium vs. the chlorotitanium enolates is consistent with examples previously reported by McCarthy and Martin.[16]

To the best of our knowledge, the data reported here for the aldol reactions of **2b** and $EtCOCHMe_2$ are the first documented examples of Type I aldol reactions in which the diastereofacial selectivity of the chiral aldehyde is reversed simply by changing the metal.[4a] We had expected at the outset that the aldol reactions of **2b** would proceed preferentially via **15** since this transition state avoids the double gauche pentane interaction present in **13** and the interactions between the Z(O)-enolate Me group and the C(11) substituents of **2b** that destabilize **14**. The data show, however, that **15** is the major pathway only when a dialkylboron enolate is used. Evidently, the "tightness" of the transition state, which is expected to be metal dependent,[17] is the key feature that determines the partition between **13/14** (Felkin selective) and **15** (anti-Felkin selective). Computational studies by Gennari[4b] suggest that the double gauche pentane interaction present in **13** can be relieved by a ca. 40° counter-clockwise rotation of the C(9)-C(10) bond, giving a transition structure intermediate between **13** and **14** that is more accessible than we originally postulated.[4a] This, together with the greater Li-O bond lengths and the relatively long developing C-C bond,[18] allow the lithium enolate aldol reaction to proceed by way of **13/14**. Similar considerations presumably contribute to the metal dependent diastereofacial selectivity of chiral ketone **3**.

In final analysis, it is apparent that the success of the rutamycin fragment assembly aldol reaction is a function of the diastereofacial selectivity preferences of the two chiral components. The reaction is a matched double asymmetric reaction when a chlorotitanium enolate is used, since both **2b** (weakly) and **3** (strongly) favor the desired stereochemical outcome. Selectivity is poor in the lithium enolate coupling since the intrinsic diastereofacial



13 14 15

preferences of **2b** and **3** are mismatched, and aldolate equilibration further erodes the diastereoselectivity. Finally, there is the interesting issue of the role of the aldehyde β-alkoxy protecting group.[6] In a related study of the diastereoselectivity of methyl ketone aldol reactions of **2a** and **2b**, we have accumulated data that suggests that dependence of selectivity on the aldehyde β-alkoxy protecting group is due to a steric interaction between the β-alkoxy group (when the protecting group is a silyl ether) and the axial metal ligand in a six membered transition state analogous to **13**.[19] This interaction should also destabilize **13/14** relative to **15** when an aldehyde like **2a** is used, resulting in diminished selectivity in chlorotitanium enolate aldol reactions.

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10. Aldol **1b** was recovered unchanged when treated with $TiCl_4$ and *i*-$Pr_2NEt$ in $CH_2Cl_2$ at -78°C for 5 h. However, it is not clear that the chlorotitanium aldolate was actually regenerated under these conditions.
11. Interestingly, anti diastereomer **5** is the major product (3 : 1 mixture, **5** : **1b**, 40% yield) of the $BF_3$•$Et_2O$ catalyzed reaction of **2b** and the TMS enol ether of **3**, and is the near exclusive (≥96% d.e.) product from the $TiCl_4$ catalyzed reaction.
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15. (a) Treatment of **8** with LiHMDS in THF at -78°C for 3 min provided a 6 : 1 mixture of **8** and **10**; **9** under these conditions equilibrated to a mixture of all three aldols (**8** : **9** : **10** = 2.1 : 3.5 : 1); while aldol **10** was completely stable under these conditions. (b) Aldols **11** and **12** equilibrate ≤3% under these conditions.
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17. Boron aldol transition states are more compact than those involving lithium or titanium enolates owing to the shorter B-O and B-C bond lengths: Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. Ti-O bond lengths (1.62-1.73Å) are intermediate between B-O (1.36-1.47Å) and Li-O (1.92-1.00 Å).
18. The developing C-C bond is believed to be longer in the lithium enolate aldol transition compared to the boron enolate aldol reaction: Li, Y.; Paddon-Row, N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481.
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