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Diastereoselective Titanium Enolate Aldol Reaction for the Total Synthesis of Epothilones

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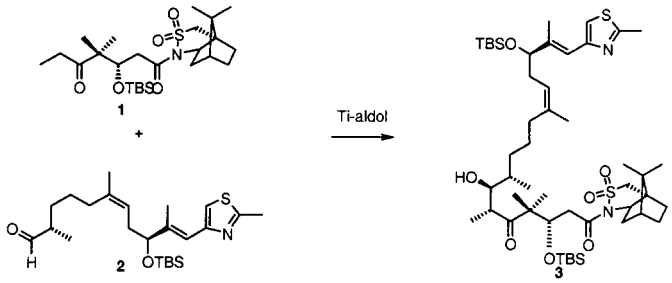
ABSTRACT



The development of a highly diastereoselective addition of the titanium enolate derived from ketone 1 to aldehyde 2 offers an efficient entry to the total synthesis of the epothilone family. The new aldol process is robust and tolerates a wide range of functional groups.

The aldol approach for the total synthesis of epothilones has been first reported by the groups of Mulzer and Nicolaou.[1] The disconnection of the C_6-C_7 bond results in a significant reduction of complexity. Many other groups closely studied this key transformation in order to develop a highly convergent synthesis of the epothilones.[2] There are the following most important lessons to be taken from these extensive investigations: The most convergent route, the aldol reaction of the free carboxylate ion enolate, is completely unselective.[2a] With protected analogues, stereoselectivities in the range of 3−5:1 in favor of the desired addition product are obtained. A significantly higher selectivity was obtained by Schinzer when using an acetonide protected enolate (10:1).[2b,c] However, the cost to be paid for the favorable selectivity is additional functional group manipulations.

Our interest for the development of a highly convergent large-scale synthesis of epothilone B prompted us to reinvestigate the aldol approach. The basic concept of our retrosynthetic analysis (Scheme 1) was the addition of the sultam-derived fragment **1** to the aldehyde **2**. Such a strategy would allow us to make use of the chiral sultam auxiliary as a carboxylate protecting group and therefore avoid additional reduction and oxidation steps.

Both building blocks were prepared according to literature procedures.[3]

(1) (a) Mulzer, J.; Mantoulidis, A. *Tetrahedron Lett.* **1996**, *37*, 9179. (b) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Yang. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166.

(2) (a) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem., Int. Ed.* **1998**, *37*, 2014. (b) Schinzer, D.; Bauer, A.; Böhm, O. M.; Limberg, A.; Cordes, M. *Chem.—Eur. J.* **1999**, *5*, 2483. (c) Schinzer, D.; Bauer, A.; Schieber, J. *Chem.—Eur. J.* **1999**, *5*, 2492. (d) Balog, A.; Harris, C.; Savin, K.; Zhang, X. G.; Chou, T.-C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2675. (e) Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K.; Glunz, P. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 7050. (f) Wu, Z.; Zhang, F.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4505. (g) Mulzer, J.; Mantoulidis, A.; Öhler, E. *J. Org. Chem.* **2000**, *65*, 7456.

(3) (a) Preparation of the aldehyde **2**: Nicolaou, K. C.; Ninkovic, S.; Sarabia. F.; Vourloumis, D.; He. Y.; Vallberg, M. R.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974. (b) Preparation of the ketone **1**: Altmann, K.-H.; Bold, G.; Caravatti, G.; Denni, D.; Flörsheimer, A.; Schmidt, A.; Rhis, G.; Wartmann, M. *Helv. Chim. Acta* **2002**, *85*, in press.

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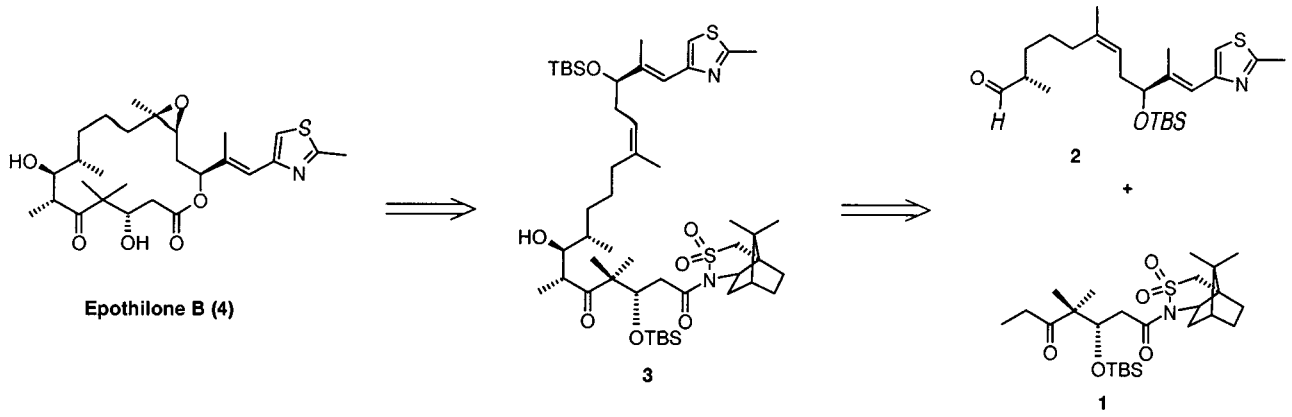
Scheme 1. Key C_6-C_7 Aldol in the Retrosynthetic Analysis for Epothilone B



In a first step, the ketone **1** was subjected to a variety of enolization conditions (Table 1). The resulting enolates were trapped with benzaldehyde in a model reaction.[4]

Table 1. Enolization Experiments with the Ketone **1**

entry	enolization conditions	product
1	1.0 eq. LDA[a)]	**5**
2	2.5 eq. $TiCl_4$ 3.0 eq. Bu_3N[b)]	**6**
3	3.3 eq. $TiCl(OiPr)_3$ 1.1 eq. LDA[a)]	**7** + **8**

[a] THF; −78 to 0 °C. [b] CH_2Cl_2; −78 to 0 °C.

LDA favors deprotonation at the α position to the amide (entry 1), whereas the titanium enolate was selectively formed at the ketone, most likely due to the higher acidity of the proton α to the ketone (entry 2). With $TiCl_4/Bu_3N$, the desired benzaldehyde addition product was formed in 86% yield with a diastereoselectivity of 3:1. Alternative conditions examined including $TiCl(OiPr)_3$, $TiCl_2(OiPr)_2$, and $TiCl_3(OiPr)/i\text{-}Pr_2NEt$ did not result in the formation of enolate. By treatment with $TiCl(OiPr)_3$/LDA (entry 3), the cyclized product **7** was isolated along with cleaved sultam auxiliary **8**. The tin and the boron enolates of **1** could not be obtained under standard conditions (Bu_2BOTf/iPr_2NEt, $(cHex)_2BCl/Et_3N$, and $SnOTf_2/Et_3N$).

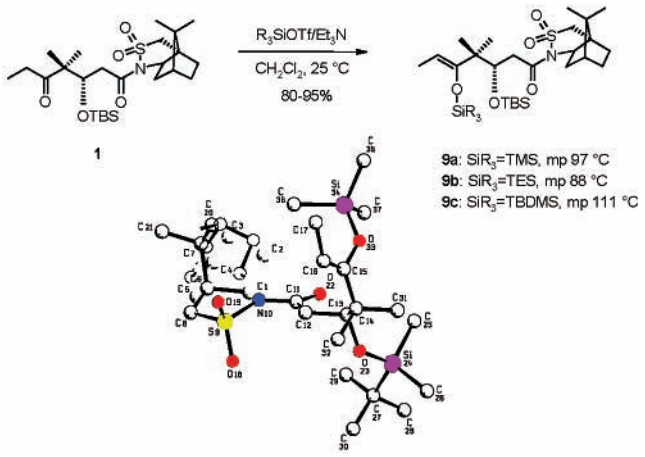
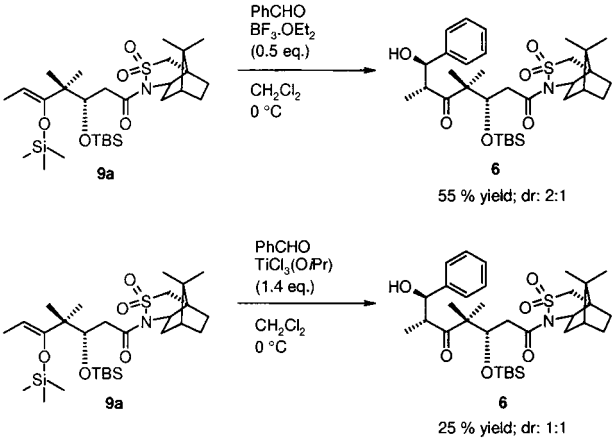


Figure 1. Formation of the silyl enol ethers **9a**−**c** and X-ray structure of the TMS-silyl enol ether **9a**.

Treatment of **1** with silyl triflates in the presence of triethylamine resulted in the selective formation of the extraordinarily stable silyl enol ethers **9a**−**c** (Figure 1) The crystal structure of the TMS derivative **9a** is shown.

Scheme 2. Mukaiyama Aldol Reactions with Benzaldehyde



Having analytically pure silyl enol ethers in hand we tested several Lewis acids ($BF_3{\cdot}OEt_2$, $MgBr_2$, $ZnCl_2$, $TiCl_4$, $TiCl_3(OiPr)$, $TiCl_2(OiPr)_2$, $Ti(OiPr)_4$, $SnCl_4$, $EtAlCl_2$, $ScOTf_3$, TMSOTf) for the Mukaiyama aldol reaction with benzaldehyde. The best results were obtained with $BF_3{\cdot}OEt_2$ and $TiCl_3(OiPr)$ (Scheme 2).

Compared to the titanium enolate of **1** (Table 1, entry 2) lower diastereoselectivities and low yields were observed when using the silyl enol ether **9a**. We therefore decided to focus on the titanium enolate addition. The model reaction was carried out with *ent*-**1** (Figure 2). Under optimized conditions, the addition product *ent*-**6** was obtained in 91% yield and 3:1 diastereoselectivity. A following crystallization afforded *ent*-**6** with >95% diastereomeric purity. From the X-ray data shown in Figure 2 and NMR analysis we concluded that the major diastereoisomer formed has the desired syn configuration.

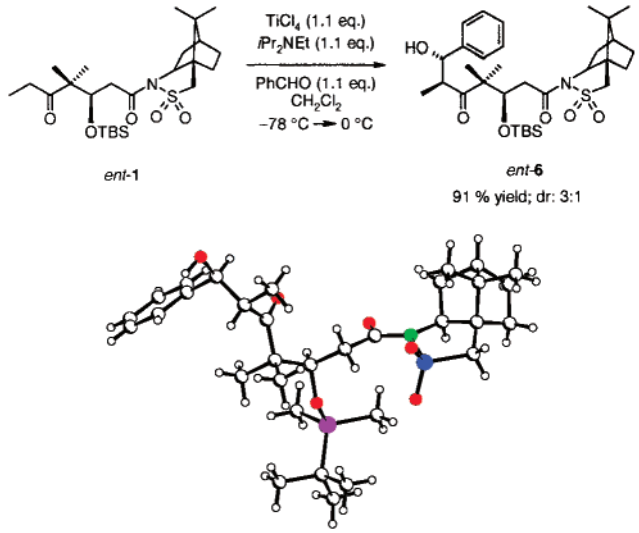


Figure 2. Ti-aldol with benzaldehyde and X-ray structure of the aldol product *ent*-**6**.

Two model reactions carried out with *ent*-**1** were monitored by ReactIR (Figure 3). Treatment with LDA at −78 °C resulted in the generation of a lithium enolate band at 1619 cm^{-1}. The same band was generated in the deprotonation of the *N*-acetyl sultam **10**. Addition of $TiCl_4$ to *ent*-**1** at −78 °C shifted the amide and ketone carbonyl frequency from 1694 cm^{-1} to lower wavenumbers at 1553 cm^{-1} for the amide-carbonyl and 1652 cm^{-1} for the ketone-carbonyl due to complexation with $TiCl_4$. After addition of base (triethylamine or tri-*n*-butylamine), only the complex-band with the ketone-carbonyl (1652 cm^{-1}) disappeared whereas the one with the amide-carbonyl (1553 cm^{-1}) remained, indicating that the titanium enolate at the ketone group was selectively formed under these conditions. After addition of the electrophile (benzadehyde), the bands of the aldol product *ent*-**6** complexed with titanium chloride appeared.

(4) For the elucidation of the configuration of **6**, vide infra.

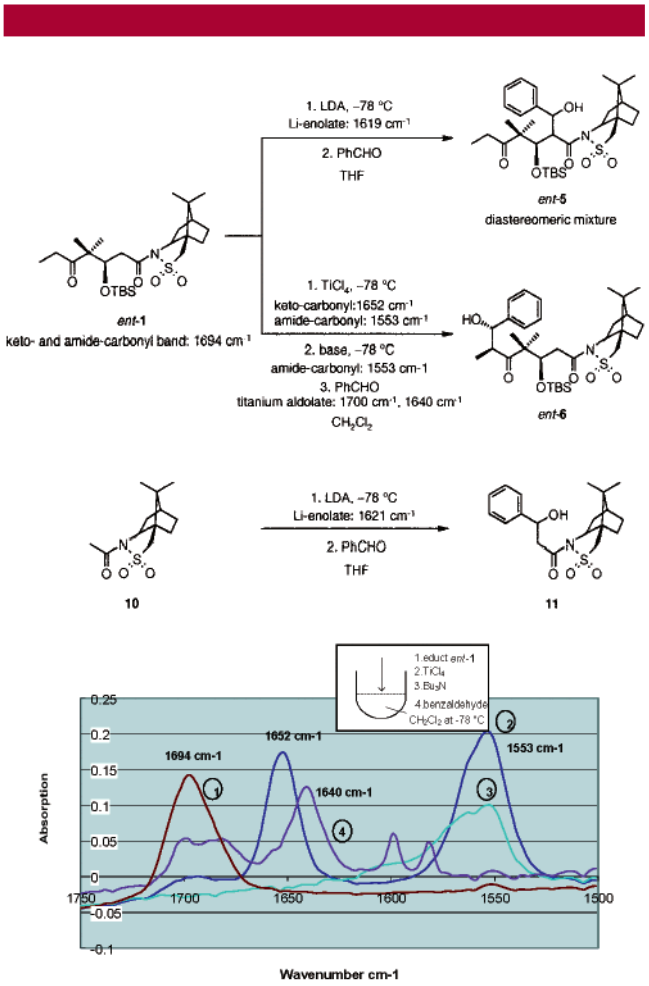


Figure 3. ReactIR analysis of the lithium and titanium enolate formation from *ent*-**1** and addition to benzaldehyde.

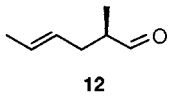
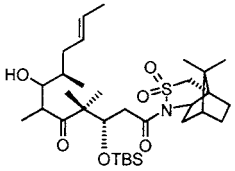
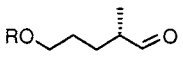
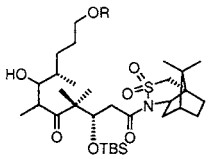
Having defined optimized conditions for the direct utilization of the sultam derived fragment **1** in a selective aldol addition to benzaldehyde we then applied the reaction conditions to a-branched aliphatic aldehydes. Whereas a diastereoselectivity of 3:2 was observed when an *R*-configured aldehyde (**12**) was utilized, excellent diastereoselectivities of >20:1 were observed for the matched case (**14a**,**b**). The results are summarized in Table 2.[5]

Finally, the titanium enolate aldol reaction between **1** and the aldehyde **2** delivered in high yield and with excellent diastereoselectivity the product **3** which is an intermediate in the synthesis of epothilone B (Scheme 3). Compound **3** was converted to the known carboxylic acid **17**[2g,3a] in two steps (TBDMSOTf, 2,6-lutidine; LiO_2H, THF/H_2O 4:1). Comparison of the analytical data of our sample of **17** with the corresponding data reported in the literature showed that the aldol product **3** with the desired stereochemistry had been obtained.[6]

(5) Treatment of **2** with $TiCl_4$ followed by trimethyl silyl enol ether **9a** at 0 °C resulted in the decomposition of the aldehyde with no formation of aldol product.

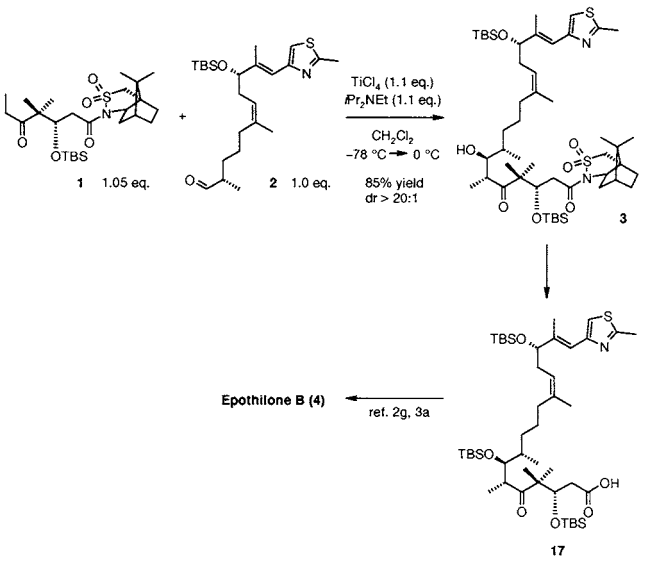
(6) The sample **17** derived from the aldol product **3** was identical with the corresponding compound described in the literature (refs 2g and 3a) with respect to all reported properties.

Table 2. Diastereoselective Aldol Reaction with Chiral Aliphatic Aldehydes

entry	aldehyde	product
1	 **12**	 **13** 63% yield[a], dr 3:2
2	 **14a** R = OBn **14b** R = OPiv	 **15a** R = OBn, 54% yield[b], dr > 20:1 **15b** R = OPiv, 84% yield[a], dr > 20:1

[a] 1.1 equiv of $TiCl_4$, 1.1 equiv of *i*PrNEt$_2$, 1.1 equiv of aldehyde, CH_2Cl_2, −78 to 0 °C. [b] 2.2 equiv of $TiCl_4$, 2.5 equiv of *i*PrNEt$_2$, 2.0 equiv of aldehyde, CH_2Cl_2; −78 to 0 °C.

Scheme 3. Titanium Enolate Aldol Reaction with Aldehyde **2** and Conversion of **3** to Known **16**



In conclusion, we have reported a highly diastereoselective key aldol coupling for an efficient synthesis of epothilones. This process is suitable for large quantity production of intermediates and results in a significant shortcut for the total synthesis of epothilones. In ongoing studies the methodology will be applied to the synthesis of interesting epothilone derivatives.

Acknowledgment. We are grateful to Alfred Schmidt for the preparation of substantial amounts of **1** and *ent*-**1** and Walter Prikoszovich for the ReactIR studies. We thank Grety Rihs for the X-rays of *ent*-**6** and **9a** and Lukas Oberer and Monique Ponelle for NMR analyses. We thank Novartis Pharma AG for support.

Supporting Information Available: Complete experimental procedures, spectral data, and structure correlation for all relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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