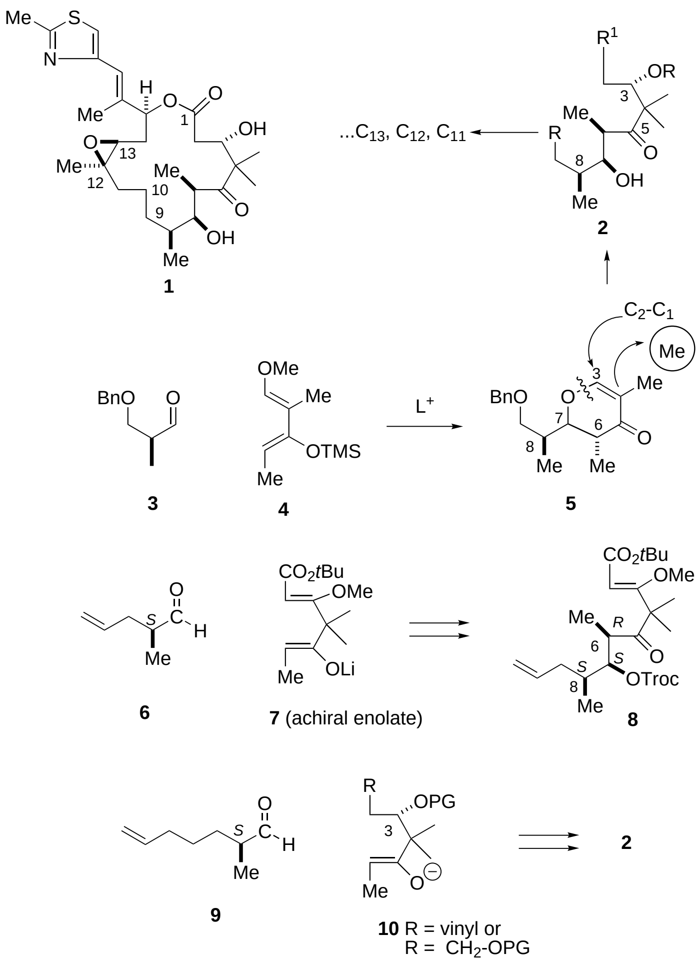
[12] The stereochemical outcome of this addition reaction is consistent with chelation control through the hydroxyl group at C4.
[13] L. J. Mathias, *Synthesis* **1979**, *11*, 561–576.
[14] The benzyl ether at C1′ was oxidized at the ozonolysis step used for installing the carboxy moiety at C5.
[15] V. V. Rheenen, *Tetrahedron Lett.* **1969**, 985–988.
[16] The diastereomeric ratio and stereochemistry at C5′ were determined by ^{1}H NMR analysis. See the Supporting Information.
[17] A. J. Robichaud, G. D. Berger, D. A. Evans, *Tetrahedron Lett.* **1993**, *34*, 8403–8406.
[18] Reaction temperature and the solvent are critical in this step. In fact, the alkyllithium reagent is not reactive to the lactone at −78 °C and unstable above −10 °C. We have used slightly modified Evans conditions. See ref. [3d].
[19] The spectral data for **19** was identical in all respects to the authentic sample which was prepared from natural zaragozic acid A.
[20] This selective protection was reported by Carreira et al.; see ref. [3c].
[21] Synthesis of the side chain at C6: K. Tomooka, A. Nagasawa, S.-Y. Wei, T. Nakai, *Tetrahedron Lett.* **1996**, *37*, 8895–8898.

Subtle Variations in the Long-Range Transmission of Stereochemical Information: Matched and Mismatched Aldol Reactions[**]

Zhicai Wu, Fei Zhang, and Samuel J. Danishefsky*

In this paper we describe findings with respect to an important question in stereospecific synthesis, that is, how might remote stereogenic loci influence the diastereofacial sense in which covalent bond formation occurs. To address this type of issue in concrete rather than abstract terms, we focused on the very promising antitumor agents, the epothilones (such as epothilone B (**1**), shown in Scheme 1). These compounds have stimulated a great deal of research from the point of view of total synthesis.[1–6] In this paper we do not directly address the total synthesis problem per se. Rather, we focus on the construction of the C6–C7 bond in the acyl sector en route to the natural products, as a paradigm for accomplishing high orders of selection by long-range induction.

By way of background we note that, originally,[1a, 1c] the stereochemical information for building the "acyl" sector of the epothilones (see **2** in Scheme 1) was stored in dihydropyrone **5** which itself arose from a cyclocondensation reaction of enantiomerically pure **3** and diene **4**. In our second-generation synthesis,[7] the enantiomerically homogenous **6** reacted with achiral enolate **7**, giving rise selectively (approximate ratio = 5.5:1) to **8**, with the required *R*, *S*, and *S* configurations at C6, C7, and C8, respectively. The configuration at C3 was subsequently induced by catalytic, reagent-based, asymmetric reduction. System **2** can now be prepared in a highly convergent fashion on a multigram scale by this synthesis.[6]



Scheme 1. Structure of epothilone B (**1**) and several methods for the construction of the C6–C7 bond in the acyl sector (**2**) of the epothilones. Bn = benzyl, TMS = trimethylsilyl, Troc = trichloroethoxycarbonyl, PG = protecting group.

The background result which was central to the program described below was reported by Schinzer and co-workers,[3a] and was subsequently used by others.[4e, 8] The essence of Schinzer's claim[9] was that aldol condensation of the enantiomerically defined lithio enolate system (see **10** in Scheme 1) with the enantiomerically defined aldehyde **9** occurs with high stereoselection in the required sense at the emerging C6–C7 bond, leading, eventually, to a product of type **2**. In essence, in the approach of Schinzer et al., the chirality at C3 had induced the required C6(*R*) and C7(S) configurations. This is in contrast to our second generation approach where the stereogenicity was induced solely by the *S* aldehyde **6**.

We undertook to revisit this type of aldol condensation for several reasons. The role of the pre-C8 *S* methyl group in **9** in delivering the high diastereofacial selectivity at C6 and C7

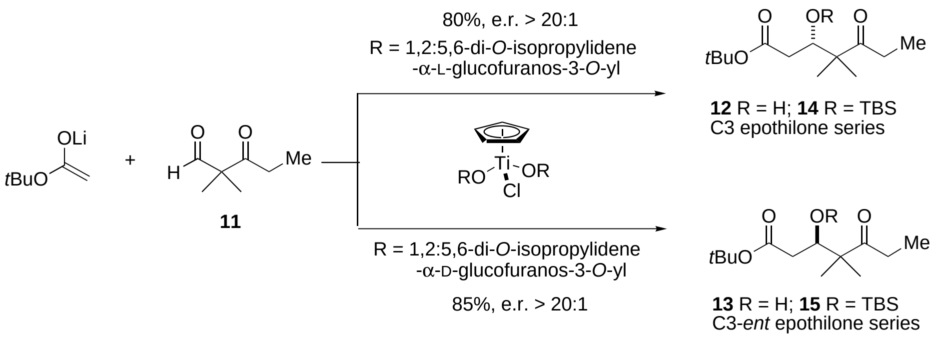
---

[*] Prof. S. J. Danishefsky, Dr. Z. Wu, F. Zhang
Department of Chemistry
Columbia University
Havemeyer Hall, 3000 Broadway, New York, NY 10027 (USA)
E-mail: s-danishefsky@ski.mskcc.org

Prof. S. J. Danishefsky
Laboratory for Bioorganic Chemistry
Sloan-Kettering Institute for Cancer Research
1275 York Avenue, New York, NY 10021 (USA)
Fax: (+1) 212-772-8691

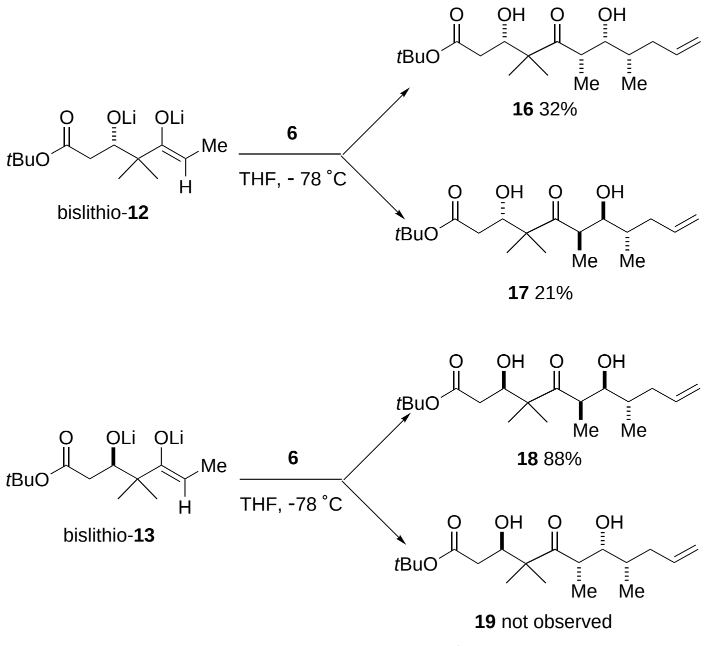
[**] This work was supported by the National Institutes of Health (Grant Nos. CA-28824 and HL-25848).

was not established. The β-hydroxy *tert*-butyl ester **12** was prepared with high enantioselectivity by the reaction of aldehyde **11** with lithio *tert*-butyl acetate following precedents and protocols described by Duthaler and co-workers in other contexts (Scheme 2).[10] With the expectation of probing the basis of Schinzer et al.'s findings in greater detail, we also prepared the *ent* β-hydroxyester **13** and converted the enantiomeric C3 alcohols into their TBS derivatives **14** and **15**. However, we were unable to effect aldol condensation between **6** and the lithio enolates derived from **12** or **13** owing to vulnerabilities in the β-siloxyester network.



Scheme 2. Asymmetric synthesis of stereogenic center C3. e.r. = enantiomeric ratio, TBS = *tert*-butyldimethylsilyl.

Given our inability to couple **14** and **15** as their lithium enolates, we examined the feasibility of using the enantiomeric β-hydroxy esters **12** and **13** in the form of their lithio enolate alkoxides, in the coupling reactions with **6** (Scheme 3).[11] In these cases, β-elimination of the C3 oxygen was not a problem and aldol condensation proceeded smoothly. The results were most interesting. When the C3(*S*) enolate corresponding to **12** was treated with enantiomerically pure aldehyde **6**, there was generated a 3:2 ratio of two products. Subsequently, it was shown by correlation (see below) that the major product, **16**, corresponds to a C6/C7 bis-*epi* version of **2** (that is, C6(*S*) and C7(*R*)), while the latter **17**, has the required epothilone configurations, C6(*R*) and C7(*S*) (in addition to being *S* at C3).

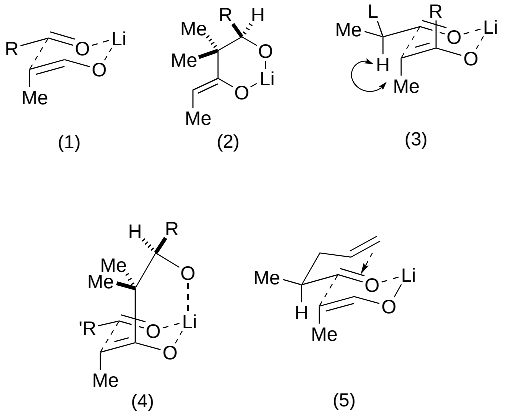


Scheme 3. Aldol reactions of the enantiomeric β-hydroxy esters **12** and **13** with **6**.

We then examined the corresponding reaction employing the enolate alkoxides derived from the *ent* precursor **13**. Remarkably, this reaction gave rise to a single aldol product (Scheme 3). Correlation with other intermediates in the program (see below) established that the C6 and C7 configurations in **18** correspond to those required to reach an intermediate such as **2**. Of course, the configuration at C3 in **18** is *R* rather than the required *S*. Hence, the use of compound **18** in a total synthesis of a naturally configured epothilone would require inversion at C3.

Nonetheless, these results are quite informative. They teach that the transition state of the aldol reaction of the C3-unprotected enolate system with **6** is very different from that of the protected enolate **10** with **9**.[3, 8] Thus, in the C3-protected series (in the case of Schinzer et al.) *S* chirality at C3 is needed to deliver the required C6(*R*),C7(*S*) configurations in the aldol product, following condensation with enantiomerically pure (*S*)-**9**. By contrast, in the C3-unprotected dilithio series (see **13**), it is the C3(*R*) enantiomer which delivers the C6(*R*),C7(*S*) configurations with the corresponding very similar aldehyde **6**.

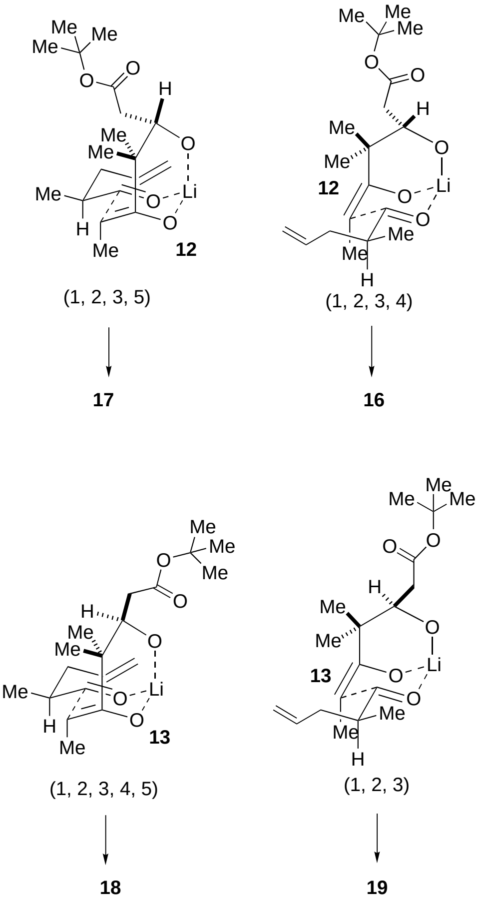
In addition to accounting for the sharp difference in outcomes as a function of the state of protection at C3, we sought to explain why the **12**+**6** case gave rise to a virtually 1:1 mixture of **16** and **17**, while the **13**+**6** combination is matched, leading cleanly to a single product **18**. We propose that there are five desiderata for such an aldol condensation (Scheme 4): 1) The usual chair transition state in the C–C bond formation,[12] 2) chelation of the lithium counterion (or counterions) by the alkoxido and enolate oxygens,[13] 3) a *syn* relationship between the C2 proton of **6** and the C6 methyl group of the



Scheme 4. Five desiderata for the aldol condensation.

enolate,[14] 4) attack by the aldehyde *anti* to the large resident R group of the enolate, and 5) attack by the enolate on the face of the aldehyde which is *anti* to the resident allyl or pentenyl group. In starting with electrophile **6**, the special γ,δ-unsaturated aldehyde effect[7b] will tend to orient the double bond of the allyl function for a favorable interaction (perhaps by π-stacking) with the aldehyde group.[7]

While the relative weightings of these factors are not known, we note that in the reaction of *R* enolate **13** with **6** to give **18**, the transition state of the aldol step shown incorporates each of the energy-lowering features (1)–(5) (Scheme 5). Thus, the two enantiotopicities of **13** and **6** are matched to produce **18**.[15] The transition state alignment that would be necessary to produce the alternative, not observed, C6,C7-*erythro* product **19**, given the incorporation of features (1)–(3), would be lacking favorable elements (4) and (5). In a similar vein, in combining the *S* enolate **12** with **6**, with inclusion of features (1)–(3) as given, each transition state is seriously unoptimal. To reach **17**, attack of aldehyde **6** must occur *syn* to the large R group projecting from the chelate. Conversely, in reaching **16**, the effect from overlap of the terminal vinyl group with the aldehyde is forfeited.

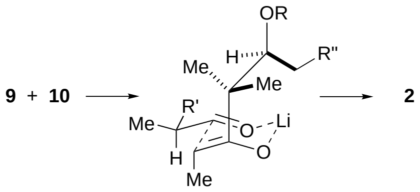


Scheme 5. Proposed transition states in the aldol reactions of **12** and **13** with **6**.

To explore these concepts further, we conducted a critical experiment to test the postulate implied in Scheme 2. We reasoned that if ensembles pre-**16** and pre-**17** correspond to mismatches, while **18** is matched, there could be measurable kinetic consequences. We probed this matter by using a racemic mixture of enolates **12** and **13** with a limiting concentration of enantiopure aldehyde **6**. In practice this experiment turned out to be most revealing. Reaction of racemic **12**:**13** (one equivalent) with lithium diisopropylamide (two equivalents) to achieve double deprotonation) was followed by addition of approximately half an equivalent of optically pure (*S*)-**6**. Remarkably, this reaction produced **18** (70% yield) virtually free of **16** or **17** (or **19**) [Eq. (1)]. In short, the matched/mismatched hypothesis has been corroborated at the kinetic level in a remarkable instance of molecular recognition in covalent bond formation through an aldol condensation.

$$\mathbf{12}\ (0.5\ \text{equiv}) + \mathbf{13}\ (0.5\ \text{equiv}) + \text{LDA}\ (2\ \text{equiv}) \longrightarrow [\text{racemic alkoxide enolates}] \xrightarrow{\mathbf{6}\ (\approx 0.5\ \text{equiv})} \mathbf{18} \tag{1}$$

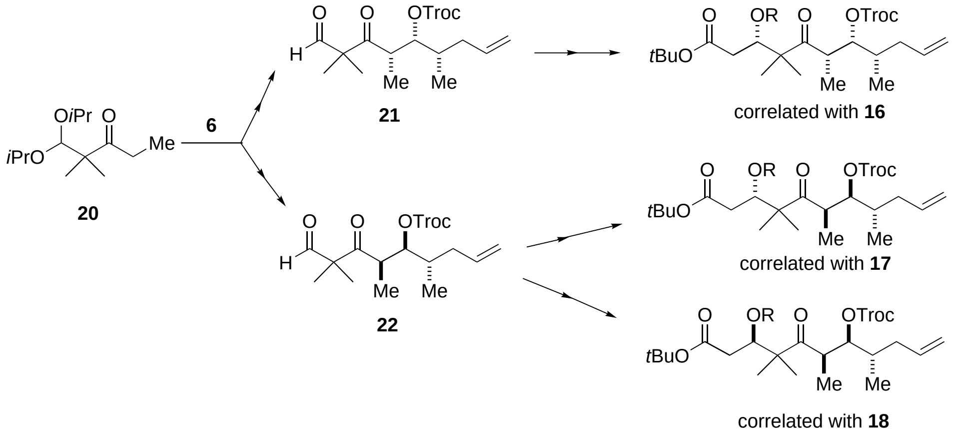
In addition, our data strongly suggest that in the C3-protected series (such as **10**), the chirality induction does not involve chelation between C3 and C5.[16] Indeed, the protecting groups which have been used at C3[3, 8] tend to be large and thus disfavor a chelate-directed conformational organization. By contrast the transition state in Scheme 6 nicely accounts for the sense of the stereochemical transmission in the C3-protected enolate series. We propose that the C3 "OR" group is positioned *anti* to the C4–C5 bond. In the C3(*S*) enolate **10**, attack of aldehyde **9** *syn* to the C3 hydrogen leads to **2**, with C6(*R*),C7(*S*) configuration (as required for the epothilones). This combination can be termed as matched. The formation of the C6(*S*),C7(*R*) product from the ensemble of **9** and **10** as proposed would require attack to occur *syn* to the CH_2R'' face of the enolate on the R′ face of the aldehyde.



Scheme 6. Proposed transition state for C3-protected series.

The structures of **16**–**18** were established by methods which demonstrate the capacity to control the configuration at C3 by the "titano" *tert*-butyl acetate method (Scheme 7).[10] Correlations started with condensation of lithio-**20** with **6** to afford the C6(*R*),C7(*S*) and C6(*S*),C7(*R*) aldol products in a 4:1 ratio. Protection of each compound as the Troc derivative and deprotection of the aldehyde function afforded compounds **21** and **22**. Following diastereospecific two-carbon homologation of these compounds, correlation with **16**–**18** was readily accomplished.

In summary, the strikingly different senses of long-range transmission (over five bonds) of stereochemical information in seemingly related aldol condensations have been rationalized by comparing the effects of resident silyl ether and "lithio alkoxy" functions. In the case of the lithio alkoxy enolates, a huge kinetic advantage favoring the matched series has been



Scheme 7. Independent synthesis of compounds for correlation with **16**–**18**.

demonstrated. Extensions of these findings to other instances of long-range transmission of stereochemical bias are a continuing area of interest in our laboratory.

Received: August 14, 2000 [Z15630]

---

[1] a) A. Balog, D. F. Meng, T. Kamenecka, P. Bertinato, D. S. Su, E. J. Sorensen, S. J. Danishefsky, *Angew. Chem.* **1996**, *108*, 2976; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2801; b) D. S. Su, D. F. Meng, P. Bertinato, A. Balog, E. J. Sorensen, S. J. Danishefsky, Y. H. Zheng, T. C. Chou, L. F. He, S. B. Horwitz, *Angew. Chem.* **1997**, *109*, 775; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 757; c) D. F. Meng, P. Bertinato, A. Balog, D. S. Su, T. Kamenecka, E. J. Sorensen, S. J. Danishefsky, *J. Am. Chem. Soc.* **1997**, *119*, 10073; d) M. D. Chappell, S. J. Stachel, C. B. Lee, S. J. Danishefsky, *Org. Lett.* **2000**, *2*, 1633; e) S. J. Stachel, M. D. Chappell, C. B. Lee, S. J. Danishefsky, T.-C. Chou, L. He, S. B. Horwitz, *Org. Lett.* **2000**, *2*, 1637.

[2] a) Z. Yang, Y. He, D. Vourloumis, H. Vallberg, K. C. Nicolaou, *Angew. Chem.* **1997**, *109*, 170; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 166; b) K. C. Nicolaou, F. Sarabia, S. Ninkovic, Z. Yang, *Angew. Chem.* **1997**, *109*, 539; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 525; c) K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, F. Roschangar, F. Sarabia, S. Ninkovic, Z. Yang, J. I. Trujillo, *J. Am. Chem. Soc.* **1997**, *119*, 7960; d) K. C. Nicolaou, Y. He, F. Roschangar, N. P. King, D. Vourloumis, T. H. Li, *Angew. Chem.* **1998**, *110*, 89; *Angew. Chem. Int. Ed.* **1998**, *37*, 84.

[3] a) D. Schinzer, A. Limberg, A. Bauer, O. M. Bohm, M. Cordes, *Angew. Chem.* **1997**, *109*, 543; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 523; b) D. Schinzer, A. Bauer, O. M. Bohm, A. Limberg, M. Cordes, *Chem. Eur. J.* **1999**, *5*, 2483; c) D. Schinzer, A. Bauer, J. Schieber, *Chem. Eur. J.* **1999**, *5*, 2492.

[4] a) S. A. May, P. A. Grieco, *Chem. Commun.* **1998**, 1597; b) J. D. White, R. G. Carter, K. F. Sundermann, *J. Org. Chem.* **1999**, *64*, 684; c) J. D. White, K. F. Sundermann, R. G. Carter, *Org. Lett.* **1999**, *1*, 1431; d) D. Sawada, M. Shibasaki, *Angew. Chem.* **2000**, *112*, 215; *Angew. Chem. Int. Ed.* **2000**, *39*, 209; e) H. M. Martin, M. Drescher, J. Mulzer, *Angew. Chem.* **2000**, *112*, 591; *Angew. Chem. Int. Ed.* **2000**, *39*, 581.

[5] a) G. H. Hofle, N. Bedorf, H. Steinmetz, D. Schomburg, K. Gerth, H. Reichenbach, *Angew. Chem.* **1996**, *108*, 1671, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1567; b) R. J. Kowalski, E. Terhaar, R. E. Longley, S. P. Gunasekera, C. M. Lin, B. V. Day, E. Hamel, *Mol. Biol. Cell* **1995**, *6*, 2137; c) P. F. Muhlradt, F. Sasse, *Cancer Res.* **1997**, *57*, 3344; for reviews, see: d) K. C. Nicolaou, F. Roschangar, D. Vourloumis, *Angew. Chem.* **1998**, *110*, 2120; *Angew. Chem. Int. Ed.* **1998**, *37*, 2015; e) C. R. Harris, S. J. Danishefsky, *J. Org. Chem.* **1999**, *64*, 8434.

[6] Given the exciting biological properties of the epothilones, the challenge nowadays lies in developing a highly processable total syntheses that produces novel epothilones for clinical trials. Our current, still unoptimized, methodology produces dEpoB[5e] on multigram scale.

[7] a) A. Balog, C. R. Harris, K. Savin, X.-G. Zhang, T. C. Chou, S. J. Danishefsky, *Angew. Chem.* **1998**, *110*, 2821; *Angew. Chem. Int. Ed.* **1998**, *37*, 2675; b) C. R. Harris, S. D. Kuduk, A. Balog, K. Savin, P. W. Glunz, S. J. Danishefsky, *J. Am. Chem. Soc.* **1999**, *121*, 7050.

[8] a) J. Mulzer, A. Mantoulidis, E. Ohler, *Tetrahedron Lett.* **1998**, *39*, 8633; b) K. C. Nicolaou, D. Hepworth, M. Ray, V. Finlay, N. P. King, B. Werschkun, A. Bigot, *Chem. Commun.* **1999**, 519.

[9] A similar boron enolate aldol reaction was reported: D. A. Evans, M. A. Calter. *Tetrahedron Lett.* **1993**, *34*, 6871.

[10] R. O. Duthaler, P. Herold, W. Lottenbach, K. Oertle, M. Riediker, *Angew. Chem.* **1989**, *101*, 490; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 495.

[11] For examples of aldol reactions of β'-hydroxy ketones, see: a) P. A. McCarthy, M. Kageyama, *J. Org. Chem.* **1987**, *52*, 4681; b) V. A. Martin, D. H. Murray, N. E. Pratt, Y.-B. Zhao, K. F. Albizati, *J. Am. Chem. Soc.* **1990**, *112*, 6965; c) G. P. Luke, J. Morris, *J. Org. Chem.* **1995**, *60*, 3013.

[12] a) H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920; b) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, J. Lampe, *J. Org. Chem.* **1980**, *45*, 1066.

[13] a) C. H. Heathcock, M. C. Pirrung, J. Lampe, C. T. Buse, S. D. Young, *J. Org. Chem.* **1981**, *46*, 2290; b) G. Frater, *Tetrahedron Lett.* **1981**, *22*, 425; c) D. Seebach, D. Wasmuth, *Angew. Chem.* **1981**, *93*, 1009; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 971; d) D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.* **1982**, *104*, 1737; e) P. Williard, J. M. Salvino, *Tetrahedron Lett.* **1985**, *26*, 3931.

[14] W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151, and references therein.

[15] For reviews on double asymmetric induction, see: S. Masamune, W. Choy, J. S. Petersen, L. R. Sita, *Angew. Chem.* **1985**, *97*, 1; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1. For early examples of double asymmetric aldol reactions, see: a) C. H. Heathcock, C. T. White, *J. Am. Chem. Soc.* **1979**, *101*, 7076; b) S. Masamune, M. Hirama, S. Mori, S. A. Ali, D. S. Garvey, *J. Am. Chem. Soc.* **1981**, *103*, 1568; c) D. A. Evans, J. Bartroli, *Tetrahedron Lett.* **1982**, *23*, 807.

[16] For proposed double chelation involving β-alkoxy aldehyde, see: ref. [4b] and J. Mulzer, A. Mantoulidis, *Tetrahedron Lett.* **1996**, *37*, 9179.