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An Efficient Total Synthesis of (−)-Epothilone B

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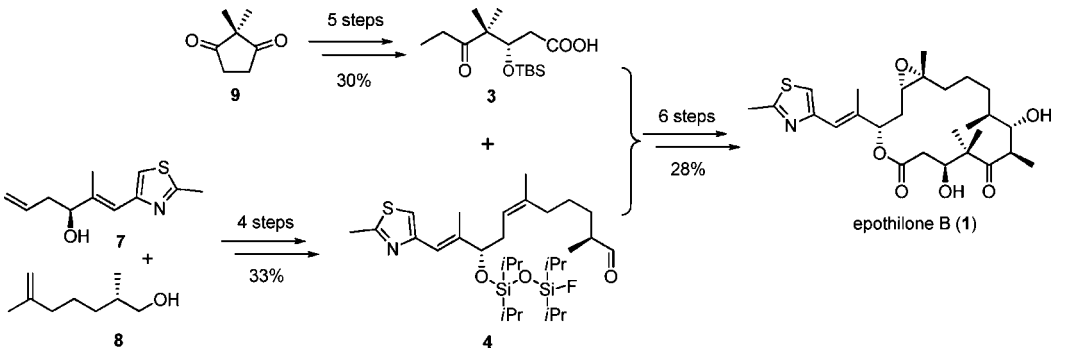
ABSTRACT



An efficient total synthesis of (−)-epothilone B has been achieved in ca. 8% yield over 11 steps from 9 (or 10 steps from 7/8), which features a bissiloxane-tethered ring closing metathesis reaction to approach the trisubstituted (*Z*) double bond and forms a new basis for further development of an industrial process for epothilone B and ixabepilone.

Epothilones A−F are a group of macrolides isolated from myxobacteria *Sorangium cellulosum*.[1] Like taxanes, epothilones interrupt the cell mitosis through interfering with the binding and functioning of tubulins. Interestingly, these natural products exhibit potent cytotoxicities even in taxol-resistant cell lines.[2] Among these, epothilone B (**1**) is the most prominent member whose *aza* analogue, ixabepilone, has been approved by the FDA as an anti-breast cancer drug (Figure 1). Moreover, investigations on the potential of **1** to fight against other types of cancers are still ongoing.

In view of the biological profile of **1**, despite the fact that these compounds can be procured quite efficiently from fermentation, the constant quest for active derivatives with optimal therapeutic indices has stimulated an ever-increasing number of total syntheses.[3] An efficient total synthesis that provides opportunities for variations on the scaffold to access new analogues is still highly desirable. Critical to an efficient synthesis of epothilone B is a convergent strategy which allows for the selective establishment of the trisubstituted (*Z*) olefin at C12−C13. Although the strategies based on palladium-catalyzed coupling reactions[4] or Wittig-type reactions[5] could address this issue with success, they generally fell short of step economy. Notably, Avery's group realized the efficient construction of the trisubstituted double bond with a Normant coupling reaction.[6]

(1) (a) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325–2333. (b) Gerth, K.; Bedorf, N.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 560. (c) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem., Int. Ed.* **1996**, *35*, 1567. (d) Höfle, G.; Glaser, N.; Kiffe, M.; H.-J. Hecht, H.-J.; Sasse, F.; Reichenbach, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1971.

(2) Bollag, D. M. *Exp. Opin. Invest. Drugs* **1997**, *6*, 867–873.

(3) For a review on syntheses of epothilones, see: (a) Altmann, K.-H.; Höfle, G.; Müller, R.; Mulzer, J.; Prantz, K. *The Epothilones: An Outstanding Family of Anti-Tumor Agents-From Soil to the Clinic*, Vol. 90; Springer: Vienna, 2009. For a most recent formal synthesis of epothilone D, see: (b) Prantz, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5030–5033.

(4) (a) Meng, D.; Bertinato, P.; Balog, A.; Su, D. S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073–10092. (b) Schinzer, K. C.; Bauer, A.; Schieber, J. *Chem.—Eur. J.* **1999**, *5*, 2492–2500.

(5) (a) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974–7991. (b) Mulzer, J.; Mantoulidis, A.; Öhler, E. *Tetrahedron Lett.* **1998**, *39*, 8633–8636.

(6) Jung, J.-C.; Kache, R.; Vines, K. K.; Zheng, Y.-S.; Bijoy, P.; Valluri, M.; Avery, M. A. *J. Org. Chem.* **2004**, *69*, 9269–9284.

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More recently, Mulzer's group devised a Grob fragmentation enabled stereospecific construction of such a double bond.[3b] Herein we report an efficient total synthesis of epothilone B featuring a bissiloxane-tethered ring closing metathesis (RCM) reaction to approach the trisubstituted (*Z*) double bond.

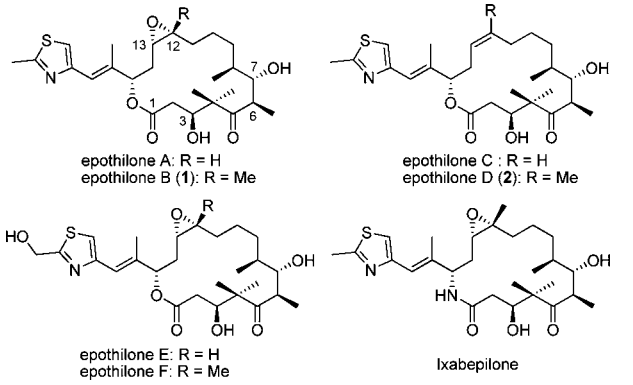
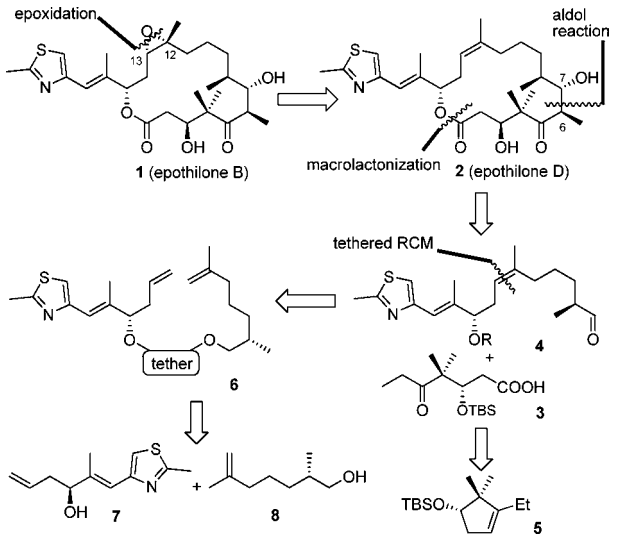


Figure 1. Epothilone A–F and Ixabepilone.

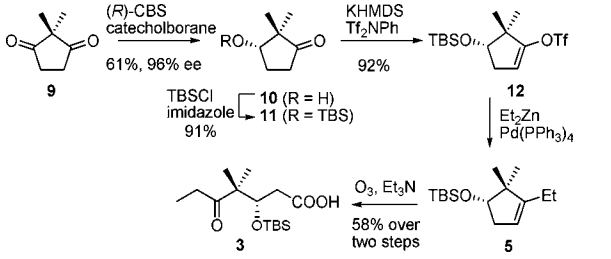
Scheme 1. Retrosynthesis of Epothilone B (**1**)



Our retrosynthesis of **1** was depicted in Scheme 1. Epothilone B (**1**) was reduced to epothilone D (**2**) by removal of the epoxide oxygen.[4a,5a] The 16-membered macrocycle of **2** was envisaged to stem from the aldol reaction of **3** and **4** and the subsequent macrolactonization.[4a,5a] Ketoacid **3** could be traced back to **5** by way of ozonolytic cleavage of the cyclopentene ring. Aldehyde **4** containing the trisubstituted *Z* double bond was anticipated to derive from a tethered RCM reaction of **6**, which in turn could be assembled from segments **7**[4a,5a] and **8**.[4b]

Our synthetic journey commenced with a novel synthesis of ketoacid **3** (Scheme 2). Thus, asymmetric reduction of 2,2-dimethyl-1,3-cyclopentandione (**9**) with catecholborane catalyzed by (*R*)-CBS delivered alcohol **10** in 61% yield with 96% ee.[7] Compound **10** was protected as TBS ether **11**, followed by treatment with KHMDS/Tf_2NPh to furnish vinyl triflate **12**. The Negishi coupling reaction of **12** with Et_2Zn proceeded smoothly in the presence of 5 mol % $Pd(Ph_3P)_4$ to generate alkene **5**, which was subsequently exposed to ozonolysis to produce **3** in 58% yield over two steps. This catalytic enantioselective procedure delivers **3** in 30% overall yield spanning five steps from **9**.

Scheme 2. Asymmetric Synthesis of **3**



Stereoseletive construction of the trisubstituted (*Z*) double bond in **1** via RCM represents a significant challenge due to the lack of stereocontrol. Usually, the (*E*) isomer was formed as the major product.[8] In 2005, Mulzer's group successfully established this double bond with 5/1 selectivity by employing a silicon-tethered RCM reaction, although the follow-up steps leading to **4** (R = TBS) were lacking step economy.[9] In our tethered-RCM strategy, the whole segment **8** would be utilized to improve the overall synthetic efficiency. It was anticipated that the stereoselectivity of the RCM reaction could be controlled by the tethers which, toward that end, would vary both sterically and electronically.

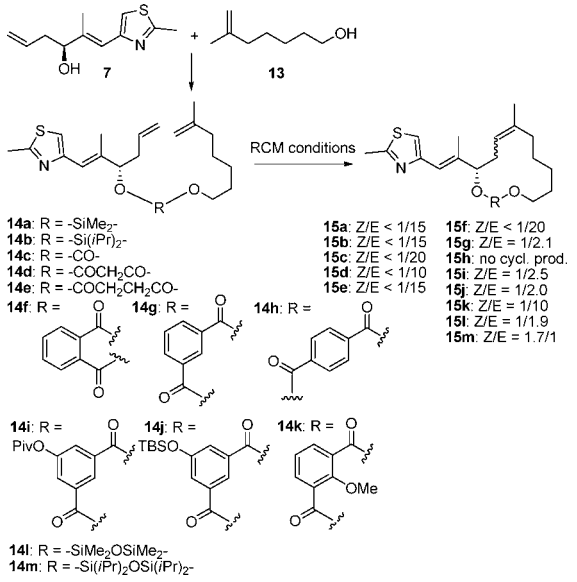
A model study was initiated by employing **7** and **13** as the components which were first assembled with various tethers to give the RCM precursors **14a**–**m** and then subjected to RCM conditions, respectively (Scheme 3). Generally, the macrocyclization was successful (**14a**–**g**, **14i**–**m**), except that the cyclophane-type substrate **14h** failed to give any cyclization product probably due to the ring strain. On the other hand, most of the tethered substrates (**14a**–**f**, **14k**) produced the (*E*) isomers predominantly (*E*/*Z* > 10/1). Interestingly, *meta*-cyclophanes (**14g**, **14i**, **14j**) delivered the isomers with improved selectivity (*E*/*Z* > 2/1). To our delight, bissiloxane-tethered substrates were found capable of producing the olefins with improved selectivities for the (*Z*) isomer. Thus, with **14l** as the substrate, alkene **15l** was obtained with a *Z*/*E* ratio of 1/1.9. Further, with **14m** as the substrate, the selectivity was enhanced to 1.7/1, favoring the (*Z*) isomer. Notably, these represent the first examples employing bissiloxane tethers for RCM reactions.

(7) Yeung, Y. Y.; Chein, R. J.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 10346–10347.

(8) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem., Int. Ed.* **1998**, *37*, 2014–2045.

(9) Mulzer, J.; Gaich, T. *Org. Lett.* **2005**, *7*, 1311.

Scheme 3. A Model Study of the Tethered RCM Reactions

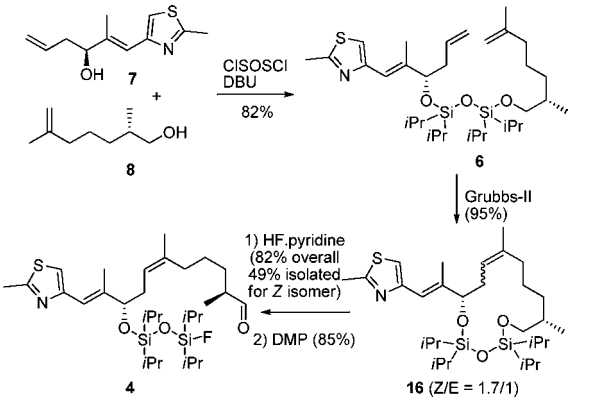


The optimal conditions obtained from the model study were applied to the construction of **4** (Scheme 4). Segments **7** and **8** were joined with $ClSi(iPr)_2OSi(iPr)_2Cl$ (ClSOSCl) in the presence of DBU to deliver **6** in 82% yield. Gratifyingly, the RCM reaction of **6** proceeded efficiently in the presence of the Grubbs-II catalyst (5 mol %) to give **16** in a nearly quantitative yield (95%) with a selectivity of 1.7/1 favoring the desired (*Z*) isomer. The subsequent cleavage of the SOS tether was critical for an efficient protecting-group manipulation. After examining several reagents, HF·pyridine was found capable of selectively cleaving the least hindered Si−O bond, generating $FSi(iPr)_2OSi(iPr)_2$ (FSOS) group attaching to the more hindered C15−O atom. After separation of the two stereoisomers by chromatography followed by oxidation of the (*Z*) isomer with Dess-Martin periodinan, aldehyde **4** was obtained in 40% yield over three steps from **6**. Notably, this new synthetic route delivers **4** in 33% overall yield covering merely four steps from **7** (**8**), which is so far the most step-economic synthesis of this key segment.[10]

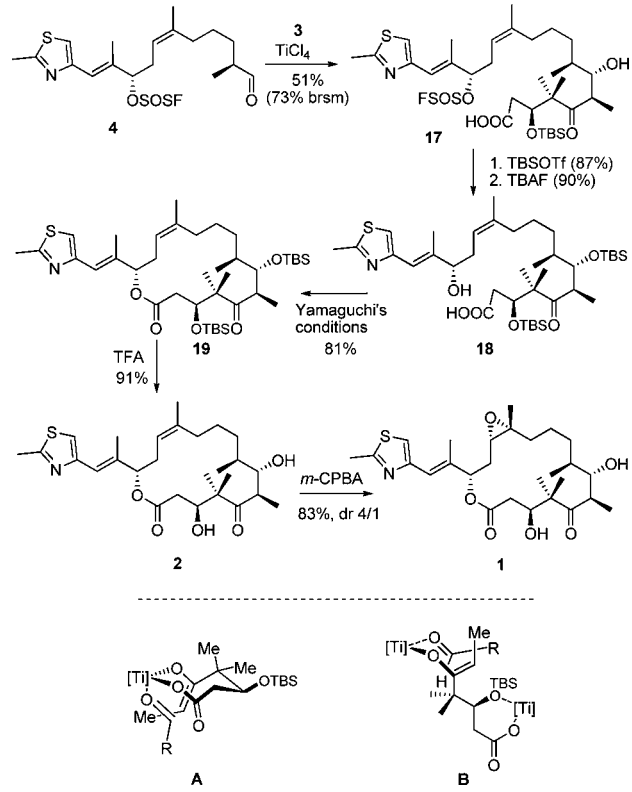
With both **3** and **4** in hand, the stage was now set for the critical aldol reaction (Scheme 5). In the previously reported syntheses, the aldol reaction with ketoacid **3** as the substrate had generally been ineffective in controlling the diastereoselectivity of the newly generated stereocenters at C6 and C7.[5a,6] To achieve efficient stereocontrol, it had been necessary to use substrates with protected alcohols[4b,6] or an auxiliary[6] in place of the free carboxylic acid. We anticipated realizing the aldol reaction with the direct use of the carboxylic acid as the substrate for higher synthetic efficiency. Employment of LDA (2.5 equiv) generated the aldol product with a diastereoselectivity of ca. 1/1. Fortunately, treatment

(10) Both **7** and **8** were synthesized in three steps. See Supporting Information for the details. For previous syntheses of **4** (R = TBS), see: References 5a (17 steps), 4b (12 steps), 9 (11 steps), and 3b (16 steps). For previous syntheses of **4** (R = SEM), see: Reference 6 (8 steps).

Scheme 4. Synthesis of **4** via Bissiloxane-Tethered RCM Reaction



Scheme 5. Total Synthesis of (−)-Epothilone D (**2**) and (−)-Epothilone B (**1**)



of **3** with $TiCl_4$/DIPEA[6] (2 equiv for each) followed by addition of **4** afforded **17** in 51% yield (73% brsm) as a single diastereomer as determined by ^1H NMR. Both the compact transition state **A** and the extended transition state **B** could account for the observed stereochemical outcome of this reaction. However, transition state **B** appears more reasonable based on the evidence that usage of 2 equiv of $TiCl_4$ was necessary for the reaction to proceed effectively.

The aldol product **17** was advanced into the targets (Scheme 5). Protection of C7-OH with TBSOTf/2, 6-lutidine followed by the selective removal of FSOS with TBAF generated **18**. Finally, by following the known procedure, **18** was converted to epothilone D (**2**) and epothilone B (**1**) successfully.[5a] Thus, **18** was exposed to Yamaguchi's conditions to effect the macrolactonization to engender **19** in 81% yield. Global deprotection with TFA afforded epothilone D (**2**) in 91% yield. Finally, treatment of **2** with *m*-CPBA produced epothilone B (**1**) and its isomer in 4/1 ratio with 83% overall yield. The spectroscopic data of synthetic **2** and **1** matched those reported for the natural products.

In conclusion, an efficient total synthesis of (−)-epothilone B (**1**) has been achieved in ca. 8% yield over 11 steps from **9** or 10 steps from **7**/**8** (each being synthesized in three steps), which forms a new basis for further development of an industrial process for epothilone B and ixabepilone. This new synthetic route of epothilone B features a novel and efficient synthesis of **3**, a bissiloxane-tethered RCM reaction which efficiently realized the assemblage of segments **7** and **8** with selective formation of the trisubstituted (*Z*) double bond, and a stereochemically well controlled aldol reaction of unmasked carboxylic acid **3** with **4**. The demonstrated success in the bissiloxane tethered RCM reactions, along with the success in the partial cleavage of the SOS tether and the selective removal of FSOS in the presence of TBS, points to the potential broader interests of SOS in organic synthesis, especially in the total synthesis of complex molecules.

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Supporting Information Available. Experimental procedures, characterization data for new compounds, and selected copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.